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Drug–Excipient **Interactions**

Although considered pharmacologically inert, excipients can initiate, propagate or participate in chemical or physical interactions with drug compounds, which may compromise the effectiveness of a medication. Excipients may also contain impurities or form degradation products that in turn cause decomposition of drug substances. This article explores some of these interactions and reactions, and calls for a better understanding of excipient properties.

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Excipients are included in dosage forms to aid manufacture, administration or absorption. Other reasons for inclusion concern product differentiation, appearance enhancement or retention of quality.[1] They rarely, if ever, possess pharmacological activity and are accordingly loosely categorized as 'inert.' However, excipients can initiate, propagate or participate in chemical or physical interactions with an active, possibly leading to compromised quality or performance of the medication. Chemical interaction can lead to degradation of the active ingredient, thereby reducing the amount available for therapeutic effect; reaction products may compromise safety or tolerance. Physical interactions can affect rate of dissolution, uniformity of dose or ease of administration. Understanding the chemical and physical nature of excipients, the impurities or residues associated with them and how they may interact with other materials, or with each other, forewarns the pharmaceutical technologist of possibilities for undesirable developments.

General considerations

Excipients may have functional groups that interact directly with active pharmaceutical ingredients. Alternatively, they may contain impurities or residues, or form degradation products that in turn cause decomposition of the drug substance.

Excipients can be a source of microbial contamination. They can also cause unwanted effects such as irritation of the skin or mucosal surfaces, sensitization reactions or adversely affect appearance or organoleptic properties. However, such effects are not usually a consequence of drug–excipient interaction per se, so are not considered in this review.

Modes of drug decomposition

Medicinal agents invariably have structural features that interact with receptors or facilitate metabolic handling. These inevitably confer some degree of lability, making them vulnerable to degradation (and interaction with other materials). Common modes of degradation are described below.

Hydrolysis. Drugs with functional groups such as esters, amides, lactones or lactams may be susceptible to hydrolytic degradation. It is probably the most commonly encountered mode of drug and product degradation because of the prevalence of such groups in medicinal agents and the ubiquitous nature of water. Water can also act as a vehicle for interactions or can facilitate microbial growth.

Oxidation. Oxidative degradation is probably second only to hydrolysis as a mode of decomposition. In contrast to hydrolysis, oxidative mechanisms are complex, involving removal of an electropositive atom, radical or electron or, conversely, addition of an electronegative moiety. Oxidation reactions can be catalysed by oxygen, heavy metal ions and light, leading to free radical formation (induction). Free radicals react with oxygen to form peroxy radicals,

which in turn interact with the oxidizable compound to generate additional free radicals to fuel further reactions (propagation). Aldehydes, alcohols, phenols, alkaloids and unsaturated fats and oils are all susceptible to oxidation.

Isomerization. Isomerization involves conversion of a chemical into its optical or geometric isomer. Isomers may have different pharmacological or toxicological properties. For example, the activity of the laevo (L) form of adrenaline is 15–20 times greater than for the dextro (D) form.

Photolysis. Reactions such as oxidation–reduction, ring alteration and polymerization can be catalysed or accelerated by exposure to sunlight or artificial light. Energy absorption is greater at lower wavelengths and, as many drugs absorb ultraviolet light, degradation by low-wavelength radiation is common. Exposure to light almost invariably leads to discolouration even when chemical transformation is modest, or even undetectable.

Polymerization. Intermolecular reactions can lead to dimeric and higher molecular weight species. Concentrated solutions of ampicillin, an amino-penicillin, progressively form dimer, trimer and ultimately polymeric degradation products.[2]

Table I lists examples of medicinal agents susceptible to such modes of degradation. Degradation may reflect vulnerability to environmental stresses such as heat, humidity, light or drug–drug interactions. Degradation may also be facilitated or promoted by excipients possessing the requisite functional groups for interaction, or containing residues that catalyse/participate in degradation processes. If excipients are also susceptible to change, this provides additional possibilities for the generation of species that participate in breakdown processes.

Direct interactions between actives and excipients

Excipients may be inorganic or organic in composition, synthetic or semi-synthetic, or derived from biological or natural sources. Many possess functional groups that can interact with other materials. It may be possible on occasion to exploit such attributes to stabilize unstable materials,[3] but more usually interactions lead to loss of quality.

