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ADVANCED PHARMACEUTICAL DOSAGE FORMS: A REVIEW

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ABSTRACT

Advanced pharmaceutics refers to the in-depth study of the science behind designing and developing drug delivery systems, focusing on complex concepts like physicochemical properties of drugs, advanced dosage forms, targeted drug delivery, and novel technologies to optimize drug absorption and therapeutic efficacy, typically studied at a graduate level in pharmacy programs; it involves a deep understanding of physical chemistry principles to effectively formulate and analyze drug products. Pharmaceutical dosage form is a combination of active pharmaceutical ingredients (API) and excipients. Excipients are included in dosage forms to aid manufacture, administration or absorption (Crowley and Martini).The ideal excipients must be able to fulfill the important functions i.e. dose, stability and release of API from the formulation.

KEYWORDS: Pharmaceutics, API, Pharmaceutical dosage form, Manufacture, Stability.

INTRODUCTION

Pharmaceutical dosage form is a combination of active pharmaceutical ingredients (API) and excipients. Excipients are included in dosage forms to aid manufacture, administration or absorption (Crowley and Martini). The ideal excipients must be able to fulfill the important functions i.e. dose, stability and release of API from the formulation. 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 are not exquisitely pure. In common with virtually all materials of

minerals, synthetic, semi-synthetic or natural origin manufacture involves using starting materials, reagents and solvents. Residues invariably remain after isolation. Often, it is the multi-component nature of the excipient that drives many of the interactions with APIs. Even for the most commonly used excipients, it is necessary to understand the context of their manufacture in order to identify potential API interactions with trace components. Excipients may have functional groups that interact directly with active pharmaceutical ingredients.[1-2]

- Properties and Limitation of API
- Properties and Limitation of excipients
- Advantage and Limitation of method(s) used

In term of development of dosage form, all three considerations are of equally important. Excipients are the substances other than API which are intentionally incorporated into pharmaceutical dosage form for specific purposes (Bhattacharya, 2006) such as;

- ✓ Improvement of the stability of API in the dosage form
- ✓ Modulation of bioavailability of active pharmaceuticals ingredients
- ✓ Maintain the pH of liquid formulation
- ✓ Maintain the rheology of semisolid dosage form
- ✓ Act as tablet binders, tablet disintegrant
- ✓ Act as antioxidant and emulsifying agents
- ✓ To allow the adequate administration
- ✓ To facilitate the manufacturing of dosage form
- ✓ For aesthetic reason
- ✓ For identification

Definition of excipients as developed by IPEC (International Pharmaceutical Excipients Council) America And IPEC Europe is, “These are the substance(s) other than the API which has been appropriately evaluated for safety and is included in a drug delivery system to either aid processing of the system during manufacturing or protect, support or enhance stability, bioavailability or patients compliances or assist in product identification and enhance any other attributes of overall safety and effectiveness of drug product during storage or use “ (Blecher, 1995).[3]

Excipients are classified according to their functions (Edward et al., 2005) as

- Binders

- Disintegrants
- Fillers (Diluents)
- Lubricants
- Glidants
- Compression aids
- Colors
- Sweeteners
- Preservatives
- Flavors
- Film formers/coatings
- Suspending/dispersing agents/surfactants

In pharmaceutical dosage form API are in intimate contact with one or more excipients. Moreover in most of dosage form the quantity of excipients are greater than the amount of API present in dosage form, for example typically a tablet contain binders, disintegrants, lubricants, and fillers, therefore excipients can have tremendous impact on the performance of API when present in dosage form. It can influence the safety and effectiveness of drug depending upon route of administration, for example in solid dosage form excipients can affect safety and effectiveness by promoting or delaying gastrointestinal release. Therefore, understanding of drug-excipients interactions is very important during selection of appropriate excipients for proposed dosage form.[4]

Key aspects of advanced pharmaceutics include

Physicochemical principles

Analyzing the physical and chemical characteristics of drugs, including solubility, stability, particle size and their impact on formulation design.

Dosage form design

Developing innovative drug delivery systems like nanoparticles, liposomes, microspheres, patches, and implants to target specific sites in the body and achieve controlled drug release.

