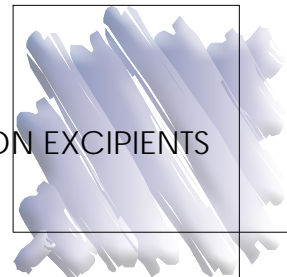




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Raising expectations of excipients

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Excipients have never shared the limelight with active pharmaceutical ingredients (APIs), nor have they historically been given the credit that they deserve in drug development, manufacturing, and delivery. An excipient's role has traditionally been viewed as merely a filler or binder contributing to the stability of the end product.

The full value that a formulation can bring to a final dosage form; or the real importance of ensuring an excipient's quality and performance; are often underestimated, overlooked, misunderstood, or disregarded. In reality, the functionality of the excipient can help determine whether or not a drug succeeds or fails.

The possible consequences of not carefully choosing the best excipient for your formulation include manufacturing complications, compromised stability, poor bioavailability of the API, unintended side-effects, reduced shelf-life of the finished product, and even serious adverse reaction or death of the patient (1). This seems the ultimate irony when therapies and pharmaceuticals are intended to help patients and improve their well-being, not harm them. To avoid these undesirable outcomes, what can you do to select the right excipient for your formulation and guarantee its quality?

While the pharmaceutical industry has been strictly regulated for years, excipients serve multiple industries as common food and cosmetic ingredients, and are often perceived only as processing aids or "inactive" additives. Because of this, regulations regarding excipients can be less stringent and regionally fragmented. It's no wonder that there is confusion about excipients and that if the misguided motivation is there, loopholes can be found to substitute or otherwise misrepresent them (2). While excipient regulation has unarguably been inconsistent, decentralized, and not in synch with the rest of the pharmaceutical industry, recently there have been more focused efforts toward harmonization and standardization of pharmaceutical excipient regulations, as well as progress toward accredited certification of manufacturing procedures. These heightened efforts can be attributed to several well-documented accidents (3) caused by adulteration of excipients and a growing appreciation for them as important functional or enabling ingredients that contribute to the ultimate success or failure in the final dosage form.

THE EVOLVING ROLE OF EXCIPIENTS

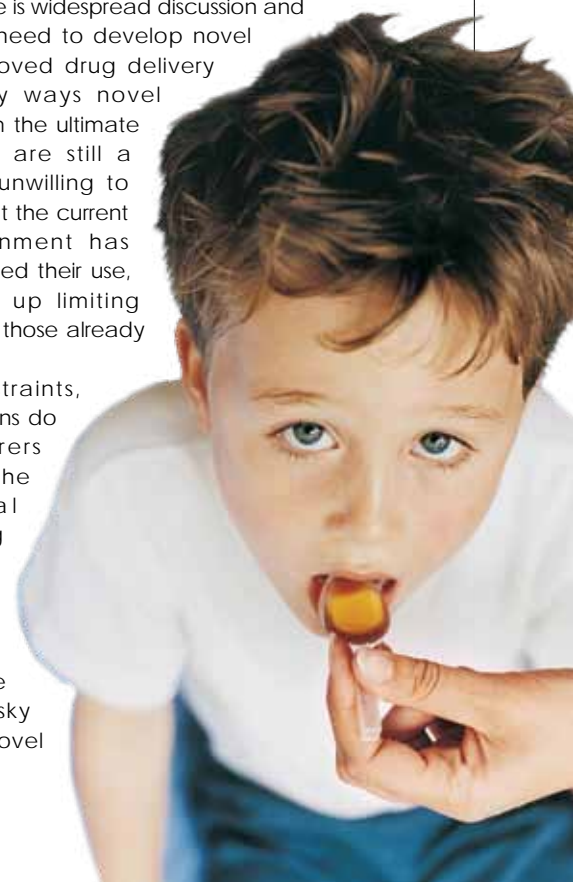
Supply chain optimization initiatives and other cost constraints in the current pharmaceutical landscape can tempt drug manufacturers to seek out low cost excipients as a way to

reduce expenses in pharmaceutical formulation and manufacturing. More recently, however, a greater understanding of the functional benefits of excipients and new applications to extend patents, enhance bioavailability, improve combined therapies, and increase stability have led manufacturers to turn to excipients as a means of improving pharmaceutical formulation, manufacturing, drug delivery, and profitability.

Due to FDA initiatives such as QbD (Quality by Design), excipient selection is starting to be considered earlier in the drug development process (4), especially since new candidates today are often less soluble. Exploring excipient functionality in the pre-formulation stage can help advance promising candidates that might otherwise be abandoned due to inadequate dissolution or bioavailability.

In a post-blockbuster era when the number of new compounds being launched is ever diminishing, novel excipients can help increase NDA (new drug application). However, for many drug manufacturers this seems a risky proposition. And they are understandably wary of jeopardizing their application if a new excipient is deemed unsafe, or they are unwilling to extend the time required to approve a new drug due to use of a novel excipient. There is widespread discussion and debate about the need to develop novel excipients for improved drug delivery solutions. In many ways novel excipients may seem the ultimate solution. But they are still a gamble most are unwilling to undertake, given that the current regulatory environment has historically discouraged their use, which often ends up limiting excipient choices to those already approved (5).

