Dosage Form Design and Development

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ABSTRACT

Background: Drugs must be properly formulated for administration to patients, regardless of age. Pediatric patients provide some additional challenges to the formulator in terms of compliance and therapeutic efficacy. Due to the lack of sufficient drug products for the pediatric population, the pharmaceutical industry and compounding pharmacies must develop and provide appropriate medications designed for children.

Objective: The purpose of this article was to review the physical, chemical, and biological characteristics of drug substances and pharmaceutical ingredients to be used in preparing a drug product. In addition, stability, appearance, palatability, flavoring, sweetening, coloring, preservation, packaging, and storage are discussed.

Methods: Information for the current article was gathered from a literature review; from presentations at professional and technical meetings; and from lectures, books, and publications of the author, as well as from his professional experience. Professional society meetings and standards-setting bodies were also used as a resource.

Results: The proper design and formulation of a dosage form requires consideration of the physical, chemical, and biological characteristics of all of the drug substances and pharmaceutical ingredients (excipients) to be used in fabricating the product. In addition, stability, appearance, palatability, flavoring, sweetening, coloring, preservation, packaging, and storage are discussed.

Conclusions: Successful development of a formulation includes multiple considerations involving the drug, excipients, compliance, storage, packaging, and stability, as well as patient considerations of taste, appearance, and palatability. (Clin Ther. 2008;30:2102-2111) © 2008 Excerpta Medica Inc.

Key words: pediatrics, dosage form, drug substances, pharmaceutical ingredients.

INTRODUCTION

The potent nature and relatively low dosage of most drugs used today preclude the expectation that the general public could obtain the proper dose of the drug from the bulk material. Consequently, dosage forms have been developed over the years for various applications and consist of the active drug in combination with ≥1 nonmedical agents that fulfill various functions in the dosage form. Through the selective use of these nonmedical agents, referred to as pharmaceutical ingredients or excipients, dosage forms of various types (eg, tablets, capsules, suspensions, creams, ointments, transdermal patches or gels) result. The pharmaceutical ingredients solubilize, suspend, thicken, dilute, emulsify, stabilize, preserve, color, flavor, and fashion medical agents into efficacious and appealing dosage forms. Each dosage form is unique in its physical and pharmaceutical characteristics.1

Formulating a drug product involves appropriate consideration of each ingredient in the final product. This includes the physical, chemical, and biological characteristics, along with the ingredients' compatibility with each other, to produce a product that will enhance compliance (by being palatable, easy to administer, and well tolerated) as well as be stable and efficacious.

The purpose of this article was to review the physical, chemical, and biological characteristics of the drug substances and pharmaceutical ingredients to be used in preparing a drug product. In addition, stability, appearance, palatability, flavoring, sweetening, coloring, preservation, packaging, and storage are discussed. These topics are among those considered by the working group from the Pediatric Formulation Initiative of the Eunice Kennedy Shriver National Institute of Child Health and Human Development in efforts to broaden the availability of pediatric patient-specific medications.
MATERIALS AND METHODS
Information for the current article was gathered from a literature review; from presentations at professional and technical meetings; and from lectures, books, and publications of the author, as well as from his professional experience. Professional society meetings and standards-setting bodies were also used as a resource.

GENERAL CONSIDERATIONS IN DOSAGE FORM DESIGN
The age of the intended patient plays a role in dosage form design. For infants and children aged <5 years, pharmaceutical liquids (rather than solid dosage forms) are preferred for oral administration. These liquids, which are flavored aqueous solutions, syrups, or suspensions, are administered directly into the infant’s or child’s mouth by drop, spoon, or oral dispenser or incorporated into the child’s food. A single liquid pediatric preparation may be used for infants and children of all ages, with the dose of the drug varied by the volume administered. When an infant is vomiting or gagging, has a productive cough, or is simply uncontrollable, there may be some question as to how much of the medicine administered is actually swallowed and how much is expectorated. In such instances, other routes of administration, such as injections, may be required. Infant-size rectal suppositories can also be used, although drug absorption from the rectum may be erratic.1-3