Charge interactions. Soluble and ionizable excipients can generate counter ions that interact with ionizable drug substances leading to the formation of insoluble drug–excipient products. Suspending agents such as sodium alginate or sodium carboxymethylcellulose dissolve in water to provide large negatively charged anions. Co-formulation in aqueous systems with drugs such as neomycin and polymyxin, the active moieties of which are positively charged and of high molecular weight, results in precipitation. Bentonite (negatively charged) and attapulgite (positive) are examples of materials of mineral origin that carry electrical charges leading to interaction with drugs of opposite charge. Such interactions are usually rapid and readily apparent in liquid systems. It is doubtful whether dosage forms containing such incompatible ingredients would progress to clinical or pharmaceutical evaluation. It can also be argued that such interactions only concern liquid dosage forms. However, the possibility cannot be ruled out that they could occur in vivo with solid dosage forms, following ingestion and hydration in the gastrointestinal tract.

Hydrogen-donating interactions. Polyvinylpyrrolidone (PVP or povidone) can interact with compounds containing hydrogen-donating functional groups. Incompatibilities of PVP with lansoprazole, famotidine and atenolol all indicate that its carbonyl group is pivotal to degradation

reactions.[4–7]

Direct drug–excipient interactions seem to be most prevalent when the interacting species are water soluble and in liquid systems. This is hardly surprising — interactions in solution are more facile than in the solid state where there is less opportunity for collision between functional groups or other reaction-enhancing events. This is why compatibility studies involving solutions give many 'false positives.' However, adsorbed moisture may promote greater molecular flexibility and consequent facilitation of interactions in solid state systems. Solution interaction studies may have some predictive capability because of such possibilities.

Reactions with lactose. Lactose can participate in complex reactions with compounds containing primary or secondary amines. These can lead to assorted low molecular weight products and high molecular weight, coloured entities. This 'Maillard reaction' has been reported for the antidepressant fluoxetine (a secondary amine) when formulated with lactose. Starch-based formulations did not yield such degradation products.[8] The reactivity of lactose in the solid state is reportedly related to the proportion of amorphous material present, as this lacks the stability provided by the crystal lattice. Amorphous lactose is also more hygroscopic, thereby increasing possibilities for moisture-assisted interactions.[9]

Reactions with silicon dioxide. Silicon dioxide can act as a Lewis acid (a substance that can accept an electron pair) under anhydrous conditions and promote reactions as diverse as dehydration, hydrolysis, epimerization, cyclization and trans-esterification. Unwelcome reactions between this excipient and diethylstilbestrol have been reported.[10] Figure 1 shows the silicon dioxide-catalysed oxidation of diethylstilbestrol to the peroxide and conjugated quinone degradation products.

Air auto-oxidation of methyl linoleate to peroxides with subsequent decomposition to aldehydes has been shown to be accelerated in the presence of colloidal silicon dioxide.[11] Interaction between chloramphenicol stearate and colloidal silica during grinding leads

Table I Modes of degradation of medicinal agents.				
Hydrolysis	**Oxidation**	**Isomerization**	**Photolysis**	**Polymerization**
Methyl dopa	Calcitonin	Tetracycline	Riboflavin	Ceftazidime
Procaine	Ascorbic acid	Vitamin A	Folic acid	Ampicillin
Penicillins	Isoprenaline	Adrenaline	Nifedipine	

to polymorphic transformation of the chloramphenicol, demonstrating that unwanted effects of excipients are not restricted to chemical transformations.[12]

Physical interactions

Some excipients are capable of adsorbing active ingredients to their surfaces and this has been used to enhance the surface area of drugs and optimize dissolution rate. However, if forces of attraction are high, desorption may be retarded and absorption compromised. In a similar context, adsorption of a novel κ-opoid agonist by microcrystalline cellulose led to incomplete drug release from capsules.[13] Adsorption of finely divided excipients on to active ingredients can also occur and, if such excipients are hydrophobic, dissolution rate and bioavailability may be retarded.

Adsorption may also initiate chemical breakdown. Colloidal silica was shown to catalyse nitrazepam degradation in tablet dosage forms, possibly by adsorptive interactions altering the electron density in the vicinity of the labile azo group and thus facilitating attack by hydrolysing entities.[14]

Although it is prudent to be aware of functional groups associated with drugs and excipients when considering possibilities for interaction, it must be stated that reactions 'on paper' may not always occur in practice, particularly in solid state. Many heterocyclic drugs contain amino groups. In accordance with the considerations above, lactose should be avoided as a formulation aid, but it is widely and successfully used in tablet and capsule dosage forms. Solution chemistry does not always translate to reactions in the solid state, particularly in terms of rate of reaction, which may be the all-important consideration in a dosage form. Stereochemistry, local environment, degree of crystallinity or indeed drug–excipient ratio can mean that some potential interactions are more a problem in concept than reality.