Given these constraints, what practical options do drug manufacturers have? Exploiting the multi-functional benefits of existing approved excipients can be an easy and safe alternative route compared to the more time consuming and risky path of pursuing novel



excipients. By working directly with the excipient manufacturer, pharmaceutical companies can learn about an excipient's full beneficial properties and have more confidence about its quality, origin, and performance.

Drug manufacturers are starting to appreciate the truly vital role excipients can play in the success of their formulation. As a result, they are turning to excipient manufacturers and contract formulators to support R&D innovation, improve manufacturing, and accelerate time to market.



This certification has multiple benefits since it assures the pharmaceutical company of GMP compliance by the excipient manufacturer and also reduces the inconvenience and expense associated with individual company audits at the excipient site.

NEW RESPECT FOR EXCIPIENTS

The world of excipients has moved well beyond just improving the stability of drugs, to creating a total solution for manufacturers and ultimately, patients. Considering the demands created by new manufacturing technologies, in addition to pressures to succeed and be profitable, there is an ever-increasing need to understand how excipients behave and why they work or fail in formulations.

With the decrease by nearly 50 percent in the number of newly launched active substances since the 1990s, and considering that nearly 40 percent of new molecular entities (NMEs) have poor aqueous solubility (10), excipients are emerging as strategic tools in an evolving

THE HUMAN SIDE OF RISK MANAGEMENT

In recent years there have been several excipient quality disasters that have heightened awareness for the need to better regulate the excipients industry.

In 2008, 84 children died in Nigeria after consuming teething formula containing glycerin contaminated with diethylene glycol (DEG). In 2006, 46 people died in Panama after taking cough syrup also contaminated with DEG (6). Several similar incidents have occurred, most often due to intentional misuse or neglectful mislabelling. With several deadly accidents related to excipients, no one can deny that there is a real need for better regulations to reduce confusion, ensure quality, and prevent such tragedies.

While various guidelines and certifications exist in the excipients industry, there is no universal standard. Globalization further confuses matters with regional differences in regulations, since excipients may change ownership and countries several times without proper documentation, accountability or ability to track chain of custody. Because excipient manufacturers are not required to register as drug manufacturers, it remains relatively easy for an ingredient not intended or suited for pharmaceutical use to be introduced into the supply chain (7). Since the excipient user bears ultimate responsibility for an excipient's quality, many pharmaceutical manufacturers have embarked on supply chain security initiatives or an excipient pedigree verification practice to mitigate risks. However, these measures only guarantee the source of the excipient, not necessarily the quality of the excipient as it is manufactured (8).

THE NEED FOR EXCIPIENTS GMP CERTIFICATION

Good Manufacturing Practice (GMP) is a requirement for nearly every component of a drug – from the packaging to the active pharmaceutical ingredient. However, a global regulatory standard does not exist for excipients. The path to accredited certification for excipients began in 2008, when the US Food and Drug Administration stated that excipient GMP conformance certification could benefit the excipient and pharmaceutical industry beyond the existing International Pharmaceutical Excipient Auditing (IPEA) program. By August 2009, IPEA and ANSI had developed an accreditation plan and process (9).

In February 2010, the first ever ANSI accredited excipient GMP certification of a quality management system was performed at W. R. Grace & Co.'s facility in Baltimore, Maryland, USA, where their Silicon Dioxide NF – Syloid® FP excipient is manufactured.



pharmaceutical model.

What can you do to select the right excipient for a formulation and guarantee its quality? Consider the patients' needs first and foremost. To fully exploit the right properties and functionalities of the excipient, maintain open communication with the excipient manufacturer and consider selecting the excipient early on in the process to maximize the potential of advancing more viable candidates to actual drugs. Also, to minimize risk, choose an excipient from a known and trusted manufacturer with accredited product quality and manufacturing certifications. And finally, for greater transparency, purchase directly from the original manufacturer, or through a secure supply chain. This will help to minimize handling errors mislabelling, and improve traceability.

The world of excipients is changing enormously. It's not just a matter of improving drug stability, it's about creating a better world for patients.

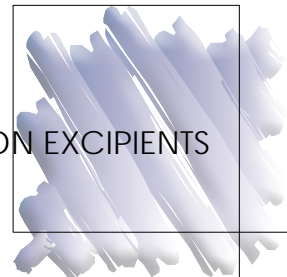
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Effects of excipients on the stability of medicinal products

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ABSTRACT *Excipients play important roles in delivery, manufacture and performance of medications. Dosage form design programmes involve choosing the most appropriate excipients, their optimum inclusion levels and the best mode of incorporation in the product. However, interactions between a drug and the excipients with which it is co-formulated in a medication can compromise the quality, efficacy or even safety of the product. Such effects may be due to direct drug: excipient interactions or reactions between drug and residues or impurities in the excipient. These may lead to the formation of new molecular constructs (degradation products) or a changed physical form of the drug. Drug substance characterization and dosage form design programs need to be explore such interaction possibilities to help choose excipients that are compatible with the drug. such investigations will reduce the risk of problems arising later in the program as instability often takes some time to be manifest.*

disputed. It also re-enforces the need for constant vigilance and a continuous efforts to get to know drug and excipients with which it may be formulated for interaction potential. This review focuses on drug-excipient interactions that might compromise quality but, as the above incident illustrates there are many other facets of drug/product interactions worthy of vigilance and study.

