Excipients as stabilizers

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Excipients are better known as promoters of degradation than as stabilizers of drug substances. This is not surprising. Functional groups or residues in excipients can have the propensity to interact with labile active ingredients, with attendant loss of molecular integrity or other changes in quality. Thus, the canon of work on excipients as stabilizers is not extensive. Nevertheless, possibilities exist to capitalize on our knowledge of how a drug substance degrades, and of the properties and composition of excipients, to convert unstable drugs into viable products. This article discusses such approaches to product stabilization.

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▼ Drug substances can be fragile entities. Environmental stresses, as well as those associated with turning a drug into a medicine, all have the potential to cause changes that compromise quality. Such stresses can cause molecular composition to change to some extent. This reduces the amount of active ingredient in the medication and might generate novel molecular entities that could compromise safety. Physical changes can lead to altered dissolution or other delivery properties. Sedimentation in liquid products, consequent to altered solubility, could present safety as well as efficacy problems.

Preformulation studies should identify propensity for change on the part of the drug substance and clarify the strategy for development of the dosage form. Drug–excipient compatibility studies might further constrain or clarify the options for formulation. Packaging suitable to protect the product offers additional scope for providing a stable product. Such 'avoidance' tactics might suffice for many dosage form development programmes, but not in all cases. Drug substances that are elaborated by semisynthetic means and those emanating from biotechnology-based programmes usually have properties that can render them 'intrinsically unstable'. Even heterocyclic compounds of low molecular mass can possess functional groups that render them susceptible, to some degree, to interactions that lead to quality being compromised.

The long shelf-lives that are usually required for medicinal products reinforce the need for quality retention as a key consideration during formulation. In contrast to foodstuffs, soft drinks and many other commodities, it is usual to expect the quality of medicines to be retained for as long as 3–5 years. Such long 'use by' periods are especially important for remote and climatically hostile regions, because of the complexities of supply and distribution. As there is no such thing as a totally impervious pack, it will be apparent that the protection afforded by the pack will be limited in an environmentally hostile environment.

It might be necessary, therefore, to consider developing a formulation that compensates for any basic deficiencies in stability of the drug substance. In such cases, excipients must play a key role in turning an unstable drug into an acceptable product.

General considerations

The potential for excipients to prevent or retard degradation will be determined by the factors that cause the molecular transformation of drug substances. These include:

- environmental components, such as water vapour and sunlight;
- stresses during conversion to the dosage form, such as size reduction, compaction or sterilizing processes;
- interactions between adjacent molecules of a drug, or between functional groups on the same molecule.

If excipients are to act as stabilizers they must obviate or attenuate such effects.

Moisture-related degradation

Water can be associated with the drug or the excipients. It can be incorporated during

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manufacture of the dosage form or acquired from the environment during processing, packaging or storage. Its ubiquitous nature and capability to exist as a vapour means that water is virtually impossible to avoid and difficult to control, particularly if the drug substance is hygroscopic. Its molecular mass is low, so modest amounts can be significant in terms of molar reactivity. It is also capable of diffusing, to a greater or lesser extent, through packaging materials, pack seals, or through compacted solid dosage forms.

Excipients with affinity for moisture might be expected to mitigate moisture sensitivity. Thus, formulation with a substance having a greater affinity for water compared with the drug could mean that moisture in the product is sequestrated by the excipient.

Perrier and Kesselring used nitrogen sorption isotherms to predict the effect of common excipients on the stability of nitrazepam[1]. They showed that stability in binary mixes was not affected by the drug/excipient ratio or by the specific surface area of the excipient. Instead, it correlated with the nitrogen adsorption energy of the excipients, determined using the BET equation. Materials with higher adsorption energies caused less degradation (Fig. 1).

The primary aim of their study was to determine the 'inertness' of excipients, rather than their utility as stabilizers. However, the approach is equally germane to ranking the desiccating capability of excipients. If the binding energy of water vapour for the excipient exceeds the binding energy for the drug, the excipient should sequestrate any available moisture and act as a stabilizer. Competition between materials with avidity for moisture should lead to its redistribution, based on relative affinity, until equilibrium is reached: the material with the greatest affinity takes the lion's share of available water. If the active ingredient in the dosage form can co-exist with its equilibrium moisture content, it will be stabilized.

