⟨1059⟩ EXCIPIENT PERFORMANCE

INTRODUCTION

Excipients are used in virtually all drug products and are essential for product manufacturing and performance. Thus, the successful manufacture of a robust product requires the use of well-defined excipients and manufacturing processes that consistently yield a quality product. Excipients used in drug products typically are manufactured and supplied in compliance with compendial standards. However, the effects of excipient properties on the critical quality attributes (CQAs) of a drug product are unique for each formulation and process and may depend on properties of excipients that are not evaluated in *USP* or *NF* monographs. The effects of variations in excipient material attributes depend on the role of an excipient in a formulation and the CQAs of the drug product. This general chapter provides a framework for applying Quality by Design (QBD) principles to excipient quality and performance.

An excipient may be used in different ways or for different purposes in a formulation and may therefore require different material attributes to achieve the desired performance. Excipient functional categories are broad, qualitative, and descriptive terms for the purpose an excipient serves in a formulation. A list of excipients grouped by functional category is included in *NF* under *Front Matter, Excipients,* which summarizes some of the more common purposes that excipients serve in drug products. Also important are the material attributes of the ingredients that must be identified and controlled to ensure the excipient performs its intended function in a drug product. A critical material attribute (CMA) is a physical, chemical, biological, or microbiological property of a material that must be within an appropriate limit, range, or distribution to ensure that drug product CQAs are maintained throughout the product life cycle. Most, but not all, CMAs become tests in a compendial monograph. In some applications, excipient suppliers and users will need to identify and control material attributes in addition to monograph specifications. Identification of CMAs requires a thorough understanding of drug product CQAs; the manufacturing process(es); and the physical, chemical, biological, or microbiological properties of each ingredient. Manufacturers should anticipate lot-to-lot and supplier-to-supplier variability in excipient properties and should have in place appropriate control measures to ensure that CMAs are maintained within the required limits. Prior knowledge, experimental designs, and risk-assessment tools can be used to prioritize and identify CMAs of excipients as well as critical process parameters. A CMA of an excipient may not be related to the major component of the excipient because, for example, the presence of minor components (e.g., peroxides, elemental impurities, or microbiological content) may affect product stability or quality. Good product development practices, which at times are termed QBD principles, require understanding excipient CMAs that contribute to consistent performance and are the foundation of a control strategy that accommodates excipient variability, consistently achieving final product CQAs.

This informational general chapter provides an overview of the key functional categories of excipients and tests or procedures that can be used to monitor and control CMAs.[1]

In this chapter, the functional categories have been organized by their most typical use in common pharmaceutical dosage forms. However, functional categories can apply to multiple dosage forms. The association of a functional category with a particular dosage form does not limit the use of an excipient to a single type of dosage form or delivery system. Each functional category includes a general description; the mechanisms by which excipients achieve their function; physical properties common to these excipients; chemical properties; and a list of *USP* general chapters that can be useful in the development of specific tests, procedures, and acceptance criteria to ensure that CMAs are adequately monitored and controlled. Because of the complex nature and interplay of formulation ingredients, processing, and dosage form performance requirements, the information provided in this chapter should not be viewed as either restrictive or completely comprehensive.

Change to read:

TABLETS AND CAPSULES

Functional Category: Diluent

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 compose a large portion of the dosage form, and the quantity and type of diluent selected often depend on its physical and chemical properties. Thus, successful and robust manufacturing and dosage form performance depend on the measurement and control of the CMAs.

FUNCTIONAL MECHANISM

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

[1] This general information chapter provides nonmandatory information that does not create compendial requirements. For additional information about nonmandatory general chapters and alternative methods and procedures, see *General Notices, 6.30 Alternative and Harmonized Methods and Procedures.*

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, 9) crystal form, and 10) 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 (e.g., silicified microcrystalline cellulose or sugar spheres), 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 can have a positive or negative effect on the drug substance physical or chemical stability and on 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 drug substance and dosage form. The detailed composition of an excipient may be important because excipient function could be influenced by the presence of minor concomitant components that are essential for proper performance. Pharmaceutical scientists may find it necessary to control the presence of undesirable components (e.g., elemental impurities or peroxides) to ensure adequate dosage form stability and performance.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in diluent functions: *Light Diffraction Measurement of Particle Size* ⟨429⟩, *Bulk Density and Tapped Density of Powders* ⟨616⟩, *Crystallinity* ⟨695⟩, *Characterization of Crystalline Solids by Microcalorimetry and Solution Calorimetry* ⟨696⟩, *Density of Solids* ⟨699⟩, *Loss on Drying* ⟨731⟩, *Optical Microscopy* ⟨776⟩, *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩, *Powder Fineness* ⟨811⟩, *Specific Surface Area* ⟨846⟩, *Water Determination* ⟨921⟩, and *Powder Flow* ⟨1174⟩.

Functional Category: Wet Binder

DESCRIPTION

Tablet and 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, and other components and the granulation liquid may be 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 of the granule properties such as flow, handling, strength, resistance to segregation, dustiness, appearance, solubility, compaction, or drug release.

FUNCTIONAL MECHANISM

Binders are soluble or partially soluble in the granulating solvent or, as in the case of native starches, can be made soluble. 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 also may modify interfacial properties, viscosity, or other properties. During drying they may produce solid bridges that yield improved residual dry granule strength.

PHYSICAL PROPERTIES

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

CHEMICAL PROPERTIES

Tablet and capsule binders can 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—influences 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 their composition.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in binder functions: *Bulk Density and Tapped Density of Powders* ⟨616⟩, *Chromatography* ⟨621⟩, *Crystallinity* ⟨695⟩, *Density of Solids* ⟨699⟩, *Loss on Drying* ⟨731⟩, *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩, *Specific Surface Area* ⟨846⟩, *Viscosity—Capillary Methods* ⟨911⟩, and *Powder Flow* ⟨1174⟩.

Functional Category: Disintegrant

DESCRIPTION

Disintegrants are functional components that are added to formulations to promote rapid disintegration into smaller units and to allow a drug substance to dissolve more rapidly. Disintegrants are natural, synthetic, or chemically modified natural polymeric substances. When disintegrants come in contact with water or stomach or intestinal fluid, they function by absorbing liquid and start to swell, dissolve, or form gels. This causes the tablet structure to rupture and disintegrate, producing increased surfaces for enhanced dissolution of the drug substance.

FUNCTIONAL MECHANISM(S)

The ability to interact strongly with water is essential to the disintegrant function. Three major mechanisms describe the function of the various disintegrants: volume increase by swelling, deformation, and capillary action (wicking). In tablet formulations, the function of disintegrants is best described as a combination of two or more of these effects. The onset and degree of the locally achieved actions depend on various parameters of a disintegrant, such as its chemical nature and its particle size distribution and particle shape, as well as some important tablet parameters such as hardness and porosity.

PHYSICAL PROPERTIES

The primary physical properties relevant to a disintegrant are those that describe the product's particle structure as a dry powder or its structure when in contact with water. These properties may include: 1) particle size distribution; 2) water absorption rate; 3) swelling ratio or swelling index; and 4) the characterization of the resulting product, whether it is still a particulate or a gel is formed.

CHEMICAL PROPERTIES

Polymers used as disintegrants are either nonionic or anionic with counterions such as sodium, calcium, or potassium. Nonionic polymers are natural or physically modified polysaccharides such as starches, celluloses, pullulan, or cross-linked polyvinylpyrrolidone. The anionic polymers mainly are chemically modified starches, cellulose products, or low-cross-linked polyacrylates. These chemical properties should be considered in the case of ionic polymers. Disintegration performance is affected by pH changes in the gastrointestinal tract or by complex formation with ionic drug substances.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in disintegrant functions: *Light Diffraction Measurement of Particle Size* ⟨429⟩, *Optical Microscopy* ⟨776⟩, *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩, and *Powder Flow* ⟨1174⟩.

Functional Category: Lubricant

DESCRIPTION

Lubricants typically are 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 before compaction. Liquid lubricants also can 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 by 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 of punches and dies in tablet presses, which helps to reduce friction. Fluid film lubricants resolidify after the pressure is removed. Liquid lubricants are released from the granules under pressure and create a fluid film. They do not resolidify when the pressure is removed but are reabsorbed or redistributed through the tablet matrix over the course of time.

PHYSICAL PROPERTIES

The physical properties that are important for the function of boundary lubricants include particle size, surface area, hydration state, and polymorphic form. Purity (e.g., stearate:palmitate ratio) and moisture content also may be important. The physical properties of possible importance for fluid film lubricants are particle size and solid state/thermal behavior. Purity also may 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), glycerides (glyceryl behenate and distearate), 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 in ensuring consistency in lubricant functions: *Light Diffraction Measurement of Particle Size* ⟨429⟩, *Crystallinity* ⟨695⟩, *Characterization of Crystalline Solids by Microcalorimetry and Solution Calorimetry* ⟨696⟩, *Loss on Drying* ⟨731⟩, *Optical Microscopy* ⟨776⟩, *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩, *Specific Surface Area* ⟨846⟩, *Thermal Analysis* ⟨891⟩, *Water Determination* ⟨921⟩, and *Characterization of Crystalline and Partially Crystalline Solids by X-Ray Powder Diffraction (XRPD)* ⟨941⟩.

ADDITIONAL INFORMATION

Certain lubricants, particularly those used in effervescent dosage forms, do not fall into the chemical categories defined above. These materials are used in special situations, and they are not suitable for universal application. Talc is an inorganic material that may have some lubricant properties. It is generally used in combination with fluid film lubricants to reduce sticking to punches and dies.

Functional Category: Glidant and/or Anticaking Agent

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 are thought to 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 among larger particles and thus may reduce friction between these particles. Anticaking agents may absorb 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. Typically they are insoluble in water. Some of these materials are complex.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in glidant or anticaking agent functions: *Light Diffraction Measurement of Particle Size* ⟨429⟩, *Loss on Drying* ⟨731⟩, *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩, *Specific Surface Area* ⟨846⟩, and *Water Determination* ⟨921⟩.

Functional Category: Coloring Agent

DESCRIPTION

Coloring agents are incorporated into dosage forms to produce a distinctive appearance that may serve to differentiate a product from others that have a similar physical appearance or, in some instances, to protect photolabile components of the dosage form. 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.

The Federal Food, Drug, and Cosmetic Act defines three categories of coloring agents:

- 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 usually are dissolved in a granulating fluid for use, although they also may be adsorbed onto carriers such as starch, lactose, or sugar from aqueous or alcoholic solutions. These latter products often are dried and used as formulation ingredients. Because of their insoluble character, lakes almost always are blended with other dry excipients during formulation. For this reason, direct-compression tablets often are 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. A coloring agent should be physically nonreactive with other excipients and the drug substances.

