DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 103

Excipient Toxicity and Safety

edited by
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Excipient Toxicity and Safety

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Foreword

Since the 1960s the producers of excipients and the drug dosage form formulation industry and regulators have slowly gained an appreciation of excipients and their specialized needs as distinct entities. There is a growing appreciation of the role that pharmaceutical excipients play in the production, shelf stability, dispensability, patient dosage acceptability, bioavailability, and delivery of the active pharmaceutical ingredient to the target organ.

As the late Dr. Shangraw, Professor of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, pointed out (*Pharmaceutical Technology*, June 1997), when I was starting out in the field, years ago, virtually all excipients were of natural origin—as either foods, food additives, or simple inorganics. They were supplied primarily by food producers or chemical suppliers. During the 1950s and 1960s development of excipients began to accelerate in the industry. The need for reproducible disintegration, dissolution, and bioavailability began to be recognized. Since available excipients were natural or well-known compounds, without obvious physiological activity, excipients were universally considered inactive and inert. Work during the 1960s alerted us to tablets, which transversed the gastrointestinal tract intact. Thus, the ''reproducible'' rate and extent of disintegration became an issue. When research indicated little or no absorption through the gut wall for certain excipients, dissolution became an issue. Bioavailability entered our active vocabulary. Polymers, sustained release agents and absorption modifiers exhibited interesting properties, but very little was known about their safety. Therefore, the need for adequate toxicological testing became apparent.

Over the years, few new potential excipients found use beyond utilization as food additives and cosmetic ingredients. As changes were made in regulations

controlling pharmaceutical production, the excipients were still not considered separate entities but only components of a final drug dosage form. The lack of regulatory status was very evident when Robert Pinco, Esq., presented a paper to a United States Pharmacopeia's Joint Pharmacopeia Open Conference on International Harmonization of Excipient Standards in 1991. He discussed this lack of regulations governing the requirements for safety evaluation of possible new excipients in Europe, Japan, and the United States. Many attendees at that conference agreed that there was a need for a regulatory road map. The time had come to recognize the unique properties of excipients and the need for appropriate and scientifically valid regulations for toxicological testing, specifications, and GMPs.

During that conference the International Pharmaceutical Excipients Council (IPEC) was conceived as a voluntary industry association of excipient producers and users. A key objective was to develop the basis for a regulatory road map, including new excipient safety evaluation guidelines for those willing to work on new excipients desired by the pharmaceutical industry. By 1992 the IPEC New Excipients Safety Evaluation Committee came into existence with members from excipient manufacturers and excipient users, academia, and the Food and Drug Administration. Many members of that committee have authored chapters in this volume, particularly the chapters in Part II. It is most significant that the committee decided to present a guideline for use by competent professionals rather than a checklist or a set of protocols. The regional IPEC-Americas, IPEC-Europe, and JPEC (Japanese organization) agreed on the principles and have, to a greater extent, harmonized the guideline. The next several years are expected to reveal progress by the regulators in the development of individual and harmonized guidelines for toxicological evaluation of excipients, for excipient drug master files, and for independent evaluation of drug master files, as well as a regulatory acceptability decision to foster the development of new materials.

This book meets a need at all levels of the pharmaceutical industry from undergraduate student through senior management, including regulators and regulatory scientists. It reviews the basics of pharmaceutical excipients, the specifications, and the regulatory status. Safety evaluation and risk assessment are reviewed. Finally, the key areas of risk communication and global harmonization are discussed. The book provides a pragmatic overview of excipients and excipient safety in pharmaceuticals.

The pharmaceutical industry is globalizing, and, therefore, the development of new concepts and new approaches to drug therapy is accelerating. A drug must be safe and effective. An excipient must be not only safe, but also suitable. My thanks to the editors and contributors for a very timely and valuable book.

Mr. Louis Blecher
Chairman
The International Pharmaceutical Excipients Council

Preface

The objective of this book is to familiarize the reader with the safe and legal use of pharmaceutical excipients. We hope to provide the reader with a comprehensive understanding of the current scientific basis for safety evalution of excipients. Excipients have not received much attention as separate entities. Until recently, excipients had been evaluated for toxicity as part of new drug formulations, with the active ingredient and all the various excipients of the formulation tested together. Until the proposal for safety evaluation procedures for new excipients by the Safety Committee of the International Pharmaceutical Excipients Council, no procedures existed for testing excipients alone. Historically, many excipients have been food additives and ''Generally Recognized As Safe'' (GRAS) by the United States Food and Drug Administration. The safety studies for such excipients have been reviewed as part of their GRAS designation. Now, the new IPEC guidelines will allow excipient manufacturers to approach their products in a scientific framework developed for this class of products.

Part I of the book defines excipients and discusses their historical use in drug formulations as inactive ingredients with specific functional properties, the requirements and importance of purity specifications, and the current regulatory requirements for excipients in the United States and Europe. Part II covers all aspects of safety evaluation of excipients as a unique class of products. The guidelines for safety evaluation of pharmaceutical excipients by various routes is an outgrowth of the Safety Committee of the International Pharmaceutical Excipients Council. The principles on which these guidelines are based and the technical details for conducting studies via each route of exposure are expounded in this section.

Part III of the book explains how data generated in toxicity studies are used

to identify hazards for use in drug formulations. Exposure assessment, a new area of excipient evaluation, is necessary to link hazard identification to risk. Principles of exposure assessment from other types of chemicals and products are used as a lens through which to view exposures to excipients, taking into consideration some of the typical exposures to drug products. Risk assessment and risk communication are the final steps in the overall understanding of the safe use of excipients. Finally, Part IV describes harmonization of existing issues for pharmaceutical excipients.

We hope that this book will be a valuable resource to pharmaceutical scientists in industry and academia, regulators, toxicologists, and risk assessors.

