

# EXCIPIENTS FOR PHARMACEUTICAL DOSAGE FORMS

Patrick J. Crowley

Luigi G. Martini

*GlaxoSmithKline, Harlow, United Kingdom*

## INTRODUCTION

Medicinal dosage forms, regardless of composition or mode of use, must meet the following requirements that underpin efficacy, safety, and quality:

1. Contain an accurate dose
2. Be convenient to take or administer
3. Provide the drug in a form for absorption or other delivery to the target
4. Retain quality throughout the shelf life and usage period
5. Be manufactured by a process that does not compromise performance and that is reproducible and economical.

Few if any active pharmaceutical ingredients have properties that allow incorporation in units that meet all these criteria. Therefore, it is necessary to add other materials to make good any shortfalls. Consequently, virtually every medicinal product is a combination of the drug substance and excipients. These are indispensable components of medicinal products and, in most cases comprise the greatest proportion of the dosage unit. It goes without saying that knowledge of the composition, function, and behavior of excipients is a prerequisite to the successful design, development and manufacture of pharmaceutical dosage forms.

The requirements listed above can be considered the prime reasons for including excipients in dosage forms since they relate directly to product performance. Issues such as regulatory acceptability, environmental effects and impact on cost of the product are also important selection criteria.

A single chapter cannot do justice to the richness and complexity of the possibilities and constraints associated with using excipients to transform a drug to a dosage form. Each topic merits a chapter, possibly a complete volume in its own right. This chapter provides a general overview of the issues involved in selecting and evaluating excipients. More detailed accounts of individual applications, performance, and associated issues may be found in the references.

## ACCURACY OF DOSE

Where the active ingredient is very potent (i.e., dose is low), it may be necessary to disperse the drug in a “diluent” or bulking agent. Otherwise, quantities being filled into capsules or dies for tableting may be so low that normal filling and other process variations translate to excessive variation in unit drug content. Likewise, low-dose medications for inhalation as dry powders may have the drug dispersed in or otherwise associated with an inert “carrier” or flow aid. For a diluent to function in this way it must form a homogenous blend with the drug. Otherwise accuracy of dose cannot be guaranteed (1).

Water may be considered a “diluent” in liquid presentations as it provides the required dose in a volume that can be accurately dispensed or administered. It is also invariably present in medications for topical or transdermal application. Water can be one of the most problematic companion materials in a dosage form because of its capability to promote hydrolysis, act as a vehicle for other molecular interactions, or simply be a medium for microbial growth. Such properties illustrate how a material that resolves one problem may pose others that in turn require the presence of additional excipients.

Liquid or semisolid preparations may require the presence of ancillary excipients to effect solvation or dispersion of the active ingredient. In particular, formulations containing drugs in the suspended state may require viscosity-enhancing agents or other additives to ensure that the drug remains homogeneously dispersed. Otherwise, the accuracy of the dose may be compromised.

## USER OR PATIENT CONVENIENCE

Drugs that are bitter or otherwise unpalatable, and administered as oral liquids may be unacceptable, particularly to younger patients. Compliance and therefore efficacy may be compromised unless the product can be made more palatable. Thus, sweeteners, flavors, or

taste-masking agents may be present in liquid oral products, in chewable dosage forms, and in effervescent or dispersible tablets that are constituted as liquids prior to use (2).

Some drugs given by injection cause local pain due to high volume, tonicity, pH, etc. An additive that evinces a local anesthetic effect may relieve such discomfort. Benzyl alcohol is employed for this purpose.

## RELEASE OF DRUG FROM THE DOSAGE FORM

Once a medication is ingested, applied to a target area, or otherwise administered, the drug must leave the dosage form for absorption or other delivery to the target. This may involve the following:

1. Dissolution in the gastrointestinal (GI) tract following oral dosage;
2. Partitioning to the skin in the case of topical or transdermal preparations;
3. Passage to pulmonary or nasal cavities (inhalation products).

Excipients can ensure that such delivery is expeditious and consistent. Their presence may be even more crucial with more esoteric forms that must be delivered to a tissue, organ, or even specific cells. Researchers are developing excipients that act as “homing devices” to guide drugs to designated targets. Such approaches will be discussed later in this chapter.

In its simplest form, designing “release” into a dosage form involves adding a disintegrant to the tablet or capsule formulation so that on ingestion the compact breaks up and drug is released for dissolution and absorption. In the case of hydrophobic drugs, dissolution may be aided by wetting agents. More complex release patterns involve using excipients to modify release from the dosage form to delay onset of action or otherwise modify the pharmacokinetics of the drug, thereby maximizing efficacy or minimizing side effects.

Excipients can influence delivery from topical and transdermal medications. The propensity of the drug to migrate from the formulation to the application surface is affected by factors such as lipophilicity of the vehicle, drug solubility in the formulation, and effects of additives on the barrier properties of the skin or mucosal surface.

## ORAL ABSORPTION ENHANCEMENT

Oral absorption is indirectly aided by excipients that promote release of drug from the dosage form, or help

dispersion and dissolution prior to passage to the systemic circulation. Excipients that promote absorption per se are less widely used. However, lipids have been used to enhance absorption of hydrophobic active ingredients. Dissolution or dispersion of drug in such materials provides a substrate for lipolysis, resulting in an emulsion of drug and lipid that provides enhanced surface area for dissolution and absorption (3).

Lipids such as oleic acid or its salts are reported to slow gastric emptying and also act as an “ileal brake.” This allows longer time for dissolution and absorption in the small intestine (4, 5). Citric acid and other organic acids also have been shown to slow gastric emptying (6). However, the levels required for such effects may be impractical for most dosage forms.