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. A coloring agent should be chemically nonreactive with other excipients and the drug substances. The quality of a coloring agent ordinarily is 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

The following general chapters may be useful in ensuring consistency in selected coloring agent functions: *Light Diffraction Measurement of Particle Size* ⟨429⟩ and *Color—Instrumental Measurement* ⟨1061⟩. Instrumental methods should be used to determine the absolute color of a coloring agent.

ADDITIONAL 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.

Functional Category: Capsule Shell

DESCRIPTION

The word "capsule" is derived from the Latin *capsula,* which means a small container. Among other benefits, capsules enable pharmaceutical powders and liquids to be formulated for dosing accuracy, as well as ease of transportation. The capsule material should be compatible with all other ingredients in the drug product. Hard capsules typically consist of two parts: both are cylindrical, and one part is slightly longer than the other and is called the body. The cap fits closely on the body to enclose the capsule. In contrast, the soft capsule is a one-piece unit that may be seamed along an axis or may be seamless. The capsule material may be derived from hydrolysis of collagen that originates from porcine, bovine, or fish sources, or it can be of nonanimal origin, e.g., cellulosic or polysaccharide chemical entities. The capsule shell also contains other additives such as plasticizers, colorants, and preservatives. In some cases, capsule shells are sterilized to prevent microbial growth. The capsule shell is an integral part of the formulation, and therefore robust manufacturing and formulation performance depends on the measurement and control of CMAs. Capsules can be used to administer drugs by oral, rectal, vaginal, or inhalation routes.

FUNCTIONAL MECHANISM

Capsules can enclose solid, semisolid, or liquid formulations. Capsules have a variety of benefits: masking unpleasant taste, facilitating blinding in clinical studies, promoting ease of swallowing, and presenting a unique appearance. Conventional capsule shells should dissolve rapidly at 37° in biological fluids such as gastric and intestinal media. However, the solubility properties of the shell can be modified (e.g., with enteric and controlled-release polymers) to control the release of the capsule contents.

PHYSICAL PROPERTIES

The primary physical properties relevant to the capsule shell are those that can have a direct effect on product performance: 1) moisture content, 2) gas permeability, 3) stability on storage, 4) disintegration, 5) compactness, and 6) brittleness. The moisture content varies with the type of capsule. Hard gelatin capsules typically contain 13%–16% water compared to hypromellose (hydroxypropyl methylcellulose or HPMC) capsules that typically contain 4%–7% water content. Moisture content has an important effect on capsule brittleness. Soft gelatin capsules contain 5%–15% water. Equilibrium water content also may be crucial to dosage form stability because water migration can take place between the shell and capsule contents. Gas permeability may be important and generally is greater for HPMC capsules than for gelatin capsules because of the presence of open structures in the former. Unlike HPMC capsules, which do not cross-link, gelatin capsules have the potential to cross-link due to environmental and chemical exposure. Gelatin capsules may undergo cross-linking upon storage at elevated temperature and humidity [e.g., 40°(75% RH)]. Gelatin shell material is also well known to cross-link due to exposure to aldehydes, ketones, and certain dyes in shell formulations. Thus, presence of these materials in excipients should be considered for gelatin encapsulated products. Cross-linking slows in vitro dissolution and often necessitates introduction of enzymes in the test

medium. Gelatin capsules should disintegrate within 15 min when exposed to 0.5% hydrochloric acid at 36°–38° but not below 30°. HPMC capsules can disintegrate below 30°.

CHEMICAL PROPERTIES

Gelatin is a commercial protein derived from the native protein, collagen. The product is obtained by partial hydrolysis of collagen derived from skin, white connective tissue, and bones of animals. Type A gelatin is derived by acid treatment, and Type B gelatin is derived from base treatment. The common sources of commercial gelatin are pigskin, cattle hide, cattle bone, cod skin, and tilapia skin. The gelatin capsule shell also typically contains coloring agents, plasticizers such as polyhydric alcohols, natural gums and sugars, and preservatives such as sodium metabisulfite and esters of *p*-hydroxybenzoic acid. The more commonly used nongelatin capsules today are made from HPMC. Different capsule types contain different moisture levels and may thus influence drug product stability. The detailed composition of an excipient may be important because the shell function can be influenced by small amounts of impurities in the excipients (e.g., peroxides in oils or aldehydes in lactose and starches) that can cause capsule cross-linking. The presence in capsule shells of undesirable materials, such as metals, odorants, water-insoluble substances, and sulfur dioxide, should be evaluated to ensure stability and performance.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected capsule shell functions: *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩, *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* ⟨62⟩, *Arsenic* ⟨211⟩, *Elemental Impurities—Limits* ⟨232⟩ and *Elemental Impurities—Procedures* ⟨233⟩, *Residue on Ignition* ⟨281⟩, *Disintegration* ⟨701⟩, *Dissolution* ⟨711⟩, *Water Determination* ⟨921⟩, and *Color—Instrumental Measurement* ⟨1061⟩.

ADDITIONAL INFORMATION

In addition to the general chapters listed above, useful information for ensuring consistency in selected capsule shell functions may be found in *Gelatin, Gel Strength (Bloom Value)*.

Functional Category: Coating Agent

DESCRIPTION

Oral tablets may be coated using compression coating, sugar coating, or film coating. Compression coating (effectively making a tablet within a tablet) typically uses the same ingredients as a conventional tablet and thus is outside the scope of this section. The term “sugar coating” refers to a process and does not require that sucrose be part of the formulation. Oral capsules can be coated using film-coating procedures. Reasons for coating pharmaceutical dosage forms include masking unpleasant tastes or odors, improving ingestion and appearance, protecting active ingredients from the environment, and modifying the release of the active ingredient (e.g., controlled-release or gastrointestinal targeting). Materials used as coating agents differ depending on the coating process used. Sugar coating was the original coating process. However, today for technical and economic reasons, sugar coating largely has been replaced by film coating. Sugar coating is a complex process that typically involves the application of several different coats including a seal coat, key coat, subcoat, smoothing coat, color coat, and polishing coat. The coating solutions or suspensions are slowly poured or otherwise applied in aliquots onto a bed of tablets in a slowly rotating pan. The coating process typically takes an extended period (potentially several days) and results in a substantial increase in tablet weight. In contrast, film coating generally is a simpler process in which coating solution or suspension is sprayed onto tablets either in a rotating pan or in a fluid-bed apparatus and results in only a modest increase in capsule or tablet weight. The materials used in both sugar coating and film coating include natural, semisynthetic, and synthetic materials. These may be solutions, suspensions, or colloidal dispersions (latexes or pseudolatexes) that can be applied as either aqueous or nonaqueous systems. In addition, waxes and lipids can be applied as coatings in the molten state without the use of solvents. They also can be applied in the solid state as a polishing coat on top of sugar coating or film coating.

FUNCTIONAL MECHANISM—SUGAR COATING

The seal coat is used to seal the surface of the tablet cores to prevent water in the coating solutions or suspensions from causing the tablet cores to disintegrate during coating. The seal coat typically is a polymer (e.g., shellac) that is insoluble in water and is applied as a thin coat from a solution in a nonaqueous solvent. The key component of the majority of sugar-coating solutions or suspensions is a solute, typically sucrose, that is highly soluble in water and forms a sticky, viscous solution (a syrup) at very high concentration. Other materials can be dissolved or suspended in the solution, depending on the stage during the coating process. As the coating dries, the dissolved coating material adheres to the surface of the tablets. The coating solution or suspension typically is applied in incremental steps, followed by drying, until the requisite coating has been achieved. The key coat is composed of another thin coat that is designed to adhere to the seal-coated cores to provide a base for the subcoat so the latter can adhere to the tablet surface. The subcoat typically contains a high concentration of suspended solids and is designed to increase the weight of the tablets comparatively quickly. The smoothing coat is designed to provide a smooth surface, and the color coat provides the final color if required. Finally, the tablets may be transferred to a polishing pan and polished using a mixture of waxes to provide a high-gloss finish.

FUNCTIONAL MECHANISM—FILM COATING

Film-coating agents are composed of film-forming materials (see *Functional Category: Film-Forming Agent*) that impart desirable pharmaceutical properties such as appearance and patient acceptance (e.g., taste masking and ease of swallowing). Film-coating agents also can serve other functional purposes such as providing a barrier against undesirable chemical reactions or untimely release of a drug from its components. After ingestion, the film coating may dissolve by processes such as hydration, solubilization, or disintegration, depending on the nature of the material used. Enteric coatings are insoluble in acidic (low pH) media but dissolve readily in neutral pH conditions. However, most common film-coating polymers do not have pH-specific solubility. The thickness of the film may vary by application and the nature of the coating agents. In the coating process, the polymer chains spread out on the core surface and coalesce into a continuous film as the solvent evaporates. Polymer solutions or dispersions with a low viscosity and high pigment-binding capacity reduce the coating time and facilitate relatively simple and cost-effective manufacturing. Plastic polymers, waxes, and lipid-based coatings can be applied without solvents by melting and atomization. When molten fluid droplets strike the surface of the fluidized drug particles, they spread and resolidify to form film layers. Therefore, film coating materials generally have the ability to form a complete and stable film around the substrate. The film coating typically is applied uniformly and is carefully dried to ensure that a consistent product is produced. Suitable plasticizers may be required to lower the minimum film-forming temperature of the polymer, and formulators should consider their potential effect on drug release.

PHYSICAL PROPERTIES

Sugar coating is a lengthy, complex process. The physical properties of the seal-coating polymer and solution are important. The physical properties of the syrup component in the subsequent layers and any dissolved or suspended solids also are important, and coating agents must be sufficiently stable during use.

Film coating is a complex process, and the characteristics of the film-forming polymer are important. The particle size of colloidal dispersions varies with their composition and manufacture (latex, pseudolatex, or redispersed powder) and can have an effect on film formation. The surface tension of coating preparations can influence the spray pattern in the manufacturing process. The film should possess sufficient elasticity and mechanical strength to withstand the stresses during coating and packaging operations. For coatings that are applied in a molten state without solvents (plastic polymers, waxes, and lipid-based coatings), melting range and melt viscosity are the primary properties that formulators must consider.

CHEMICAL PROPERTIES

Coating components can be of natural, semisynthetic, or synthetic origin and also can be available in different chemical grades. They comprise a diverse variety of different chemical materials. Formulators must consider the nature of the material and its intended use when they identify and quantitate chemical CMAs to ensure consistent performance.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected coating agent functions: *Fats and Fixed Oils* ⟨401⟩, *Light Diffraction Measurement of Particle Size* ⟨429⟩, *Dissolution* ⟨711⟩, *Tensile Strength* ⟨881⟩, *Thermal Analysis* ⟨891⟩, *Viscosity—Capillary Methods* ⟨911⟩, *Viscosity—Rotational Methods* ⟨912⟩, and *Viscosity—Rolling Ball Method* ⟨913⟩. In addition, the general chapters listed under *Functional Category: Film-Forming Agent* (below) also may be appropriate for the evaluation of film-coating polymers.

