

On the right track



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Excipients can enhance product performance, patient acceptability and compliance. But some also interact with the active ingredient, thereby compromising performance. We talk to **Professor Luigi G Martini**, of King's College London, and **Patrick Crowley**, of Callum Consultancy, about how pharma manufacturers can select the right excipient for their formulation.

Virtually all medications contain excipients. They may be included for reasons linked to manufacturing, quality or patient acceptability. They can also modify a drug's action, rendering it more effective or safer. Therefore, it is important during product and process development, manufacturing, testing, troubleshooting or process enhancement that their behaviour is taken into account.

Multifunctional aspects of excipients

Excipients may have more than one function (Table 1, right). Multifunctionality can be exploited to reduce the overall excipient load; for example, microcrystalline cellulose can aid flow, compression and disintegration of tablets. An unwanted effect might concern over-mixing magnesium stearate, compromising wettability and dissolution rate. Secondary attributes may not always be important. It depends on the drug, or drug-excipient environment; however, when considering using a material with a desirable functionality it is wise to be aware of other characteristics that make it unsuitable for the drug or dosage form.

Excipient sources

Excipients can be synthetic, mineral or biological in origin. They may be natural products, semi-synthetics, relatively pure or a complex mixture of materials. They can usually be multisourced and their use is not confined to medications. Far greater amounts may be used in foodstuffs, beverages and other products. The pharmaceutical manufacturer's offtake is relatively tiny, making it difficult to obtain bespoke materials; however, were pharmaceutical manufacturers to present a united front requiring excipients of appropriate quality for their use (most dosage forms of a particular kind contain essentially the same excipients), a vendor might be willing to provide 'specials' at a suitable price.

Excipient impurities

Impurities in excipients may comprise residues from starting materials, processing or isolation. They may be acquired during storage or transport. Levels may be extremely low but, if drug content in a dosage

Table 1. Functionalities and other attributes of tableting excipients.

Material	Functionality	Other attributes
Magnesium stearate	Lubricates punch/die interface	Hydrophobicity (inhibits dissolution/release)
Microcrystalline cellulose	Compression and flow aid	Can adsorb agents, hygroscopic
Polymeric materials (eg, cellulose-based)	Granulation aids, release modifiers, viscosity enhancers etc	Low molecular mass residues
Colloidal silicon dioxide	Compression aid (solids)	Adsorbent, can catalyse degradation
Polyvinyl pyrrolidone	Binder, release modifier	Can contain peroxides
Gelatin	Capsule component, release modifier	Can pass moisture to contents

form is low, the excipient-drug ratio is high. If the nature of the dosage form is such that interaction between impurity and drug is feasible, then drug-related impurities may be formed.

The most common residue in excipients is water, being present at the outset or adsorbed from the environment during handling and storage. In some cases it can accentuate excipient functionality. Dried microcrystalline cellulose has poorer compressibility than when hydrated; however, moisture can cause hydrolysis in susceptible drugs in the solid state because of its following properties:

- high vapour pressure – facilitates penetration through solids
- low molecular mass – a little can go a long way in reactivity.

Some excipients may contain additives, residues or impurities. These can interact with some drugs under appropriate conditions. Historically, pharmacopoeial monographs did not usually contain such information; thankfully this is changing. Monographs on vegetable oils and lipids now invariably require that the nature and level of added antioxidant be

listed. Residues in polymeric excipients, mostly monomers or structural deviants, are being increasingly named in monographs. This makes it easier to consider the potential for and risks of interaction.

The presence of residues does not necessarily lead to interactions. Conditions and environment must be favourable. Even drugs susceptible to hydrolysis can tolerate some moisture. Factors such as diffusion rate (water vapour) or relative hygroscopicities of excipient and active can determine sensitivity. Impurities may be so strongly associated with the excipient that they are non-reactive. Heat of friction during operations such as size reduction or compaction may drive off volatiles, but could also free those that are tightly bound. It is important accordingly to use drug-excipient compatibility studies that reflect the process and proximity in the dosage form (for example, test compacts of drug and excipient).

Impurities in excipients may change during storage or handling.

Ethoxylated surfactants such as the Tweens and polysorbates are oxidised by atmospheric oxygen to hyper peroxides, peroxides and carbonyl compounds such as formaldehyde. Peroxide levels in Tween 20 increase following opening and storage in fluorescent light at ambient conditions. Air oxidation of polyethylene glycol (PEG) can also generate peroxides, aldehydes and carboxylic acids. Low aldehyde liquid PEGs and polysorbates are now available commercially, but the effects of storage conditions and use on product quality should be evaluated so that storage and usage conditions are defined.

Biopharmaceutical agents can be particularly susceptible to excipient-related effects. Their multiple modes of degradation present many possibilities for interaction, with potentially severe consequences if reaction products are immunogenic. Such degradation may be process or formulation-induced. Succinate buffer was shown to crystallise during freezing in a lyophilisation cycle, generating lower pH and unfolding of the gamma interferon active. When the human growth hormone was lyophilised in the presence of sodium chloride, aggregation, precipitation, oxidation and deamidation followed.

Safety of excipients

Many products have been reformulated to remove undesirable components such as alcohol in child medication. Some preservatives have also been removed, particularly in parenterals. Controversy still surrounds many in use. Table 2, overleaf, summarises some reported side effects with preservatives.

There have been calls for the removal of preservatives from injectables and making

products in preservative-free single dose units; however, increased use of auto injectors and patient-friendly devices that facilitate parenteral administration to treat chronic conditions (those not requiring frequent injection) need to be considered in such discussions. The potential for undesirable reactions needs to be balanced against the benefits of better modes of dosage, enhanced compliance and better therapy with such devices, and a consequent need for multidose presentations.