The small intestine is drained by the hepatic portal vein, making the liver the first “port of call” for orally absorbed drugs. Therefore, high hepatic metabolism will compromise systemic availability. Formulation to enhance lymphatic absorption offers the potential for avoiding such first-pass metabolism. It could also target anticancer agents to lymphatic carcinomas (7). Table 1 lists various materials and associated therapeutic agents that have been formulated for lymphatic delivery.

Oleic acid has been used in a novel approach to boost the bioavailability of propranolol (Fig. 1). The effect was ascribed to preferential uptake by the lymphatic system and avoidance of the extensive first-pass metabolism that would follow passage through the hepatic portal system (8). Formulation with triglycerides also enhanced lymphatic absorption of the antimalarial drug halofantrine (9). However, the low lymph/blood flow ratio limits lymphatic absorption to drugs that are highly lipophilic ( $\log P > 5$ ) and that have significant solubility in long-chain triglycerides ( $>50$  mg/mL).

Strategies to breach physical and enzymatic barriers in the intestinal epithelium that hinder passage to the systemic circulation have included enhancing paracellular flux by disrupting “tight junctions” (10, 11). Inhibition of the P-glycoprotein (PGP) that ejects unrecognized or unwanted materials also has been studied (12). Certain lipids are reported to be PGP inhibitors but there are no reports of successful application to commercial products or use in clinical trials.

Yet another approach to intestinal absorption enhancement concerns the inhibition of intestinal Cytochrome P450 3A4, an enzyme responsible for the prehepatic metabolism of many drugs. Grapefruit juice is reported to be a powerful inhibitor of this enzyme and is known to enhance the bioavailability of cyclosporin, triazolam, nifedipine, and other drugs. Studies have been carried out to identify the components in grapefruit juice that evince

**Table 1** Drug carriers for lymphatic targeting

Lymphotropic carrier	Drug	Type of interaction
Dextran sulphate	Bleomycin	Ion-pair
Dextran	Mitomycin C	Covalent binding
$\beta$ -Cyclodextrin oligomer	1-Hexylcarbamoyl-5-fluorouracil	Hydrophobic inclusion
L-Lactic acid oligomer microsphere	Aclarubicin, cisplatin	Incorporation
Gelatin microsphere	Mitomycin C	Incorporation
Intrinsic protein complex	Vitamin B <sub>12</sub>	Complex
Styrene-maleic acid anhydride-co-polymer	Neocartinstation	Covalent binding
Liposome	Ara-C	Encapsulation
S/O emulsion	5-Fluorouracil, Bleomycin	Encapsulation
Lipid mixed micelle	Inteferon, TNF	Hydrophobic binding
Chylomicron, LDL	Cyclosporine, vitamin A, coenzyme Q, DDT	Incorporation
Carbon colloid	Ethynylesteradiol 3-cyclopententyl ether Mitomycin C, Aclarubicin	Hydrophobic adsorption

(From Ref. 7.)

this effect (13, 14). It could be argued that inclusion of such materials (thought to be flavinoids), as “excipients” in the dosage form would lead to not only more complete but also more consistent systemic levels by counteracting inconsistencies brought about by enzyme inhibitors in food and drink (such as grapefruit juice). Time will tell whether the ongoing interest in this area will lead to new “excipients” that modulate absorption in this way.

Excipients that are bioadhesive or that swell on hydration can promote absorption by increased contact with epithelial surfaces, by prolonging residence time in the stomach, or by delaying intestinal transit. Cellulose ethers, gums of natural origin, and synthetic acrylic acid polymers have been evaluated for such purposes. The range of materials available and their differing viscoelastic and rheological behaviors mean that it is possible, by

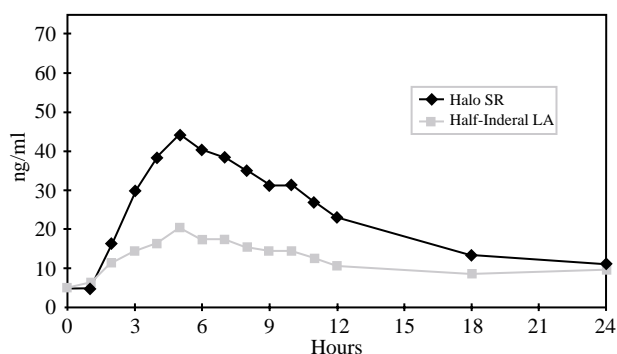
judicious admixture, to develop delivery units with balanced properties so that adhesion, density, hydration, drug release rate, etc. can be tailored to the drug in question and the physiological characteristics of the target delivery site (15).

### Enhancers for Other Modes of Absorption

Many physical and enzymatic barriers can prevent successful delivery of active pharmaceutical ingredients by noninvasive, nonoral routes. It is not surprising, therefore, that there is great interest in excipients that can overcome such obstacles.

Transdermal delivery is a case in point. The skin, particularly the stratum corneum presents a formidable barrier to diffusion. Materials used to enhance its permeability have ranged from simple solvents such as ethanol or propylene glycol to aromatic chemicals such as terpenoids. Such penetration enhancers appear to work by disrupting the lipid domains in the stratum corneum that reduce permeability (16). A bespoke penetration enhancer, laurocapram (Azone), was developed in the late 1970s for use in transdermal delivery but its use in commercial products appears to be limited (17).