Perrier and Kesselring assumed that the binding energy for water vapour was comparable to that for nitrogen, or was of the same rank order. This assumption can be questioned. The forces of attraction between water vapour and nitrogen for an excipient substrate could be very different because of differences in dipole moment. Nevertheless, the rank order seen in Fig. 1 is impressive and the approach merits further study. It might be that dynamic vapour sorption instrumentation, which, in recent years, has been greatly enhanced in terms of sensitivity and precision, could be usefully employed to determine the binding energies of common excipients for water vapour (or to confirm the rank order relationship in Fig. 1). Such characterization would be a boon to the formulator dealing with moisture-labile materials.

Moisture is not the only residue with a significant vapour pressure that can be present in dosage forms. Lower alcohols

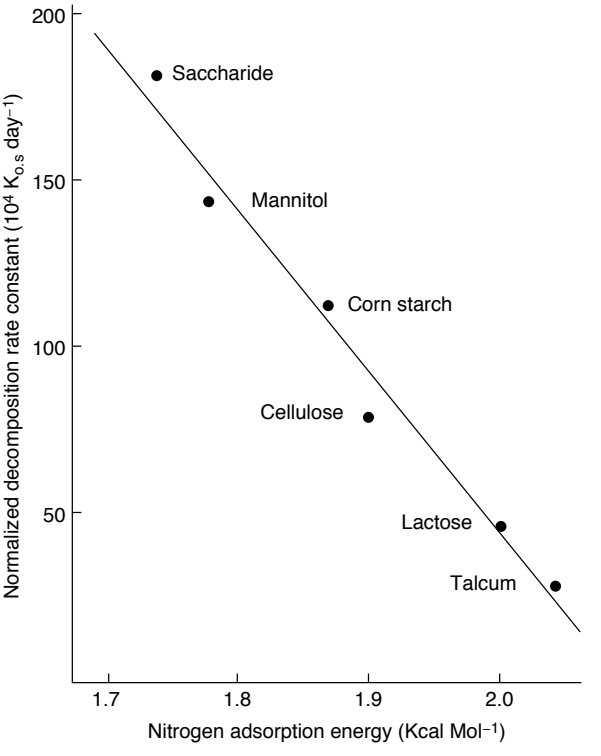

Figure 1. Normalized decomposition rate constants of nitrazepam in relation to nitrogen adsorption energy of various materials. Figure reproduced, with permission, from Ref. 1.

(methanol, ethanol, isopropanol) might be present from the synthesis and isolation of the drug, or from the process used for manufacturing the dosage form. Formaldehyde has the capability to participate in most of the known reactions of aldehydes and is present in many materials, including components of packaging[2,3]. Parts per million levels might cause significant degradation because of its low molecular weight. The capability of formaldehyde to be adsorbed by and interact with a drug substance can be determined during preformulation[4]. If it cannot be eliminated it might well be that it too, like moisture, can be sequestrated by an excipient.

Materials such as amorphous silica and microcrystalline cellulose are powerful sorbents[5–7] and might thus be capable of functioning as 'scavengers' of volatile residues. Care should be taken, however, to ensure that desorption does not occur during subsequent handling or storage of product. Thus the factors that affect desorption of the residue from the excipient substrate should be carefully studied.

Degradation by oxidation

Oxidation is probably second only to hydrolytic breakdown as a cause of loss of quality. The reactions are usually complex and

precipitated by many factors that are difficult to separate and clarify. The facile notion that stabilization is a matter of formulating with an antioxidant is rarely so simple in practice, especially with solid-state systems. The molecular association required to attenuate a reaction might not be readily attainable in solid-state dispersions.

However, formulation additives have been effective stabilizers in vitamin preparations. Tocopherol, butylated hydroxyanisole, butylated hydroxytoluene and propylgallate have all been used to stabilize vitamins A and D_3 (Refs 8–11). Ascorbic acid solutions have been stabilized by a combination of chelating agent and antioxidant[12]. Ascorbic acid has also been stabilized by magnesium, calcium or aluminium stearate[13]. It is not clear, however, whether these materials effected stabilization *per se* or whether it was produced by antioxidants that are usually present in stearates and other fatty acids.

Oxidation can be catalysed by exposure to air or light, the presence of trace residues (for example, heavy metals), or by other components in the formulation. It can also result from a combination of all of these. Different mechanisms require different approaches to stabilization. It is only by acquiring a basic understanding of the degradation process that a rational approach to stabilization can be developed.