INTRODUCTION

Drug and product instability can have many causes and have serious technical and commercial consequences. A recent incidence in the US, involving a paracetamol (acetaminophen)-containing medication, Tylenol lead to a multiplicity of product recalls.

The recalls followed complaints by some users that product had an objectionable odour and caused nausea. The root cause was subsequently traced to low levels of a phenolic compound, tribromoanisole (TBA) in the product. The TBA was apparently a breakdown

product of a preservative used to treat the wood used to make pallets on which product was stored at the site of manufacture. Its volatile nature and characteristic odour meant that diffusion through the plastic wrapper and packaging material resulted in the off-odour (1).

This incident illustrates how subtle and difficult-to-predict interactions between drug or product, and environmental components can have serious consequences for products, and the organisations that develop, manufacture and sell them. It resulted in severe censure of the Manufacturer by the FDA for lack of oversight, inadequate Incident Management processes and failure to report to the Agency in a timely manner. This might be seen as over-reaction to a complex incident, the root cause of which cannot have been readily apparent but the consequences for the product and manufacturer cannot be

When designing dosage forms it is important to be aware of the potential for excipients to adversely affect quality

GENERAL CONSIDERATIONS

Drug substances are designed to interact with receptors to devince their therapeutic effect. Various functional groups are necessary for such interaction, and for metabolism and clearance by mechanisms such as glucoronidation, oxidation and hydrolysis. Prodrugs are designed to transform to the active component after administration. Such "fragility" may be desirable in an ecological sense (and a pre-requisite for activity in the case of prodrugs). Potent stable materials consumed as medications could, on excretion persist in the environment, enter food chains and affect population health and safety. At the same time such propensity to transform can also make a drug vulnerable to degradation by environmental stresses, process residues or by the materials with which it is formulated.

Drugs may interact directly with excipients or with residues or impurities therein. Such interactions may be modest, slow and take time to be detected in conventional stability studies. This can complicate and even delay project progression. When designing dosage forms therefore it is important to be aware of the potential for excipients to adversely affect quality.

Such adverse interactions can be broadly categorised as follows:

- Direct drug-excipient (chemical) interactions.
- Interactions between drug and residues in excipients (or vice versa).
- Interactions leading to physical (non-chemical) changes.

Other interactions that may affect performance parameters such as dissolution rate, drug absorption or processing characteristics are not considered in this review.

MODES OF DEGRADATION

Molecular structure determines the propensity of a material to transform to another structure. The environment

a material encounters, be it another substance or stresses such as humidity, light or temperature may also be pivotal in promoting the following changes.

Hydrolysis

Drugs that are esters, amides, lactones or lactams may undergo hydrolytic degradation. Such entities, formulated in aqueous media may be especially vulnerable to hydrolysis. However the rate of degradation may be so slow that losses are minimal. Nevertheless potential for hydrolysis in the presence of excipients should be considered and explored as excipients may promote degradation, either directly or by altering the aqueous environment in liquids or semi solids. Degradation, in solution or suspension may be influenced by pH, ionic strength, dielectric constant and these in turn may be influenced by excipients, particularly if water-soluble.

Potential for interactions in the liquid state can possibly be reliably predicted by studies at different temperatures to determine the effects of the above-listed variables. Solution studies are more amenable to conventional kinetic analysis than solid state reactions. Studies at stressful temperatures with extrapolation to temperatures likely to be encountered during manufacture, transport and storage of product may provide an accurate estimate of interaction potential and consequences for quality. A caveat is that it may be difficult to keep conditions like pH constant at different temperatures, or throughout a study, when excipients are present. Partly soluble excipients may also complicate such studies as increased levels in solution at higher temperatures may alter ionic strength and affect reaction rates (2).

Hydrolysis in the solid state is more complex but very common for the following reasons:

- water (moisture) is virtually ubiquitous, being present in the environment as water vapour, in drugs, excipients and in packaging materials.
- its low molecular mass (18 cf ca 400 for most "small molecules") means that "a little can go a long way" in terms of fractional degradation.
- it has a relatively high vapour pressure. This, combined with its low molecular mass confers good penetration properties, whether into solids during processing or through product or packaging during storage.

Excipients that are hydrates or contain residual moisture can promote hydrolysis in the solid state by acting as a source of water. Under appropriate conditions such moisture may be "donated" to the drug if conditions and dynamics favour such transfer. Conversely, if an excipient has avidity for moisture that is greater than that of the drug substance viz is more hygroscopic it may sequester residual moisture from a moisture-sensitive drug, rendering it more stable. Desiccants such as silica gel or molecular sieve can act as stabilizers in this way.