ADDITIONAL INFORMATION

Additives often are included in a coating formulation. Fillers (e.g., sugar alcohols, microcrystalline cellulose, calcium carbonate, and kaolin) may be added to increase the solids content of the coating agent without increasing viscosity. Stearic acid can be used to improve the protective function/moisture barrier of a coating. Coloring agents (e.g., titanium dioxide and iron oxides) may be added to modify appearance.

Functional Category: Plasticizer

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. Plasticizers 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 intermolecular and intramolecular mobility of the macromolecules that comprise polymeric materials. They achieve this by interfering with the normal intermolecular 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 also are 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°) and can be volatile (i.e., exert an appreciable vapor pressure) at ambient temperature. Plasticizers can reduce the glass transition temperature (T_g) of the system to which they are added.

CHEMICAL PROPERTIES

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 in ensuring consistency in selected excipient functions: *Residual Solvents* ⟨467⟩, *Melting Range or Temperature* ⟨741⟩, *Refractive Index* ⟨831⟩, *Specific Gravity* ⟨841⟩, *Thermal Analysis* ⟨891⟩, and *Water Determination* ⟨921⟩.

ADDITIONAL 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.

Functional Category: Film-Forming Agent

DESCRIPTION

Film-forming agents typically are polymers that can be used to prepare polymer films to coat tablets or capsules for oral administration, to modify appearance, to modify drug release, or to serve other purposes such as melt-in-the-mouth formulations. Polymeric materials used as film-forming agents can be derived from natural, semisynthetic, or synthetic sources, and they can be supplied as powders, granules, pre-prepared solutions, or colloidal dispersions. Colloidal dispersions may contain other components such as plasticizers, surface-active agents, preservatives, or stabilizers. Film-forming agents can be applied as colloidal dispersions (latexes or pseudolatexes) or as aqueous, hydroalcoholic, or nonaqueous polymeric solutions.

FUNCTIONAL MECHANISM

Film-forming agents typically are composed of polymeric materials that possess the ability to form films after solvent evaporation from a solution of the polymer or from the continuous phase of a colloidal dispersion. Thus, the polymer alone must be a solid at ambient temperature and humidity. Some polymers can form films without the inclusion of added components, but other polymers may require the use of additional components such as plasticizers.

PHYSICAL PROPERTIES

Many polymeric film-forming agents are available in a variety of physical grades that typically are based on the nominal viscosity of the particular grade. The physical properties of the polymer usually are those of a solid, and many polymers are available as powders and granules. In addition to the normal properties of bulk powders and granules, other important physical properties of a polymeric film-forming agent are the molecular weight distribution, which is linked to the nominal viscosity of the grade, and the glass transition temperature (T_g). If the film-forming agent is provided as a pre-prepared solution or dispersion, the viscosity of the solution or dispersion can affect performance and should be monitored.

CHEMICAL PROPERTIES

Film-forming agents comprise a diverse group of materials, including natural, semisynthetic, and synthetic materials as discussed above. They may have ionizable functional groups that impart pH-dependent properties and also can be available in different chemical grades (e.g., with different degrees of chemical substitution). Pharmacopeial monographs often describe classes of polymeric materials that allow a considerable range of composition. Formulators should consider these factors when they identify critical material attributes and establish specifications to ensure consistent performance.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected film-forming agent functions: *Fats and Fixed Oils* ⟨401⟩, *Light Diffraction Measurement of Particle Size* ⟨429⟩, *Bulk Density and Tapped Density of Powders* ⟨616⟩, *Chromatography* ⟨621⟩, *Density of Solids* ⟨699⟩, *Dissolution* ⟨711⟩, *Optical Microscopy* ⟨776⟩, *pH* ⟨791⟩, *Tensile Strength* ⟨881⟩, *Thermal Analysis* ⟨891⟩, *Viscosity—Capillary Methods* ⟨911⟩, *Viscosity—Rotational Methods* ⟨912⟩, *Viscosity—Rolling Ball Method* ⟨913⟩, *Bulk Powder Sampling Procedures* ⟨1097⟩, *Near-Infrared Spectroscopy—Theory and Practice* ⟨1856⟩, ▲*Raman Spectroscopy—Theory and Practice* ⟨1858⟩▲ (CN 1-Aug-2020), *Pharmaceutical Dosage Forms* ⟨1151⟩ *Powder Flow* ⟨1174⟩, and *Scanning Electron Microscopy* ⟨1181⟩.

Functional Category: Flavor and Fragrance

DESCRIPTION

A flavor is a single chemical entity or a blend of chemicals of natural or synthetic origin that has the ability to elicit a taste or aroma (i.e., fragrance) response when orally consumed or smelled. The primary purpose of flavor that is added to a pharmaceutical preparation is to provide all or part of the taste and aroma of the product taken into the mouth. Flavors commonly are used in pharmaceutical oral disintegrating tablets, oral solutions, and oral suspensions to mask objectionable drug taste and to make the formulation more palatable, thus promoting patient compliance.

FUNCTIONAL MECHANISM

Chemicals dissolved in saliva excite chemoreceptors on taste buds that reside primarily on the tongue and thus arouse taste perception. Dissolution also releases volatile chemicals that reach the olfactory receptors, triggering aroma perception. The total of taste and odor responses constitutes flavor. Humans can distinguish among five components of taste: sourness, saltiness, sweetness, bitterness, umami (savory), and a wide range of specific odors. Flavor enhancers and taste modifiers can be used to modify the sweetness profile of a sweetening agent or to mask off-flavors. For example, organic acids, such as aspartic and glutamic acids, are known to reduce bitterness.

PHYSICAL PROPERTIES

Taste perception depends on physicochemical, physiological, and psychological factors. Physical properties such as particle size, solubility, humectancy, texture, and color all influence the senses. In addition to flavor, the sensory attributes of sight (e.g., appealing color), sound (e.g., crunch of a chewable tablet), and mouth feel (e.g., viscous, slimy, chalky, cloying, or watery) also contribute to and influence the overall sensory experience.

CHEMICAL PROPERTIES

Chemicals that provide one of the five basic tastes possess a wide variety of structures, functional groups, and molecular weights. Chemicals used to flavor pharmaceuticals by providing both odor and taste tend to have low molecular weights (<250 Da) and polar functional groups such as esters, ketones, aldehydes, amines, or alcohols. To increase the stability of the flavor(s) in a solid dosage form and to minimize flavor–drug interactions, formulators can add flavors in an encapsulated or spray-dried form.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in flavor functions: *Light Diffraction Measurement of Particle Size* ⟨429⟩, *Chromatography* ⟨621⟩, *Congealing Temperature* ⟨651⟩, *Loss on Drying* ⟨731⟩, *Melting Range or Temperature* ⟨741⟩, *Optical Rotation* ⟨781⟩, *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩, *Refractive Index* ⟨831⟩, and *Specific Gravity* ⟨841⟩.

Functional Category: Release-Modifying Agents

Release-modifying agents are used to control drug release in extended-release formulations (also referred to as prolonged-release or controlled-release formulations). Sustained-release and enteric coating agents are included under *Functional Category: Coating Agent.*

DESCRIPTION

Release-modifying agents change a medicinal product's drug-release pattern to achieve the desired drug plasma profile for a given time. The majority of release-modifying agents are polymers that differ in solubility, ease of erosion, rate of swelling, or sensitivity to the biological environment in which they are placed. These polymers have been used to fabricate matrix- or membrane-based drug delivery systems for oral, parenteral, transdermal, and other routes of administration. Matrix controlled-release drug delivery systems can be classified as hydrophilic eroding matrices, hydrophilic noneroding matrices, or hydrophobic matrices. In membrane controlled-release drug delivery systems, the drug reservoir is coated by a rate-controlling polymeric membrane that may consist of a blend of polymers to control release. Such devices may take the form of tablets, capsules, microspheres, vesicles, fibers, patches, and others. In addition to polymers, certain lipid-based excipients also can be used as release-modifying agents in hydrophobic matrix devices and other types of modified-release systems. Typically, these lipid-based materials are fats and waxes or related materials with melting ranges above 45°.

FUNCTIONAL MECHANISM

Upon contact with a biological fluid, release-controlling polymers may undergo a variety of physical changes such as swelling, gelling, dissolution, or erosion, each of which can be triggered by simple aqueous exposure or can be modulated by pH, osmotic stress, or interactions with bile or other intestinal contents. In addition to physical changes, polymers may undergo chemical degradation by acids, bases, enzymes, water, heat, and others. Any or all of these mechanisms may act in concert to control the rate at which the drug is released from the delivery system.

For hydrophilic matrices in which drug diffusion dominates release rate, the rate of drug release depends on the properties of the polymer gel and the nature of the continuous phase in the interstices of the gel influences the dissolution and diffusion

rates of the drug. In the case of eroding matrices, the gel erodes because of the mechanical action of the gastrointestinal tract as the water uptake increases, and the gel becomes more dilute, thus reducing the diffusion distance or releasing drug particles that subsequently dissolve. Hydrophobic matrix-forming materials are not soluble. Drug release from such systems is governed by drug diffusion through the tortuous pores that remain as soluble components dissolve.

Membrane-based drug delivery systems include polymer-coated tablets, capsules, and microspheres. Drug-release mechanisms from such systems are complex and depend on physicochemical characteristics of the drug and polymers or lipids used as well as biological factors in the case of biocompatible and biodegradable systems. Most commonly, drug release from such systems is governed by drug diffusion through the hydrated rate-controlling membrane.

Other modified-release systems for parenteral use include solid lipid nanoparticles and liposomes. The release mechanisms for these systems often involve a complicated interplay with biological processes such as potential clearance through the reticulo-endothelial system, targeted delivery, and cellular uptake.

Osmotic pump devices are a special case of membrane delivery systems. The rate-controlling polymer is insoluble and semipermeable—i.e., it will allow water but not drug molecules—to diffuse through the membrane. Release is controlled by the osmotic pressure of the core components and the viscosity of the resulting solution or suspension. The drug, either in solution or as a suspension, is forced out of a hole in the membrane, which is typically drilled by a laser during product manufacture.

PHYSICAL PROPERTIES

The physical properties of the release-controlling excipient depend on the chemical type: hydrophilic polymer, hydrophobic polymer, semipermeable polymer blends, or lipid, wax, or biodegradable polymer (which can be hydrophilic or hydrophobic).