Pediatric patients, developmentally disabled patients, some elderly, and even other adult patients may have difficulty swallowing solid dosage forms, especially uncoated tablets. For this reason, some medications are formulated as chewable tablets that can be broken up in the mouth before swallowing. These tablets, which may be comparable in texture to an after-dinner mint, break down into a pleasant-tasting, creamy material. New, rapidly disintegrating/dissolving tablets are available that dissolve in the mouth in ~10 to 15 seconds; this allows the patient to take a tablet but actually swallow a liquid.3

PREFORMULATION STUDIES
Before the formulation of a drug substance into a dosage form, it must be chemically and physically characterized. Preformulation studies supply the information needed to define the nature of the drug substance. This information is then used as the framework for the drug’s combination with pharmaceutical ingredients in the fabrication of a dosage form.3-6

Drug Substance Characteristics
It is important to have an understanding of the characteristics of a drug substance before dosage form development. Most drug substances in use today are solid materials and most are pure chemical compounds of either crystalline or amorphous constitution; some occur as optical isomers and some are anhydrous or hydrous.3,5 The selection of the proper form of the drug (eg, base, salt, anhydrous, hydrate) is critical to ensure solubility, absorption, and stability characteristics. The purity of the chemical substance is essential for its identification as well as for the evaluation of its chemical, physical, and biological properties. Chemical properties include the structure, form, and reactivity of the drug. Properties that can affect the drug’s dissolution and bioavailability include physical characteristics such as particle size, crystalline structure, and solubility. Other physical properties of importance include physical description and melting point. The ability of the drug to pass through various biological membranes to reach its site of action, ultimately eliciting a biological response, is included in the biological properties of the drug.

Microscopic Examination
Microscopic examination of the raw drug substance provides an indication of particle size and particle size range of the drug substance, as well as its crystal structure. During some processing procedures, the solid drug powders must flow freely and not become entangled or agglomerated. Spherical and oval-shaped powders flow more easily than needle-shaped powders and may facilitate processing.3-5

Melting Point Depression
A characteristic of a pure substance is a defined melting point or melting range. If not pure, the substance will exhibit a depression or lowering of its melting point as compared with the pure substance. This phenomenon is commonly used to determine the purity of a drug substance and, in some cases, the compatibility of various substances before inclusion in the same dosage form (including the active drug with pharmaceutical ingredients and pharmaceutical ingredients with each other). Compatibility between substances can be determined by observation of the melting point data of different ratios/combinations of the substances.

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Particle Size

Particle size distribution affects certain physical and chemical properties of drug substances, such as drug dissolution rate, bioavailability, content uniformity, taste, texture, color, and stability. Flow characteristics and sedimentation rates (suspensions) are also important factors related to particle size. It is essential to establish, as early as possible in the formulation process, how the particle size of the drug substance may affect formulation and product efficacy. Of special interest is the effect of particle size on the drug's absorption. Particle size influences the oral absorption profiles of certain drugs. For example, drugs with poor solubility may have poor absorption when present as large particles. Reduction of the drug to small particles often results in better dissolution and absorption of the drug. Also, satisfactory content uniformity in solid dosage forms depends to a large degree on particle size and the equal distribution of the active ingredient throughout the formulation. When the particle size of the substances is uniform, there is less tendency of the particles to separate, with the smaller particles generally settling to the bottom and the larger ones rising to the top of the mixture.

Polymorphism

Whether a drug substance is a crystal or amorphous form is a principal factor in formulation. Polymorphic forms (ie, different crystalline forms of the same drug) may exhibit different physicochemical properties, including melting point and solubility. The occurrence of polymorphic forms with drugs is relatively common, and it has been estimated that polymorphism is exhibited by at least one third of all organic compounds.

In addition to the polymorphic forms in which compounds may exist, they can occur in noncrystalline or amorphous forms. The energy required for a molecule of drug to escape from a crystal is much greater than that required to escape from an amorphous powder. Therefore, the amorphous form of a compound is always more soluble than a corresponding crystal form.