Propensity for moisture uptake is defined by the Critical Water Activity/Relative Humidity (CRH) of a drug or excipient. Values for some excipients and other common materials are listed in Table 1 (reproduced with permission from Reference 3).

When a material is in an environment where the Relative Humidity exceeds its CRH it gains moisture from that environment. Thus sodium carboxymethyl cellulose would be expected to "sequester" moisture from a companion drug if the ERH of the active exceeded 84 percent. The high CRH values exhibited by the materials listed in Table 1 suggest that the capability of most common excipients to desiccate and stabilize moisture sensitive drugs is virtually non-existent, or where potential exists the material in question (eg calcium chloride) is not a suitable excipient. Most moisture-sensitive drugs probably require environments that are much "drier" than achievable by the materials listed in Table 1.

Excipient	Critical Relative Humidity (%)	
	20°C	40°C
Dextrose	100	88
Fructose	72	64
Lactose	100	100
Mannitol	100	100
Sorbitol	80	69
Sucrose	86	83
Xylitol	91	73
Ascorbic Acid	100	98
Fumaric Acid	100	100
Tartaric Acid	84.5	78
Calcium Chloride	29	21
Potassium Chloride	84	82
Potassium Sulphate	97	97
Sodium Chloride	75	75
Sodium Citrate	60.5	78
Hydroxypropylmethylcellulose	100	100
Polyethylene Oxide	100	96
Polyethylene Glycol (PEG)	94	85
Sodium Carboxymethylcellulose	84	84
Hydroxyethyl cellulose	93	91
Pluronic F127	96	99
Pluronic F87	88	92.5

Table 1. Critical relative humidity (CRH) values for excipients.

Microcrystalline cellulose (MCC) is widely used in tablet manufacture. Adsorbed moisture is not bound very tightly but readily equilibrates with its environment (Figure 1). There is no body of evidence however that micro crystalline cellulose destabilizes moisture sensitive drugs. This may be due to the fairly common practice of pre-drying prior to incorporation in product containing hygroscopic drug.

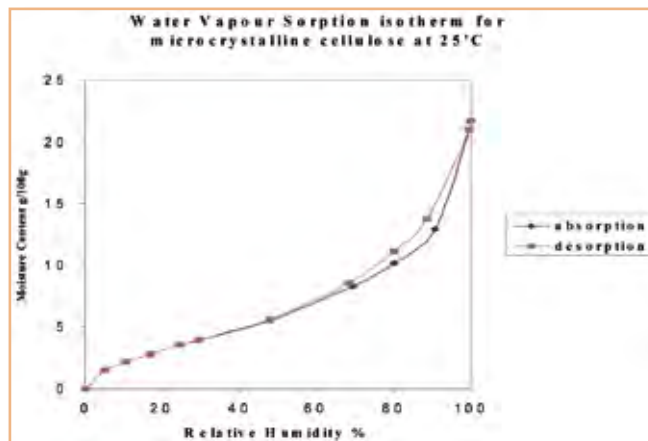


Figure 1. Water vapour sorption isotherm for microcrystalline cellulose at 25°C.

Starch and starch derivatives also contain moisture at levels that reflect equilibration with the environment to which they are exposed. Moisture transfer from such materials to drug also needs to be considered where the active is moisture sensitive and hygroscopic. Gelatin, while strictly not an excipient is in intimate contact with the drug formulation in capsule products so can act as a source of moisture. Its moisture sorption profile shows distinct hysteresis at relative humidity values below about 80 percent; some of the loosely bound moisture is readily removed (4). Hard gelatin capsule shells contain about 15 percent moisture at Relative Humidities in the range 35-60

percent. Hence, there is a risk of moisture transfer from shell to drug if the latter is hygroscopic throughout or below this RH range. Drying the capsules to obviate such transfer renders the shells brittle and in danger of breaking during encapsulation. In the light of such considerations it may be prudent to avoid formulating moisture sensitive hygroscopic drugs as hard gelatin capsules. Capsule shells made from hydroxypropyl methylcellulose (HPMC) are now available. HPMC has a narrower range of moisture than gelatin at normal processing/storage conditions (Figure 2). It is claimed that such units are more suitable for drugs that may be susceptible to moisture (5)

Alumino silicates ("Molecular Sieve") have traditionally been used as package inserts with moisture sensitive tablet dosage forms. An amorphous silicate (magnesium aluminometasilicate

Subtle and difficult-to-predict interactions between drug or product, and environmental components can have serious consequences for products

Excipient	Critical Relative Humidity (%)	
	20°C	40°C
Dextrose	100	88
Fructose	72	64
Lactose	100	100
Mannitol	100	100
Sorbitol	80	69
Sucrose	86	83
Xylitol	91	73
Ascorbic Acid	100	98
Fumaric Acid	100	100
Tartaric Acid	84.5	78
Calcium Chloride	29	21
Potassium Chloride	84	82
Potassium Sulphate	97	97
Sodium Chloride	75	75
Sodium Citrate	60.5	78
Hydroxypropylmethylcellulose	100	100
Polyethylene Oxide	100	96
Polyethylene Glycol (PEG) 3500	94	85
Sodium Carboxymethylcellulose (CMC)	84	84
Hydroxyethyl cellulose	93	91
Pluronic F127	96	99

Figure 2. Equilibrium moisture contents of gelatin-based and HPMC-based capsules.