Hydrophilic polymers gel in contact with water or aqueous media. Because they should provide resistance to the mechanical action of the gastrointestinal tract during passage, they typically are higher molecular weight grades of the polymers. At the concentrations typically used during in vivo release, these high molecular weight polymers often do not exhibit Newtonian properties except in very dilute solution (if they are soluble). Formulators should monitor the kinetic and viscoelastic properties of the gels formed in the release medium.

Hydrophobic polymers are insoluble in water, and their solution properties are determined in nonaqueous solutions. The polymers used in the preparation of semipermeable membranes in osmotic pump devices also are insoluble in water, and similarly their solution properties are determined in nonaqueous solutions. Similarly, hydrophobic lipid-based materials are insoluble in water.

CHEMICAL PROPERTIES

Release-controlling agents have many different types and origins and are available in a range of grades that reflect the considerable variation in their chemical structures and properties. Formulators must consider these variables during any chemical investigation and when they consider the effects of chemical structure on excipient performance. Properties of interest may include chemical composition for copolymers and cellulosic derivatives, degree of ionization, molecular weight, degree of cross-linking, or, for lipids, fatty acid composition. Residual impurities from the manufacturing process, e.g., monomers, initiators, quenching agents, peroxides, and aldehydes, may affect drug substance stability and should be monitored.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected functions of release-modifying agents: *Fats and Fixed Oils* ⟨401⟩, *Light Diffraction Measurement of Particle Size* ⟨429⟩, *Crystallinity* ⟨695⟩, *Characterization of Crystalline Solids by Microcalorimetry and Solution Calorimetry* ⟨696⟩, *Dissolution* ⟨711⟩, *Loss on Drying* ⟨731⟩, *Melting Range or Temperature* ⟨741⟩, *Nuclear Magnetic Resonance Spectroscopy* ⟨761⟩, *Optical Microscopy* ⟨776⟩, *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩, *Specific Surface Area* ⟨846⟩, *Mid-Infrared Spectroscopy* ⟨854⟩ and *Ultraviolet-Visible Spectroscopy* ⟨857⟩, *Tensile Strength* ⟨881⟩, *Thermal Analysis* ⟨891⟩, *Viscosity—Capillary Methods* ⟨911⟩, *Viscosity—Rotational Methods* ⟨912⟩, *Viscosity—Rolling Ball Method* ⟨913⟩, *Water Determination* ⟨921⟩, *Characterization of Crystalline and Partially Crystalline Solids by X-Ray Powder Diffraction (XRPD)* ⟨941⟩, *Powder Flow* ⟨1174⟩, and *Scanning Electron Microscopy* ⟨1181⟩.

ADDITIONAL INFORMATION

Some release-modifying agents may include additives such as an antioxidant or an anticaking agent.

Change to read:

ORAL LIQUIDS

Functional Category: pH Modifier (Acidifying/Alkalizing/Buffering Agent)

DESCRIPTION

The hydrogen ion concentration, $[H^+]$, in an aqueous solution is expressed as $pH = -\log(H^+)$. The pH of pure water is 7 at 25°. An aqueous solution is acidic at pH <7 and alkaline at pH >7. An acid can be added to acidify a solution. Similarly, a base can be used to alkalize a solution. A buffer is a weak acid (or base) and its salt. When a buffer is present in a solution, the addition of small quantities of strong acid or base leads to only a small change in solution pH. Buffer capacity is influenced by salt/acid (or base/salt) ratio and total concentration of acid (or base) and salt. The pH of pharmaceutical solutions typically is controlled using acidifying/alkalizing and buffering agents to: 1) maintain a pH close to that of relevant body fluid to avoid irritation, 2)

improve drug stability where it is found to be pH dependent, 3) control equilibrium solubility of weak acids or bases, and 4) maintain a consistent ionization state of molecules during chemical analysis, e.g., high-performance liquid chromatography.

FUNCTIONAL MECHANISM

The ionization equilibria of weak bases, weak acids, and water are the key to the functions of acidifying, alkalizing, and buffering agents. The autoprotolytic reaction of water can be expressed as:

$$H_2O + H_2O \leftrightarrow H_3O^+ + OH^-$$

The autoprotolysis constant (or ion product) of water is $K_w = 1 \times 10^{-14}$ at 25° and varies significantly with temperature. Because the concentrations of hydrogen and hydroxyl ions in pure water are equal, each has the value of approximately 1×10^{-7} mol/L, leading to the neutral pH of 7 at 25°. When an acid, base, or salt of a weak acid (or base) is added, the ionization equilibrium of water is shifted so that $[H^+][OH^-]$ remains constant, thus resulting in a solution pH that is different from 7.

PHYSICAL PROPERTIES

pH modifiers typically are dissolved in liquid dosage forms. Physical properties may be important and should be considered because they may influence processing requirements (e.g., particle size may influence mixing time required to dissolve a pH modifier).

CHEMICAL PROPERTIES

Buffers and pH modifiers influence solution pH, buffer capacity, osmolality, osmolarity, and water conductivity. When used in chemical analysis, buffers must be chemically compatible with the reagents and test substance. Buffers used in physiological systems should not interfere with the pharmacological activity of the medicament or the normal function of the organism.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected pH-modifier or buffering-agent functions: *Water Conductivity* ⟨645⟩, *Osmolality and Osmolarity* ⟨785⟩, and *pH* ⟨791⟩.

Functional Category: Wetting and/or Solubilizing Agent

DESCRIPTION

Solubilizers can be used to dissolve otherwise insoluble molecules. They function by facilitating spontaneous phase transfer to yield a thermodynamically stable solution. A number of solubilizers are available commercially. Acceptable solubilizers for pharmaceutical applications have been fully evaluated in animals for safety and toxicology. Wetting agents increase the spreading and penetrating properties of a liquid by lowering its surface tension.

FUNCTIONAL MECHANISM

Wetting and solubilizing agents comprise a variety of different chemical structures or classes. Some solubilizers have unique chemical structures. For example, a hydrophilic moiety may be tethered with a hydrophobic moiety to yield distinct micelle shapes and morphologies in water, thus facilitating solubilization. The mechanism of solubilization often is associated with a favorable interaction of the insoluble agent and the interior core of the solubilizer assembly (e.g., micelles). In other cases, unique hydrophobic sites that are capable of forming inclusion complexes are present. Other types of solubilizers use a range of polymeric chains that interact with hydrophobic molecules to increase solubility by dissolving the insoluble agent into the polymeric chains.

PHYSICAL PROPERTIES

Wetting and solubilizing agents are typically solid, liquid, or waxy materials. Their physical properties depend on their chemical structures. The physical properties and performance of the wetting agents and solubilizers, however, depend on the surface-active properties of the solubilizers and on the hydrophilic–lipophilic balance (HLB). Materials with lower HLB values behave as emulsifiers, whereas those with higher HLB values typically behave as solubilizing agents. For example, the commonly used wetting and solubilizing agent sodium lauryl sulfate (HLB 40) is hydrophilic and highly water soluble and, upon dispersion in water, spontaneously reduces surface tension and forms micelles that function to solubilize lipophilic materials.

The unique hydrophilicity and hydrophobicity properties of solubilizers can be characterized by their chemical structures, aggregate numbers, or critical micelle concentrations (CMCs). The CMC value is unique to an individual solubilizer that bears hydrophilic, lipophilic, and/or hydrophobic chains. CMC is a measure of the concentration at which the surface-active molecules aggregate. These molecular aggregates can solubilize the solute by incorporating part into the hydrophobic interior. Such interactions with the insoluble molecule further stabilize the molecules in the entire assemblies without precipitation.

CHEMICAL PROPERTIES

The chemical and surface-active properties depend on the structures of the solubilizers. Because of the complex nature of solute–solvent–solubilizer interactions, pharmaceutical scientists must carefully consider, identify, and control the CMAs of solubilizers.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected solubilizing agent functions: *Fats and Fixed Oils* ⟨401⟩, *Light Diffraction Measurement of Particle Size* ⟨429⟩, *pH* ⟨791⟩, *Specific Gravity* ⟨841⟩, *Specific Surface Area* ⟨846⟩, *Mid-Infrared Spectroscopy* ⟨854⟩ and *Ultraviolet-Visible Spectroscopy* ⟨857⟩, *Thermal Analysis* ⟨891⟩, *Viscosity—Capillary Methods* ⟨911⟩, *Viscosity—Rotational Methods* ⟨912⟩, *Viscosity—Rolling Ball Method* ⟨913⟩, and *Scanning Electron Microscopy* ⟨1181⟩.

Functional Category: Antimicrobial Preservative

DESCRIPTION

Antimicrobial preservatives are used to kill or prevent growth of bacteria, yeast, and mold in the dosage form.

FUNCTIONAL MECHANISM

Preservatives work by a variety of mechanisms to control microbes. Most work at the cell membrane, causing membrane damage and cell leakage. Other modes of action include transport inhibition, protein precipitation, and proton-conducting uncoupling. Some preservatives are bactericidal (kill bacteria or yeast and mold); some are bacteriostatic (inhibit growth of microorganisms); and others are sporicidal (kill spores). Several of the preservatives can act synergistically (e.g., combinations of parabens).

PHYSICAL PROPERTIES

Antimicrobials generally are soluble in water at concentration ranges at which they are effective. The vapor pressure of these agents is important, especially if the dosage form is intended for lyophilization or spray drying. Several of these agents are flammable. Understanding an excipient's partition coefficient is important because partitioning of a preservative into an oil phase can diminish the preservative's concentration in the aqueous phase, which in turn can reduce its value as a preservative.

CHEMICAL PROPERTIES

Phenolic preservatives can undergo oxidation and color formation. Incompatibilities of preservatives (cationic and anionic mixtures, adsorption to tubes or filters, or binding to surfactants and proteins) should be taken into account during product development.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected antimicrobial functions: *Injections and Implanted Drug Products* ⟨1⟩, *Antimicrobial Effectiveness Testing* ⟨51⟩, *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩, *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* ⟨62⟩, and *Antimicrobial Agents—Content* ⟨341⟩.

ADDITIONAL INFORMATION

Safety and labeling requirements regarding the use of antimicrobial preservatives should be considered.

Functional Category: Chelating and/or Complexing Agents

DESCRIPTION

Chelating agents form soluble complex molecules with certain metal ions (e.g., copper, iron, manganese, lead, and calcium) and essentially remove the ions from solution to minimize or eliminate their ability to react with other elements and/or to precipitate. The agents are used in pharmaceuticals (oral, parenteral, and topical formulations), cosmetics, and foods to sequester ions from solution and to form stable complexes. Chelating agents also are referred to as chelants, chelators, or sequestering agents.

Complexing agents form soluble complex molecules (e.g., inclusion complexes) with other solutes (e.g., drug substances) and can influence physical and chemical properties such as solubility and stability.