Solubility

An important physicochemical property of a drug substance is solubility, especially aqueous system solubility. A balance between aqueous and lipid solubility is important for dissolution (aqueous) and absorption across biological membranes (lipid). A drug must possess some aqueous solubility for therapeutic efficacy. For a drug to enter the systemic circulation to exert a therapeutic effect, it must first be in solution. Relatively insoluble compounds, such as erythromycin, may exhibit incomplete or erratic absorption. If the solubility of the drug substance needs improvement, the methods to accomplish this will depend on the chemical nature of the drug and the type of drug product under consideration. The chemical modification of the drug into salt or ester forms may be used to obtain more soluble (and sometimes less soluble) compounds. For example, erythromycin is available as the stearate (tablets) and ethylsuccinate (suspension) esters for oral administration and as the lactobionate (solution) for injection.

Solubility and Particle Size

Although solubility is normally considered a physicochemical constant, small increases in solubility may be accomplished by particle size reduction.

Solubility and pH

If the drug is to be formulated into a liquid product, another technique to enhance solubility involves adjusting the pH of the solvent in which the drug is to be dissolved. However, there are many drug substances for which pH adjustment is not an effective means of improving solubility. Weak acidic or basic drugs may require extremes in pH that are outside accepted physiologic limits or may cause stability problems with formulation ingredients. Adjustment of pH may have little effect on the solubility of nonelectrolytes, such as dextrose and prednisone. In other cases, it is desirable to use cosolvents or techniques such as complexation, micronization, or solid dispersion to improve aqueous solubility.

Dissolution

Variations in the biological activity of a drug substance may be brought about by the rate at which it becomes available to the organism. The dissolution rate, or the time it takes for the drug to dissolve in the fluids at the absorption site, may be the rate-limiting step in the absorption process. This is true for drugs administered orally in solid forms such as tablets, capsules, or suspensions, as well as drugs administered intramuscularly in the form of pellets or suspensions. When the dissolution rate is the rate-limiting step, any factors that affect it will also affect absorption. Consequently, dissolution rate can affect the onset, inten-
sity, and duration of response, as well as influence the overall bioavailability of the drug from the dosage form.

The dissolution rate of drugs may be increased by decreasing the drug’s particle size, resulting in an increase in its surface area. It may also be raised by increasing its solubility in the diffusion layer, as in buffered aspirin. In this case, the diffusion layer is at a higher pH, resulting in faster dissolution due to increased solubility. An effective means of obtaining higher dissolution rates is to use a highly water-soluble salt of the parent substance. Although a soluble salt of a weak acid will subsequently precipitate as the free acid in the bulk phase of an acidic solution, such as gastric fluid, it will do so in the form of fine particles with a large surface area.

Early formulation studies should include the effects of pharmaceutical ingredients on the dissolution characteristics of the drug substance.

Membrane Permeability

To produce a biological response, the drug molecule must first cross a biological membrane. This membrane acts as a lipid barrier to most drugs and permits the absorption of lipid-soluble substances by diffusion, while lipid-insoluble substances can diffuse across the barrier only with some difficulty, generally involving facilitated diffusion or active transport. The interrelationship of the dissociation constant, lipid solubility, and pH at the absorption site and absorption characteristics of various drugs are the basis for the pH partition theory. Absorption can be enhanced by the drug in its nonionized state, which can be accomplished by an adjustment of the medium containing the drug.

In the latter stages of preformulation testing or early formulation studies, animals and humans must be assessed to determine the absorption efficiency and pharmacokinetic parameters and to establish a possible in vitro/in vivo correlation for dissolution and bioavailability.