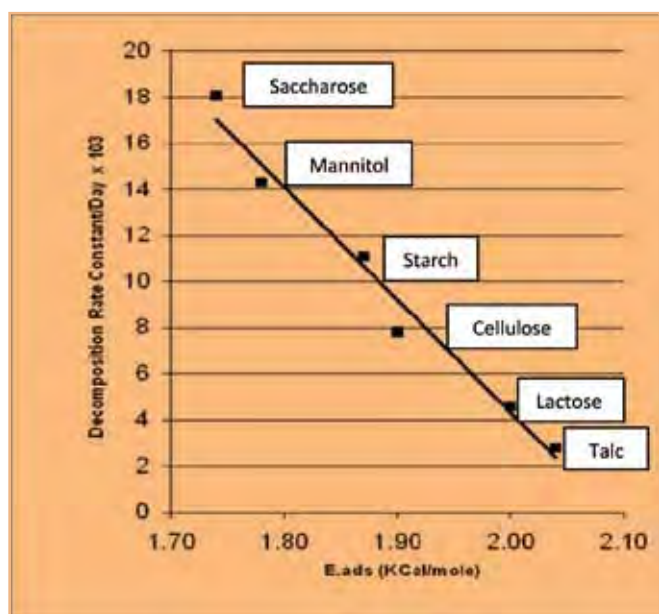


Figure 3. Degradation (decomposition) rate constants for nitrazepam in drug-excipient mixtures. effect of the nitrogen adsorption energies of the excipients. Reproduced with permission from reference (8).

or Neusilin™) has become available (6). Its primary purpose is to act as a scavenger of moisture and stabilizer of moisture sensitive drugs. Moisture sorption capacity varies with environmental Relative Humidity. Neusilin also enhances compact hardness at low inclusion levels.

The inclusion of excipients as desiccating agents in a formulation raises the possibility that moisture sorption during manufacturing operations (eg vacuum transfer, film coating, fluidisation or granulation) will saturate the excipient and nullify any stabilising effect. Hence, impressive performance in laboratory studies may not be readily replicated in a manufacturing environment unless processing conditions are carefully considered and simulated.

Perrier and Kesselring showed that nitrazepam stability in drug/excipient binary mixes varied linearly with the nitrogen adsorption energies of the excipients (Figure 3). On the assumption that adsorption energy for water vapour parallels that for nitrogen they suggested that "water binding energy" of the excipient determines its capability to adsorb and retain water ie act as a stabiliser (7).

Process-related stresses such as grinding and drying can release "bound" water from drug or excipient that may then participate in hydrolytic reactions (9, 10). Such phenomena may mean that testing simple drug-excipient blends in excipient screening studies may not predict interactions in formulated product. Compression, attrition or other crystal-disrupting stresses may be the catalyst for interaction and merit simulation in preformulation screening.

Oxidation

Aldehydes, alcohols, phenols and compounds containing such groups may be susceptible to oxidation. Such interactions may be promoted by heavy metal ions, peroxides or light. Mechanisms can be complex involving free radical formation (induction) and interaction with oxygen to form peroxy radicals. These can then interact with the oxidisable drug to generate additional free radicals to propagate further reactions. Degradation products may be manifold and difficult to identify (11).

The following excipients may have low level residues from manufacture that can lead to oxidative degradation in susceptible compounds (Table 2 and Reference (12)).

Excipient	Residue
PVP, Cross-linked PVP	Peroxides
Polyethylene Glycol	Peroxides
Polysorbate 80	Peroxides
Talc	Heavy Metals

Table 2. Excipient residues that are potential oxidising agents. Reproduced with permission from reference (12).

N-oxide formation in tablets and drug-excipient mixtures of the osteoporosis drug, raloxifene hydrochloride was traced to the presence of peroxides in the excipients Povidone and Crospovidone (13). Hydrogen peroxide has also been shown to accumulate in stored samples of the polyether surface active agent, Tween 80 (Polysorbate 80) and other non ionic surfactants (14). "Low Peroxide" grades of such materials are now available. However, as peroxide accumulation occurs during storage it remains to be seen whether such grades are particularly beneficial. Storage requirements (conditions and time viz shelf life) should be validated by making product with suitable "aged" surfactant and testing appropriately.

There are no reports of peroxide accumulation in polyether surfactants after such materials are incorporated in product. Indeed it would be difficult to detect such change in the complex environment of many products. Nevertheless, the possibility cannot be discounted and might explain instability in formulated product.

Peroxides may also be present in organic solvents, vegetable oils and lecithin (15). Acetaldehyde and formaldehyde have also been detected in Tween 80 (16). Labile residues in excipients may vary with source, from batch to batch, or change over time. "Fresh" excipient may not elicit an effect that may occur with aged material (and vice versa). The possibilities for different effects by "new" and "aged" samples could be usefully explored during dosage form design and evaluation. Stability studies in dosage forms manufactured using fresh and older excipients might be a useful component of Control and Risk Mitigation strategies.