Entry via nasal or buccal mucosa allows the delivery of peptides or other labile drugs that are highly potent (low-dose drugs) and that do not have steep dose-response relationships. Absorption enhancement requires increased contact time and reduced clearance rate (in the case of nasal delivery), thereby optimizing conditions for mucosal diffusion. Excipients that enhance nasal absorption include



**Fig. 1** Effect of oleic acid on propranolol bioavailability. (From Ref. 8.)

phospholipids to enhance mucosal permeability and agents that imbibe water and become mucoadhesive (e.g., glyceryl mono oleate). In addition, the gelling agents hydroxypropyl cellulose and polyacrylic acid promote absorption of insulin in dogs (18). These findings, however, have not been used to find a commercially viable product for intranasal delivery of insulin, presumably due to insulin's narrow therapeutic index. However, intranasal delivery systems for calcitonin, a macromolecule with a much safer dose-response relationship, have been commercialized.

## EXCIPIENTS FOR DRUG TARGETING

The 1990s saw an explosion in knowledge and understanding of the roles that natural mediators play in physiological and pathological processes. At the same time, biotechnology has made it feasible to manufacture such mediators relatively cheaply and in large quantities, thereby affording possibilities for use as therapeutic agents. However, effective delivery remains a formidable challenge from the efficacy, safety, and patient-convenience perspective. Most natural mediators are highly potent, extremely labile, and may need to be delivered to a specific organ or cellular target. Conventional oral dosage is not usually feasible due to the hostile environment and enzymatic barriers along the GI tract. Parenteral administration is hardly desirable for chronic therapy. Therefore, many biotechnology products need to be combined with materials that afford protection against destruction, reduce elimination rate, or target a specific site so that activity is enhanced and toxicity minimized. The level of interest and activity in this area supports the view that more effective delivery systems are required if the promise of biotechnology is to be realized. Hence, it is likely that the search for absorption-enhancing excipients for such materials will continue unabated.

Carriers for biopharmaceutical therapeutic agents range from well-established excipients of natural origin to custom-made synthetic materials with putatively enhanced protective or targeting features. Natural or semisynthetic materials predominate however. Sources as diverse as primitive marine plants (chitosans and alginates), plant or animal phospholipids (egg and seed lecithin), and mammalian collagens (gelatin) are being mined for useful delivery or targeting aids, as well as for components of complex formulations such as microemulsions or liposomes. The wide use of biological materials may mean that Mother Nature produces more suitable biopolymers than the synthetic chemist. More plausibly, it may reflect

the need for long and expensive safety evaluation of novel synthetic materials prior to use in man. This hinders timely evaluation other than in vitro or animal models.

More esoteric materials that confer target specificity include glycoproteins, recombinant proteins, or monoclonal antibodies (19). To date, clinical performance of such carrier systems has been disappointing. Further refinement of concepts and materials may be necessary before the performance matches the promise.

Attenuated adenoviruses have been used as vectors where delivery to cell nuclei is required (e.g., in gene medicine). It is a moot point whether these or other targeting or carrier materials are "excipients" part of a prodrug or something in-between. The boundaries between "active" and "inactive" materials are much less clear in such cases. The traditional approach of evaluating a novel entity in its own right in animal safety programs and then formulating with "inert" materials is inappropriate with sophisticated delivery systems because of the important effect of the adjuvant on disposition and kinetics of the active ingredient.

## EXCIPIENTS AS STABILIZERS

Product quality can be compromised during manufacture, transport, storage or use. The causes of deterioration can be manifold and product-specific. They include microbial spoilage or chemical transformation of the active or physical changes that alter performance in vivo. Deterioration can compromise safety or make the medication less attractive, which means it may not be used. Excipients can contribute to or cause such changes unless carefully screened for possible interactions in preformulation studies.

Cases where excipients have the opposite effect and stabilize labile drugs are less common. Nevertheless, they have been shown to reduce degradation rates of drugs that are photolabile, oxidizable, or degradable consequent to inter- or intramolecular reactions (20). Stabilization strategies include the following:

1. Formulation with an excipient whose light absorption spectrum overlaps that of the photolabile drug. This is the so-called spectral overlay approach;
2. Using an antioxidant in formulations that are susceptible to degradation by oxidation. This approach has been particularly successful in vitamin-containing products
3. Using an excipient that "hinders" association of groups in the same molecule, in adjacent molecules, or in the vehicle that can interact and cause degradation. There

are several reports of cyclodextrins effecting such “steric stabilizations.” Polyethylene glycol also has been shown to stabilize an ointment formulation by preventing formation of inactive rearrangement products.

Less esoteric but equally important stabilizers include preservatives in liquid products to prevent microbial growth and buffers to provide an environment conducive to good stability where degradation is pH-related. Chelating agents also are used as stabilizers to prevent heavy metals from catalyzing degradation.

## EXCIPIENTS AS PROCESS AIDS

The vast majority of medicinal products are manufactured by high-speed, largely automated processes for reasons that are related as much to safety and quality as to cost of goods. Excipients that aid in processing include the following:

1. The almost universal use of lubricants such as stearates in tablets and capsules to reduce friction between moving parts during compression or compaction;
2. Excipients that aid powder flow in tablet or capsule manufacture. Materials such as colloidal silica improve flow from hopper to die and aid packdown in the die or capsule shell. Accuracy and consistency of fill and associated dose is thereby improved
3. Compression aids to help form a good compact, whether on dry granulation (slugging) prior to tableting or on tablet compression. Most are derived from plant, animal, or mineral origin (microcrystalline cellulose, lactose, or magnesium carbonate)
4. Agents such as human or bovine serum albumin that are used in the manufacture of biotechnology-based products. These avoid adsorption of the protein to flexible tubing, filters, and other process equipment
5. Stabilizers to protect the drug from processing conditions that might otherwise be deleterious. It is common to use “cryoprotectants” such as sugars, polyhydric alcohols or dextrans in lyophilized parenteral biotechnology products to prevent inactivation during freezing. A similar approach has also been used to prevent liposomal aggregation and leakage (21).