Partition Coefficient

In formulation development, the octanol-water partition coefficient is commonly used for estimating the permeability potential and lipophilicity of the drug. It is defined as: \( P = \frac{\text{concentration of drug in octanol}}{\text{concentration of drug in water}} \), where \( P \) is dependent on the drug concentration only if the drug molecules have a tendency to associate in solution. For an ionizable drug, the following equation is applicable: \( P = \frac{\text{concentration of drug in octanol}}{1 - \alpha} \) [concentration of drug in water], where \( \alpha \) equals the degree of ionization.

pKa/Dissociation Constants

Among the physicochemical characteristics of interest is the extent of dissociation/ionization of drug substances. The extent of ionization influences the formulation and pharmacokinetic parameters of the drug. The extent of dissociation/ionization is highly dependent on the pH of the medium containing the drug. In formulation, the vehicle may be adjusted to a certain pH to obtain a particular level of ionization of the drug for solubility and/or stability purposes. In terms of pharmacokinetics, the extent of ionization of a drug influences the extent of absorption, distribution, and elimination. The extent of ionization helps predict precipitation in solutions and in the calculation of the solubility of drugs at certain pH values.

Drug and Drug Product Stability

Preformulation studies evaluate the physical and chemical stability of the pure drug substance. Stability studies conducted in the preformulation phase include solid-state stability of the drug alone, solution-phase stability, and stability in the presence of expected excipients. Initial investigations begin with knowledge of the drug’s chemical structure, which allows the preformulation scientist to anticipate the possible degradation reactions.

Kinetics and Shelf-Life

Stability is defined as the extent to which a product retains, within specified limits and throughout its period of storage and use (ie, its shelf-life), the same properties and characteristics that it possessed at the time of its manufacture.

There are 5 types of stability that are of interest to health care providers: (1) chemical—each active ingredient must retain its chemical integrity and labeled potency, within the pharmacopoeial-specified limits; (2) physical—the original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability, must be retained; (3) microbiologic—sterility or resistance to microbial growth must be retained according to the specified compendial requirements, and antimicrobial agents that are present...
ent must retain effectiveness within specified limits; (4) therapeutic—the therapeutic effect must remain unchanged; and (5) toxicologic—no significant increase in toxicity should occur.

Chemical stability must be considered when selecting storage conditions (temperature, light, humidity), when choosing the proper container for dispensing (glass vs plastic, clear vs amber or opaque, cap liners), and for anticipating interactions when mixing drugs and dosage forms. Chemical stability and expiration dating are based on chemical reaction kinetics (ie, the study of the rate of chemical change and the way this rate is influenced by conditions of concentration of reactants, products, and other chemical species that may be present, and by factors such as solvent, pressure, and temperature).

ENHANCING THE STABILITY OF
DRUG PRODUCTS

Stability Procedures
Pharmaceutical ingredients (excipients) may be used to achieve the desired dosage form of a drug substance. Some of these agents may be used to achieve the appropriate physical and chemical characteristics of the product or to enhance its appearance, odor, and taste. Other substances, such as buffers and antioxidants, may be used to increase the stability of the drug substance, particularly against the hydrolytic and oxidative processes. In each instance, the added pharmaceutical ingredient must be compatible with and must not detract from the stability of the drug substance in the particular dosage form prepared.

Hydrolysis
There are several approaches to the stabilization of pharmaceutical preparations containing drugs subject to deterioration by hydrolysis. Perhaps the most obvious is the reduction, or the elimination, of water from the pharmaceutical system. In liquid preparations, water can frequently be replaced or reduced in the formulation through the use of substitute liquids such as glycerin, propylene glycol, and alcohol. In certain injectable products, anhydrous vegetable oils may be used as the drug’s solvent to reduce the chance of hydrolytic decomposition.3,5

Decomposition by hydrolysis may be prevented for other drugs to be administered in liquid form by suspending them in a nonaqueous vehicle (such as vegetable oils) rather than by dissolving them in an aqueous solvent. In other instances, particularly for certain unstable antibiotic drugs, when an aqueous preparation is desired, the drug may be commercially supplied in a dry form for reconstitution at the pharmacy by adding a specified volume of purified water just before dispensing. The dry powder supplied commercially is actually a mixture of the antibiotic, suspending agents, flavorants, and colorants, which, when reconstituted, remains a stable suspension or solution of the drug for the time period in which the preparation is normally consumed.1,3,4 Storage under refrigeration is advisable for most preparations considered unstable due to hydrolytic causes.