Many drug candidates are poorly soluble, stimulating interest in their solubilisation to enhance delivery and absorption. Notable advances have been made, but there have been reports of adverse events with some solubilisers in parenteral products. Cremophor EL is a polyethoxylated castor oil, used as a solubiliser in parenteral formulations of the anti cancer agents, paclitaxel, docetaxel and ixapebilone, the immunosuppressant cyclosporin and the antifungal miconazole. It is possible that, without this material, these valuable

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Table 2. Common preservatives and reported side effects/cautions.

Preservative	Comment
Benzyl alcohol	Not recommended for parenterals
2-Phenylethanol	Can be a mild irritant to skin, eye and mucous membranes
Benzoic acid	Gastro-irritant; mildly irritant to skin, eyes and mucous membranes
Sorbic acid	Sensitisation reported but relatively uncommon
Parabens	Unsuitable for parenteral or ophthalmic use due to irritancy
Chlorocresol	Irritant to skin, eyes and mucous membranes. Cannot be used in intrathecal, intra-cisternal or peridural injections
Quaternary ammonium compounds (eg benzalkonium chloride)	Irritants; can exacerbate pre-existing dermatoses, particularly mucosal tissues. Should not be used in contact lens solutions as can bind to lenses and induce ocular irritation
Thimerosal	Potent sensitiser, particularly in topical products
Phenylmercuric salts	Skin irritants at concentrations exceeding 0.1%

therapeutic agents could not have been developed as practical medications; however, there have been reports of anaphylactoid hypersensitivity, erythrocyte aggregation and peripheral neuropathy ascribable to its presence. These products treat patients with severe clinical conditions. Use of such excipients should be considered in a risk-benefit context. Cremophor EL does not seem to elicit the above-mentioned reactions when used in oral or topical products.

Excipients as solubilisers

Drugs with good specificity and potency can be poorly soluble. This can constrain absorption on oral dosage and prevent parenteral administration. Strategies to solubilise include dissolution in cosolvent-water mixtures (for parenteral administration), use of surfactants or solubilising agents, or a combination of these. Organic solvents used in injectables include ethanol, propylene glycol, benzyl alcohol or PEG. Products containing them are invariably diluted with aqueous systems at administration, requiring adequate drug solubility in the diluted system. Use is frequently limited to medication for severe clinical conditions.

Surfactants usually comprise vegetable oils or fatty acids/esters that have been covalently linked with polyoxethylene or sorbitan structures to confer balanced hydrophobic and hydrophilic properties. They have limited utility as solubilisers, unless they comprise part of an emulsion for a liquid product. Levels need to be low if the product is for injection.

If a hydrophobic drug can interact with a complexing agent that is water soluble, such that the complex disguises the hydrophobic moiety while presenting hydrophilic groups to the aqueous environment, it may be possible to design a soluble drug product. Dissociation (release) can occur in the gastrointestinal tract, the drug being displaced from the cavity by materials such as cholesterol or bile salts. Release on parenteral administration is facilitated by the presence of similar endogenous materials in systemic circulation. The cholesterol metabolite, sodium cholesteryl sulphate has been used to solubilise the antifungal amphotericin B. Complexation also alters drug distribution, reducing systemic toxicity.

Cyclodextrins are cyclic glucose polymers with a hydrophobic inner core and hydrophilic external groups. The dimensions and nature of the internal environment facilitate complexation of aromatic structures of a molecular mass of about 500 – many drug substances. The external groups determine solubility. The original α , β and γ cyclodextrins have limited aqueous solubility. Modified β cyclodextrins in contrast have much better solubility, being one of the few novel solubilising excipients that have become available in recent times. They are safe, available in low-endotoxin form and are suitable for oral or parenteral use.

Modifying drug release

Excipients play key roles in controlling drug release from dosage forms to optimise absorption, onset or duration of drug action or align performance with clinical or patient requirements. They can be broadly categorised as:

- cellulose-based or similar polymers that constrain release by means of a coat or matrix, which must dissolve, or through which the drug must diffuse for release; polymers can be water soluble or insoluble
- pH-sensitive (enteric) polymers applied as a coat or as a drug/polymer matrix to localise delivery in a specific region of the gastrointestinal tract; they can prevent release at low pH or deliver to the proximal or distal regions of the small intestine.

Such functionality may be provided by a single material or mixtures providing the requisite hydration, swelling or erosion properties. Agents such as 'pore formers' can be included to influence release rates; plasticisers are added to maintain coat flexibility.

The majority of controlled release medications concern oral dosage; however, the vagaries of the gastrointestinal tract in terms of transit and absorption and the advent of more user-friendly injection devices have increased interest in parenteral delivery. Concepts are similar to oral delivery but excipients may differ due to the need for systemic biodegradability, low endotoxin content and capability to be sterilised. Lipids and sterols are used, although they must be given by intramuscular injection unless formulated as oil in water emulsions or liposomes. They can be good vehicles for lipid-soluble drugs but drug solubility must be very high or drug dose low.

Drug targeting

Targeting drugs to cancerous organs or tissues may enhance efficacy and reduce toxicity. Lymphatic targeting illustrates the concept. Lymph is a primary pathway for tumour metastasis, with evidence that immunomodulators are more active in lymphatics than in blood. Lymph could be an important thoroughfare for delivery of oncology drugs. Oral delivery to lymph requires a drug to be highly lipophilic (Log P>5) and solubility in long chain triglycerides (>50mg/ml). Parenteral delivery does not require such properties. Intramuscular or intradermal dosage seems to be a better gateway for lymph targeting than intravenous administration. Materials such as dextrans, gelatin, polylactic acid and lactide-glycolide copolymers are being evaluated for lymphatic targeting in preclinical models. ■