Myra L. Weiner
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1
What Are Excipients?

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I. INTRODUCTION

A. What Are Excipients?

There are several definitions for an excipient. In some cases, the definition is simple; in others, the definition is more encompassing and complex. Webster (1) defines an *excipient* as ''inert substance (as gum arabic or starch) that forms a vehicle (as for a drug).''

The *National Formulary* (2), a book of standards that provides monographs for pharmaceutical ingredients used in drug dosage forms, defines an *excipient* as any component, other than the active substance(s), intentionally added to the formulation of a dosage form. It is not defined as an ''inert'' commodity or an ''inert'' component of the dosage form. *The United States Pharmacopeia* (*USP*) and *National Formulary* (*NF*) are recognized in the Federal Food, Drug and Cosmetic Act. According to section 501 of the act, assays and specifications in the monographs of the *USP* and *NF* constitute legal standards. Most commonly recognized are *USP* and *NF* standards for determining the identity, strength, quality, and purity of the articles (''excipients'').

The *Handbook of Pharmaceutical Excipients*, originally published in 1986, was the first English-language publication to comprehensively and systematically describe the physical and chemical properties of pharmaceutical excipients. The second edition (1994) of the *Handbook of Pharmaceutical Excipients (3) defines excipients* as the additives used to convert pharmacologically active compounds into pharmaceutical dosage forms suitable for administration to patients.

In the spring of 1991, the International Pharmaceutical Excipients Council (IPEC) was formed. IPEC membership includes both companies that manufacture

*Retired

pharmaceutical excipients and companies that use excipients in the manufacture of drug dosage forms. *Pharmaceutical excipients*, as defined by IPEC (4), are any substance other than the active drug or prodrug that has been appropriately evaluated for safety and is included in a drug delivery system for any of the following purposes:

1. Aid processing of the system during manufacture
2. Protect, support, or enhance stability and bioavailability
3. Assist in product identification
4. Enhance any other attribute of the overall safety and effectiveness of the drug product during storage or use

As can be seen from the foregoing paragraphs, there are many definitions for an excipient. However, the intent in all cases is to define an excipient as a material(s) that has been evaluated for safety, aids in the manufacture of the dosage form, and protects, supports, or enhances stability and bioavailability of the drug or active ingredient.

This chapter will provide the reader with an appreciation and understanding of excipients: what they are; how they are employed; and what is their role in turning active ingredients into efficient and effective medicines.

II. EXCIPIENTS FOR USE IN ORAL MEDICINES

By far the most frequently employed dosage form used today throughout most areas of the world is the compressed tablet. *Tablets* may be defined as solid pharmaceutical dosage forms containing drug substances, with or without suitable diluents (excipients), and prepared either by compression or molding methods (5). The use of a tablet as a dosage form can be traced to well over 1,000 years ago when a procedure for molding solid forms containing medicinal ingredients was recorded (6). Tablets have been in widespread use since the latter part of the 19th century, and their popularity continues. Tablets remain popular because of the numerous advantages over other oral medicines, some of which are (a) accuracy of dosage, (b) compactness and portability (c) ease of administration, (d) durability of physical characteristics for extended periods of storage, and (e) stability of the chemical and physiological activity of the drugs.

For purposes of this chapter, excipients used mainly in the manufacture of compressed tablets will be discussed. Many of these excipients are also used in other oral dosage forms, including capsules and other types of tablets, which include chewables, effervescent, bilayer, multiple compressed, topical tablets, and tablets for solution. They are also used in tablets for specific modes of action (i.e., buccal or sublingual release and modified or controlled release).

Excipients perform very important functions in tablet formulations (7) specifically as

Fillers or diluents
Binders
Disintegrants or super disintegrants
Lubricants
Antiadherents
Glidants
Wetting and surface-active agents
Colors and pigments
Flavors, sweeteners, and taste maskers

Excipients may be classified according to the role they play in the finished tablet. Those excipients that help impart satisfactory processing and compression characteristics to the formulation include fillers–diluents, binders, glidants, and lubricants. The second group of excipients helps impart additional desirable physical characteristics to the finished tablet. Included in this group are disintegrants, colors and pigments, and wetting and surface-active agents. For chewable tablets, flavors, sweeteners, and taste-modifiers are employed. For controlled- or modified-release tablets, polymers or waxes or other solubility-retarding or modifying excipients are used. Chowan (7) recently provided a list (Table 1) of excipients commonly used in the manufacture of compressed tablets. Although not all-inclusive, the excipients are listed according to their intended use: direct-compression excipients, wet-granulation excipients, and those excipients that help to impart additional desirable physical characteristics to the finished tablet. The choice of excipients in a tablet formulation depends on the active ingredient, the type of tablet, the desired tablet characteristics, and the process used to manufacture the tablet. Compacted or compressed tablets are produced from powder mixtures or granulations made by one of the following general techniques:

Direct Compression. Direct compression consists of compressing tablets directly from powdered material without modifying the physical nature of the material itself. The process consists of mixing and blending the active ingredient with the appropriate excipient(s) before compression.

Wet Granulation. Wet granulation consists of weighing and mixing the active ingredient and excipient(s), granulation with a binder (low- or high-shear mixing), screening the damp mass (granulation), drying of the granulation, dry screening, lubrication, and compression. The wet granulation method is labor-intensive and time-consuming relative to tablets prepared by the direct compression technique.