“Flow aids” also can help performance in cases where the delivery device is an integral part of the medication. Products for pulmonary delivery are often formulated as dry powders that are inhaled via the oral cavity. The fine-particle nature of the medicinal agent, which may be vital for efficient delivery to the

bronchial target area, militates against good flow. Materials such as lactose or mannitol (of appropriate particle size) can enhance flow or act as a “carrier” from the dose unit (usually a capsule) through the inhalation delivery device to the oral cavity on inspiration. They are widely used for these purposes in inhalation formulations of anti-asthmatic agents such as salbutamol and budesonide (22, 23). The recombinant therapeutic proteins human deoxyribonuclease (used to treat cystic fibrosis) and human granulate colony stimulating factor (g-CSF) are also formulated with “carriers” to aid pulmonary delivery (24).

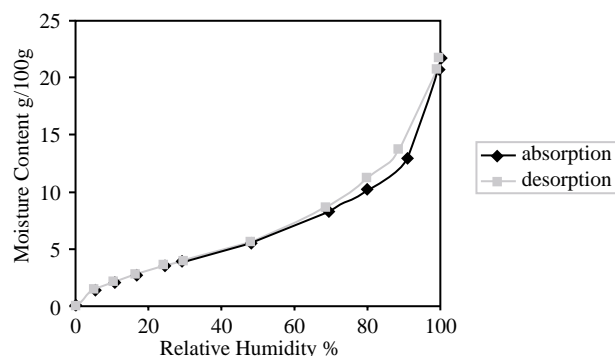
The adherence of very fine particles to larger ones can solve segregation problems when mixing powders containing particles of differing size or shape. If the fine particles can associate with their larger companions due to some surface effect, “ordered mixing” ensues and homogeneity is assured during subsequent processing (25).

Process aids do not usually contribute to the performance of the dosage form in terms of quality or in vivo performance. Indeed, lubricants, because of their hydrophobic nature, can hinder disintegration and dissolution of solid dosage forms unless the level and mode of incorporation is carefully characterized and controlled. Thus, in addition to drug-excipient interactions, the potential for interexcipient competition and incompatibility must be considered and studied.

## DRUG–EXCIPIENT INTERACTIONS

Despite the earlier account of excipients acting as stabilizers, it is fair to state that there are far more cases on record of excipients adversely affecting quality. Degradation may be caused by interaction between functional groups in the excipient and those associated with the drug. Many small-molecule drugs contain primary, secondary, or tertiary amino groups and these have the propensity to interact with aldehydic groups in sugars or volatile aldehydes present as residues. Chemical interaction can result in degradation of the drug substance to inactive moieties with loss of efficacy where degradation is excessive. Even when degradation is modest, it is possible that the formed degradation products may compromise safety.

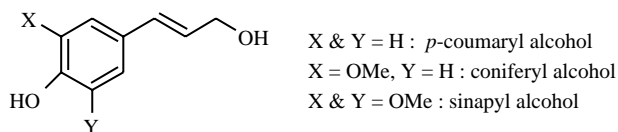
Physical interactions between drug and excipient also can compromise quality. Adsorption of drug by microcrystalline cellulose resulted in drug dissolution being less than complete (26). Interaction between chloramphenicol stearate and colloidal silica during grinding led to polymorphic transformation (27).



**Fig. 2** Water vapor sorption isotherm for microcrystalline cellulose at 25°C. (From Ref. 30.)

Excipients may contribute to degradation even when not directly interacting with active moieties. Soluble materials may alter pH or ionic strength, thereby accelerating hydrolytic reactions in liquid presentations. Such effects may be accentuated during processing. For instance, sterilization by autoclaving, while of short duration, may cause significant degradation product formation because of the high temperature involved. Dextrose is widely used in parenteral nutrition solutions or as a tonicity modifier in other parenterals. Sterilization by autoclaving can cause isomerization to fructose and formation of 5-Hydroxymethyl furfuraldehyde in electrolyte-containing solutions (28). At the other extremes of processing, succinate buffer was shown to crystallize during the freezing stage of lyophilization, with associated reduction of pH and unfolding of gamma interferon (29). It is important to identify and characterize such “process stresses” during dosage-form development and tailor processing conditions accordingly.

Microcrystalline cellulose is a partially depolymerized cellulose that is part-crystalline/part noncrystalline and hygroscopic. Adsorbed water is not held in any “bound” state but will rapidly equilibrate with the environment during processing or storage (30) (Fig. 2). Thus, it is possible that in a dosage form, water can be sequestered by a more hygroscopic active ingredient. If the drug is moisture sensitive, degradation may follow. Stabilization may be possible by drying prior to use, but loss of water may make it a less effective compression aid (31).



**Fig. 3** Potential residues in microcrystalline cellulose.

Microcrystalline cellulose may also contain low levels of nonsaccharide organic residues. These emanate from lignin, a cross-linked biopolymer made up primarily of the three allylic alcohols/phenols in the wood chip starting material (Fig. 3) (32).

It is also possible that degradation products of these phenols, or free radical combinations, may be present, with potential for chemical interaction with the drug.