It is also possible that an additive in the excipient (such as an antioxidant) can be a surreptitious stabilizer. If this additive is replaced or removed by the supplier (for perfectly valid reasons), the impact on product stability could be disastrous. Knowledge of the basic mechanism of stabilization means that effective change control arrangements can be negotiated with the providers of excipients.

Photodegradation

Exposure to light can precipitate a plethora of degradation reactions. These can include addition reactions in unsaturated systems, substitution reactions, polymerization, isomerization and photo-oxidation[14]. Suitable light-resistant packaging can, in many cases, prevent or reduce degradation. However, degradation during product use is also a possibility and it might be necessary to stabilize the formulation itself.

The concept of spectral overlay was pioneered by Thoma and Klimek[15,16]. This approach involves formulating with a material whose UV absorption spectrum overlaps (or substantially overlaps) that of the compound requiring stabilization. The impact of damaging radiation will thus be attenuated as the excipient 'competes' with the active compound for the photons from the radiation source. Thoma showed that the photolabile calcium antagonist nifedipine can be effectively stabilized by the natural food colorant curcumin, or by riboflavine[15]. Neither of these additives provided complete spectral cover but stability enhancement was significant (Fig. 2).

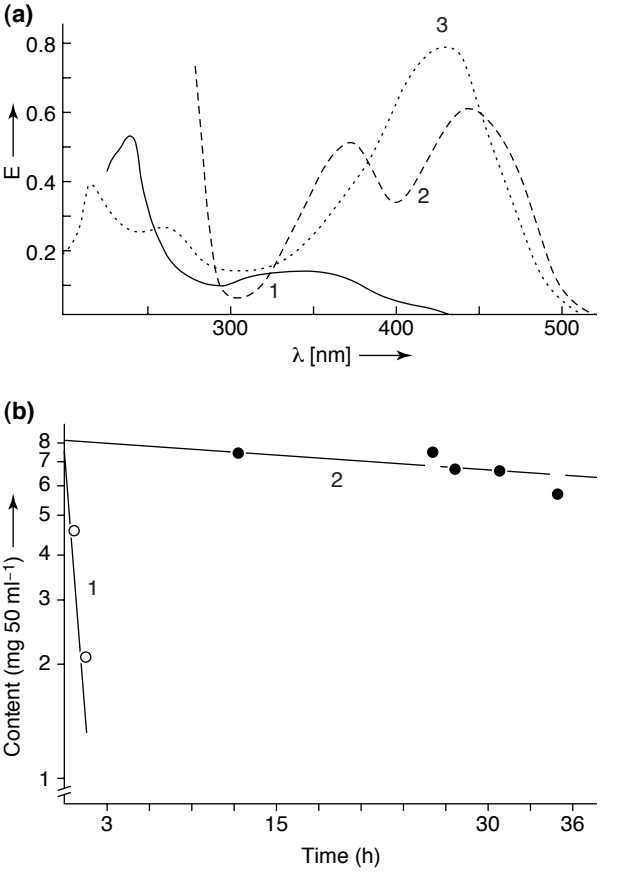

Figure 2. Spectral overlay for stabilization of photolabile drugs. **(a)** UV absorption spectra of nifedipine (1) and the stabilizers riboflavine 5-phosphate (2) and circumin (3). **(b)** Solution stability of nifedipine (1) in the presence and absence of curcumin (2). Figure reproduced, with permission, from Ref. 15.

Spilgies used the spectral overlay approach to stabilize solutions of a photolabile β-lactam using acceptable food colorants having UV spectra that went some way to providing spectral cover[17] (Fig. 3).

A similar approach was used by Sanderson *et al.* to stabilize a potential anti-psoriasis agent for application as an ointment[18]. Although stable in the formulated, packaged product, the active ingredient was photolabile. Isomerization and polymerization reactions occurred when the ointment was exposed as a thin film to simulated sunlight. In-use degradation was therefore a possibility and stabilization needed to be considered.

Table 1 shows the effect of including benzophenones (agents used in sunscreens) on photostability. The reduced degradation can be ascribed to the partial spectral overlay provided by the benzophenones (Fig. 4).