Dry Granulation (by Roller Compaction or Slugging). The third process for making the ''running'' powder blend for tableting is the dry granulation process. This process requires five steps: (a) mixing, (b), roller compaction or slug-

Table 1 Tablet Excipients

Direct compression excipients	Wet granulation excipients
Cellulose	*Binders*
Avicel PH Microcrystalline Cellulose NF, Ph.Eur., JP, BP	Avicel PH Microcrystalline Cellulose NF, Ph.Eur., JP, BP
Microfine cellulose	Cellulose derivatives
Lactose	*Povidone USP*
Super-Tab Spray-Dried Lactose Monohydrate NF, Ph.Eur., JP, BP	*Gelatin NF*
Anhydrous lactose	Natural gums
Other sugars	Starch paste
Compressible Sugar NF	*Pregelatinized Starch NF*
Dextrose Excipient NF	*Sucrose NF*
Dextrates NF	Other binders
Starch and starch derivatives	Others
Native starches	*Disintegrants*
Pregelatinized Starch NF	Ac-Di-Sol Croscarmellose Sodium NF, Ph.Eur, JPE
Sodium Starch Glycolate NF	*Sodium Starch Glycolate, NF,* Explotab, Primojel
Inorganic salts	*Crospovidone NF*
Dibasic Calcium Phosphate USP	*Lubricants*
Tribasic Calcium Phosphate NF	Magnesium stearate
Calcium Sulfate NF	Calcium stearate
Polyols	Stearic acid
Mannitol USP	Sodium stearyl fumarate
Sorbitol NF	Hydrogenated vegetable oils
Xylitol NF	Mineral oil
	Polyethylene glycols
	Antiadherents
	Glidants

Source: Ref. 7.

ging, (c) milling, (d) screening, and (e) final blending. The same excipients that are used in direct compression can also be used in dry granulation.

A. Direct Compression Excipients

The direct compression process generally involves mixing a drug with excipients before compression. Direct compression excipients must have good flow and compression characteristics. In addition, direct compression excipients must exhibit low lubricant sensitivity to compression; have good stability; promote tablet disintegration and drug dissolution; and exhibit noninterference with bioavailability of the active ingredient.

1. Cellulose

The process of direct compression was revolutionized by the introduction of Avicel PH microcrystalline cellulose (MCC) in the early 1960s, although spray-dried lactose had been introduced at an earlier data. In combination, MCC and spray-dried lactose are used together in varying ratios in most direct compression formulas. Microcrystalline cellulose is described in the *National Formulary* (*NF*) as a purified, partially depolymerized cellulose prepared by treating α-cellulose, which is obtained as a pulp from fibrous plant material, with mineral acids. Avicel PH MCC is the excipient most often used in tableting as a filler, disintegrant, flow aid, and dry binder in directly compressible tablets.

MCC has extremely good binding properties as a dry binder. It improves flow and has good lubrication and disintegration properties. Tablets prepared with MCC generally exhibit excellent hardness and low friability. Aivcel PH MCC is available in various particle size, density, and moisture grades (Table 2) to meet the various tablet requirements. Microfine cellulose (Elcema) is a mechanically produced cellulose powder. The granular grade (G-250) may be used in direct compression because of its improved flow and compression properties. Microfine cellulose possesses a poor dilution potential relative to MCC. *Dilution potential* is defined as the ability of a given quantity of an excipient to bind a specified amount of an active ingredient to form an acceptable tablet (7). The greater the quantity of active ingredient the excipient is able to bind or carry, the better is its dilution potential.

2. Lactose

Lactose is the most commonly used filler in tablet formulations. it is a natural disaccharide produced from cow's milk. Some forms of lactose meet the require-

Table 2 Avicel PH Microcrystalline Cellulose—Typical Average Particle Size, Bulk Density, and Loss on Drying at the Time of Shipment

Grade	Typical average particle size (μm)	Bulk density (g/mL)	Loss on drying (%)
PH-101	50	0.28	4
PH-102	90	0.30	4
PH-103	50	0.28	2
PH-105	20	0.25	3
PH-112	90	0.30	1
PH-113	50	0.30	1
PH-200	180	0.32	4
PH-301	50	0.38	4
PH-302	90	0.39	4

ments for a direct-compression excipient. Hydrous lactose does not flow, and its use is limited to tablet formulations prepared by wet granulation. Spray-dried lactose monohydrate (Super-Tab) and anhydrous lactose (Sheffield) have good flowability and compressibility. Spray-dried lactose monohydrate is specifically engineered for direct compression and is ideally suited for drugs that do not compress well.

3. Other Sugars

Large crystals of sucrose flow very well through a hopper, but their compaction properties are poor. *Compressible Sugar NF* consists mainly of sucrose that is processed to have properties suitable for direct compression. It also may contain small quantities of starch, dextrin, or invert sugar. Compressible sugar is a sweet, white crystalline powder and is complete water solubility. Because of the high water solubility, tablets containing compressible sugar as an excipient do not disintegrate, but rather, the sugar dissolves, releasing the drug. It is widely used for chewable vitamin tablets because of its natural sweetness.

Dextrose Excipient NF is available in the anhydrous and monohydrate forms. The compression properties are poor and the tablet compacts are soft.

Dextrates are prepared from a controlled enzymatic hydrolysis of starch. Because their sweetness and negative heat of solution, dextrates are recommended for chewable tablets.

4. Starch and Starch Derivatives

Starch and starch derivatives are among the most commonly used excipients in tablet formulations. They can function as disintegrants, binders or fillers. Native starches used as excipients are obtained from corn, wheat, rice, tapioca, and potatoes, but cornstarch is most commonly used. Native starches are used as disintegrants, but with introduction of the super disintegrants in the late 1970s, they are no longer the disintegrant of choice. Because of poor flow, loss of binding and compressibility in the presence of a lubricant, they are less suitable for direct compression tablet formulations. Starch, when used as a paste, makes a good binder, particularly when the drug is insoluble and in high concentrations. The native starches are used as a binder that comes in the form of a 5%–10% paste cooked in a double boiler, and the concentration of starch in the formulation may vary between 2 and 5%.

