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White Paper

API Stability in Solid Dose Formulation:

Exploring the Myth of Inert Excipients

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Introduction

Stable active pharmaceutical ingredients (APIs) represent a critical success factor for drug formulation for four main reasons.

Firstly, the potential instability of APIs can represent a critical threat to patient safety. This risk can be generated through the decline in the actual dosage of the drug as its content degrades over time, or via the creation of toxic degradation products.

Secondly, the stability of an API is a prerequisite for regulatory acceptance of the drug. Thirdly, greater API instability reduces the potential shelf-life of a drug, risking excessive wastage and damaging revenues and profits if demand is lower than anticipated.

Finally, API instability can increase the complexity and cost of drug storage requirements, such as extra cooling, which also harms the economic viability of the drug, increasing costs and eroding convenience for both physicians and patients.

The factors that cause an API to become unstable include, but are not limited to:

- **Exposure to heat and/or changes in temperature**
- **Exposure to moisture**
- **Oxidation**
- **pH sensitivity**
- **Biological contamination**
- **Light sensitivity**
- **Interaction with other formulation components**

The relevance of each factor is dependent upon the API used. This also means that preventive measures have to be considered on a case-by-case basis. However, exposure to heat, moisture and oxidation are factors that are known to induce instabilities across a broad range of APIs.

This white paper examines the potential impact of poor API stability in solid dose drug development, explores the causes of instability and explains how excipients can help in creating stable APIs. Finally, it also presents some case studies to illustrate their potential effectiveness.

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The role of excipients

There has been a paradigm shift in assumptions about excipients in solid dose drug formulations. In the past, excipients in formulation were assumed to be inert, but it is now clear that this is not usually the case in reality. The contemporary view is that excipients are not inert and their functionalities are becoming increasingly important, even in more traditional approaches to pharmaceutical formulation such as direct compression.

Whereas fillers were once regarded simply as fillers, today they are chosen according to specific functionalities. For example, without excellent flowability, compressibility and uniformity, the direct compression of very high and low dose formulations in particular would not be possible.

The range of excipient functions includes:

Physical action: Including lubricants, flow enhancers, disintegrants, binders, coatings or pigments.

Chemical activity: pH adjustment, preservatives, antioxidants, scavengers, and taste modifiers.

Bioavailability enhancement: Including the ability to, for example: increase solubility; limit the tendency of recrystallization of amorphous drugs; enhance permeability; enable in situ salt formation or even complexation with the API.

Addressing excipient stability issues using traditional approaches

The most common types of API instabilities can be induced in the following ways: Direct interaction/reactivity with the excipients; moisture content; oxidation; compression force; impurities; hygroscopicity; and the granulation process. These issues and how they are usually addressed are explored in more detail below:

Direct interaction/reactivity: Direct interaction or reactivity provides a good example of how excipients used with APIs are not necessarily as inert as was assumed in the past. Lactose, for example, is a reducing sugar that reacts primarily with amine groups in the so-called Maillard reaction.[1]

And yet, lactose is very commonly used in solid dose formulations, despite the fact that a reaction with the API might occur. As another example, magnesium stearate is very often used as a lubricant, but is incompatible with acidic APIs such as acetylsalicylic acid and most alkaloid APIs. The standard strategy in formulation is to avoid the use of excipient/API combinations that are obviously incompatible as far as the chemistry is concerned.

Moisture content/hygroscopicity: Table 1 lists the maximum water content of commonly applied filler excipients as specified in pharmacopoeial monographs. For example, a water content as high as 15% is still within compendial specifications for starch, while only 0.3% is applicable for mannitol.

Substance	Water Content
Starch	≤ 15%
MCC	≤ 7%
Isomalt	≤ 7%
Excipient System A*	≤ 5.75%
Excipient System B*	≤ 3.5%
Excipient System C*	≤ 3%
Lactose monohydrate	≤ 1%
DC-Sucrose	≤ 1%
DC-Mannitol	≤ 0.3%

Table 1:
Water content of commonly used fillers in solid dose formulation
(data based on Rowe et al. or manufacturer's information)[2]

*Excipients systems A-C are ready-to-use systems of the following composition:
- A: lactose monohydrate, povidone, crospovidone
- B: lactose monohydrate, cellulose
- C: lactose monohydrate, maize starch

This complexity derives from the fact that different measurement methods are applied, and even different parameters are specified such as moisture content or loss on drying.