This focus on residues associated with microcrystalline cellulose is not to denigrate it as an excipient. It is and will remain a most valuable formulation aid that can help compression, disintegration, and flow, as well as acting as a general diluent in solid-dose formulation (33). It can also be a useful additive in liquid products. Indeed, the knowledge available on microcrystalline cellulose interactions probably reflects the level of interest in such a useful material. Rather, the intent is to illustrate how excipients, or residues contained in them, can interact with active ingredients in a number of ways. The first commandment for the formulator is arguably to “know your drug,” but it is also important to be aware of the composition, residues, and other behaviors of excipients.

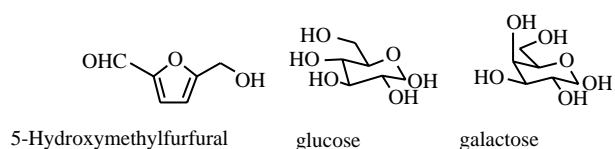
## STABILITY OF EXCIPIENTS

Excipients can lose quality over time. Oils, paraffins, and flavors oxidize; cellulose gums may lose viscosity. Polymeric materials used in film coating or to modify release from the dosage form can age due to changes in glass transition temperature. This can lead to changes in elasticity, permeability, and hydration rate and associated changes in release properties or appearance (34).

Preservatives such as benzoic acid or the para hydroxybenzoates are volatile and can be lost during product manufacture if the process involves heating. Loss during product storage is also feasible if containers are permeable to passage of organic vapors. Acetate buffer is volatile at low pH and can be lost during the drying stages of lyophilization. Such behaviors reinforce the need to know the behaviors of excipients as well as of the active ingredient so that appropriate processing, storage conditions, and “use by” periods are stipulated where necessary.

## IMPURITIES IN EXCIPIENTS

Excipients, like drug substances contain process residues, degradation products or other structural deviants formed during manufacture. Historically, it was not unusual for



**Fig. 4** Potential residues in lactose.

adulterants to be added to “bulk up” the commodity. Thankfully, a combination of better analytical techniques, vendor certification programs, and quality audit systems should mean that adulteration is largely a thing of the past. However, constant vigilance is necessary. As recently as 1996, renal failure in children in Haiti was ascribed to use of glycerol contaminated with diethylene glycol in a liquid paracetamol product (35).

Residues in excipients can affect quality and performance by interacting with the drug or other key components. Reducing sugar impurities in mannitol were responsible for the oxidative degradation of a cyclic heptapeptide (36).

Lactose is one of the most widely used excipients in tablet manufacture. It is available in a number of different forms, differing in hydration and crystal states. Isolation and purification may involve treatment with sulphur dioxide (37). However, there are no reports of complications from residues of this powerful oxidizing agent.

Lactose is a disaccharide comprised of glucose and galactose units. These reducing sugars are reported to be present in spray dried lactose (38), as is the hexose degradant 5-hydroxymethyl furfural (39). This aldehyde has the potential for additional reactions with primary amino groups, Schiff Base formation and color development (Fig. 4) (40).

Drugs containing secondary amine groups also can be degraded. Maillard reaction products have been reported in capsules containing lactose and the antidepressant fluoxetine (41). This reaction is also reported extensively in publications concerned with the food industry. High temperatures and low moisture contents associated with food processing induces caramelization of sugars and oxidation of fatty acids to aldehydes, lactones, ketones, alcohols, and esters (42, 43). It would not be surprising if such degradation products were generated in the same materials used in pharmaceutical dosage forms. Unfortunately, most pharmacopoeial monographs do not list such organic contaminants. Also, some excipient vendors are reluctant to share information on residues and contaminants with customers. The pharmaceutical industry generally represents only a small proportion of business for such commodity providers. Hence, it is difficult to be persuasive on the need for individualized standards and controls. Therefore, the following list (Table 2) cannot be

**Table 2** Potential residues in common excipients

Excipient	Residue
PVP, Polysorbates, benzyl alcohol	Peroxides
Magnesium stearate, fixed oils, paraffins	Antioxidants
Lactose	Aldehydes, reducing sugars
Benzyl alcohol	Benzaldehyde
Polyethylene glycol	Aldehydes, peroxides, organic acids
Microcrystalline cellulose	Lignin, hemicelluloses

considered as comprehensive because of this unsatisfactory state of affairs.

Excipient residues may also compromise safety or tolerance. Wool fat or lanolin derived from sheep wool may contain low levels of insecticides from sheep treated for parasites. These insecticide levels are probably too low to cause direct toxicity, but may cause allergic reactions when lanolin in cosmetics or topical medicaments is applied to the skin.

Paradoxically, excipient residues such as antioxidants may inadvertently act as stabilizers of the drug substance. Unheralded removal by the vendor or replacement by a different type of stabilizer could precipitate an unheralded product stability crisis leading to recall from the market. Such a possibility highlights the need for agreed change control systems between the pharmaceutical manufacturer and the excipient vendor.

## SAFETY OF EXCIPIENTS

Although excipients have traditionally been considered “inert,” it is now well accepted that some carry the potential for untoward effects. These can range from the inconvenient to the serious, be general or patient-specific, and may or may not be dose-related. The effect may be ascribable to the excipient itself or to a residue from the starting material or the process of manufacture.

Lactose is one of the most widely used tablet excipients. However, 5–10% of the population of the United Kingdom suffers from lactose malabsorption (44), nor is there reason to suppose that this percentage is lower in other countries. Lack of the lactase enzyme leads to fermentation by colonic bacteria, with formation of lactic acid and carbon dioxide causing stomach cramps, diarrhea, and vomiting (45). Whether such clinical symptoms are manifest following ingestion of the levels

normally present in dosage forms is not known, but such phenomena may sometimes explain minor side effects regularly reported during the monitoring that accompanies volunteer Phase I studies.