Sanderson *et al.* also noted that stability could be enhanced by the addition of a 'blocker' such as titanium dioxide and by

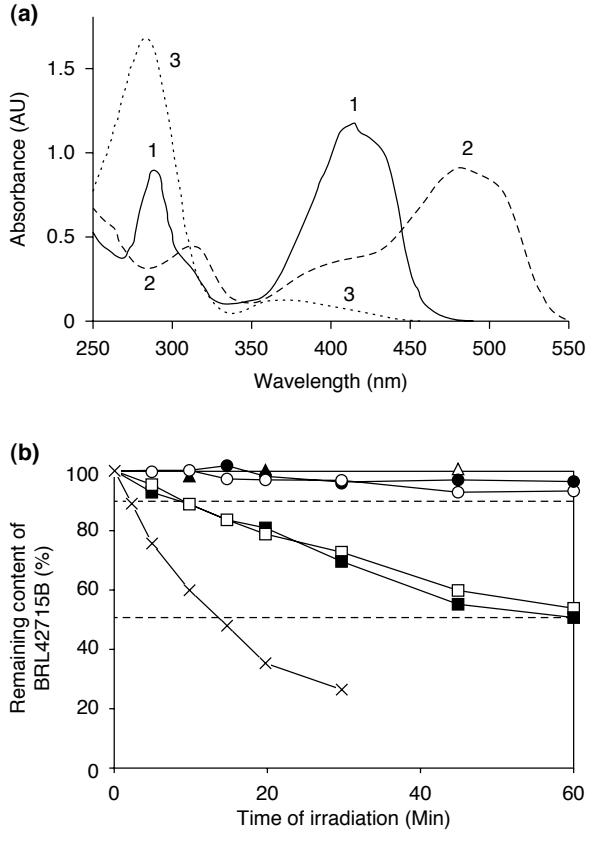

Figure 3. Effect of food colorants on the stability of the β-lactam BRL42715B. **(a)** UV absorption spectra. In an aqueous solution of 20 μg ml^{-1}, quinoline yellow (1); yellow-orange S (2); and BRL42715B (3). **(b)** Effect of additives on solution stability. Yellow-orange S 5.0 mg ml^{-1} (black triangle), 0.5 mg ml^{-1} (black circle), 0.05 mg ml^{-1} (black square) and water (control sample) (cross); quinoline yellow 5.0 mg ml^{-1} (white triangle), 0.05 mg ml^{-1} (white circle), and 0.05 mg ml^{-1} (white square). Figure reproduced with permission from H. Spilgies (unpublished).

using a brand of soft paraffin with a UV spectrum that provided partial spectral cover (Table 2 and Fig. 5). It can be seen from Table 2 that the presence of the antioxidant α-tocopherol did not augment the stabilizing effect of the grade of paraffin in question. Thus the enhancement seen is more likely to be a spectral overlay effect (Fig. 5). Some aromatic residue or other additive in the paraffin might be responsible for the spectral cover. These findings highlight the need to be aware of the basic stabilization mechanism and the need for change control systems for excipients. Change of supplier of paraffin could lead to a less-stable product in this case.

In a similar vein, the presence of the UV absorber oxybenzone in the film coat was shown to stabilize sulphisomidine tablets[18].

Successful application of the spectral overlay approach requires excipients with the appropriate absorption spectra. Obviously they must also be free from pharmacological activity and be non-toxic. Hence, the list of potentially useful materials is limited. Nevertheless, it is an elegant approach to stabilization if the pack cannot be relied on to provide the requisite protection.

Other modes of degradation

Some degradation reactions do not involve species other than the active ingredient. Isomerization, dimerization and polymerization and other forms of molecular rearrangement are not uncommon, particularly for drugs of large molecular mass or those of biological origin. No other species need be involved in such reactions, although they might act as catalysts or initiators. Ostensibly, it might seem that molecules with an intrinsic 'self-destruct' capability would be the most difficult to stabilize. It is paradoxical, therefore, that some of the more successful attempts to stabilize labile drugs have concerned materials that are derived either directly or indirectly from biological sources.