Pregelatinized starch is obtained by a chemical or mechanical process that ruptures the starch granules in the presence of water. Partially pregelatinized starch acts as a binder as well as a distintegrant. If starch is fully pregelatinized, it loses its disintegrant properties and acts only as a binder.

Sodium starch glycolate is the sodium salt of a carboxymethyl ether of

starch. It is used as a super disintegrant, which will be discussed later in this chapter.

5. Inorganic Salts

The most commonly used direct compression inorganic salts are dibasic calcium phosphate, tricalcium phosphate, and calcium sulfate.

Dibasic Calcium Phosphate Dihydrate USP is the most commonly used directly compressible filler-bind. *Dicalcium Phosphate Dihydrate* (Di-Tab), in its unmilled form, has good flow properties and compressibility. Because it has no inherent lubricating or disintegrating properties, other excipients must be added to prepare a satisfactory tablet formulation.

Tribasic calcium phosphate is available as a directly compressible filler–binder for tablets. Tribasic calcium phosphate has shortcomings in that it has a high tendency to adhere to punches and dies, and it has a deleterious effect on dissolution, especially after aging of the tablets.

Calcium Sulfate NF (terra alba) is available as a specially processed grade of excipient for direct compression. It is an inexpensive filler.

6. Polyols

Polyols for pharmaceutical use include sorbitol, mannitol, and xylitol.

Sorbitol NF is closely related to glucose, which can be obtained from starch or sucrose. Direct compression grades of sorbitol, available from several manufacturers, can be used for the preparation of chewable tablets, lozenges, and disintegrating tablets. However, the hygroscopicity of sorbitol limits its use in tableting.

Mannitol is a popular excipient for chewable tablets, owing to its pleasant taste and mouthfeel, resulting from its negative heat of solution. Mannitol powder has poor flow and compression properties. It is available in granular form, for direct compression, which has good flow and compression properties, and it is not hygroscopic.

Xylitol is used as a noncariogenic sweetening agent in tablets, syrups, and coatings.

B. Wet Granulation Excipients

The most widely used and most general method of tablet production is the wet-granulation method. The excipients that agglomerate drug, filler, and other excipients together and cause them to form granules are the binders. There is a twofold purpose for agglomeration of the drug and excipients: (a) to improve the powder flow to minimize weight variation and content uniformity problems; and (b) to improve compressibility, resulting in tablets with low friability and good tensile

strength. The choice of binding agent depends on the binding force required to form granules. Most binders are hydrophilic and soluble in water. Natural gums and polymers function by forming a thin film on the surface of the particles, which then agglomerate during the granulation step. Table 3 provides a partial listing of binders commonly used in wet granulation.

Microcrystalline cellulose (MCC) functions as a wet granulation binder. MCC permits faster addition of the granulation solution through a rapid wicking action in the wet phase. It also produces less screen blockage during wet screening, speeds drying, minimizes or prevents case hardening, and eliminates or reduces color mottling. Microcrystalline cellulose is the only wet granulation binder that also works well in directly compressible formulations.

Polymers (cellulose derivatives), including *Carboxymethyl Cellulose Sodium USP*, *Hydroxypropyl Cellulose NF*, *Hydroxypropyl Methylcellulose USP*, *Methylcellulose USP*, and *Hydroxyethyl Cellulose NF*, all are examples of excipi-

Table 3 Binders Used in Wet Granulation

Name	Concentration used (% of formulation)	Solvents
Microcrystalline cellulose	10–50	Water
Polymers (cellulose derivatives)	1–5	Water
Carboxymethyl cellulose sodium		
Hydroxypropyl cellulose		
Hydroxypropyl methylcellulose		
Methyl cellulose		
Hydroxyethyl cellulose		
Ethyl cellulose	2–7	Alcohol
Povidone (PVP)	2–5	Alcohol, water
Gelatin	1–3	Water
Natural gums	1–5	Water
Acacia		
Tragacanth		
Guar		
Pectin		
Starch	2–5	Water (paste)
Pregelatinized starch	10–25	Water
Sucrose	2–20	Water
Others		Water
Corn syrup		
Polyethylene glycols		
Sodium alginate		
Magnesium aluminum silicate		

ents used as wet binders. The concentration of the binder is 1–5% of the formulation, and the solvent is water. *Ethylcellulose NF* is also employed as a binder. It is soluble in solvents such as alcohol. In some formulations, and depending on the drug, ethylcellulose may provide controlled release of drug.

Povidone USP (PVP) is one of the most commonly used binders. PVP or polyvinyl pyrrolidone is a synthetic polymer with several grades available, differing only in the molecular weight of the polymer. The most common grade used is povidone K-29/32. It is normally used in concentrations of 2–5% of the formulation.

Gelatin NF as a binder has largely been replaced by synthetic polymers. However, when used, its level of use is 1–3% of the formula. Natural gums, such as acacia, tragacanth, guar, and pectin, are still employed at 1–5% concentrations. Natural gums have been largely replaced by the synthetic polymers owing to variability in quality of the gums.

Cornstarch is widely used as a binder as starch paste. It is prepared by suspending 5–10% starch in cold water, followed by heating in a double boiler until fully gelatinized. The concentration of starch may vary between 2 and 5% in the formulation. A significant improvement to starch paste is *Pregelatinized Starch NF* (i.e., partially pregelatinized [Starch 1500] or fully gelatinized starch). The concentration of pregelatinized starch in the formula will vary depending on the type used, but is usually in the 10–25% range. Pregelatinized starch provides good binding properties and acts as a disintegrant.