Providers may include antioxidants in materials such as paraffins, fatty acids and non ionic surfactants, presumably to counter the presence of oxidising agents. Tween 20 may contain the antioxidant butylated hydroxyl toluene (BHT) (16). Removal from an excipient, replacement by a supposedly superior alternative, or change to a new excipient Provider could precipitate a stability crisis in cases where the additive was unknowingly stabilising the active ingredient as well as the excipient. Risk management and mitigation in such a context means having an agreed change control and notification process in place with excipient Providers so that any proposed change is considered and evaluated prior to adoption.

Antioxidants may have limited use in stabilizing drugs or excipients, particularly in solid state formulations. This may be due to the complexity and variety of interactions. Furthermore, the "intimate" molecular association that may be necessary for effectiveness may not be attainable in the solid state. However, tocopherol, butylated hydroxyanisole, butylated hydroxytoluene and propyl gallate have all been used to stabilize Vitamins A and D3. Ascorbic Acid (albeit solutions) have been stabilized by a combination of chelating agent and antioxidant and by magnesium, calcium or aluminium stearate (17). It is not clear, however, whether these latter materials directly acted as stabilisers *per se*. The benefit may have been due to antioxidants present in stearates and other fatty acids.

Photolysis

Reactions such as oxidation-reduction, ring alteration and polymerisation can be catalysed or accelerated by exposure to sun or artificial light. Energy absorption is greater at lower wavelengths and, as many drugs absorb ultra-violet light, degradation by low-wavelength radiation is a risk. Photolytic degradation can be very complex, the products of such degradation being numerous and difficult to identify. Exposure to light can cause discolouration of both drugs and excipients even when degradation is modest and not even detectable analytically. This can lead to "off colour" product, perceived by the patient as a quality deficiency.

It may be possible to utilise some excipients to reduce photodegradation. Thoma and Klimek (18) showed that the photolabile calcium antagonist, Nifedipine was stabilised by the food colourant curcumin and by riboflavin, both of which had similar UV absorbance to the drug (Figure 4 and Reference (19)). The impact of damaging radiation is attenuated as the excipient "competes" with the active compound for the photons from the radiation source. Neither the curcumin nor riboflavin provided complete spectral cover but stability enhancement was significant. Spilgies used a similar approach to stabilise solutions

of a photolabile beta lactamase inhibitor, BRL 42715 (Figure 5 and (19)).

A well designed risk assessment and mitigation plan, which may include relevant drug-excipient interaction testing, can reduce the risk of quality being compromised or programmes delayed

The benzophenone derivatives, oxybenzone and dioxybenzone used as UV blockers in sunscreens may be useful stabilisers in topical formulations that are exposed to light during use. However, concern has been expressed about their skin penetration and photosensitization (20). Sulphisomidine tablets were stabilised by incorporating the UV absorber, oxybenzone in the film coat (21). The parent structure, benzophenone is used as a UV blocker in plastics.

Isomerisation and molecular rearrangement

Isomerisation involves conversion of a chemical into its optical or geometric isomer that may have pharmacological or toxicological properties different from the parent drug. Retinyl

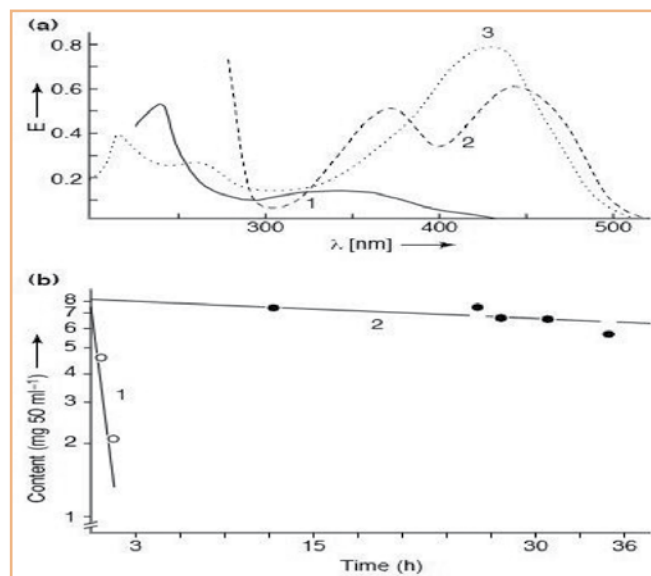


Figure 4. UV Absorption spectra (a) and effect on stability of nifedipine (b). a) UV Spectra of Nifedipine (1), Riboflavin (2) and Curcumin (3) b) Stability in Solution of Nifedipine with (●) and without (○) Curcumin Reproduced with permission from reference (19).