Malabsorption of the cereal protein gluten is another potential source of untoward effects from excipients. This condition demands a gluten-free diet. Most starches utilized in medicinal products are now gluten-free but gluten-containing materials have been used as film formers in microencapsulated products (46). There is also a possibility that gluten could be present in excipients that utilize cereal derivatives as starting materials or bases (e.g., dry powder flavors that sometimes use maltodextrin bases).

Sucrose is a very effective sweetener, particularly for liquids dosed to children. Its propensity to cause dental caries and the complications it poses in the management of diabetes may have contributed to its progressive removal from medicinal products despite its continuing widespread use in foods and confectionery. Sorbitol is another excellent sweetening agent and has been used as a replacement for sucrose in oral liquid products. It has the propensity to cause diarrhea and flatulence, although the effect may only be manifest at high doses. However, there may be additive effects (e.g., if it is formulated with active ingredients that are also associated with GI intolerance, such as antibiotics).

Synthetic sweeteners have had checkered careers as excipients (47). Cyclamate was banned in the United States following reports of carcinogenicity and withdrawal of generally regarded as safe (GRAS) status in 1969. It remains banned despite additional studies to clarify safety and attempts at reinstatement. It remains acceptable in Europe.

Saccharin is equally controversial. It also is suspected as being a carcinogen due to cyclohexylamine formation, possibly by gut flora, on ingestion (48). It was banned as a food additive by the Food and Drug Administration (FDA) in 1977, but has remained available consequent to regular congressional moratoria on the proposed ban. It is not permitted in Canada except for diabetic beverages and foods.

The flavoring agent sodium glutamate is sometimes used to flavor protein supplements or liver extracts. Flushing, headache, and chest pain have been ascribed to its presence, albeit after food intake rather than medication. This is the background to the so-called Chinese restaurant syndrome (49).

Aspartame is a newer sweetener/flavor enhancer but it too may cause angiodema and urticaria. It is contraindicated in patients suffering from phenylketone urea, as hydrolysis can lead to formation of phenylalanine.

Aspartame also can hydrolyze in solution to form a diketopiperazine derivative and can participate in Michael-type addition reactions with olefines susceptible to nucleophilic attack. The products of such interactions, if they occur, will be drug and formulation-specific, and it is likely that their safety characteristics will be unknown (45).

The use of benzyl alcohol as a local anesthetic was previously discussed. It is also used as a preservative in parenteral dosage forms. However, there is some evidence that benzyl alcohol is neurotoxic and its use is contraindicated in the United Kingdom in children under 3 years of age (50).

The literature is replete with reports of various allergic-type reactions to preservatives (parabens, chlorocresol), antioxidants (propyl gallate, metabisulphite), surfactants and solvents. The list is too long to be discussed in this article but Ref. 48 contains a very useful compilation and discussion of immunotoxic events seen with various dosage form additives.

Many of these studies involved application of copious amounts to animal skin or to human volunteers in Phase I studies. Others concerned reports of reactions in people suffering from pre-existing allergic conditions. Reports of side effects must, therefore, be viewed from such perspectives and the possibilities for side effects weighed against the widespread use of the same materials in food, confectionery, cosmetic, and household products as well as in medicines. This is not to belittle the hypersensitivity and other reported reactions but unless these are put into context, there may be further constraints on excipient usage and unrealistic demands for "totally inert" formulation adjuvants.

Adverse reactions may be caused by the excipient *per se* but by a residue. HIV infection in humans and spongiform encephalopathies in cattle have raised the specter of viral transmission by materials as diverse as human and bovine serum albumin, lactose, gelatin, fatty acids, or their salts, as well as polyols such as glycerol. It is generally accepted that screening procedures for blood donors and the heat treatment usually employed for sterilizing human serum albumin (minimum 10 h at 60°C), originally introduced to guard against hepatitis infection, provides good lethality against the HIV virus. However, the prions associated with spongiform encephalopathies are so resistant to heat and other forms of sterilization that removal is more problematic. Consequently, the use of vegetable sources for fatty acid and organic alcohol-type excipients is becoming more common. Whether gelatin capsules will be replaced by starch or cellulose gum-based alternatives (for the same reason) remains to be seen.



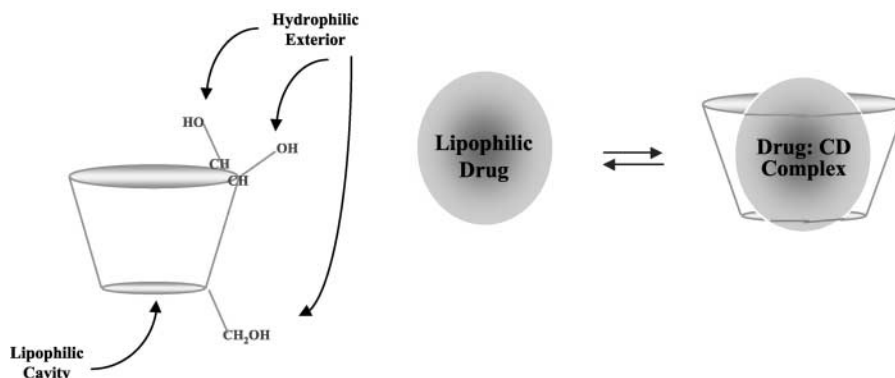


Fig. 5 Mechanism of solubilization by cyclodextrins. (Reproduced from CyDex Inc.)