While Karl Fisher titration is water-specific and measures only the water content in a sample, loss on drying also includes other volatile impurities. As a result, they are not directly comparable with one another. Also, the differentiation in water content in the monograph is related to the hygroscopicity of the excipients.

Figure 1 compares the water absorption of commonly used fillers in solid formulation such as mannitol, microcrystalline cellulose (MCC), and sorbitol.

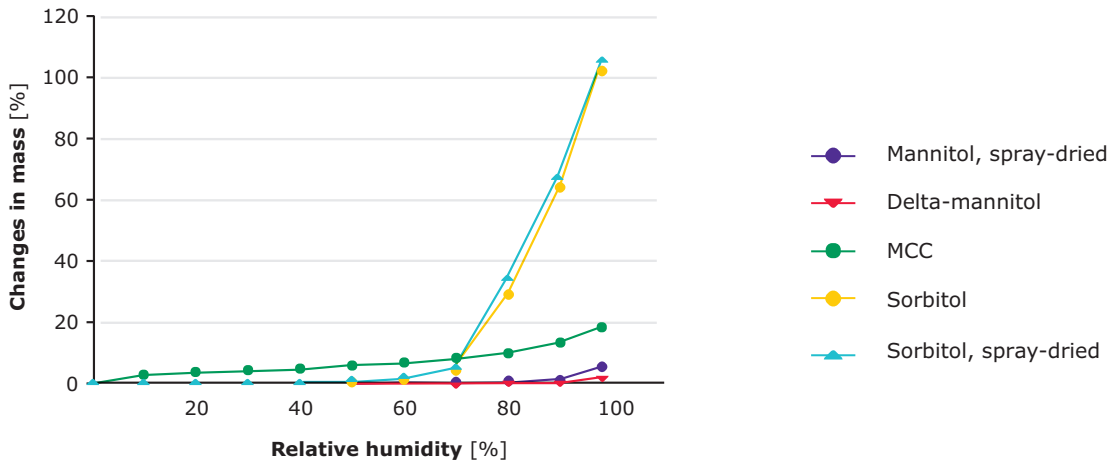


Figure 1:
Dynamic vapor sorption (DVS) results of spray-dried beta-polymorphic mannitol, delta-polymorphic mannitol, MCC and spray-dried and crystallized sorbitol

The data show that sorbitol, which is generally regarded as highly hygroscopic, is actually only hygroscopic in an environment with a relative humidity of 65% or more. In contrast, MCC exhibits higher hygroscopicity at a relative humidity of 65% and less and absorbs water regardless of how much moisture is present in the environment.

Still, formulators often hesitate to use sorbitol because of its hygroscopicity, even though it is clearly of concern only when specific conditions are present.

These environmental conditions can be controlled during the production process, and the packaging type and material selected helps to prevent any effects that may otherwise occur during storage of the final formulation.

Impurities: A meta-study into reactive impurities in excipients by Wu Y. et al in 2011 identified the excipients and impurities listed in Table 2 as being particularly significant.[3] For example, MCC as a commonly used filler in solid formulation contains, in addition to water, several different types of impurities such as the reducing sugar glucose, aldehydes, free radicals and peroxides, all of which may promote API instabilities.

Also, it can directly interact with the API via hydrogen bonding, which may result in a retardation of the API release kinetics.

Table 2:

Example excipients commonly used in pharmaceutical formulation and their typical impurities

• MCC	Water, glucose (reducing sugar), hydrogen bonding (→ retardation), aldehydes, free radicals/peroxides
• Glucose, lactose	Water, aldehydes, formic acid, reducing sugar
• Starch	Water, reducing sugar, aldehydes
• HPMC	Water, reducing sugar, retardation, aldehydes
• PEG, Tween®	Aldehydes, peroxides
• Povidone	Peroxides, aldehydes, retardation
• Crospovidone	Peroxides, aldehydes

It is important to consider the last two excipients shown in Table 2, povidone and crospovidone, in more detail. The former is used as a binder, and the latter as a superdisintegrant. With similar chemistry, both of them contain peroxides, aldehydes and may form molecular adducts with certain APIs, affecting API release kinetics.