Along with temperature, pH is a major determinant in the stability of a drug prone to hydrolytic decomposition. The hydrolysis of most drugs depends on the relative concentrations of the hydroxyl and hydronium ions, and a pH at which each drug is optimally stable can easily be determined. For most hydrolyzable drugs, the pH of optimum stability is acidic (ie, pH between 5 and 6). Therefore, through judicious use of buffering agents, the stability of otherwise unstable compounds can be increased.

Oxidation
Pharmaceutically, the oxidation of a susceptible drug substance is most likely to occur when it is maintained in other than the dry state in the presence of oxygen, exposed to light, or combined in formulation with other chemical agents without proper regard for their influence on the oxidation process. The oxidation of a chemical in a pharmaceutical preparation may alter the color of that preparation. It may also result in precipitation or a change in the usual odor of a preparation.3-5

The oxidative process is diverted, and the stability of the drug is preserved, by use of antioxidants, which react with free radicals in the drug to prevent progression of the oxidative chain reaction. In general, antioxidants act by providing electrons and easily available hydrogen atoms that are accepted more readily by the free radicals than those of the drug being protected. Antioxidants used in aqueous preparations include sodium sulfite (at high pH values), sodium bisulfite (at intermediate pH values), sodium metabisulfite (at low pH values), hypophosphorous acid, and ascorbic acid. In oleaginous (oily or unctuous) preparations, α-tocopherol, butylhydroxyanisole, and ascorbyl palmitate are useful.
The proper use of antioxidants involves their specific application only after appropriate biomedical and pharmaceutical studies. In certain instances, other pharmaceutical additives (eg, phenylmercuric acetate) can inactivate a given antioxidant when used in the same formulation. Certain antioxidants can react chemically with the drugs they were intended to stabilize, without a noticeable change in the appearance of the preparation.

Trace metals originating in the drug, solvent, container, or stopper are a constant source of difficulty in preparing stable solutions of oxidizable drugs. These trace metals must be eliminated from labile preparations by thorough purification of the source of the contaminant or by chemically complexing or binding the metal through the use of chelating agents that make the metal chemically unavailable for participation in the oxidative process. Examples of these chelating agents include edetate calcium disodium and ethylenediaminetetraacetic acid.

Light can also act as a catalyst to oxidation reactions. As a photocatalyst, light waves transfer their energy (photons) to drug molecules, making the latter more reactive through increased energy capability. As a precaution against the acceleration of the oxidative process, sensitive preparations are packaged in light-resistant or opaque containers.

Because most drug degradations proceed more rapidly with an increase in temperature, it is also advisable to maintain oxidizable drugs in a cool place. Another factor that could affect the stability of an oxidizable drug in solution is the pH of the preparation. Each drug must be maintained in solution at the pH most favorable to its stability. For example, aspirin is most stable at a pH of ~2.5. The pH of optimum stability, in fact, varies from preparation to preparation and must be determined on an individual basis for the drug in question.

Thus, for easily oxidizable drugs, the respective preparations may be stabilized by the selective exclusion from the system of oxygen, oxidizing agents, trace metals, light, heat, and other chemical catalysts to the oxidation process. Antioxidants, chelating agents, and buffering agents may be added to create and maintain a favorable pH.

Other Processes

In addition to hydrolysis and oxidation, other destructive processes such as polymerization, chemical decarboxylation, and deamination may occur in pharmaceutical preparations. However, these processes occur less frequently and are peculiar to only small groups of chemical substances.