Biopharmaceutics

Studying the relationship between the physicochemical properties of a drug and its absorption, distribution, metabolism, and excretion within the body.

Molecular pharmacology

Understanding how drug molecules interact with cellular receptors and biological systems to achieve therapeutic effects.

Pharmacokinetics and Pharmacodynamics

Applying mathematical models to study the absorption, distribution, metabolism, and excretion of drugs, as well as their therapeutic effects on the body.

Drug Stability and Compatibility

Evaluating the factors influencing drug degradation and ensuring the safety and efficacy of pharmaceutical products over time.

Mode 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 degradation because of the prevalence of such groups in medicinal agents and ubiquitous nature of water. Water can also act as a vehicle for interactions or facilitates microbial growth.

Oxidation

Oxidative degradation is 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 catalyzed by oxygen, heavy metal ions and light, leading to free radical formation. Free radicals react with oxygen to form peroxy radicals which in turn react with oxidizable compound to generate additional free radicals to fuel further reactions. 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 levo (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 catalyzed or accelerated by exposure to sunlight or artificial light. Energy absorption is greater at lower wavelengths and, as many as drugs absorb UV light; degradation by low wavelength radiation is common. Exposure to light almost invariably leads to discoloration 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-pencillin, progressively form dimer, trimer and ultimately polymeric degradation products (Bundgaard, 1976). Table 1 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 catalyze/participate in degradation processes. If excipients are also susceptible to change, this provides additional possibilities for the generation of species that participate in break-down processes.

Table 1: Modes of degradation of medicinal agents.

Hydrolysis	Oxidation	Isomerization	Photolysis	Polymerization
Methyldopa	Calcitonin	Tetracycline	Riboflavin	Ceftazidime
Procaine	Ascorbic acid	Vitamin A	Folic acid	Ampicillin
Penicillins	Isoprenaline	Adrenaline	Nifedipine	

Direct interactions between actives and excipients[5]

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.

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.

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 transesterification. Unwelcome reactions between this excipient and diethylstilbestrol have been reported.[10] Figure 1 shows the silicon dioxidecatalysed 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 to polymorphic transformation of the chloramphenicol, demonstrating that unwanted effects of excipients are not restricted to chemical transformations.

Mechanism of drug-excipients interaction[6]

Exact mechanism of drug excipients interaction is not clear. However, there are several well documented mechanisms in the literature. Drug-excipients interaction occurs more frequently than excipient-excipient interaction (Pifferi et al., 2003; Cavatur et al., 2004). Drug-excipients interaction can either be beneficial or detrimental, which can be simply classified (Moreton, 2006) as

1. Physical interactions
2. Chemical interactions

Physical interactions

It is quite common, but is very difficult to detect. A physical interaction doesn't involve any chemical changes. Physical interactions are frequently used in manufacturing of dosage form, for example to modify drug dissolution. However many of the physical interactions are unintended which usually causes the problems. Physical interaction can either be beneficial or detrimental to product performance.

An example of a physical interaction between an API and an excipient is that between primary amine drugs and microcrystalline cellulose. When dissolution is carried out in water a small percentage of the drug may be bound to the microcrystalline cellulose and not

released. For high-dose drugs, this may not be a major issue, but for low dose drugs it can lead to dissolution failures. This has caused problems in the past, but the phenomenon can be remedied by carrying out dissolution using a weak electrolyte solution for the dissolution medium (e.g., 0.05 M HCl). Under these revised dissolution test conditions, adsorption onto the microcrystalline cellulose is very much reduced and 100% dissolution may be achieved even for low-dose APIs (Edge et al., 2003).

A general example of a physical interaction is interactive mixing. In this smaller particles (typically the APIs) interact with the surface of the larger carrier particles (typically the excipients) through physical forces. In this way we obtain a more homogenous powder blend. After the medicine, e.g., a tablet has been administered to the patient, the aqueous environment of the gastrointestinal tract (GIT) either causes the smaller API particle or other carrier particles to dissolve or causes the surface interactions to change to allow the smaller particles to be released from the larger carrier particles.

But as we have already stated, physical interactions can also be detrimental, and magnesium stearate is recognized within the pharmaceutical industry for causing problems such as reduced tablet “hardness” and dissolution from tablets and capsules.