FUNCTIONAL MECHANISM

Chelating agents are used to sequester undesirable metal ions from solution. The chemical structure of chelating agents allows them to act as a "claw" to associate with the metal atom by forming a heterocyclic ring structure. Complexing agents function similarly but mechanistically and do not (by definition) require a two-point claw structure because they can associate via one or more binding sites. All chelating agents are complexing agents, but not all complexing agents are chelating agents.

Chelating agents are used as antioxidant synergists, antimicrobial synergists, and water softeners. By sequestering metal ions from solution, chelating agents reduce the propensity for oxidative reactions. Chelating agents also have the ability to enhance antimicrobial effectiveness by forming a metal-ion–deficient environment that otherwise could feed microbial growth.

Complexing agents generally form soluble complex molecules with solutes (e.g., drug molecules) that can influence physical, chemical, and drug delivery properties. Complexing agents that form inclusion complexes typically contain a hydrophobic cavity into which a drug substance can enter and an outer, more hydrophilic region.

PHYSICAL PROPERTIES

Chelating and complexing agents generally are soluble in water and typically are dissolved in liquid dosage forms. Physical properties may be important and should be considered because they may influence processing requirements (e.g., particle size may influence mixing time required to dissolve). Chelating and complexing agents exhibit different degrees of hygroscopicity. Because chelating agents are used in low levels, particle size distribution can be important to enable acceptable dosage form content uniformity.

CHEMICAL PROPERTIES

Chelating agents complex with metal ions via any combination of ionic and covalent bonds. Dilute aqueous solutions may be neutral, acidic, or alkaline. Edetic acid and its salts are incompatible with strong oxidizers, strong bases, and polyvalent metal ions (e.g., copper and nickel). Specific agents are selected for a formulation based on their solubility, affinity for the target metal ion, and stability. Edetate salts are more soluble than the free acid. Unlike other edetate salts and the free acid, edetate calcium disodium does not sequester calcium and therefore is preferred to prevent hypocalcemia. It is also preferred to chelate metals with the release of calcium ions. Alternatively, disodium edetate can be used to treat hypercalcemia. Edetic acid will decarboxylate if heated above 150°.

Complexing agents generally form molecular complexes with drug substances that are dependent on complexing agent physical and chemical properties. The ability of a solute to form an inclusion complex is dependent on complexing agent molecular weight, chemical structure, and the dimensions of the hydrophobic cavity.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected chelating and complexing functions: *Antimicrobial Effectiveness Testing* ⟨51⟩, *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩, *Elemental Impurities—Limits* ⟨232⟩ and *Elemental Impurities—Procedures* ⟨233⟩, *Iron* ⟨241⟩, *Lead* ⟨251⟩, *Antimicrobial Agents—Content* ⟨341⟩, *Light Diffraction Measurement of Particle Size* ⟨429⟩, *Loss on Drying* ⟨731⟩, *pH* ⟨791⟩, *Water Determination* ⟨921⟩, and *Cell-based Advanced Therapies and Tissue-based Products* ⟨1046⟩.

Functional Category: Antioxidant

DESCRIPTION

This category applies to antioxidants used as in vitro stabilizers of pharmaceutical preparations to mitigate oxidative processes. Antioxidants used for their biological activity in vivo may be regarded as active ingredients with therapeutic effects and are not discussed. Antioxidants delay the onset of and/or significantly reduce the rate of complex oxidative reactions that could otherwise have a detrimental effect on the drug substance. Antioxidants also can be considered for protecting nonactive components such as unsaturated oils, pegylated lipids, flavors, and essential oils. Thus, antioxidants preserve the overall integrity of the dosage form against oxidative stress. Antioxidants are most effective when incorporated in the formula to prevent or delay the onset of chain reactions and to inhibit free radicals and hydroperoxides from engaging in the cascading processes described above. Effective application of antioxidants and evaluation of their efficacy necessitate an understanding of oxidative mechanisms and the nature of the byproducts they generate. Autoxidation is initiated when oxygen reacts with a substrate to form highly reactive species known as free radicals ($RH \rightarrow R\cdot$). After "initiation" the free radicals in the presence of oxygen can trigger chain reactions ($R\cdot + O_2 \rightarrow ROO\cdot$ and $ROO\cdot + RH \rightarrow R\cdot + ROOH$) to form peroxy radicals, hydroperoxides, and new alkyl radicals that can initiate and then propagate their own chain reactions. The cascading reactions during the propagation phase can be accelerated by heat, light, and metal catalysts. In the presence of trace amounts of metal catalysts (Cu^{+}, Cu^{2+}, Fe^{2+}, and Fe^{3+}), hydroperoxides (ROOH) readily decompose to $RO\cdot$ and $ROO\cdot$ and subsequently can trigger reactions with the API and/or the excipients (e.g., hydrocarbons) to form hydroxyl acids, keto acids, and aldehydes that can have further undesirable effects. Note that hydroperoxides are not solely the reaction products of oxidative mechanisms within a formulation. Residual amounts of hydroperoxides also can be found in commonly used excipients like polyethylene glycols, polyvinylpyrrolidone, and polysorbates. The initiation phase generally is slow and has a limited effect on the quality of the finished product. The propagation phase, in contrast, involves rapid, irreversible degradation of chemical species.

FUNCTIONAL MECHANISM

Antioxidants can be grouped by their mode of action. Phenolic antioxidants that block free radical chain reactions also are known as true or primary antioxidants. This group consists of monohydroxy or polyhydroxy phenol compounds with ring substitutions. They have very low activation energy to donate hydrogen atom(s) in exchange for the radical electrons that are rapidly delocalized by free radicals. By accepting the radical electrons, they stabilize free radicals. The reaction yields antioxidant free radicals that also can react with lipid free radicals to form other stable compounds. Thus, they can block oxidative chain reactions both in the initiation and propagation stages. Because of their solubility behavior, phenolic antioxidants are most effective in protecting oils and oil-soluble actives against oxidative stress. Reducing agents generally are water-soluble

antioxidants (e.g., L-ascorbic acid) with lower redox potential than the drug or the excipient they are protecting. They delay the onset and the rate of oxidative reactions by sacrificially reacting with oxygen and other reactive species. The oxygen-scavenging potential of the reducing agents may be sensitive to pH and also can be negatively affected in the presence of trace elements. Chelating agents bind with free metals (Cu^{+}, Cu^{2+}, Fe^{2+}, and Fe^{3+}) that may be present in trace amounts in the formulation. The newly formed complex ions are nonreactive. Chelating agents therefore remove the capacity of the metal catalysts to participate in oxidative reactions that occur during the propagation stage.

The utility of antioxidants can be maximized by synergistic use of one or two primary antioxidants along with reducing and chelating agents. The combined effect often is greater than the sum of the individual effects of each antioxidant (synergistic effect).

PHYSICAL PROPERTIES

Solubility of the antioxidant should be greatest in the formulation phase (oily, aqueous, or emulsion interface), where the drug substance is most soluble. The temperature at which the antioxidant decomposes is critical for autoclaved preparations, where loss of antioxidant activity may occur. Stability of the antioxidant also must be considered and may be a function of pH and processing conditions. Metal ions may react with propyl gallate to form colored complexes. At alkaline pH, certain proteins and sodium salts may bring about discoloration of *tert*-butylhydroquinone.

CHEMICAL PROPERTIES

Activation energy, oxidation–reduction potential, and stability at different formulation (e.g., pH) and processing (e.g., heat) conditions are important chemical properties. If the dosage form's expected shelf life depends on the antioxidant's function, the concentration must be factored in and periodically assessed to ensure that a sufficient amount of antioxidant remains throughout the product shelf life.

GENERAL CHAPTERS

The following general chapters may be useful for assessing selected excipient antioxidant functions: *Iron* ⟨241⟩, *Chromatography* ⟨621⟩, *Crystallinity* ⟨695⟩, *Melting Range or Temperature* ⟨741⟩, *Specific Surface Area* ⟨846⟩, and *Water Determination* ⟨921⟩.

Functional Category: Sweetening Agent

DESCRIPTION

Sweetening agents are used to sweeten oral dosage forms and to mask unpleasant flavors. See *Functional Category: Flavor and Fragrance* for more details.

FUNCTIONAL METABOLISM

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. These properties may be formulation dependent.

CHEMICAL PROPERTIES

Sweeteners can be divided into three 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 in which the manufacturing processes involve heating.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected sweetening functions: *Light Diffraction Measurement of Particle Size* ⟨429⟩, *Loss on Drying* ⟨731⟩, *Melting Range or Temperature* ⟨741⟩, *Optical Rotation* ⟨781⟩, and *Water Determination* ⟨921⟩.

ADDITIONAL 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/day 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, and some sweeteners are incompatible with certain preservatives.

SEMISOLIDS, TOPICALS, AND SUPPOSITORIES

Functional Category: Suppository Base

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°), 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 melting range. In general, suppository bases melt between 27° and 45°. However, individual bases usually have a much narrower melting range within these temperature boundaries, typically 2°–3°. 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 also may contain ethoxylated fatty acids. They are available in many different grades that are 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. Polyethylene glycols that show appropriate melting behavior are examples of hydrophilic suppository bases.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected suppository base functions: *Fats and Fixed Oils* ⟨401⟩, *Congealing Temperature* ⟨651⟩, *Melting Range or Temperature* ⟨741⟩, and *Pharmaceutical Dosage Forms* ⟨1151⟩.

ADDITIONAL INFORMATION

Some materials included in suppositories based on hard fats have much higher melting ranges. These materials typically are microcrystalline waxes that help stabilize molten suspension formulations. Suppositories also can be manufactured from glycerinated gelatin.

Functional Category: Suspending and/or Viscosity-Increasing Agents

DESCRIPTION

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

FUNCTIONAL MECHANISMS

A number of mechanisms contribute to the dispersion stabilization or viscosity-increasing effect of these agents. The most common is the increase in viscosity—because of 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 their characterization.

CHEMICAL PROPERTIES

The majority of the suspending and viscosity-increasing agents are: 1) hydrophilic carbohydrate macromolecules (acacia, agar, alginic acid, carboxymethylcellulose, carrageenans, dextrin, gellan gum, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, maltodextrin, methylcellulose, pectin, propylene glycol alginate, sodium alginate, starch, tragacanth, and xanthan gum); and 2) noncarbohydrate hydrophilic macromolecules, including gelatin, povidone carbomers, polyethylene oxide, and polyvinyl alcohol. Minerals (e.g., attapulgite, bentonite, magnesium aluminum silicate, and silicon dioxide) comprise the second-largest group of suspending and viscosity-increasing agents. Aluminum monostearate is the one non-macromolecular, nonmineral excipient in this functional category. It consists chiefly of variable proportions of aluminum monostearate and aluminum monopalmitate.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected viscosity-increasing functions: *Viscosity—Capillary Methods* ⟨911⟩, *Viscosity—Rotational Methods* ⟨912⟩, and *Viscosity—Rolling Ball Method* ⟨913⟩.