Table 1. Effect of UC-absorbing agents on stability of an anti-psoriatic compound in a paraffin-based ointment (samples exposed for one hour in a Sol-2 light cabinet)

Stabilizer	Level (% w/w)	Degradation %
None	–	49
Oxybenzone	0.25	35
Oxybenzone	0.5	26
Oxybenzone	1	24
Dioxybenzone	0.25	20
Dioxybenzone	0.5	9
Dioxybenzone	1	9

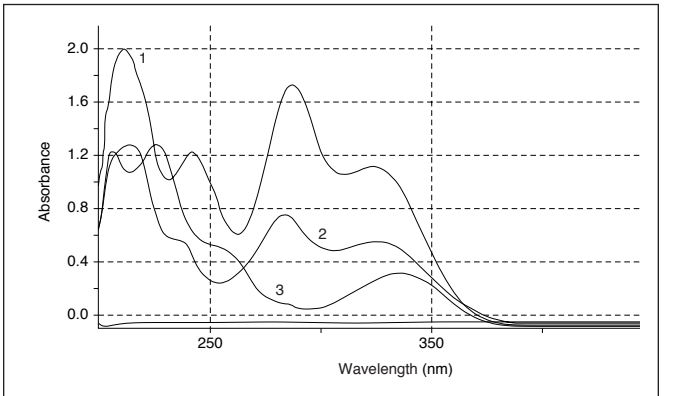

Figure 4. UV spectra of anti-psoriasis drug and benzophenones. Oxybenzone (1); Dioxybenzone (2); and Anti-psoriasis drug (3). Figure reproduced, with permission, from Ref. 17.

Table 2. Effect of grade of paraffin and use of 'Blocker' on stability

Sample	Description	Degradation %
1	Control (normal grade paraffin)	47
2	'Witco-N' paraffin	26
3	As '2' plus 1% titaniun dioxide	11
4	As '2' plus 250 ppm alpha-tocopherol	27

Cyclodextrins are cyclic glucose polymers with the unique capability to accommodate hydrophobic 'guest' moieties within the annulus. Non-covalent links 'anchor' guest to host. Cyclodextrins have been widely reported as enhancing the solubility and dissolution rate of poorly soluble drugs. Their use as stability enhancers also capitalizes on their unique molecular complexation capability. This can result in improved stability of compounds with a tendency to sublime, such as clofibrate and isosorbide[19,20]. Chemical stability can be enhanced when the reactive groups are accommodated in the cyclodextrin cavity, thereby preventing inter- or intramolecular reactions. The effect of such molecular encapsulation is shown in Table 3 for a prostaglandin E_1 (PGE_1) derivative[21]. There was apparently a double benefit with the use of this compound in that the dissolution rate was also significantly enhanced.

Prostaglandins, being derivatives of arachidonic acid, have a basic molecular structure that is characterized by a cyclopentane nucleus with two hydrocarbon side-chains giving a 'hairpin' configuration. Like many materials of natural origin, prostaglandins readily degrade both in solution and as solids, and such behaviour can limit their utility. However, it appears that cyclodextrins are uniquely suited to the stabilization of these labile materials and several successful attempts have been reported. Stable complexes have been formed with PGE_1 (prostacyclin) and PGF_2 (Refs 22,23). It is interesting that, in the latter case, stabilization is effected by both the α- and the β-forms of cyclodextrin, although the mode of molecular encapsulation is different for each type. The α-form accommodates the cyclopentane portion of the molecule within the cavity, whereas, in the case of β-cyclodextrin, one of the side-chains of the prostaglandin is inserted as shown in Fig. 6 (Ref. 24). Either way it would appear that the reactive moieties are rendered less labile by 'spatial' effects.

The molecular inclusion properties of cyclodextrins would suggest that their suitability as stabilizers is limited to cases in which degradation is the result of molecular rearrangement. It is interesting, therefore, that cyclodextrin complexation inhibits the oxidative degradation of vitamin D_3 (Ref. 25). On reflection, this is not surprising. Positioning of the labile moiety within the cyclodextrin cavity might render it less vulnerable, in the steric sense, to attack by many kinds of degrading species.

It should be stated that cyclodextrin complexation is no guarantee that instability will be remedied. In some cases, the effect might be opposite to that desired. It has been reported that incorporation in β-cyclodextrin accelerates vitamin K decomposition in solution[26], and there are other accounts of complexation being of little benefit or of variable effects[27]. This ought not to be surprising. Generally, the hydrophobic part of the guest molecule will be accommodated within the cyclodextrin cavity, but the labile group(s) might reside in a different part and not be protected by encapsulation. Indeed, they could be rendered more vulnerable. Here again, knowledge of the basic modes of degradation should indicate the chances of successful stabilization by molecular incorporation.