Sucrose NF is the form of a 50–70% solution is used as a binder. The actual concentration of sucrose in the formula may vary between 2 and 20%. Generally, granules formed using sucrose as a binder are hard, and excessive tablet machine pressure is required to make a tablet.

C. Other Tablet Excipients

Excipients may be classified according to the role they play in manufacture of the finished tablet. As discussed previously, fillers–diluents and binder help to impart satisfactory processing and compression characteristics to the formulation. Lubricants, glidants, and antiadherents also help to impart satisfactory processing and compression characteristics. A second group of excipients helps impart additional desirable physical characteristics to the finished tablet. Included are disintegrants, colors and pigments, wetting and surface-active agents and, for chewable tablets, flavors, sweeteners, and taste modifiers.

1. Disintegrants

A *disintegrant* is an excipient added to a table formation to cause the tablet to break apart or disintegrate after administration. The drug must be released from the tablet matrix as quickly as possible to permit its rapid dissolution.

Starch is the oldest and was the first most commonly used disintegrant in compressed tablets (Table 4). Because of requirements for faster dissolution and problems with compression and tablet softening, starch is being largely replaced with the newly developed "super disintegrants."

The name *super disintegrant* comes from the low use levels (2–8%) at which they are effective. Croscarmellose sodium, sodium starch glycolate, and crospovidone are examples of a cross-linked cellulose, cross-lined starch, and a cross-linked polymer. Cross-linking serves to greatly reduce water solubility, while allowing the excipient to swell and absorb many times its weight of water, causing the tablet to break apart or disintegrate.

2. Lubricants

Lubricants have various functions in tablet manufacture. To prevent adhesion of the tablet material to the surface of the dies and punches (Fig. 1), reduce interparticle friction, and facilitate ejection of the tablet from the dye. Commonly used lubricants include magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils, polyethylene glycols, and sodium stearyl fumarate.

Magnesium stearate is the most commonly used and effective lubricant for tablets. Its use level is 0.2–2.0% (max). Calcium stearate is employed at the same use level, but is not as popular as magnesium stearate. Stearic acid, hydrogenated vegetable oils, and mineral oil are frequently used if there is a chemical and physical incompatibility of the active ingredient with magnesium stearate. In some formulations, however, stearic acid is used in combination with magnesium stearate.

Table 4 Most Commonly Used Disintegrants and Recommended Levels in a Formulation

Disintegrant	Example	Level (%)
Starch NF	Corn, wheat, potato, rice (Corn most commonly used)	5–10 in dry granulation
	Pregelatinized starch (Starch 1500)	Binder and a disintegrant, 5–20 in wet granulation
Croscarmellose Sodium NF	Ac-Di-Sol	2–4 in wet or dry granulation
Sodium Starch Glycolate NF	Primogel, Explotab	2–8 in dry granulation
Crospovidone NF	Crospovidone	2–5 in wet or dry granulation

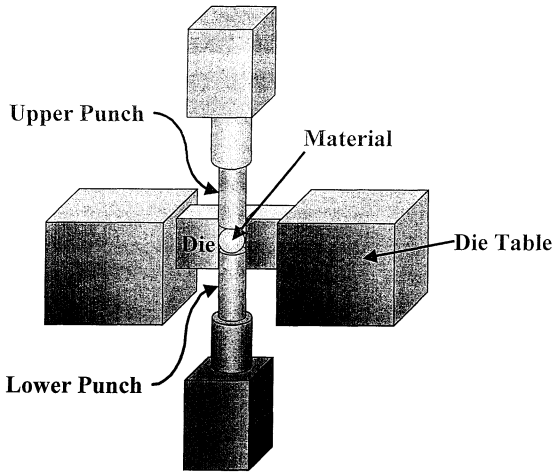

Figure 1 Simple tableting system.

3. *Antiadherents*

Antiadherents prevent sticking of the tablet blend to the die wall and punch face. They are used in combination with magnesium stearate when sticking becomes a problem. Commonly used antiadherents and use levels include cornstarch (5–10%) and talc (1–5%).

4. *Glidants*

A glidant is an excipient used in tablet formulations to improve flow of the powder mixture. Glidants are mixed, in low concentrations, into the final tablet blend in dry form just before compression. Colloidal silicon dioxide (Cab-O-Sil, Syloid, and Aerosil) is the most commonly used gliant. It is used in low concentrations (0.1–0.2%). Talc (asbestos-free) is also used (0.2–0.3%) and may serve the dual purpose of lubricant and glidant. In certain formulations, the alkali stearates and starch are employed.

5. *Coloring Agents*

Colors in compressed tablets serve several functions: (a) making the dosage form more esthetic in appearance; (b) helping the manufacturer to control the product during its preparation; and (c) serving as a means of identification to the patient. Any of the approved, certified water-soluble FD&C dyes, mixtures of the same, or their corresponding lakes may be used to color tablets. A color lake is a combi-

nation of adsorption of a water-soluble dye to a hydrous oxide of a heavy metal (usually aluminum), resulting in an insoluble form of the dye. Each country has its own list of approved colorants that must be taken into consideration when designing a formulation for international markets.

6. Wetting Agents

Sodium lauryl sulfate, in combination with disintegrants, such as starch, is an effective disintegrant. It has been suggested that effectiveness of surfactants in improving tablet disintegration is due to an increase in the rate of wetting.

7. Flavors and Sweeteners

Flavoring agents and sweeteners are seldom found in standard compressed tablets, but frequently in chewable tablets. Flavors are available as oils, liquid mixtures, and spray-dried products from several flavor houses. In addition to the sweetness added by the excipients mannitol, sorbitol, or sucrose, artificial sweeteners may be added to the chewable tablet formulation. Aspartame (Searle), a new synthetic sweetner, has found applications in pharmaceutical tablet and liquid formulations.