Reducing sugars, which react with APIs that carry a primary amine group in the Maillard reaction, recur throughout the list. To control the occurrence of this reaction, pharmacopoeias limit the reducing sugar level to 0.1% for polyols such as mannitol or sorbitol. However, the question then arises as to whether this level is sufficient to ensure acceptable API stability.

Figure 2 shows an HPLC chromatogram of two different formulations using the same API but different types of mannitol. When comparing the analysis results directly after blending the components to the results after one week of storage at 60 °C, different levels of impurity can be noted after approximately 7.5 minutes of elution.

Mannitol A complies with the compendial limit of 0.1% reducing sugars, showing a level of 1.9% of API degradation product after storage. Mannitol B contains lower reducing sugar levels, which results in lower API degradation product content of only 0.6% after storage.

Figure 2:

HPLC chromatograms comparing formulations of a model API and mannitol excipients containing different levels of reducing sugars and the resulting amount of API degradation product after storage at 60 °C for 7 days to the blend tested immediately after preparation.

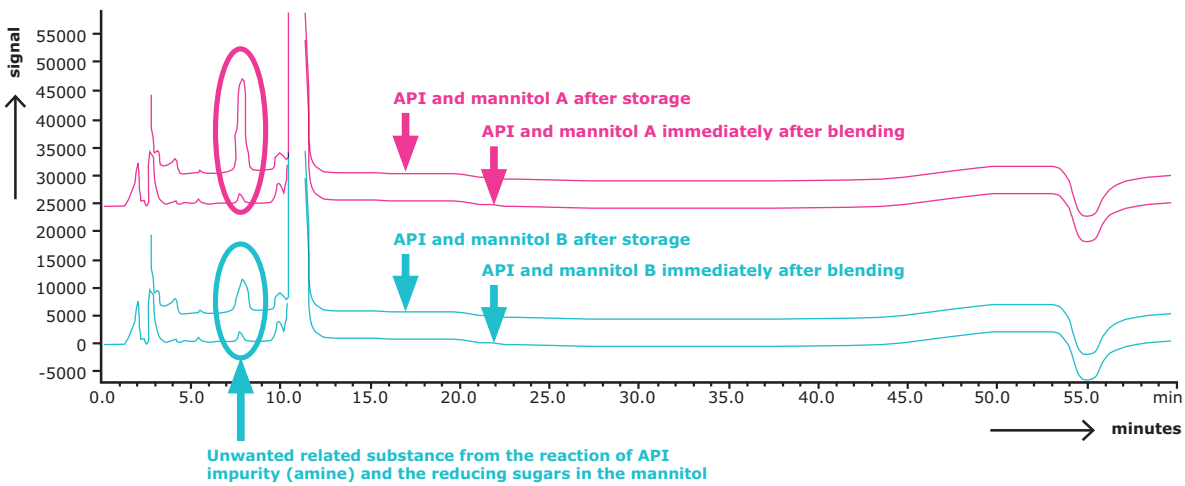


Figure 3 shows another example using the API pramipexol. Again, formulations using mannitol A and B were compared using HPLC. While mannitol A resulted in API degradation levels of 6.5%, mannitol B resulted in lower API degradation of 1.5% and a lesser variety of degradation products. Similarly to the previous example, this is a direct result of the lower amount of reducing sugar impurity in mannitol B.

Of course, it is also important to bear in mind that the limits stated within a product's certificate of analysis (CoA) are not the same as actual values, because suppliers need to ensure a margin of error to ensure the CoA guarantee is upheld. Out of specification results would result in serious supply disruptions.

Figure 3:

HPLC chromatograms comparing the amount of API degradation product in formulations of model API pramipexol and mannitol excipients containing different levels of reducing sugars.