Adsorption of drug molecules onto the surface of excipients can render the drug unavailable for dissolution and diffusion, which can result in reduced bioavailability. For example, antibacterial activity of cetylpyridinium chloride was decreased when magnesium stearate was used as lubricants in tablet containing cetylpyridinium chloride; this was due to adsorption of cetylpyridinium cation by stearate anion on magnesium stearate particle (Mackay et al., 1996). In one of the investigation, it was observed that dissolution of drug was decreased due to adsorption of drug on the surface of microcrystalline cellulose. In a similar context, adsorption of novel k-opoid agonist by microcrystalline cellulose led to incomplete drug release from the capsules. Adsorption may also initiate chemical breakdown. Colloidal silica was shown to catalyze nitrozepam degradation in tablet dosage form, possibly by adsorptive interactions altering electron density in the vicinity of the labile azo group and thus facilitating attack by hydrolyzing entities (Czaja and Mielck, 1982).

Complexing agents usually bind reversible with drugs to form complex, which do not allow them to dissolve, complexing agent such as cyclodextrin are often used to increase the bioavailability of poorly water soluble drugs (Rajewski and Stella, 1997).

However, it was found that complexation of cyclodextrin with non-steroidal anti-inflammatory drug (NSAID) naproxen and tolbutamide (Hoffman et al., 1993) increased the dissolution, but there was no corresponding increase in bioavailability. Phenobarbital formed an insoluble complex with PEG-400, which resulted in slower dissolution and decreased absorption (Bhatia et al., 1996). In-vitro evaluation of complexation of steroids prednisolone with water soluble excipients, showed increased dissolution, but the complexes were having high molecular weight and might be too large to diffuse through GI membrane, therefore it may be possible that in-vivo bioavailability of prednisolone would be lower (Fincher et al., 1973)

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.[7]

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.

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

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.

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[8]

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.

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. 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.

Chemical interactions

Chemical interaction involves chemical reaction between drugs and excipients or drugs and impurities/ residues present in the excipients to form different molecules. Chemical interactions are almost detrimental to the product because they produce degradation products, different degradation product are classified as in ICH guideline ICHQ3B (ICH guideline ICHQ3B, 2008). Different types of chemical drug-excipients interaction have been reported in the literature.

Chemical interactions between drug and excipients[9]

Primary amine group of chlorpromazine undergoes Maillard reaction with glycosidic hydroxyl group of reducing sugar dextrose to form imine, which finally breakdown to form Amidori compounds.

In one another study it was observed that release of diclofenac sodium from matrix tablet was inhibited by polymer chitosan at low pH, most possibly via formation of ionic complex between diclofenac sodium and ionized cationic polymer (Block et al., 1997).

Secondary amines may also interact with reducing sugars. However, the reaction cascade does not proceed beyond the formation of the imine, and thus no coloration develops (Baertschi et al., 1998)

Primary amines may interact with double bonds in a reaction analogous to a Michael addition reaction (e.g., fluvoxamine maleate, where the fluvoxamine primary amine group can interact with the double bond in the maleic acid counterion). Examples of excipients that contain double bonds include sodium stearyl fumarate and sorbitan monooleate.

Certain APIs are susceptible to oxidation, e.g., atorvastatin and cytidine nucleoside analogues. Fumed metal oxides (e.g., fumed silica, fumed titania, and fumed zirconia) can promote such oxidation reactions.

These reactions are more complex in some ways, and less easy to predict. Lactone formation because of the close proximity of heteroatoms and an active hydrogen atom in the molecule, e.g., benazepril.

Suspending agents such as sodium alginate dissolve in water to form large negatively charged anions, co-formulation in aqueous systems with drugs such as neomycin and polymixin (active mioties of which are positively charged) result in precipitation.

Silicon dioxide catalyzes 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 (Tischinger et al.). Interaction between chloramphenicol stearate and colloidal silica during grinding leads to polymorphic transformation of the chloramphenicol, demonstrating that unwanted effects of excipients are not restricted to chemical transformations (Forni et al., 1988).