## NOVEL EXCIPIENTS

It might be expected that the increased knowledge of pathological processes and drug-receptor dynamics, along with the relentless pressure for manufacturing efficiencies and economies of scale that have been the hallmark of the 1990s, would also demand and generate new and better formulation aids. This has not happened. Indeed, some have implied that excipients available in 2000 A.D. are not very different from those that were available in 2000 B.C. (51). While clearly calculated to amuse, the assertion contains a grain of truth. Only a handful of novel excipients have emerged over the past 20 years.

The reasons for this are not difficult to understand. Like novel pharmacological agents, a novel excipient must go through numerous safety and metabolic evaluation processes before it can be used in humans. In essence, it would be necessary to apply for a Type 4 Drug Master File in the United States, or a Certificate of Suitability in European Union (EU) countries (50). Such safety and filing programs are expensive and time-consuming. Furthermore, it is difficult to prove “lack of activity” in any material. Excipients are not subject to prescription or pharmacovigilance monitoring, therefore, they need to be “squeaky clean” before “blanket approval” is forthcoming. While a novel excipient can be evaluated at the same time as a novel drug, few organizations wish to put their investment in a novel drug at risk by partnering it with an unproven excipient. Therefore, novel excipients are likely to remain scarce commodities. However, a number of materials considered as “novel” are evincing interest as formulation aids.

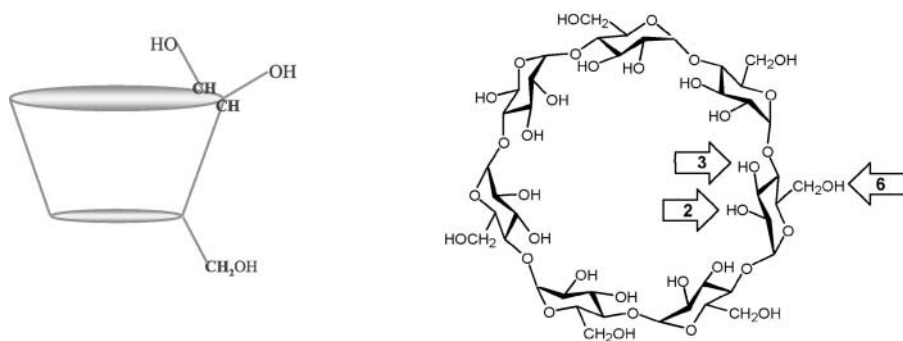
### Cyclic Glucose Polymers

Cyclodextrins are not new molecular entities. They were first reported a century ago. However, it is only relatively

recently that their potential as formulation aids has been recognized. Their capability to stabilize labile drugs has already been mentioned. They can also be used to solubilize highly insoluble molecules as, with the insertion of the drug in the annulus, the complex largely acquires the solubility characteristics of the cyclodextrin (52) (Fig. 5). Inclusion complexes have also been used to successfully mask taste or odor, reduce sublimation of drugs with high volatility (53), and enhance thermal stability (54).

The so-called parent cyclodextrins viz the alpha, beta, and other forms (Fig. 6) have properties that may have prevented widespread use as formulation adjuvants. The moderate solubility and the perceived need to form molar complexes meant that their use would be limited to low-dose, highly potent compounds. Furthermore,  $\beta$ -Cyclodextrin in particular could not be used parenterally because of renal nephrotoxicity. This was ascribed to its low solubility possibly associated with the propensity to form a molecular complex with cholesterol *in vivo* and precipitate in the proximal renal tubule. Thus, the potentially most useful application viz dissolution of poorly soluble compounds for injection could not be countenanced. However,  $\beta$ -Cyclodextrin is currently a well-established excipient in oral dosage forms and has recently been allocated monographs (as Betadex) in the European Pharmacopoeia (EP) 2000 and in the U.S. National Formulary, NF 19.

It is also encouraging that derivatized cyclodextrins with greater solubility are now available. The hydroxypropyl and sulphobutyl ether derivatives of  $\beta$ -Cyclodextrin (Fig. 7) have much greater solubilities than the parent material. Indeed, sulphobutyl ether was deliberately developed for use with parenterals in the knowledge that many novel drug substances are poorly soluble. Both these forms have been subjected to comprehensive safety evaluation programs (parenteral in the case of the sulphobutyl ether), and Drug Master Files have been lodged with the FDA. Such



Parent Cyclodextrin	a	b	g
Glucose Units	6	7	8
Molecular Weight	973	1135	1297
Water solubility (g/100 mL)	14.5	1.85	23.2
Cavity Diameter (Å)	4.7-5.3	6.0-6.5	7.5-8.3
Cavity Volume (Å) <sup>3</sup>	~174	~262	~472

**Fig. 6** Properties and functional groups of some cyclodextrins. (Reproduced from CyDex Inc.)

initiative and commitment on the part of the manufacturers of these newer agents is particularly praiseworthy in light of the costly safety evaluation programs. It may well be that with the availability of such “more suitable” cyclodextrins, they will find a valuable niche in the armamentarium of the formulation scientist. The references cited below comprise two excellent reviews of the promise, properties, and limitations of cyclodextrins (55, 56).

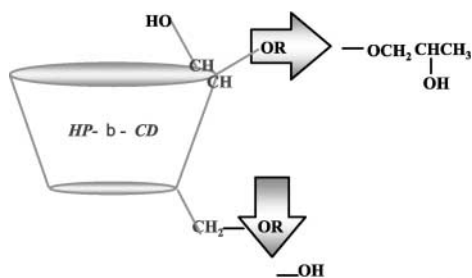
Thus, cyclodextrins are a family of excipients, each with somewhat different properties that allow the

possibility of matching individual cyclodextrins to specific drugs to compensate for a deficiency or to aid performance in some way.