Functional Category: Ointment Base

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 can be suspended as a stable mixture.

Ointment bases are classified as: 1) oleaginous ointment bases that are anhydrous, do not absorb water readily, are insoluble in water, and are not removable by water (e.g., petrolatum); 2) absorption ointment bases that are anhydrous and absorb some water but are insoluble in water and are not water removable (e.g., lanolin); 3) emulsion ointment bases that are water-in-oil or oil-in-water emulsions and are hydrous, absorb water, and are insoluble in water (e.g., creams of water, oils, waxes, or paraffins); and 4) 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 CHAPTERS

The following general chapters may be useful in ensuring consistency in selected ointment base functions: *Congealing Temperature* ⟨651⟩, *Viscosity—Capillary Methods* ⟨911⟩, *Viscosity—Rotational Methods* ⟨912⟩, and *Viscosity—Rolling Ball Method* ⟨913⟩.

Functional Category: Stiffening Agent

DESCRIPTION

A stiffening agent is an agent or a mixture of agents that increases the viscosity or hardness of a preparation, especially in ointments and creams.

FUNCTIONAL MECHANISM

In general, stiffening agents are high melting point solids that increase the melting point of ointments or increase the consistency or body of creams. Stiffening agents can be either hydrophobic (e.g., hard fat or paraffin) or hydrophilic (e.g., polyethylene glycol, high molecular weight).

PHYSICAL PROPERTIES

The primary physical property relevant to stiffening agents is their high melting point or melting range. Typical melting ranges for stiffening agents range from 43° to 47° (cetyl esters wax), 53° to 57° (glyceryl distearate), 69° to 74° (glyceryl behenate), and 85° to 88° (castor oil, hydrogenated).

CHEMICAL PROPERTIES

Stiffening agents comprise a diverse group of materials that include glycerides of saturated fatty acids, solid aliphatic alcohols, esters of saturated fatty alcohols and saturated fatty acids, saturated hydrocarbons, blends of fatty alcohols and a polyoxyethylene derivative of a fatty acid ester of sorbitan, and higher ethylene glycol polymers.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected stiffening-agent functions: *Congealing Temperature* ⟨651⟩, *Melting Range or Temperature* ⟨741⟩, *Viscosity—Capillary Methods* ⟨911⟩, *Viscosity—Rotational Methods* ⟨912⟩, and *Viscosity—Rolling Ball Method* ⟨913⟩.

ADDITIONAL INFORMATION

Some of the materials included as stiffening agents increase the water-holding capacity of ointments (e.g., petrolatum) or function as co-emulsifiers in creams. Examples include stearyl alcohol and cetyl alcohol.

Functional Category: Emollient

DESCRIPTION

Emollients are excipients used in topical preparations to impart lubrication, spreading ease, texture, and softening of the skin and to counter the potentially drying/irritating effect of surfactants on the skin.

FUNCTIONAL MECHANISM

Emollients help form a protective film and maintain the barrier function of the epidermis. Their efficacy may be described by three mechanisms of action: protection against the delipidizing and drying effects of surfactants, humectancy due to occlusion (by providing a layer of oil on the surface of the skin, emollients slow water loss and thus increase the moisture-retention capacity of the stratum corneum), and lubricity, adding slip or glide to the preparation.

PHYSICAL PROPERTIES

Emollients impart one or more of the following attributes to a pharmaceutical preparation: spreading capacity, pleasant feel to the touch, softness of the skin, and indirect moisturization of the skin by preventing transepidermal water loss.

CHEMICAL PROPERTIES

Emollients are either oils or are derived from components of oils as esters of fatty acids. Depending on the nature of its fatty acid ester, an emollient may be liquid, semisolid, or solid at room temperature. Generally, the higher the molecular weight of the fatty acid moiety (carbon chain length) the richer the feel and softness of the touch. Fluidity generally is imparted by shorter chain length and higher degree of unsaturation in the fatty acid moiety. The degree of branching of ester bonds also influences the emollient properties.

GENERAL CHAPTER

The following general chapter may be useful in ensuring consistency in selected emollient functions: *Fats and Fixed Oils* ⟨401⟩.

PARENTERALS

Functional Category: Pharmaceutical Water

DESCRIPTION

Water is used as a solvent, vehicle, diluent, or filler for many drug products, especially those supplied in liquid form. These may include injectable drugs, ophthalmic drugs, inhalation solutions, and others. Water also is a vehicle for buffers and antimicrobial agents and is a volume expander for infusion solutions.

USP includes monographs for eight grades of pharmaceutical waters. Water for Injection is intended for use in the preparation of parenteral solutions. Where used for the preparation of parenteral solutions subject to final sterilization, use suitable means to minimize microbial growth, or first render the Sterile Water for Injection and, thereafter, protect it from microbial contamination. For parenteral solutions that are prepared under aseptic conditions and are not sterilized by appropriate filtration or in the final container, first render the Sterile Water for Injection and, thereafter, protect it from microbial contamination. Do not use Purified Water in preparations intended for parenteral administration. Where used for sterile dosage forms other than for parenteral administration, process the article to meet the requirements under *Sterility Tests* ⟨71⟩, or first render the Sterile Purified Water and, thereafter, protect it from microbial contamination. *USP* also contains references to other types of water, such as distilled water, deionized water, and others according to 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° or lower, and it vaporizes at a normal boiling temperature of 100°, depending on 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 to gases in the air. Exposure to atmospheric carbon dioxide lowers water's pH. Storage 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 over time.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected pharmaceutical water functions: *Injections and Implanted Drug Products* ⟨1⟩, *Bacterial Endotoxins Test* ⟨85⟩, *Total Organic Carbon* ⟨643⟩, *Water Conductivity* ⟨645⟩, *Water for Hemodialysis Applications* ⟨1230⟩, and *Water for Pharmaceutical Purposes* ⟨1231⟩.

Functional Category: Bulking Agent

DESCRIPTION

Bulking agents used in lyophilized pharmaceuticals, also referred to as freeze-dried products, include various saccharides, sugar alcohols, amino acids, and polymers. The primary function of bulking agents is to provide a pharmaceutically elegant freeze-dried cake with noncollapsible structural integrity that will reconstitute rapidly before administration. In addition, bulking agents are selected to prevent product loss caused by blow-out during freeze drying, to facilitate efficient drying, and to provide a physically and chemically stable formulation matrix. Complementary combinations of bulking agents, e.g., mannitol and a polymer, frequently are used to improve performance.

FUNCTIONAL MECHANISM

A bulking agent that readily crystallizes during lyophilization helps maintain the structural integrity of the cake formed during primary drying, thereby preventing macroscopic collapse and maintaining pharmaceutical elegance. Microscopic collapse of amorphous components in the formulation can still occur (with some potentially undesirable results) but does not result in macroscopic collapse or "meltback" if the bulking agent's properties and concentration are adequate. The bulking agent also should possess a high eutectic melting temperature with ice to permit relatively high primary drying temperatures with commensurate rapid and efficient drying and subsequent rapid reconstitution upon usage. Functional cake-forming excipients, such as mannitol, frequently are used because they crystallize during freezing, thereby allowing efficient drying and the formation of a structurally robust and stable cake. Amino acids and cosolvents also have been used to achieve this effect. Most biopolymer active ingredients remain amorphous upon freeze-drying, and bulking agents such as disaccharides can function as lyoprotectants by helping to maintain a stable amorphous phase during freezing and drying to prevent denaturation. Solubility enhancement of an insoluble crystalline active ingredient sometimes is achieved with the use of a biopolymer that enhances solubility or prevents crystallization during lyophilization or subsequent reconstitution. Bulking agents also are selected on the basis of biocompatibility, buffering capability, and tonicity-modifying properties.

Lyoprotectant properties of bulking agents (i.e., those that protect the drug substance during lyophilization) typically are achieved by the formation of a highly viscous glassy phase that includes the biopolymer drug substance in combination with low molecular weight amorphous saccharides such as sucrose, trehalose, or certain amino acids. A typical approach for protein pharmaceutical formulation is to combine a sugar alcohol that readily crystallizes and an amorphous diluent. This mixture acts as a lyoprotectant.

PHYSICAL PROPERTIES

Bulking agents are dissolved in aqueous solution before lyophilization. Therefore, chemical purity and the absence of bioburden and pyrogenic materials are essential properties of the excipient. However, the physical form and particle properties of the excipient generally are not relevant to the final properties of the lyophilized formulation. The solubilization process and the drying process can be facilitated by the use of volatile cosolvents such as ethanol or tertiary butyl alcohol.

The physical properties that are essential to product performance during and after lyophilization include the glass transition temperature (T_g) of the amorphous frozen concentrate before drying, the glass transition temperature of the final dried formulation cake, and the eutectic melting temperature of the crystalline bulking agent with ice. The glass transition temperature (T_g) of the formulation depends on the glass transition temperatures of the individual components, concentrations, and interactions. Although approximations can be made based on reported transition temperatures for individual components,

current practice includes the measurement of formulation glass transition temperatures by thermal analysis or freeze-drying microscopy.

The physical states of the bulking agent during and after lyophilization are important physical properties. Both formulation composition and processing parameters play roles in determining whether the bulking agent is amorphous or takes a specific crystalline form. Rate of freezing, drying temperatures, and annealing are among the important process parameters used to control the physical state of the formulation and its components. Moisture retention and adsorption after lyophilization also can contribute to formulation instability and poor reconstitution.

CHEMICAL PROPERTIES

Reactivity of the bulking agent with other formulation components, especially the active ingredient, may be critical. Reducing sugars are well known to react with aromatic and aliphatic amines. Glycols may contain trace peroxide levels that can initiate oxidative degradation. The ability of saccharides and polyhydric alcohols to form hydrogen bonds to biopolymers may play a role in their lyoprotection effects.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selecting bulking agent functions: *Injections and Implanted Drug Products* ⟨1⟩, *Crystallinity* ⟨695⟩, *Characterization of Crystalline Solids by Microcalorimetry and Solution Calorimetry* ⟨696⟩, *Thermal Analysis* ⟨891⟩, *Pharmaceutical Dosage Forms* ⟨1151⟩, and *Water–Solid Interactions in Pharmaceutical Systems* ⟨1241⟩.

Functional Category: Tonicity Agent

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 requires that the effective osmotic pressure of solutions for injection must be approximately the same as that of blood. When drug products are prepared for administration to membranes, such as eyes or nasal or vaginal tissues, solutions should be made isotonic with respect to these tissues.