D. Excipients for Other Oral Dosage Forms

Capsules are solid oral dosage forms in which the drug is enclosed in either a hard or soft, soluble shell of gelatin. Excipients commonly used in manufacture of hard gelatin capsule dosage forms include microcrystalline cellulose, lactose, and starch. Depending on the formulation and equipment used to encapsulate the powder blend, lubricants, such as magnesium stearate or stearic acid, and glidants, such as colloidal silicon dioxide or talc, are also employed.

Liquid-filled soft gelatin capsules are a popular dosage form for delivery of vitamins (e.g., vitamin E). Excipients commonly used in the liquid fill are natural vegetable oils which, in some cases, are in a water-dispersible form. Preservatives, parabens, are used on occasion, depending on the formulation requirements.

Effervescent tablets are used to deliver oral medications, such as antacids and analgesics. In addition to the active ingredient, excipients are sodium bicarbonate and organic acids, such as tartaric or citric acid. In the presence of water, these excipients react, liberating carbon dioxide, which acts as a disintegrant and produces effervescence.

III. EXCIPIENTS FOR VARIOUS ROUTES

The objective of the following discussion of excipients for various routes is to provide the reader with an appreciation of excipients, how they function, and

how they are employed. The list of excipients is quite extensive. In the interest of brevity, only the more commonly employed excipients in each category of use are discussed. The reader is referred to the standard pharmaceutical texts, such as *Remington's Pharmaceutical Sciences*, 18th ed. (8) for a more thorough discussion of excipients and their categories of use.

A. Topical and Transdermal Delivery System

Drugs are applied to the skin or inserted into various body orifices in liquid, semisolid, or solid form. Semisolid preparations generally refer to therapeutic ointments, creams, salves, or pastes. These preparations are generally viscous in consistency when intended for application to the skin. Newer modes of drug delivery include transdermal delivery systems. These systems have been developed to optimize drug delivery or to overcome the shortcomings of some of the earlier delivery preparations.

The USP recognizes four general classes of ointment bases. Block (9) categorized the ointment bases into five classes for purposes of showing differences in the performance properties of the bases (Table 5).

Petrolatum and mineral oil are perhaps the best examples of hydrocarbon (oleaginous) bases. *Petrolatum USP* is tasteless, odorless, smooth, and greasy in texture and appearance. It is often used externally for its emollient properties. Petrolatum, when used as an ointment base, has exhibited a high degree of compatibility with a variety of active ingredients. Mineral oil is obtained from petroleum, as petrolatum, by collection of a particular viscosity-controlled fraction. The lower viscosity grades of mineral oil are preferred for semisolid products, because they are less tacky and greasy. The main disadvantage of the hydrocarbon or oleaginous ointment bases is that they are greasy. The greasy or oily material, when used topically, may stain clothing, and it is difficult to remove the stain.

Absorption bases are hydrophilic, anhydrous materials that have the ability to absorb additional water. The word absorption refers only to the ability of the base to absorb water. There are two types of absorption bases: the anhydrous form and the emulsion form. *Hydrophilic Petrolatum USP* and anhydrous lanolin are examples of anhydrous bases that absorb water to form water-in-oil emulsions. Anhydrous lanolin is an example of a hydrous base that is a water-in-oil emulsion having the ability to absorb additional amounts of water.

Water-washable bases or emulsion bases are commonly referred to as creams. Vanishing cream bases fall into this category. These preparations are the most commonly used type of ointment base. The vast majority of commercial dermatological products are formulated as an emulsion or cream base. Emulsion bases are washable and can be removed easily from the skin or clothing. The list of excipients used to prepare water-washable bases is numerous and includes stearic acid, stearyl alcohol, cetyl alcohol, glycerol monostearate, lanolin, glyc-

Table 5 Classification and Properties of Ointment Bases

Hydrocarbon bases (oleaginous)
Example: White petrolatum
Properties:
1. Emollient
2. Occlusive
3. Non–water-washable
4. Hydrophobic
5. Greasy

Absorption bases (anhydrous)
Examples: Hydrophilic petrolatum; anhydrous lanolin
Properties:
1. Emollient
2. Occlusive
3. Absorb water
4. Anhydrous
5. Greasy

Emulsion bases (water/oil type)
Examples: Lanolin, cold cream
Properties:
1. Emollient
2. Occlusive
3. Contain water
4. Some absorb additional water
5. Greasy

Emulsion Bases (Oil/Water Type)
Example: Hydrophilic ointment
Properties:
1. Water-washable
2. Nongreasy
3. Can be diluted with water
4. Nonocclusive

Water-soluble bases
Example: Polyethylene glycol ointment
Properties:
1. Usually anhydrous
2. Water-soluble and washable
3. Nongreasy
4. Nonocclusive
5. Lipid-free

Source: Ref. 9.

erin, and others. Frequently, preservatives (methyl and propyl paraben) are added to maintain potency, and integrity of the product and to control microbial growth. Emulsifiers, anionic, cationic, and nonionic, are important components of water-washable bases. Sodium lauryl sulfate is an example of anionic emulsifier. Cationic emulsifiers are used infrequently owing to irritation to skin and eyes and to considerable incompatibility problems. Many nonionic surfactants are condensation products of ethylene oxide groups with a long-chain hydrophobic compound. Examples of nonionic surfactants are the Span and Tween products.

Water-soluble bases are prepared from mixtures of high and low molecular weight polyethylene glycols, which have the general formula:

$$HOCH_2\ (CH_2OCH_2)_nCH_2OH$$

Polyethylene glycols of interest include the 1500, 1600, 4000, and 6000 products, ranging from soft, waxy solids (1500 is similar to petrolatum in consistency) to hard waxes. Polyethylene glycol 6000 is an example of a hard wax-like material.