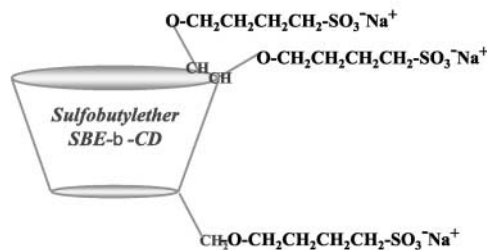
### Fluorocarbons

The replacement of chlorofluorocarbon (CFC) propellants with the nonozone-depleting hydrofluorocarbons (HFCs) merit mention for two reasons. First, it illustrates how environmental impact can be an important selection

#### Hydroxypropyl Beta Cyclodextrin



#### Sulphobutyl ether derivative of Beta Cyclodextrin



**Fig. 7** Functional groups of novel cyclodextrins. (Reproduced from CyDex Inc.)

criterion at a time when “green” issues are high profile. Second, HFCs were developed and evaluated for safety and delivery capability by a consortium of pharmaceutical companies, with costs shared and evaluation programs defined by prior agreement between end-users and propellant manufacturers. Such collaboration could be employed usefully in the future to develop novel excipients for delivery or targeting. The benefits would undoubtedly accrue to all.

### **Polymeric Targeting or Delivery Aids**

Many publications, particularly from academic institutes, contain information concerning synthetic or semisynthetic polymers, which are designed to enhance targeting or delivery properties. However, evaluation of the effect of such material on performance has been invariably confined to *in vitro* work or perhaps studies in rodents. Clearance for use in humans has not been obtained. Therefore, these substances cannot be considered as excipients that are readily available to the formulation technologist.

If few novel delivery materials become available in the future, the formulation scientist may have to rely on using mixtures of established excipients that, in combination, have properties that are “greater than the sum of the parts” in terms of viscoelasticity, diffusivity, tissue/organ specificity or other desirable targeting or delivery features. Such approaches seem likely to provide considerable scope for creative approaches, and for the formulation technologist, it should be an exciting and fulfilling road to travel.

### **EXCIPIENT SELECTION**

The nature and properties of the active ingredient dictate the choice of an excipient, the dosage form to be elaborated, and the process by which it is manufactured. It is also important to know the patient group and clinical condition. The mode of use of the medication and the envisaged dose must also be considered. Candidate excipients should then be evaluated to demonstrate that they function in the manner intended (do what they are meant to do) and do not adversely interact with the drug, or with other excipients. Obviously, they should not have any pharmacological effect and should not otherwise compromise safety or tolerance.

It is also necessary to consider the regulatory status of excipients and any country-specific requirements or constraints. The U.S. and Japanese regulatory agencies

publish lists of excipients used in medicinal products (57, 58). The materials listed in these compendia can generally be considered suitable for administration by the route for which they are already being used. For materials with no history of previous use, evidence must be provided that they do not compromise patient safety nor induce any other undesirable effects.

### **SOURCING EXCIPIENTS**

Excipients can be crucial determinants of product performance and quality. Thus, they should be sourced directly from a reputable vendor who has quality systems in place to ensure consistent manufacture and control. Procurement from brokers is to be discouraged. Auditing such providers for the presence of quality systems and controls should be the norm, particularly if they are new suppliers to the pharmaceutical industry. A validation program should be put in place to establish reliability of the supply source (59). This program should take the following into account:

1. The nature of the excipient and medicinal product in which it will be used
2. The conditions under which the materials are manufactured and controlled
3. The nature and status of the supplier, and his understanding of the Good Manufacturing Practice (GMP) requirements of the pharmaceutical industry
4. The Quality Assurance system of the manufacturer. Excipients, unlike active ingredients, are not currently subject to regulatory control in terms of GMP unless they are novel materials (in which case preapproval inspection for GMP compliance is necessary). However, the Guide to Good Manufacturing Practice for Bulk Pharmaceutical Excipients, elaborated by the International Pharmaceutical Excipients Councils (IPEC) of Europe and the U.S. while not having any regulatory status, provides much useful information on quality systems and is a good reference for performing audits of excipient facilities (60, 61).

A particular drug or dosage form may have features that rely on the presence of excipients for stabilization, delivery, or other performance parameters. Alternatively, the excipient may need to have additional features to render it suitable for the product in question (e.g., density, absence of a particular residue, etc.). In such cases it may be necessary to agree to extra quality tests and limits over and above those demanded by pharmacopoeias or applied by the vendor.

It is also prudent to be aware of the materials, reagents, and solvent used in the manufacture of the excipient and consider potential interactions between such residues and the active ingredient. It may also be advisable to agree to a Change Control notification procedure with the vendor, to avoid the introduction of new materials in the manufacture of the excipient without prior consideration of the possible impact on the medicinal product.

## CONCLUSION

Traditional attitudes that viewed excipients as "inert" materials are long outmoded. It is now well accepted that they are not merely place fillers but can be true "partners" of the active ingredient in many medicinal products and have the potential to enhance or possibly adversely affect performance. As such, their choice, quality control, mode of inclusion, stability, and performance characteristics merit the same attention as the active ingredient. Thus, knowledge of excipients, their foibles, and requirements for handling, processing, and storage are powerful assets in the armamentarium of the pharmaceutical technologist.

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