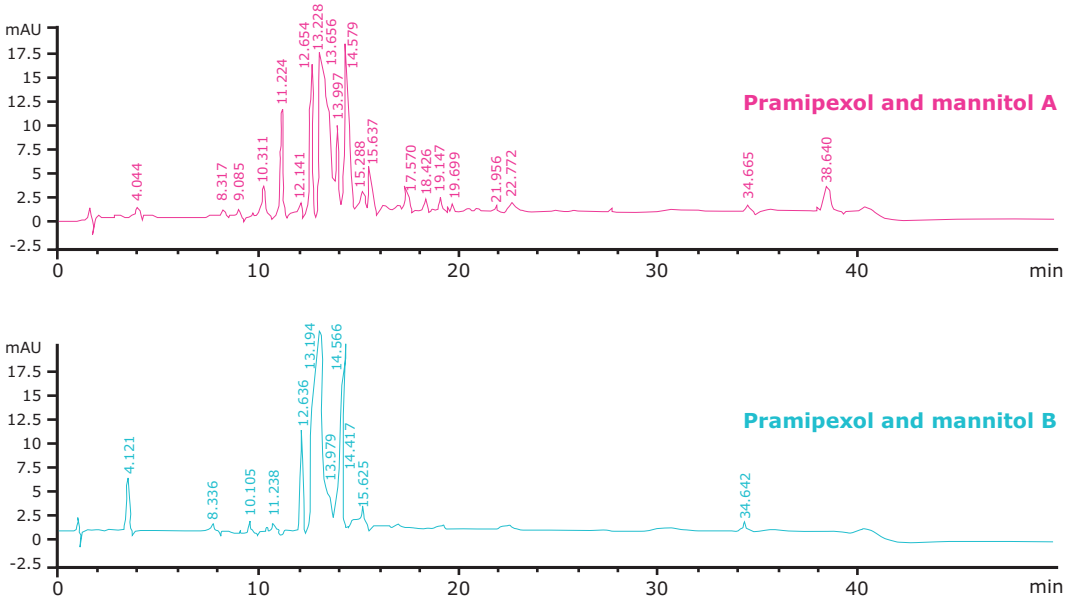


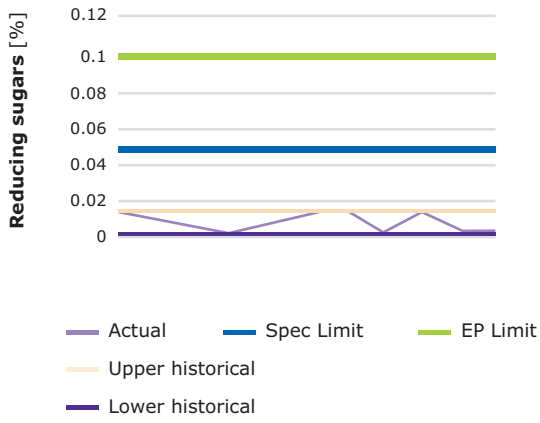
Figure 4 shows how the actual values of reducing sugar content are in relation to the limit values specified for particle-engineered mannitol Parteck® M. With a specified limit of 0.05% and actual levels of reducing sugars below 0.02%, the margin of error is sufficiently large that the CoA guarantee can easily be upheld.

Another aspect is that batch-to-batch variations in reducing sugar level within the specified limits may affect the performance of the final formulation.

It is therefore critical to choose an excipient with a sufficiently specified level and confirmed low variation from batch to batch.

Figure 4:

Batch-to-batch variation of reducing sugar levels in particle-engineered, mannitol-based Parteck® M excipient, showing very low levels of reducing sugars.

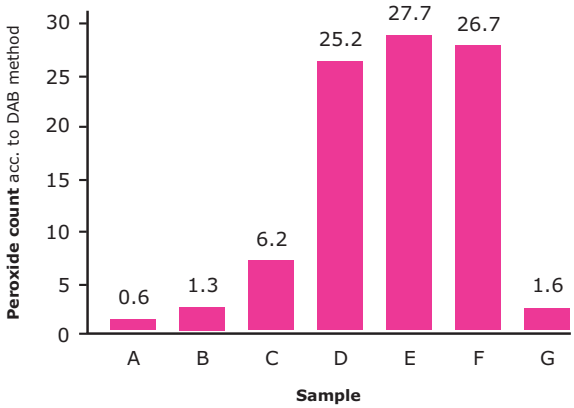


Batch	Reducing Sugars
1	0.014%
2	0.011%
3	0.008%
4	0.005%
5	0.011%
6	0.015%
7	0.016%
8	0.006%
9	0.015%
11	0.008%
12	0.008%

Oxidation: Oxidation is often mentioned as an important factor by formulators. Simple exposure to air as the source of oxidation can be easily prevented via coatings or packaging type and material and, typically, is not directly affected by the choice of excipients. However, excipients may contain peroxides as an impurity which may effect oxidation. Povidone and crospovidone as sources of peroxides are often part of excipient systems used for orally disintegrating tablets (ODTs).