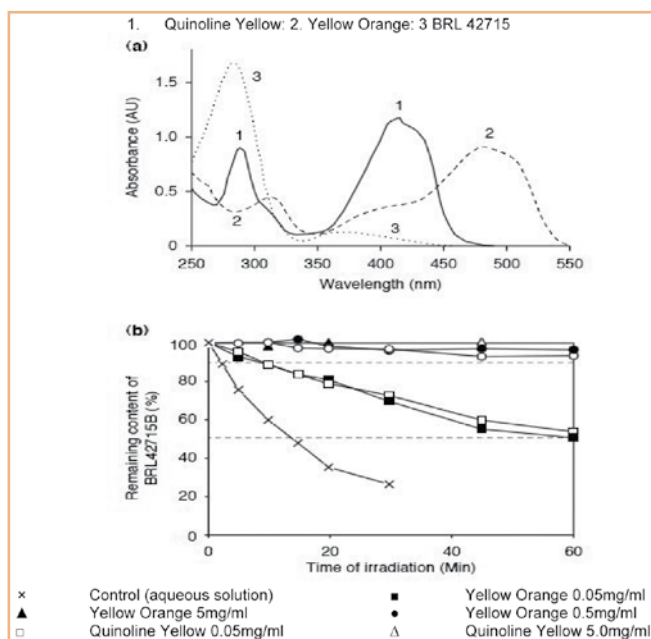


Figure 5. Effect of food colourants on stability in aqueous solution of BRL 42715. Reproduced with permission from reference (25).

palmitate (Vitamin A) is susceptible to isomerisation in the presence of light. Molecular rearrangement comprises transformation that involves no other species ie neither addition nor removal of atoms or groups. The topical antibacterial, mupirocin degrades in this manner in both solid state and in solution (22).

Isomerisation was significant in the solid state but was greatly attenuated when dissolved in Polyethylene Glycol 400 (Table 3) and (23, 24), a rare example of a drug in solution being more stable than in the solid state.

Stability of Mupirocin as a Solid and dissolved in PEG 400			
Time (months)	Condition °C	% Degradation	
		Drug Substance (Solid)	Solution (2%) in PEG 400
2	37	100 *	3
8	20	22	5
	30	100 *	9
12	20	42	6
		* material had melted	

Reproduced from Reference 24.

Table 3. Stability of Mupirocin as a Solid and dissolved in PEG 400. Reproduced with permission from reference (24).

Physical transformation

Drugs can transform to different crystal forms (polymorphs or pseudo polymorphs), or from crystalline to the amorphous form (and vice versa) under the influence of stresses such as temperature, compression or grinding. Time-related transformation is also possible. Excipients may promote or, retard such change. Chloramphenicol Stearate transformation from Polymorph A to the B and non crystalline forms occurred on grinding in the presence of colloidal silica (25). Buxton and co-workers showed that the anti depressant drug, Paroxetine Hydrochloride transformed from a crystalline anhydrate to a hemihydrate when compacted, as would be the case during tablet compression. Rate of compaction was directly influenced by compaction force (26). The effect of excipients on such transformation was not studied.

The polymeric excipient, polyvinyl pyrrolidone (PVP) has been evaluated for capability to stabilize amorphous forms of drugs in cases where solubility and dissolution rate might need to be enhanced for biopharmaceutical purposes. The retarding effect of PVP on amorphous-to-crystalline transformation of the anti inflammatory, indomethacin was shown to be related to particle size (27). The same authors noted that moisture sorption properties of such dispersions may differ from those of the component parts (28).

Impurities in Common Excipients	
Excipient	Impurities
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	" "
hydroxypropylmethyl/ethyl celluloses	glyoxal

Reproduced with permission from Reference 12.

Table 4. Impurities in common excipients. Reproduced with permission from reference (12).

Other interactions

Reactive chemical entities can be present in widely used excipients (Table 4) and their makeup may well determine the nature and extent of interaction with drug.

Such presence and potential for interaction is also important with respect to Biopharmaceuticals. These are becoming increasingly prominent as therapeutic agents and, while most of the materials listed in Table 4 are unlikely to be incorporated in such products other additives may present challenges. Biopharms are generally complex and fragile structures. Transformation can take many forms and, in addition to potency loss structural changes can lead to safety being compromised. Formation of high molecular mass products leads ultimately to less soluble aggregates.

The non-ionic surfactant polyoxyethylene sorbitan monooleate (Polysorbate 80 or Tween 80) is sometimes used as an anti-aggregant in biopharmaceuticals and vaccines. Comments made earlier in this review, with respect to the presence of Peroxides are also germane to biopharmaceuticals. Formaldehyde is also reported to have been formed in Tween 80 on exposure to air. Acetaldehyde was also found to be present but did not increase on exposure (29). The degradation of O-benzyl guanine was ascribed to residual formaldehyde in PEG 400. Such potential makes it advisable to pay particular attention to the storage, stability and routine monitoring of the quality of these excipients.

This review commenced with an account of an incident that illustrated the complexity of product stability performance. Interactions are also possible between an excipient, and residues therein and primary packaging. Solvents such as propylene glycol can act as plasticisers and alter rigidity of plastic containers on long term storage. A report by Sides et al. (30) relates how headspace analysis was used to identify an odour from an interaction product that had been formed by ethanol residues in the tablet disintegrant, sodium starch glycollate and a stabiliser used in the PVC component of a blister pack. The interaction product, ethyl 2-mercapto acetate, although present at a level that was hardly detectable analytically had a readily-noticed and objectionable odour, human olfactory sensitivity surpassing detection limits of modern analytical techniques. In the general sense, odour, while not affecting drug content, efficacy or safety may be readily noticed by patients and has to be considered as compromising overall product quality.