Stability Testing

As a drug development program progresses, so does the requisite data to demonstrate and document the drug/drug product’s stability profile. Before approval for marketing, a product’s stability must be assessed with regard to its formulation, the impact of pharmaceutical ingredients present, the influence of the container and closure, the manufacturing and processing conditions (eg, heat), the packaging components and conditions of warehousing/storage, the anticipated conditions of shipping (temperature, light, and humidity), and anticipated duration and conditions of pharmacy shelf-life and patient utilization. It is important to recognize that the “holding” of intermediate product components (as drug granulations for tableting) for undue lengthy periods before processing into finished pharmaceutical products could affect the stability of both the intermediate component and the finished product. Therefore, in-process stability testing, including the retesting of intermediate components, is important.

Product containers, closures, and other packaging features must be considered in stability testing. For instance, tablets or capsules packaged in glass or plastic bottles, blister packs, or strip packaging require specific stability test protocols. Parenteral and other sterile products must meet sterility test standards to ensure protection against microbial contamination. Any preservatives used must be tested for effectiveness in the finished product.

Drug products must meet stability standards for long-term storage of ~2 to 3 years at room temperatures and under conditions of relative humidity. Products are also subjected to accelerated stability studies as an indication of shelf-life stability. It is a requirement of the US Food and Drug Administration (FDA) in a New Drug Application that if not submitted in the approved application, the first 3 postapproval production batches of a drug substance be placed on long-term stability studies and the first 3 postapproval production batches of drug product be subject to both long-term and accelerated stability studies.

Under usual circumstances, most manufactured products require a shelf-life of ≥2 years to ensure their stability at the time of patient consumption. Commer-
Pharmaceutical Ingredients/Excipients
Definitions and Types

To prepare a drug substance into a final dosage form, pharmaceutical ingredients are required. For example, in the preparation of pharmaceutical solutions, ≥1 solvents are used to dissolve the drug substance; flavors and sweeteners are used to make the product more palatable; colorants are added to enhance product appeal; preservatives may be added to prevent microbial growth; and stabilizers (eg, antioxidants, chelating agents) may be used to prevent drug decomposition. In the preparation of tablets, diluents or fillers are commonly added to increase the bulk of the formulation, binders to cause the adhesion of the powdered drug, and pharmaceutical substances, antiadherents, or lubricants to assist the smooth tableting process; disintegrating agents are used to promote tablet breakup after administration; and coatings are used to improve stability, control disintegration, or to enhance appearance. Ointments, creams, and suppositories achieve their characteristic features due to the pharmaceutical bases that are utilized. Thus, for each dosage form, the pharmaceutical ingredients establish the primary features of the product and contribute to the physical form, texture, stability, taste, and overall appearance.

A few of the more common and widely used pharmaceutical excipients, including flavors, sweeteners, colors, and preservatives, are discussed here. Packaging and storage are also discussed.

Appearance and Palatability

Although most drug substances in use today are unpalatable and unattractive in their natural state, modern pharmaceutical preparations are presented to the patient as colorful, flavorful formulations and/or are acceptable in terms of appearance, smell, and taste. These qualities, which are the rule rather than the exception, are aimed at eliminating the natural reluctance that patients may have to taking medications because of disagreeable odor or taste.1,3,4

There is some psychological basis to drug therapy and to drug therapy adherence. Odor, taste, and color of a pharmaceutical preparation can play a part in compliance. An appropriate drug will have its most beneficial effect when it is accepted and taken as directed by the patient. The proper combination of flavor, taste, and color in a pharmaceutical product contributes to its acceptance.
**Flavoring Pharmaceuticals**

The flavoring of pharmaceuticals applies primarily to liquid dosage forms intended for oral administration. Medication in liquid form comes into immediate and direct contact with the patient's taste buds. By adding flavoring agents to liquid medication, the disagreeable taste of drugs may be successfully masked.