Excipient residues

Excipients (like drug substances) are not exquisitely pure. In common with virtually all materials of mineral, synthetic, semi-synthetic or natural origin, manufacture involves using starting materials, reagents and solvents. Residues invariably remain after isolation. Low levels of residue can have a greater impact than might be expected, however — particularly where the ratio of excipient to drug is high, or where the residue has low molecular weight or acts as a catalyst. This is particularly true where an interaction product may pose safety questions and needs to be 'qualified' by toxicology studies. Such complications often arise after mainstream safety studies have commenced, and can result in delayed or complicated programmes.

Table II illustrates how reactive chemical entities are commonplace in widely used excipients. The list is not comprehensive, perhaps reflecting the absence of such information in most pharmacopoeial monographs, as well as the reluctance of excipient providers to be forthcoming about modes of manufacture and types of residues in their products.

Lactose. Lactose is one of the most widely used excipients in tablets. Purification during isolation may involve treatment with sulphur dioxide,[15] but no complications caused by residues of this powerful oxidizing agent have been reported nor are limits stipulated for residues in the pharmacopoeial monographs. Perhaps the volatility of sulphur dioxide results in very effective removal during isolation and drying.

Lactose is a disaccharide of glucose and galactose (see Figure 2). These reducing sugars have been found in spray-dried lactose,[16] as has the hexose degradation product, 5-hydroxymethylfurfural, probably generated by heat encountered during spray-drying.[17] As an aldehyde, 5-hydroxymethylfurfural can participate in addition reactions with primary amino groups, resulting in Schiff base formation and colour development.[18]

Dextrose is widely used in parenteral nutrition solutions or as a tonicity modifier in parenterals. Sterilization by autoclaving has been

Table II Impurities found in common excipients.	
Excipient	**Residue**
Povidone, crospovidone, polysorbates	Peroxides
Magnesium stearate, fixed oils, lipids	Antioxidants
Lactose	Aldehydes, reducing sugars
Benzyl alcohol	Benzaldehyde
Polyethylene glycol	Aldehydes, peroxides, organic acids
Microcrystalline cellulose	Lignin, hemicelluloses, water
Starch	Formaldehyde
Talc	Heavy metals
Dibasic calcium phosphate dihydrate	Alkaline residues
Stearate lubricants	Alkaline residues
Hydroxypropylmethyl/ethyl celluloses	Glyoxal

Figure 2 Glucose and galactose, and the hexose degradation product 5-hydroxymethylfurfural, are found in spray-dried lactose.
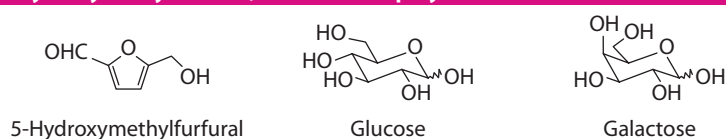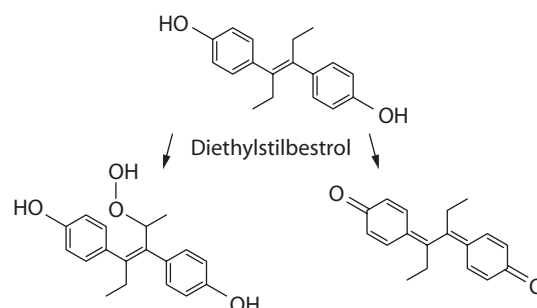

5-Hydroxymethylfurfural   Glucose   Galactose

Figure 1 Degradation pathways of diethylstilbestrol.