PERSPECTIVES AND CONCLUSIONS

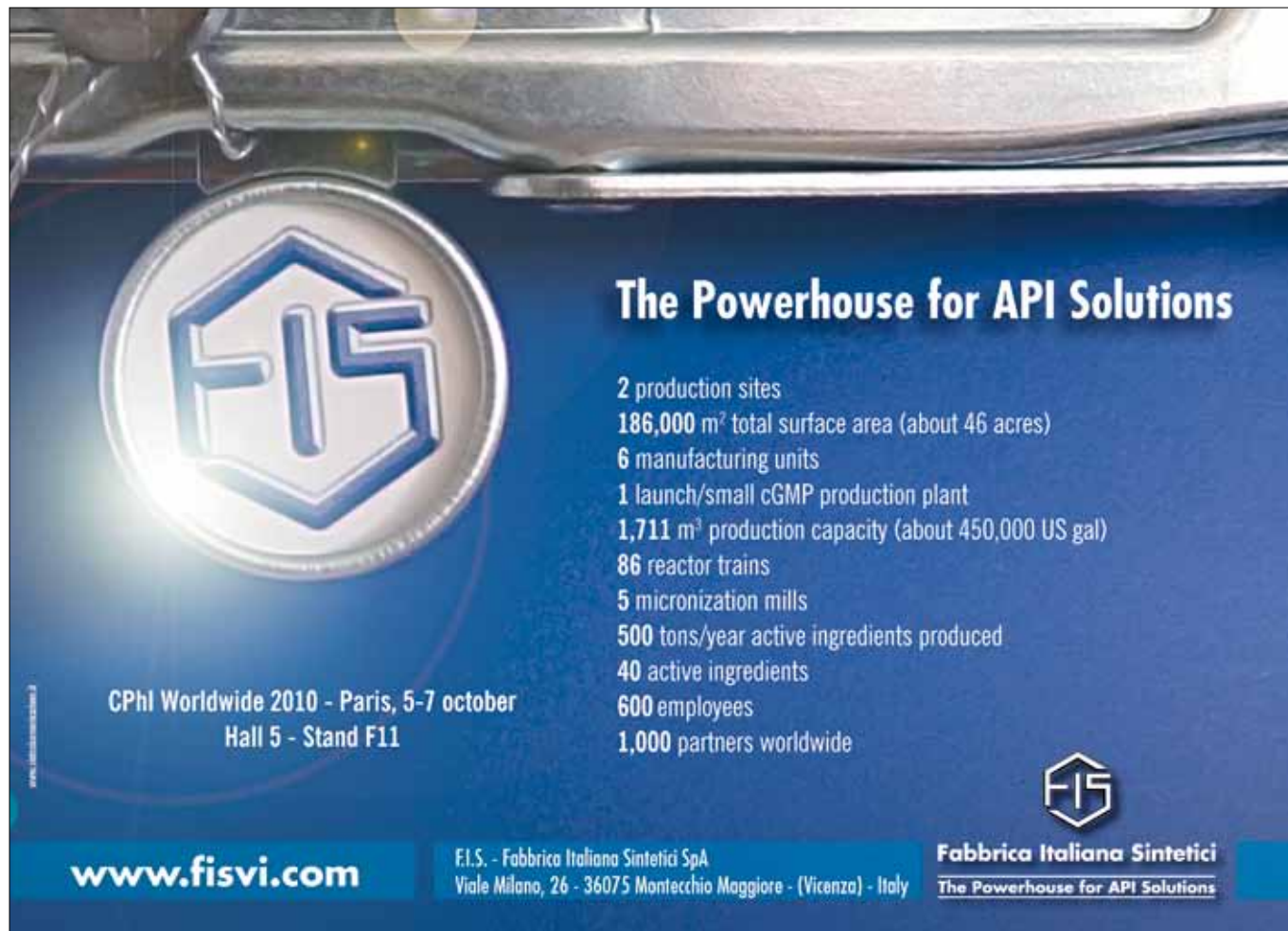
Excipients may possess functional groups or residues that may interact with the drug (or other components in the product) to compromise quality. Such presence does not necessarily mean that interactions will occur. Solubility may be extremely low such that reactions are negligible or non-existent. Steric hindrance or other effects may also rule out interaction possibilities in the solid state. However, the potential for interactions should be considered because, even if interaction generates only low levels of degradation product these have to be considered for potential to affect safety.

Screening for drug excipient interactions often comprises simply heating mixes at stressful conditions and monitoring the effect on drug quality. Such studies can produce many "false positives" and exclude useful materials that might otherwise enhance the medication. A more scientific and desirable approach concerns combining knowledge of the mechanisms by which a drug may degrade with awareness of what functional groups and residues may be present in excipients. A well designed risk assessment and mitigation plan

that may include relevant drug-exipient interaction testing can then be designed and implemented.

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