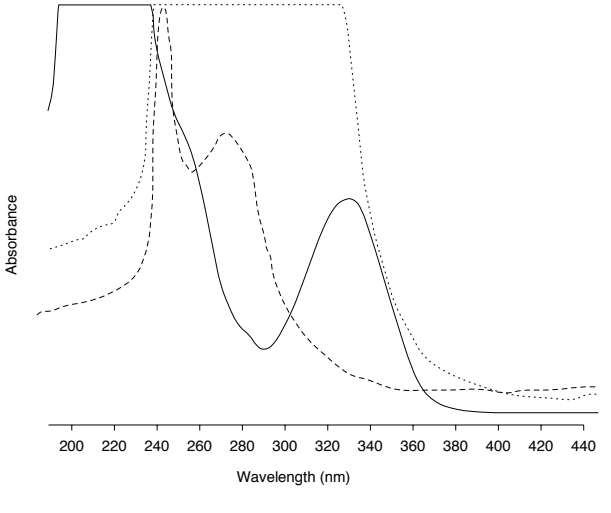

Figure 5. UV absorption spectra of anti-psoriasis drug and soft paraffins. Anti-psoriasis drug (SB 201993) (hatched line); Oxybenzone (dotted line); Dioxybenzone (hatched line). Figure reproduced, with permission, from Ref. 17.

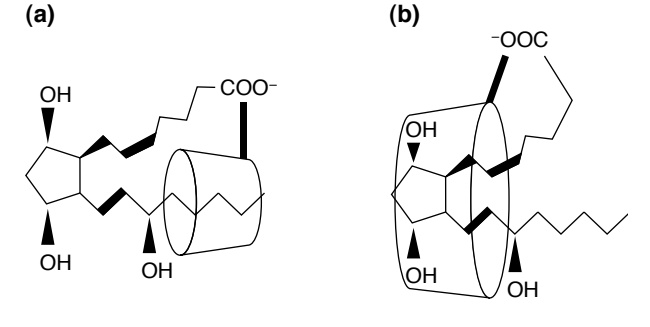

Figure 6. Modes of encapsulation of prostaglandin F_2 and cyclodextrins. **(a)** Shows α-cyclodextrins, and **(b)** shows β-cyclodextrins. Figure reproduced, with permission, from Ref. 24.

Table 3. Effect of cyclodextrin complexation on stability of dimethyl prostaglandin E1 (storage at 60°C)

Time (Days)	Degradation %	
	Drug 'as is'	Cyclodextrin complex
1	2.2	0.1
3	8.8	0.5
8	30.2	2.5
14	54	4

Table reproduced, with permission, from Ref. 21.

The molecular size of cyclodextrins, relative to most drug substances, means that their use is limited to highly potent, low-dose drugs. Otherwise, the large cyclodextrin/drug ratio in an equimolar complex means that a dosage form is likely to be too large to be practical. The process for preparation of the complex can also be a drawback. The most effective mode of complex formation appears to involve dissolution of the drug and cyclodextrin in a suitable solvent, standing to allow the complex to form, and then drying. If the drug is very unstable, there could be problems with maintaining molecular integrity during the solution phase, particularly if heating is required and the time for complex formation is prolonged. Dry encapsulation (micro grinding) also appears to be feasible, but the consistency of such a preparative technique might be open to question.

Like all 'novel' excipients, cyclodextrins cannot be used without due consideration of the safety implications. Both α- and β-cyclodextrins are present in a number of commercial products, although approval seems to vary from country to country. Their use in oral preparations seems to be gaining general acceptance. Inclusion in parenteral products is more problematical, particularly if inclusion levels are high. Renal toxicity has been reported for both forms, possibly as a result of depressed solubility in the environment of the proximal tubule. The hydroxypropyl derivative appears to be a safer option for parenteral administration (see the recent excellent review on cyclodextrins by Stella and Rajewski for a more comprehensive treatise on many facets of cyclodextrin properties[28]).

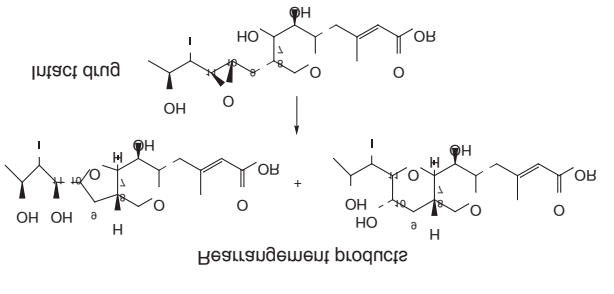

Figure 7. Modes of degradation of mupirocin.