Suitable combinations of high and low molecular weight polyethylene glycols yield products that have ointment-like consistency. They soften or melt when applied to the skin. No water is required for their manufacture.

In addition to preservations, antioxidants are frequently added to semisolid ointment bases whenever oxidative deterioration is expected. Often two antioxidants are used, because the combination is often synergistic. Common antioxidants include butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and propyl gallate.

B. Parenteral Systems

Parenteral products are intended for use by injection under or through one or more layers of the skin or mucous membranes. Most frequently they are solutions or suspensions. Because this route of administration circumvents the highly efficient protective barriers of the human body, exceptional purity of the parenteral dosage form must be achieved. Products for the eye and ear, although not introduced into internal body cavities, are placed in contact with tissues that are very sensitive to contamination. Thus, similar standards of sterility and purity are required for ophthalmic and otic dosage forms.

The excipient of greatest importance for parenteral products is water. Water of suitable quality for parenteral administration must be prepared either by distillation or reverse osmosis. *Water for Injection USP* is a high-purity water intended to be used as a vehicle for injectable preparations. It is manufactured by exacting standards and meets stringent monograph requirements. *Sterile Water for Injection USP* (SWFI) is an excipient intended to be used as a packaged and sterilized product.

Certain aqueous vehicles are used as isotonic vehicles to which an active ingredient may be added at the time of administration. These vehicles include sodium chloride injection, Ringer's injection, and others. Several water-miscible solvents are used primarily to improve solubility of certain active ingredients and to reduce hydrolysis. The most important solvents in this group are ethyl alcohol, propylene glycol, and the liquid series polyethylene glycols. The most important group of nonaqueous vehicles are the fixed oils, including corn oil, cottonseed oil, peanut oil, and sesame oil. Fixed oils are used particularly as vehicles for certain hormone preparations (i.e., testosterone injection).

Buffers are employed to stabilize a solution against the chemical degradation that may occur if the pH changes significantly. Acetate, citrate, and phosphate are the most common buffers used in parenteral products. Antioxidants are frequently required to preserve products because of the ease with which many drugs are oxidized. Sodium bisulfide is the most frequently used antioxidant.

Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations contained in multiple-dose containers. Their

purpose is to prevent the multiplication of microorganisms inadvertently introduced into the container while withdrawing a portion of the contents with a hypodermic needle and syringe. Benzyl alcohol is the most commonly used antimicrobial. Parabens are the next most common preservatives.

For a thorough review of "Excipients and Their Use in Injectable Products," the reader is referred to a recent review article by Nema et al. (10).

C. Emulsions and Suspensions

Emulsions may be defined in any number of ways, but essentially an emulsion is a two-phase system prepared by combining two immiscible liquids, one of which is dispersed uniformly throughout the other phase. Generally, one of the liquids is water and the other is some type of lipid or oil. Most emulsions incorporate an aqueous phase into a nonaqueous phase (or vice versa).

The list of excipients used to prepare emulsions is quite extensive. Choice of excipients for the oil phase includes various grades of mineral oil, a number of edible vegetable oils, and other such. Many emulsifying agents (or emulsifiers) are available, including natural emulsifying agents, finely divided solids, and synthetic emulsifying agents. Again, the list is too cumbersome for this presentation. Standard pharmaceutical texts (i.e., *Remington's Pharmaceutical Sciences*, 18th ed.; (8), can be consulted for more detailed information on excipients used for preparation of emulsions.

A *suspension* is a dispersion or dispersed system in which the internal, or suspended, phase is dispersed uniformly throughout the external phase, called the suspending medium or liquid. It is a two-phase system consisting of a finely divided solid (active ingredient) dispersed in a liquid, suspending medium. There are three general classes of pharmaceutical suspensions: (a) orally administered suspensions, (b) externally applied suspensions (topical lotions), and (c) injectable (parenteral) suspensions.

Suspending agents are used to impart greater viscosity and retard sedimentation. Suspending agents include cellulose derivatives, clays, natural gums, and synthetic gums. The list of agents is too extensive to be covered in this presentation. Excellent reviews of pharmaceutical suspensions (11,12) contain more detailed information on suspending agents (excipients).

D. Intranasal and Inhalation Delivery Systems

Nasal solutions or suspensions are usually aqueous systems designed to be delivered to the nasal passages in drops or sprays. Many of the excipients used to prepare pharmaceutical solutions or suspensions are used in the preparation of nasal products. In addition to water, cellulosics, surfactants, and buffering agents are commonly employed. Aqueous nasal solutions usually are isotonic and

slightly buffered, for example, sodium chloride and dextrose, to maintain a pH of 5.5–6.5. Antimicrobial preservatives similar to those used in ophthalmic preparations are employed on occasion.

Aerosol dosage forms for oral and topical use were developed in the mid-1950s. The aerosol product itself consists of two components: (a) concentrate (containing the active ingredient(s); and (b) propellant(s) (13). The propellant provides the internal pressure that forces the product out of the container when the valve is opened and delivers the product in its desired form. Excipients for aerosols are divided into two categories: (a) those for the drug concentrate; and (b) those for the propellant.

1. Drug Concentrate

The drug(s) may be solubilized or micronized and suspended in the concentrate. Antioxidants (i.e., ascorbic acid) and dispersing agents (i.e., sorbitan trioleate, oleic acid, and such), are employed, especially if the drug is micronized. Solvent blends include water, ethanol, and glycols.