Diethylstilbestrol

reported as causing some isomerization to fructose and also formation of 5-hydroxymethylfurfural in electrolyte-containing solutions.[19] Parenteral solutions that are sterilized by heating would clearly be vulnerable not only to such excipient degradation but to further reactions with the drug, leading to the type of reaction products described earlier with regard to lactose.
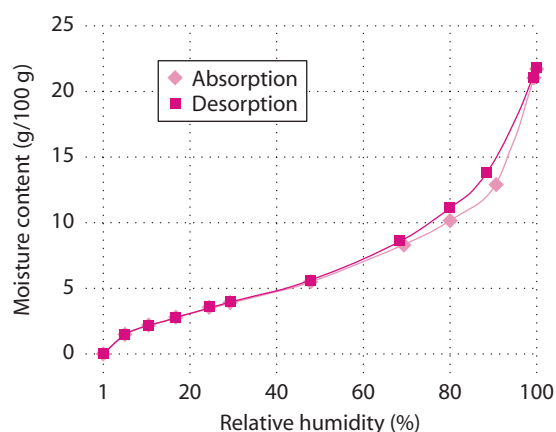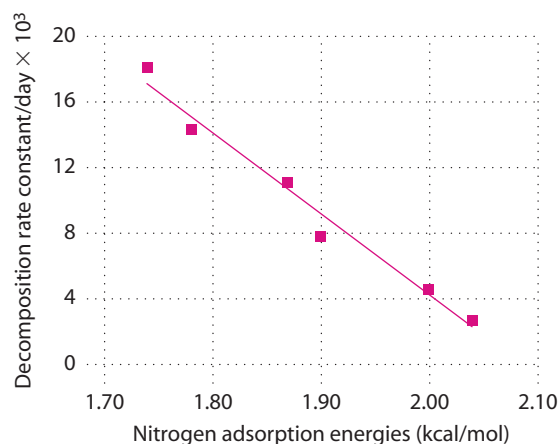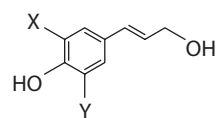
X and Y = H: *p*-coumaryl alcohol
X = OMe, Y = H: coniferyl alcohol
X and Y = OMe: sinapyl alcohol

Effect of pH. The presence of pH-modifying residues can accelerate hydrolytic degradation or have more esoteric effects. Most medicinal agents are salts of organic acids or bases. Residues that modify pH may lead to free base or acid formation during long-term storage. Such products may be volatile and lost by sublimation from the dosage form. This 'disappearance' without concomitant formation of degradation products can be mystifying and requires much time and effort to elucidate. Thorough characterization of the drug substance and awareness of residues in excipients may help resolve or obviate such mysteries.

Effect of processing. A number of food industry publications provide useful insights into how processing can lead to impurity formation in food additives that are also pharmaceutical excipients. High temperatures and low moisture contents can induce caramelization of sugars and oxidation of fatty acids to aldehydes, lactones, ketones, alcohols and esters.[20,21] Such degradation products may also be present in the same materials used in pharmaceutical dosage forms. Unfortunately, pharmacopoeial monographs rarely list such organic contaminants.

Microcrystalline cellulose. This compound is a partially depolymerized cellulose that is part crystalline and part non-crystalline; it is also hygroscopic. Adsorbed water is not held in a 'bound' state, but will rapidly equilibrate with the environment (see Figure 3).[22] It is possible that, in a dosage form, such water can be sequestrated by a more hygroscopic active ingredient leading to degradation if the drug is moisture sensitive. Drying prior to use will remove unwanted moisture but may make it a less effective compression aid.[23] In a similar context, Perrier and Kesselring showed that nitrazepam stability in binary mixes with commonly used excipients was directly proportional to their nitrogen adsorption energies (see Figure 4). They suggested that water-binding energy, not contact surface energy, may be the stability determinant.[24]

Water-based reactions. Several studies with drug substances have shown that process operations such as grinding and drying can release

bound water, which is then 'free' to participate in hydrolytic reactions.[25–28] Such process stresses can also be expected to loosen bound water in excipients, which may then degrade moisture sensitive drugs with which they are formulated. Such possibilities make it easy to understand why testing simple drug–excipient mixtures in excipient screening studies may not predict interactions in formulated product. Compression, attrition or other crystal disrupting stresses may be the catalyst for interaction but these are rarely mentioned as meriting investigation.

Reactions with residues or impurities. Peroxide residues in povidone (binder) and crospovidone (disintegrant) were shown to be responsible for the enhanced formation of the N-oxide degradation product of the oestrogen receptor modulator, raloxifene. Correlation between residual peroxide levels and N-oxide formation enabled a limit to be set for peroxide content of the excipients.[29]

Microcrystalline cellulose may contain low levels of non-saccharide 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 (see Figure 5).[30] It is possible that degradation products of these phenols, or free radical combinations may be present in microcrystalline cellulose, thereby conferring the potential for chemical interaction with the drug.

Organic solvents may also contain peroxides and, furthermore, these increase with storage time.[31] Solvent residues from crystallization or isolation of active pharmaceutical ingredients are present in most drug substances, albeit at low levels. They may also be present in excipients, having the same provenance. Peroxides introduced to the dosage form in such a way could fuel the generation of novel impurities.