Cyclodextrins will not be a panacea for all stability problems, but clearly they have a niche and are being increasingly used in commercial pharmaceutical products.

The experiences with cyclodextrins illustrate the potential of 'steric stabilization'. If a drug can be 'fixed' to an excipient, by adsorption or other non-covalent means, the possibility exists that, on occasion, labile groups will be made less available to incoming moieties with which it might react. The possibility that dissolved drugs can be 'structured' by using appropriate solvent systems or soluble additives is an attractive concept for stabilization. In this context, prostacyclin is stabilized by various albumins[29]. Human serum albumin also inhibits the aggregation and oxidation of solutions of iron protoporphyrin. Materials as diverse as polyvinylpyrrolidone (PVP), caffeine, niacin and antioxidants also enhanced protoporphyrin stability in solution and in lyophilized solid[30]. The beneficial effects of albumins on prostacyclin stability suggest that Mother Nature might have evolved ways of stabilizing natural mediators. This could be fertile ground that merits exploration for strategies for stability enhancement.

Mupirocin (pseudomonic acid A) is an antibacterial for topical infections. It is of natural origin, being derived from fermentation of *Pseudomonas fluorescens*. It readily degrades in solution and in the solid state[31]. Degradation in the solid state is initiated by rupture of the epoxide ring followed by rearrangement to two bicyclic compounds (Fig. 7). No other molecular species appears to be involved and it was therefore difficult to conceptualize strategies for stabilization. However, the finding that rearrangement was reduced when the compound was dissolved in polyethylene glycol was capitalized on to develop a viable commercial ointment formulation[32]. What was surprising was that the drug dissolved in this vehicle was more stable than as a solid, reversing the normal trend for materials to be more stable in the solid state than in solution (Table 4). Although the basic means of stabilization has not been elucidated, it is difficult to

Table 4. Effect of formulation on stability of mupirocin

Time (months)	Condition (°C)	Degradation %	
		Drug substance (solid)	Drug in solution (2% in PEG 400)
2	37	100 (melted)	3
8	20	22	5
	30	100 (melted)	9
12	20	42	6

avoid the conclusion that some steric hindrance effect prevents degradation by rearrangement.

Overview

Many products contain excipients that can be categorized as stabilizers in a general sense. Using suspending agents to prevent sedimentation, adding a preservative to prevent microbial spoilage or a buffer to adjust pH for optimum stability are all examples of excipients being added to enhance product stability. However, such approaches are part of the stock-in-trade of the formulator and are expounded in many articles and textbooks. Hence, they have not been discussed here. Instead, this review has attempted to focus on cases in which fundamentally unstable drugs can be transformed into viable medicinal products by formulating with appropriate excipients that have some direct effect on the molecular integrity of the active ingredient.

The question can be posed whether a strategy for stabilization is appropriate. In the era of combinatorial chemistry and genomics-based research, the view of the pundits seems to be that unstable entities should be 'selected out' early in the discovery and development process. After all, poorly stable therapeutic agents are likely to progress slowly (or not at all) to the marketplace. In the environment promised by genomics, it is postulated that there will be an embarrassment of riches in terms of compounds to select for clinical evaluation, thus attempts to stabilize a poorly stable material might not seem warranted.

However, there are other reasons why the capability to stabilize labile materials should remain an option for the formulator of medicinal products. The activity, specificity and freedom from toxicity might be directly related to molecular fragility. Materials derived from biotechnological or other natural sources are a case in point. Stabilization using appropriate excipients might be the only way in which many of these materials can be converted into viable products.

Furthermore, in the context of environmental impact, the use of excipients to stabilize an unstable active ingredient is an attractive concept. A product could be developed that retains its quality while the drug and other formulation components are in close association. Rapid breakdown would follow disposal (or ingestion) with the attendant separation of drug and stabilizer. Stable residues of potent materials would not be an issue.

It should also be noted that turning an unstable entity into a stable product offers possibilities for intellectual property claims, as evidenced by the number of patent claims referenced in this article. Thus there are potential commercial advantages for organizations with the will to make the effort and the skills to provide inventive approaches to stabilization.

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