The selection of an appropriate flavoring agent depends on several factors but primarily on the taste of the drug substance itself. Certain flavoring materials are more effective than others in masking or disguising the particular bitter, salty, sour, or otherwise undesirable taste of medicinal agents. Although individuals' tastes and flavor preferences differ, cocoa-flavored vehicles are considered effective for masking the taste of bitter drugs. Fruit or citrus flavors are frequently used to combat sour- or acid-tasting drugs, and cinnamon, orange, raspberry, and other flavors have been successfully used to make preparations of salty drugs more palatable. 1,3,4

The age of the intended patient should also be considered in the selection of the flavoring agent, as certain age groups appear to prefer certain flavors. Children prefer sweet, candy-like preparations with fruity flavors, but adults appear to prefer less sweet preparations with a tart rather than a fruit flavor. 3

When flavoring a product, some options include oil- or water-soluble liquids and dry powders; most are diluted in carriers. Oil-soluble carriers include soybean and other edible oils; water-soluble carriers include water, ethanol, propylene glycol, glycerin, and emulsifiers. Dry carriers include maltodextrins, corn syrup solids, modified starches, gum arabic, salt, sugars, and whey protein. Because flavors can degrade as a result of exposure to light, temperature, headspace oxygen, water, enzymes, contaminants, and other product components, they must be carefully selected and checked for stability.1,3,4

**Sweetening Pharmaceuticals**

In addition to sucrose, a number of artificial sweetening agents have been used in foods and pharmaceuticals over the years. These include aspartame, acesulfame potassium, saccharin, and cyclamate; some have faced challenges by the FDA and restrictions to their use and sale. 3,4 At high doses, some of these artificial sweeteners have unpleasant (ie, bitter, irritating) tastes. Other sweeteners include fructose, polyalcohols, sorbitol, glycerin, and stevia (a relatively new, natural sweetening agent introduced in the United States in the past decade). 3

**Coloring Pharmaceuticals**

A distinction should be made between coloring agents that have inherent color and those agents that are used as colorants. A colorant becomes an integral part of a pharmaceutical formulation, and its exact quantitative amount must be reproducible each time the formulation is prepared or else the preparation's appearance will differ from batch to batch. This requires a high degree of pharmaceutical skill, for the amount of colorant generally added to liquid preparations ranges between 0.0005% and 0.001% depending on the colorant and the depth of color desired. 1,4

Because of their color potency, dyes are generally added to pharmaceutical preparations in the form of diluted solutions rather than as concentrated dry powders. This permits greater accuracy in measurement and more consistent color production. 3

In addition to esthetics and the certification status of a dye, the dyes to be used in a particular formula must be selected based on the physical and chemical properties of those dyes available. Of prime importance is the solubility of a prospective dye in the vehicle. In general, most dyes are broadly grouped into those that are water soluble and those that are oil soluble; few, if any, are both. A water-soluble dye may also be adequately soluble in commonly used pharmaceutical liquids such as glycerin, alcohol, and glycol ethers. Oil-soluble dyes may also be soluble to some extent in these solvents, as well as in liquid petrolatum (mineral oil), fatty acids, fixed oils, and waxes. 1,4

A great deal of solubility is not required, as the concentration of dye in a given preparation is rather minimal. 3

Another important consideration when selecting a dye for use in a liquid pharmaceutical is the pH and pH stability of the preparation to be colored. Dyes can change color with a change in pH, and a dye must be selected for a product so that any anticipated pH change will not alter the color during the usual shelf-life. The dye also must be chemically stable in the presence of the other formulative ingredients and must not interfere with the stability of those agents. To maintain their original colors, FD&C dyes must be protected from oxidizing agents, reducing agents (especially metals such as iron, aluminum, zinc, and tin), strong acids and alkalis, and excessive heating. Dyes must also be reasonably photostable; that is, they
must not change color when exposed to light of anticipated intensities and wavelengths under the usual conditions of shelf storage. Certain medicinal agents, particularly those prepared in liquid form, must be protected from light to maintain their chemical stability and their therapeutic effectiveness. These preparations are generally maintained and dispensed in dark amber or opaque containers.\textsuperscript{1,3,4}