Interaction of drug with excipient residues/ impurities[10]

Exicipients are not exquisitely pure. In common with virtually all materials of minerals, synthetic, semi-synthetic or natural origin manufacture involves using starting materials, reagents and solvents. Residues invariably remain after isolation. Low levels of residues may have a greater impact than might be expected, however- particularly where the ration of excipient to drug is very high, or where the residue has low molecular weight or acts as a catalyst.

Table 2 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.

Table 2: Impurities found in common excipients.

Excipients	Residues
Povidone, crospovidone, polysorbates	Peroxides
Magnesium stearate, fixed oils, lipids	Antioxidants
Lactose	Aldehydes, reducing sugars
Benzyl alcohol	Benzaldehyde
Microcrystalline cellulose	Lignin, hemicelluloses, water
Starch	Formaldehyde

Talc	Heavy metals
Dibasic calcium phosphate dehydrate	Alkaline residues
Stearate lubricants	Glyoxal

Dextrose is widely used as tonicity modifier in the parenterals dosage form and it is used as nutrition solution. Sterilizations by autoclaving of such parenteral preparations containing dextrose can cause isomerization of dextrose in fructose and formation of aldehyde(5-hydroxymethyl furfuraldehyde), which can react with primary amino group to form shiff base and colour development (Almond and Janicki, 1974). Wirth et al showed that Maillard reaction product was also found in capsule containing lactose and antidepressant Fluoxetine (Baertschi, 1998). Lactose is a disaccharide of glucose and galactose. These reducing sugars have been found in spray-dried lactose (Brownley et al., 1963) as has the hexose degradation product, 5- hydroxymethylfurfural, probably generated by heat encountered during spray-drying (Brownley et al., 1964). As an aldehyde, 5- hydroxymethylfurfural can participate in addition reactions with primary amino groups, resulting in Schiff base formation and colour development (Almond et al., 1974).

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 longterm 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. For example Oxazolam degrades in the presence of microcrystalline cellulose may be attribute to carboxylic acid groups on the cellulose surface in addition to effect of water.

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 (Puttipipathkachorn et al., 1990; Nakagawa, 1982; Takahashi et al., 1984). 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. For example high moisture content of polyvinyl pyrrolidine and urea enhances aspirin hydrolysis (Figure 2). Excipients can form hydrates may enhance drug degradation by giving up their water of crystallization during grinding. Lactose hydrate enhances degradation of 4-methylphenylamino acetate hydrochloride upon grinding.

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.

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 (Aidrian, 1982; Danehy 1986). Such degradation products may also be present in the same materials used in pharmaceutical dosage forms. Unfortunately, pharmacopoeial monographs rarely list such organic contaminants.

Applications of advanced pharmaceutics[11]

Targeted drug delivery

Developing drug formulations that specifically target diseased tissues or cells, minimizing side effects.

Sustained release formulations

Designing drugs that release the active ingredient slowly over an extended period, reducing dosing frequency.

Transdermal drug delivery

Developing patches that deliver drugs through the skin.

Inhalation drug delivery

Formulating drugs to be inhaled for pulmonary treatment

Gene therapy:

Designing delivery systems to transfer genetic material into cells for therapeutic purposes.

Biopharmaceutical products

Non-ionic surfactants have traditionally been used as emulsion formers in topical and oral products, and more recently assolubilizers and stabilizers in biotechnology products. They are susceptible to hydrolysis (Bates et al., 1973) and auto-oxidation (Azaz et al., 1978). Peroxide levels in polyethylene glycol solutions have been shown to increase with concentration in solution and storage time (Ding, 1993). 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 (Decker et al., 1999). 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 hydroxyl toluene (BHT) has been shown to inhibit peroxide formation in Tween 20 during storage (Jaeger et al., 1994). 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 (Lam et al., 1996). Human growth hormone, lyophilized in the presence of sodium chloride, showed severe aggregation and precipitation, as well as accelerated oxidation and deamidation (Pikal et al., 1991).

CONCLUSION

Drug-excipient interactions may take a long time to be manifested in conventional stability testing programmes, and are not always predicted by stress and pre-formulation studies. They can complicate and compromise a development programme or the viability of a commercial

product. 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.

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.

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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