The presence of a residue with interaction capability does not necessarily mean that degradation follows, or does so to any significant extent. The conditions, physical form and environment for interaction may not be appropriate (and drug–excipient ratio could be important). However,

if residues are volatile, liquid or otherwise 'mobile,' possibilities for destabilization cannot be discounted and warrant investigation.

Biopharmaceutical products

The relative fragility of the proteinaceous materials in biopharmaceutical products, and the frequent need for more sophisticated systems for their delivery places constraints and demands on excipients. The physical state of most biopharmaceutical products can favour interaction. The amorphous nature of most lyophiles means that destabilizers such as residual moisture are not held in a structured milieu. This amorphous state also affords greater molecular flexibility and consequent opportunities for reactions. Constant vigilance and rigorous screening are required if physical and chemical interactions that compromise quality, performance or safety are to be avoided. The reducing sugars in mannitol, an excipient widely used in parenterals, have been reported as responsible for the oxidative degradation of a cyclic heptapeptide.[32]

Non-ionic surfactants have traditionally been used as emulsion formers in topical and oral products, and more recently as solubilizers and stabilizers in biotechnology products. They are susceptible to hydrolysis[33] and auto-oxidation.[34,35] Peroxide levels in polyethylene glycol solutions have been shown to increase with concentration in solution and storage time.[36] Continuing generation of powerful oxidizing agents could be very damaging to protein structures containing cysteine, histidine, methionine or other terminal groups susceptible to oxidation.

Lipid excipients may be used to form micro-emulsions or other drug targeting systems. Most food grade lipids contain peroxides that decompose under the influence of heat and UV radiation. This can lead to free radical formation, which can in turn oxidize unsaturated groups leading to deterioration of the delivery system and also, possibly, the active ingredient.[37] Storage conditions, use periods and limits for residues need to be established for such excipients. Such information needs to be generated by rigorous and suitably controlled investigative studies.

An antioxidant butylated hydroxy toluene (BHT) has been shown to inhibit peroxide formation in Tween 20 during storage.[38] It is common to include such stabilizers in oxidizable excipients. Inadvertent removal, or replacement by the excipient provider, could precipitate a stability crisis in a product where the additive was unknowingly stabilizing the active ingredient as well. Such possibilities make it imperative that change control and notification agreements are in place between provider and pharmaceutical manufacturer, particularly for biopharmaceutical products, as these cannot be subject to the same definitive analytical characterization as small molecule medicinal agents.

Excipients may be an indirect cause of degradation in biopharmaceutical products. Succinate buffer was shown to crystallize during the freezing stage of a lyophilization cycle, with associated pH reduction and unfolding of gamma interferon.[39] Human growth hormone, lyophilized in the presence of sodium chloride, showed severe aggregation and precipitation, as well as accelerated oxidation and deamidation.[40] Such examples of chemical and physical stability of excipients re-enforce the desirability of performing process-simulating stress testing.

Conclusions and perspectives

Many stability problems encountered during development and post-commercialization can be ascribed to inadequate matching of the ingredients in dosage forms, lack of awareness of the complexities of chemical and physical interactions, or the unheralded presence of a residue in one of the excipients. Many such issues concern low levels of novel entities formed by drug–excipient interactions that pose questions concerning safety or tolerance. Such incidents have probably been increased by the growing sophistication of analytical techniques to detect, identify and quantitate low level impurities.

Drug–excipient interactions may take a long time to be manifested in conventional stability testing programmes, and are not always predicted by stress and preformulation studies. They can complicate and

compromise a development programme or the viability of a commercial product.[41] It is possible to reduce the probability of such undesirable and costly scenarios by allying knowledge of the propensity of a drug to undergo degradation reactions with an awareness of excipient reactivity and of the residues that they may contain. Such awareness may help to anticipate undesirable interactions and avoid their occurrence. A judicious choice of excipients or control of their quality will exclude or limit residues promoting degradation. It is surprising, therefore, that there is a paucity of information in compendia or other publications on potentially damaging residues in even the most common excipients. It is a sphere of activity that groups attempting to harmonize excipient monographs do not seem to have addressed, and it is to be hoped that 'least common denominator' considerations in harmonization initiatives do not exacerbate the situation. Perhaps it could be a subject for a future initiative.

In summary, knowledge of drug–excipient interactions is a necessary prerequisite to the development of dosage forms that are stable and of good quality. It is hoped that this review provides some perspective of this important area of pharmaceutical technology.

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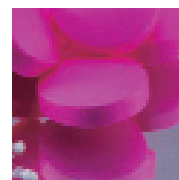
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