**Preservation**

Preparations that are particularly susceptible to microbial growth because of the nature of their ingredients are protected by the addition of an antimicrobial preservative. Preparations that are at risk for contamination by microbes are most aqueous preparations, especially syrups, emulsions, and suspensions, and some semisolid preparations, particularly creams. Certain hydroalcoholic and most alcoholic preparations may not require the addition of a chemical preservative when the alcoholic content is sufficient to prevent microbial growth.\textsuperscript{1,3,4}

Microorganisms involved include molds, yeasts, and bacteria, with bacteria generally favoring a slightly alkaline medium and the others an acidic medium.\textsuperscript{3} Although few microorganisms can grow at a pH <3 or >9, most aqueous pharmaceutical preparations are within the pH range of 3 to 9, which is favorable for growth of microorganisms, and therefore they must be protected against microbial growth with the use of preservatives. To be effective, a preservative agent must be dissolved in sufficient concentration in the aqueous phase of a preparation. Furthermore, only the undissociated fraction or molecular form of a preservative possesses preservative capability, because the ionized portion is incapable of penetrating the microorganism. Thus, the preservative selected must be largely undissociated at the pH of the formulation being prepared. Acidic preservatives, such as benzoic, boric, and sorbic acids, are more undissociated and thus more effective as the medium is made more acidic. Conversely, alkaline preservatives are less effective in acidic or neutral media and more effective in alkaline media. Thus, it is important to discuss the pH of the system when addressing the effectiveness of a preservative at specific concentrations and the resulting undissociated concentration of the preservative is calculated or otherwise determined to be appropriate. Also, if formulative materials interfere with the solubility or availability of the preservative agent, its chemical concentration may not be a true measure of the effective concentration. Many incompatible combinations of preservative agents and other pharmaceutical adjuncts have been discovered in recent years, and undoubtedly many more will be uncovered in the future as new preservatives, pharmaceutical adjuncts, and therapeutic agents are combined for the first time.\textsuperscript{4} Many of the recognized incompatible combinations that result in preservative inactivation involve macromolecules such as various cellulose derivatives, polyethylene glycols, and natural gums such as tragacanth. These macromolecules can attract and hold preservative agents, such as the parabens and phenolic compounds, rendering them unavailable for their preservative function.\textsuperscript{3,4} It is essential to consider all formulative ingredients, as one may interact with and affect the other, to assure that each can do its intended job successfully.

In addition, the preservative must not interact with the container, such as a metal ointment tube or a plastic medication bottle, or with the enclosure, such as a rubber or plastic cap or liner. Such an interaction could result in the decomposition of the preservative or the container closure, or both, with resultant product decomposition and contamination. Appropriate tests should be devised and conducted to ensure against this type of preservative interaction.

**Packaging and Storage**

The selected packaging must be appropriate to enhance stability and compliance. The selection of a container depends on the physical and chemical properties of the compounded preparation and the intended use of the preparation. Packaging materials should not interact physically or chemically with the preparation. Materials that are reactive, additive, or absorptive can alter the identity, strength, quality, and purity of the compounded drug beyond the specifications for an acceptable preparation. Characteristics of concern in container selection include inertness, visibility, strength, rigidity, moisture protection, ease of reclosure, and economy of packaging.

Compounded medications should be stored according to commercial or pharmacist-generated labeling. Generally, medications are stored at room temperature (20°C to 25°C), refrigerated temperature (2°C to 8°C), or in the freezer (−25°C to −20°C). Some products, such as suspensions and protein products, should not be frozen. Freezing of suspensions will result in particle size redistribution and potential difficul-
ties in resuspending the particles and, if an injectable, in withdrawing the product into a syringe through a needle. Proteins can become denatured if frozen, possibly resulting in a change in their activity and other characteristics.

CONCLUSIONS
Due to the lack of sufficient drug products for the pediatric population, the pharmaceutical industry and compounding pharmacies must develop and provide appropriate medications designed for children. Successful development of a formulation includes multiple considerations involving the drug, excipients, compliance, storage, packaging, and stability, as well as patient considerations of taste, appearance, and palatability.

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