FUNCTIONAL MECHANISM

Tonicity is equal to the sum of the concentrations of the solutes that have the capacity to exert an osmotic force across a membrane and thus reflects overall osmolality. 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 that it can pass through the cell membrane freely and is not factored when determining the tonicity of a solution. In contrast, sodium chloride is impermeant and cannot pass through a membrane without the help of a concentration gradient and, therefore, contributes 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 glucose solutions of the same molar concentration. This is because when glucose dissolves, it remains one particle, but when sodium chloride dissolves, it becomes two particles: Na^+ and Cl^-. Several methods are available to calculate tonicity.

CHEMICAL PROPERTIES

Tonicity agents may be present as ionic or nonionic types. Examples of ionic tonicity agents are alkali metal or earth metal halides such as calcium chloride ($CaCl_2$), potassium bromide (KBr), potassium chloride (KCl), lithium chloride (LiCl), sodium iodide (NaI), sodium bromide (NaBr) or sodium chloride (NaCl), sodium sulfate (Na_2SO_4), or boric acid. Nonionic tonicity agents include glycerol, sorbitol, mannitol, propylene glycol, or dextrose. Sodium or potassium chloride and dextrose commonly are added to adjust tonicity.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected tonicity agent functions: *Injections and Implanted Drug Products* ⟨1⟩, *Osmolality and Osmolarity* ⟨785⟩, and *Pharmaceutical Calculations in Pharmacy Practice* ⟨1160⟩.

AEROSOLS

Functional Category: Propellant

DESCRIPTION

Propellants are compounds that are gaseous under ambient conditions. They are used in pharmaceuticals (nasal sprays and respiratory and topical formulations), cosmetics, and foods to provide force to expel contents from a container.

FUNCTIONAL MECHANISM

Propellant substances are low boiling point liquids or compressed gases that are relatively inert toward active ingredients and excipients. They can be characterized by three properties: whether they form a liquid phase at ambient temperatures and useful pressures, their solubility and/or miscibility in the rest of the formulation, and their flammability. Their performance is judged by their ability to provide adequate and predictable pressure throughout the usage life of the product.

Propellants that have both a liquid and gas phase in the product provide consistent pressures as long as there is a liquid phase present—the pressure in the headspace is maintained by the equilibrium between the two phases. In contrast, the pressure provided by propellants that have no liquid phase may change relatively rapidly as the contents of the container are expelled. As the headspace becomes larger, the pressure within the container falls proportionately. Propellants that have no liquid phase but have significant pressure-dependent solubility in the rest of the formulation have performance characteristics between those of the other two systems. In such cases, as the headspace increases the propellant comes out of solution to help to maintain the pressure of the system.

In metered-dose inhalers, the propellant has a liquid phase that is an integral part of the dispensed pharmaceutical product. Actuating the metering valve dispenses a defined volume of the liquid contents. The propellant spontaneously boils and provides atomizing and propulsive force. A predictable change in active concentration occurs from the beginning to the end of the container life cycle as the liquid phase of the propellant vaporizes to reestablish the equilibrium pressure of the system as the headspace increases.

PHYSICAL PROPERTIES

Propellants have boiling points well below ambient temperatures. A propellant's density for disperse systems and its solubility properties may be significant considerations when one selects a propellant. Apaflurane and norflurane have liquid-phase densities that are greater than that of water. Hydrocarbon propellants (butane, isobutane, and propane) and dimethyl ether have liquid-phase densities that are less than that of water.

CHEMICAL PROPERTIES

Propellants typically are stable materials. The hydrocarbon propellants (butane, isobutene, and propane) and dimethyl ether are all flammable materials. Apaflurane, carbon dioxide, nitrogen, and norflurane are nonflammable. Nitrous oxide is not flammable but supports combustion. Chlorofluorocarbon propellants are considered to be ozone-depleting substances. Their use in foods, drugs, devices, or cosmetics is regulated by 21 CFR 2.125. Albuterol metered-dose inhalers formulated with chlorofluorocarbon propellants have not been available in the United States since January 1, 2009.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected propellant functions: *Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests* ⟨601⟩, *Chromatography* ⟨621⟩, and *Water Determination* ⟨921⟩.

DRY POWDER INHALERS

Dry powder inhalers (DPIs) commonly contain few functional excipients. For example, DPIs may contain a carrier and may use a capsule shell. Other useful excipients include glidants to improve flow during manufacture of the active carrier mix. A discussion of the use of a lubricant can be found in the tablet or capsule sections above in addition to the carrier properties discussed below.

Functional Category: Carrier

DESCRIPTION

Carriers are used to help deposit the active ingredient in the lung and may have a secondary role in diluting the active to ensure that dosages can be properly metered.

FUNCTIONAL MECHANISM

The carriers are used to promote drug deposition into the lungs for better penetration or absorption in the appropriate lung location. In addition, the carrier is used to decrease the concentration of the active so the latter is adequately dosed in a uniform manner.

PHYSICAL PROPERTIES

The physical properties of carriers include appropriate morphology, hydration state, flowability, surface energy, and particle size distribution.

CHEMICAL PROPERTIES

Carriers must have suitable purity, including low microbial content and no extraneous proteins or impurities, to avoid interactions with the patient's immune system.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected carrier functions: *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩, *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* ⟨62⟩, *Elemental Impurities—Limits* ⟨232⟩ and *Elemental Impurities—Procedures* ⟨233⟩, *Light Diffraction Measurement of Particle Size* ⟨429⟩, *Nitrogen Determination* ⟨461⟩, *Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests* ⟨601⟩, *Bulk Density and Tapped Density of Powders* ⟨616⟩, *Crystallinity* ⟨695⟩, *Characterization of Crystalline Solids by Microcalorimetry and Solution Calorimetry* ⟨696⟩, *Density of Solids* ⟨699⟩, *Loss on Drying* ⟨731⟩, *Optical Microscopy* ⟨776⟩, *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩, *Powder Fineness* ⟨811⟩, *Mid-Infrared Spectroscopy* ⟨854⟩ and *Ultraviolet-Visible Spectroscopy* ⟨857⟩, *Water Determination* ⟨921⟩, *Characterization of Crystalline and Partially Crystalline Solids by X-Ray Powder Diffraction (XRPD)* ⟨941⟩, and *Powder Flow* ⟨1174⟩.

Functional Category: DPI Capsule Shells

DESCRIPTION

Capsule shells sometimes are used in DPIs. The capsule shell is used to contain the dosage amount and safeguard the inhalable powder in a DPI.

FUNCTIONAL MECHANISM

The use of capsule shell may speed pharmaceutical development because it does not require a complex device and can use premeasured drug substance or formulation. A capsule shell must not fragment into inhalable portions and should remain intact after the shell breaks to expose the powder for inhalation.

PHYSICAL PROPERTIES

Capsule shell composition generally is dictated by the drug substance's moisture content, brittleness, and electrostatic interactions with the inhalable powder.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected DPI capsule shell functions: *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩, *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* ⟨62⟩, *Arsenic* ⟨211⟩, *Elemental Impurities—Limits* ⟨232⟩ and *Elemental Impurities—Procedures* ⟨233⟩, *Residue on Ignition* ⟨281⟩, *Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests* ⟨601⟩, *Disintegration* ⟨701⟩, *Dissolution* ⟨711⟩, *Loss on Drying* ⟨731⟩, *Optical Microscopy* ⟨776⟩, *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩, *Uniformity of Dosage Units* ⟨905⟩, *Water Determination* ⟨921⟩, *Color—Instrumental Measurement* ⟨1061⟩, and *Water–Solid Interactions in Pharmaceutical Systems* ⟨1241⟩.

additional information

In addition to the general chapters listed above, useful information for ensuring consistency in selected capsule shell functions may be found in *Gelatin, Gel Strength (Bloom Value)*.

OPHTHALMIC PREPARATIONS

Functional Category: Antimicrobial Preservatives

DESCRIPTION

The preservative system acts as a safeguard to kill or inhibit the growth of microorganisms that may be inadvertently introduced in the product after the manufacturing process either during storage or use.

FUNCTIONAL MECHANISM

Antimicrobial preservatives work by a number of mechanisms. Quaternary ammonium compounds affect microbial cell membranes via charge interactions with phospholipids, leading to disruption of the cell membrane. Parabens also disrupt cell membrane integrity. Alcohols such as chlorbutanol and benzyl alcohol work via lipid (membrane) solvation and protein denaturation. *N*-[3-(Dimethylamino)propyl]tetradecanamide has greater antimicrobial effectiveness toward fungi and protozoa than do quaternary ammonium compounds. Similar to quaternary ammonium compounds, it disrupts plasma membrane integrity. Sorbic acid works by reduction of the sulfhydryl groups of proteins. Hypochlorite is a strong oxidizing agent. Reactions of chloramines with the amine groups of proteins can cause changes in conformation and thus loss of protein activity. Chlorine released by these reactions can react with cellular constituents, such as proteins and lipid. Polyaminopropyl biguanide accumulates in the cell membrane, blocking the entry of nutrients.

PHYSICAL PROPERTIES

To serve as an ophthalmic antimicrobial preservative, a compound should be at least sparingly soluble in water, thus providing an appreciable range of usable concentrations.

CHEMICAL PROPERTIES

A preservative must be compatible with the active and inactive ingredients of the finished product. For example, quaternary ammonium compounds are incompatible with anionic surfactants. Benzyl alcohol is incompatible with oxidizing agents. Chlorbutanol is incompatible with some nonionic surfactants. Compatibility between compounds varies with the pH of the formula. The preservative should be stable in solution at the formulation pH, usually from 5 to 8. Formulation pH can affect preservative activity by influencing how the preservative partitions between the formulation and microbes and how the preservative interacts with the target sites of the microbial cell. For example, preservatives that must pass through cell membranes before exerting activity should be formulated at a pH at which the preservative is mainly in its un-ionized state.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistent functions of selected antimicrobial preservatives: *Antimicrobial Effectiveness Testing* ⟨51⟩, *Sterility Tests* ⟨71⟩, *Bulk Density and Tapped Density of Powders* ⟨616⟩, *Chromatography* ⟨621⟩, *Density of Solids* ⟨699⟩, *Loss on Drying* ⟨731⟩, *Pharmaceutical Dosage Forms* ⟨1151⟩, *Powder Flow* ⟨1174⟩, *Sterility Assurance* ⟨1211⟩, and *Validation of Microbial Recovery from Pharmacopeial Articles* ⟨1227⟩.

Functional Category: Polymers for Ophthalmic Use

DESCRIPTION

Polymers are used in ophthalmic preparations to enhance the retention of active ingredients by reducing the amount of product that is lost from the eye when the patient blinks. In addition, polymers also can be components of artificial tears. Most water-soluble polymers commonly used as film-forming agents in ophthalmic preparations can be categorized as follows: 1) cellulose-based substances, 2) biologically produced gums, and 3) synthetically produced substances.