2. Propellant

Compressed gases, such as nitrogen, nitrous oxide, and carbon dioxide, have been used as aerosol propellants. Unlike the liquified gases, compressed gases possess little, if any, expansion power and will produce a fairly wet spray. Liquified gas compounds are widely used as propellants because they are extremely effective in dispersing the active ingredients into a fine mist or foam. The fluorinated hydrocarbons (fluorocarbons) are nonflammable relative to the flammable hydrocarbons. Because of environmental issues, fluorinated hydrocarbons have limited use in specifically exempted metered-dose inhalers and contraceptive vaginal foams (i.e., metered-dose steroid drugs for intranasal or oral inhalation, and such). Alternatives to the fluorocarbons are now under study and development. Hydrocarbons, *n*-butane, propane, and *iso*-butane, have largely replaced the fluorocarbons for topical pharmaceutical aerosols. Although of low order toxicity, flammability tends to limit their use.

E. Mucosal, Vaginal, and Rectal Preparations

Suppositories are solid dosage forms of various sizes (weights) and shapes, usually medicated, for insertion into the rectum, vagina, or the urethra. After insertion, they soften, melt, or dissolve in the cavity fluids. Typically, a suppository consists of a dispersion of the active ingredient(s) in an inert matrix, generally composed of a rigid or semirigid base. The *USP* lists the following as usual suppository bases: cocoa butter, glycerinated gelatin, hydrogenated vegetable

oils, mixtures of polyethylene glycols of various molecular weights, and fatty acids esters of polyethylene glycol.

Cocoa butter, or theobroma oil, is a fatty material composed of a mixture of C_{16}–C_{18} saturated and unsaturated fatty acid triglycerides from the roasted seed of Theobroma cacao Linné. Cocoa butter is used extensively in manufacture of suppositories. It is well tolerated, but presents several problems when formulated in suppositories, including its unique melting point, slow rate of crystallization, and changes in the marketplace (i.e., pricing and availability can be erratic).

Glycerinated gelatin is usually used as a vehicle for vaginal suppositories. These suppositories typically contain preservatives, such as the parabens.

Water-soluble or dispersible suppository bases are of comparatively recent origin. Most are composed of polyethylene glycols or glycol–surfactant combinations. Because they are not dependent on a melting point approximating body temperature, they have a distinct advantage over cocoa butter or cocoa butter-like bases. Suppositories of varying melting points and solubility can be prepared by blending polyethylene glycol polymers (Carbowax) of various molecular weight. Water-miscible or water-dispersible suppositories are also prepared by using selected nonionic surfactant excipients. For example, Polyoxyl 40 stearate is a white, water-soluble solid, melting above body temperature. Water-dispersible suppository bases may also include other surfactants that are either soluble (Tween, Myrj) or water-dispersible (Arlacel), used either alone or in combination with other wax or fatty materials.

IV. SUMMARY

To reiterate, an excipient is a material that aids in the manufacture of the dosage form and protects, supports, or enhances stability and bioavailability of the drug. Excipients play many roles in turning active ingredients into efficient and effective dosage forms. There are numerous examples discussed in the chapter. Some excipients are used in distinctly different dosage forms. A good example is hydroxypropyl methylcellulose (HPMC). HPMC is used as a binder in the preparation of tablet granulations. It is also used as suspending–thickening agent in numerous pharmaceutical suspensions. HPMC is also used as a polymeric film coating for granules, pellets, and tablets (not discussed in this chapter). Another example is sodium lauryl sulfate. It is employed as a wetting agent in tablets to improve tablet disintegration, and as an emulsifier for pharmaceutical emulsions, creams, ointments, and such.

REFERENCES

1. Webster's New Collegiate Dictionary, A Merriam-Webster. Springfield, MA: G&C Merriam Co, 1980, pp. 395.

2. The National Formulary NF 18. Rockville, Maryland: United States Pharmacopeial Convention, 1995, pp. 2201, pp. liii, pp. 1982.
3. Handbook of Pharmaceutical Excipients, 2nd ed. Washington, DC: American Pharmaceutical Association, 1994, Preface XI.
4. L Blecher. Excipients—the important components. Pharm Proc, January 1995, p. 6.
5. E Rudnic, JB Schwartz. Oral solid dosage forms. In: AR Gennaro, ed. Remington's Pharmaceutical Sciences. 18th ed. Easton, PA: Mack Publishing, 1990, pp. 1633–1635.
6. WC Gunsel, CJ Swartz, JL Kanig. Tablets. In: The Theory and Practice of Industrial Pharmacy. Philadelphia: Lee & Febiger, 1970, pp. 305.
7. ZT Chowan. Tablet ingredients. In: Problem Solver and Reference Manual. Philadelphia: FMC Corp, 1998, pp. 1–18.
8. AR Gennaro. Remington's Pharmaceutical Sciences. 18th ed. Easton, PA: Mack Publishing, 1990.
9. LH Block. Medicated applications. In: AR Gennaro, ed., Remington's Pharmaceutical Sciences. 18th ed. Easton, PA: Mack Publishing, 1990, pp. 1602–1607.
10. S Nema, RJ Washkuhn, RJ Brendel. Excipients and their use in injectable products. PDA J Pharm Sci Technol 1997; 51(no. 4), pp. 166–171.
11. RA Nash. Pharmaceutical suspensions. In: HA Lieberman, MM Rieger, GS Banker, eds. Pharmaceutical Dosage Forms Disperse Systems. vol. 1. New York: Marcel Dekker, 1988, pp. 151–185.
12. CM Ofner, RL Schnaare, JB Schwartz. Oral aqueous suspensions. In: HA Lieberman, MM Rieger, GS Banker, eds. Pharmaceutical Dosage Forms Disperse Systems. vol. 1. New York: Marcel Dekker, 1988, pp. 231–252.
13. JJ Sciarra, AJ Cutie. Aerosols. In: AR Gennaro, ed. Remington's Pharmaceutical Sciences. 18th ed. Easton, PA: Mack Publishing, 1990, pp 1694–1712.