FUNCTIONAL MECHANISM

Film-forming agents for ophthalmic preparations can enhance the retention of active ingredients in the eye by a number of mechanisms. They can be used as simple viscosity-modifying agents to reduce the flow of the product, thereby slowing the rate of product loss after administration. They also can be used to form films on the surface of the eye so the drug remains deposited on the eye after the liquid portion of the product has been expelled or has evaporated. These agents can be formulated to produce a film or a gel when the product warms to body temperature (upon contacting the surface of the eye), mixing with the tear film, and/or evaporating. Some polymers have shown bio-adhesive properties on the cornea and can increase drug retention.

PHYSICAL PROPERTIES

To serve as an ophthalmic film-forming agent, a polymer typically must be at least slightly soluble in water, thus providing an appreciable range of usable concentrations. Such polymers often increase viscosity or exhibit film- or gel-forming properties when warmed to body temperature, when exposed to the pH or solute composition and ionic strength of the tear film, or when the product evaporates.

CHEMICAL PROPERTIES

The finished product viscosity range that can be obtained with a film-forming agent is related to its chemical structure and molecular weight. Functional groups such as the pyruvate and acetate groups of xanthan gum can affect the relationship between viscosity and solution pH and ionic strength and also can determine film- and gel-forming properties. Polymer charge can influence interactions with the mucous layer of the eye. Molecular conformation, chain mobility, and degree of cross-linking also can affect the degree of swelling and thus performance.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistent functions of polymers for ophthalmic use: *Bulk Density and Tapped Density of Powders* ⟨616⟩, *Chromatography* ⟨621⟩, *Density of Solids* ⟨699⟩, *Loss on Drying* ⟨731⟩, *Particulate Matter in Ophthalmic Solutions* ⟨789⟩, *Viscosity—Capillary Methods* ⟨911⟩, *Viscosity—Rotational Methods* ⟨912⟩, *Viscosity—Rolling Ball Method* ⟨913⟩, *Pharmaceutical Dosage Forms* ⟨1151⟩, and *Powder Flow* ⟨1174⟩. In addition, the general chapters listed under *Functional Category: Film-Forming Agents* also may be appropriate for the evaluation of polymers for ophthalmic use.

TRANSDERMALS AND PATCHES

Functional Category: Adhesive

DESCRIPTION

Topical drug delivery systems (e.g., transdermals or skin patches) require the use of adhesives to maintain contact between the applied drug delivery system and the skin. Adhesives can be intercalated as a separate layer between the formulation matrix and the skin surface, incorporated as a part of the formulation matrix itself, or applied to the periphery of the topical delivery system.

FUNCTIONAL MECHANISM

Adhesion is the tendency of dissimilar surfaces to adhere to one another as a result of one or more types of interactions. For topical drug delivery systems, these adhesive interactions generally are chemical (primarily electrostatic) or dispersive (van der Waals and/or hydrogen bonding) in nature, although there is the possibility of mechanical interaction via the interlocking of microscopic asperities.

PHYSICAL PROPERTIES

In general, the adhesives used in transdermals or skin patches are pressure-sensitive materials whose performance is best characterized by physical test methods for tackiness and viscoelasticity of the adhesive per se and viscosity of a solution of the adhesive.

CHEMICAL PROPERTIES

In transdermals, the most widely used pressure-sensitive adhesives are acrylic, rubber, and silicone polymers. Acrylic polymer adhesives include various esters of acrylic or methacrylic acid, acrylamide, methacrylamide, *N*-alkoxyalkyl, or *N*-alkyl-acrylamides. Polyisobutylenes and polysiloxanes are among the most common rubber-based and silicone-based adhesives, respectively. The molecular weight and compositional distribution of the polymers are critical to the replication of the adhesive's efficacy from batch to batch.

GENERAL CHAPTERS

The following general chapters may be useful in evaluating the suitability of adhesives used in transdermals: *Tensile Strength* ⟨881⟩ and *Viscosity—Capillary Methods* ⟨911⟩.

Functional Category: Film-Forming Agent

DESCRIPTION

Film-forming agents used as the formulation matrix of topical drug delivery systems (e.g., transdermals or skin patches) or in conjunction with such systems comprise a flexible, nontacky but adherent film, in whole or in part, applied to the skin surface.

FUNCTIONAL MECHANISM

Film formation results from the progressive loss of solvent (or dispersion medium) from a solution (or dispersion) of a film-forming agent, whether in particulate or molecularly dispersed form. Solvent (or dispersion medium) loss leads to closer molecular or particulate packing and increased interaction among the film-forming agent molecules or particles. Ultimately, a continuous film is formed as a result of increased molecular entanglement or particulate sintering.

PHYSICAL PROPERTIES

Properties critical to successful film formation include the film-forming agent's glass transition temperature (T_g), the viscosity of the solution or dispersion, and the surface characteristics of the substrate. Viscoelastic properties such as elastic modulus, viscous modulus, and intrinsic or complex viscosity describe functional characteristics, such as adhesion, for a pressure-sensitive adhesive component. Adhesion to a substrate and tack and shear tests can be used for batch release.

CHEMICAL PROPERTIES

Typical film-forming agents are thermoplastic or thermosetting high molecular weight polymers or copolymers, often in the form of aqueous dispersions or latex compositions. Cellulosic polymers, vinyl polymers and copolymers, and acrylic and methacrylic acid polymers and copolymers frequently are used in topical delivery systems as film-forming agents.

GENERAL CHAPTERS

The following general chapters may be useful in evaluating the suitability of film-forming agents used in transdermals and patches: *Thermal Analysis* ⟨891⟩, *Viscosity—Capillary Methods* ⟨911⟩, *Viscosity—Rotational Methods* ⟨912⟩, and *Viscosity—Rolling Ball Method* ⟨913⟩.

RADIOPHARMACEUTICALS

Radiopharmaceuticals commonly contain categories of excipients that also are used in conventional drugs. For example, radiopharmaceutical capsules may contain diluents and necessarily use a capsule shell, and parenteral radiopharmaceuticals may contain pharmaceutical water, diluents, tonicity agents, pH modifiers, antimicrobial preservatives, chelating and/or complexing agents, and antioxidants. Many radiopharmaceuticals differ from conventional drugs, however, because their preparation (reconstitution) involves one or more chemical reactions that require unusual excipients. Furthermore, the self-absorption of emitted radiation may result in the radiolytic decomposition of many radiopharmaceuticals. Hence, several excipients are used predominately in radiopharmaceutical formulations, although they occasionally may be used for other drugs.

Functional Category: Reducing Agent

DESCRIPTION

Reducing agents generally are required for technetium Tc 99m radiopharmaceuticals. Technetium Tc 99m, in the chemical form of sodium pertechnetate (+7 oxidation state), must be reduced to a lower oxidation state so that it can be chelated or otherwise complexed by the intended ligand to form the final Tc 99m radiopharmaceutical. The reducing agent, typically a stannous salt, generally is formulated in the kit for the preparation of the technetium Tc 99m radiopharmaceutical.

FUNCTIONAL MECHANISM

The reducing agent (e.g., stannous ion) must be present in sufficient quantity to reduce all of the technetium atoms to the intended oxidation state but must not produce undesired reduction products or other impurities (e.g., stannous hydroxide precipitates).

PHYSICAL PROPERTIES

Reducing agents (e.g., stannous salts) must be readily soluble in water.

CHEMICAL PROPERTIES

Reducing agents (e.g., stannous salts) are sensitive to oxidation by atmospheric oxygen and oxidizing species in solution. Hence, lyophilized contents of kit vials must be filled with a nonoxidative gas such as nitrogen or argon. The reducing agent also must be stable at the intended pH of the formulated product.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected reducing agent functions: *Chromatography* ⟨621⟩ and *Radioactivity* ⟨821⟩.

Functional Category: Transfer Ligand

DESCRIPTION

In the preparation of certain radiopharmaceuticals, the radiometal (e.g., stannous-reduced technetium Tc 99m) is first chelated by a relatively weak chelating ligand and then is transferred to the principal chelating ligand or complexing moiety. Examples of such transfer ligands include citrate, gluconate, and tartrate.

FUNCTIONAL MECHANISM

Transfer ligands typically undergo rapid reactions with reduced technetium to form weak chelates, thus keeping the reduced technetium in a soluble form until it is transferred to the principal ligand. This procedure is especially useful when the kinetics of complexation with the principal ligand is slow or when a heating step is necessary to expose chelating groups on the principal ligand.

PHYSICAL PROPERTIES

Transfer ligands must be readily soluble in water.

CHEMICAL PROPERTIES

Transfer ligands must have rapid complexation kinetics and must form relatively weak chelates compared to complexation with the principal ligand.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected transfer ligand functions: *Chromatography* ⟨621⟩ and *Radioactivity* ⟨821⟩.

Functional Category: Colloid Stabilizing Agent

DESCRIPTION

Lyophobic colloids tend to clump together and form large aggregates to minimize their surface-area-to-volume ratio. Colloid stabilizing agents are relatively large lyophilic molecules that coat the surface of each individual colloid particle and prevent or inhibit clumping. Examples of colloid stabilizing agents include gelatin and dextran.

FUNCTIONAL MECHANISM

The colloid stabilizing agent coats the surface of the lyophobic colloid particles, making them appear lyophilic. Additionally, the colloid stabilizing agent may be charged, thus causing the coated colloid particles to repel one another.

PHYSICAL PROPERTIES

Colloid stabilizing agents must be readily soluble in water.

CHEMICAL PROPERTIES

Colloid stabilizing agents must be capable of coating the lyophobic colloid particles, e.g., by electrostatic attraction of an opposite charge.

GENERAL CHAPTERS

The following general chapters may be useful in ensuring consistency in selected colloid stabilizing agent functions: *Chromatography* ⟨621⟩ and *Radioactivity* ⟨821⟩.

Functional Category: Free Radical Scavenger

DESCRIPTION

Radiation interactions with water and other molecules frequently produce free radicals. Free radical scavengers preferentially interact with oxidative or reductive free radicals that otherwise would result in degradation of formulation components. In the case of radiopharmaceuticals, free radical scavengers can be used to enhance radiochemical purity. Examples of free radical scavengers include methylene blue and aminobenzoic acid.

FUNCTIONAL MECHANISM

Free radical scavengers preferentially interact with radiolytically produced free radicals before these free radicals can interact with the radiopharmaceutical and produce radiochemical impurities.

PHYSICAL PROPERTIES

Free radical scavengers must be readily soluble in water.

CHEMICAL PROPERTIES

Free radical scavengers must be capable of preferentially interacting with free radicals without causing other effects.