Figure 5 shows that the peroxide levels of ODT excipient systems C-F, which contain povidone and crospovidone, are up to 46 times higher than those of ODT excipient systems without povidone and crospovidone (A, B and G). Therefore, when dealing with an oxidation sensitive API, the use of povidone and crospovidone is best avoided.

Figure 5:
Amount of peroxides in commercially available ready-to-use ODT excipient systems



Composition of ready-to-use ODT excipient systems:

A: Mannitol, croscarmellose sodium
B: Lactose, starch
C: Mannitol, crospovidone, povidone, polyvinyl acetate
D: Mannitol, xylitol, microcrystalline cellulose (MCC), crospovidone, calcium dihydrogen phosphate dihydrate
E: Mannitol, xylitol, MCC, crospovidone, Mg Al silicate
F: Mannitol, fructose, MCC, solicon dioxide, crospovidone
G: Mannitol, starch

Compression: There are three ways in which the compression force used in solid dose formation can affect API stability. Firstly and perhaps surprisingly, the pressure exerted in the tableting process can create observed localized temperatures of above 160°C within a tablet. Essentially, the action of pressure and speed during the compression process on the friction created at excipient contact points is high enough to create melting in, for example, mannitol.

So, if a temperature-sensitive API is used that was stable in the powder mixture but degradation products can be observed after compression, this may be due to local temperature increases during the tableting process.

Secondly, certain polymorphic forms of an API which are, for example, intended to achieve better bioavailability in the body due to an improved apparent solubility of the API, are temperature-sensitive. The temperature increase during the tableting process could also result in a partial change of the API's polymorphic form and, therefore, a different final formulation performance than initially intended.

Finally, the shear force that is applied in the tableting process may break up large molecules or coated API particles. Coated API particles may have been formulated with the intention of masking a bitter API's taste, modifying the release kinetics or improving API stability. The application of shear force results in particle break-up, compromises the coating layer and impairs the intended effect of the particle coating.

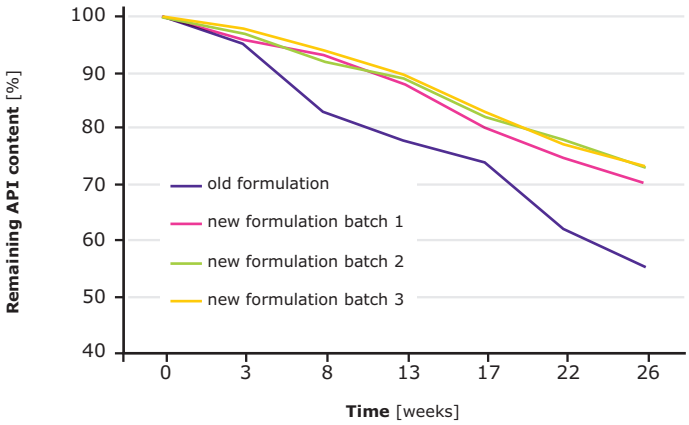
Figure 6 shows the impact of this effect on oxidation-sensitive vitamin D as model API in a design of experiment (DOE) study using mannitol for direct compression. Vitamin D tablets are created with API particles bearing a protective, antioxidant coating to improve its stability. The results show that reducing compression force increases API stability:

By changing to a mannitol with improved compressibility, the compression pressure was reduced from 18 kN to 2 kN and API stability was increased.

In other words, with lower compression force, the temperature rise caused by the tableting process is minimized and the break-up of particles is prevented.

Figure 6:

Enhanced stability of vitamin D_3 by reduced compression force



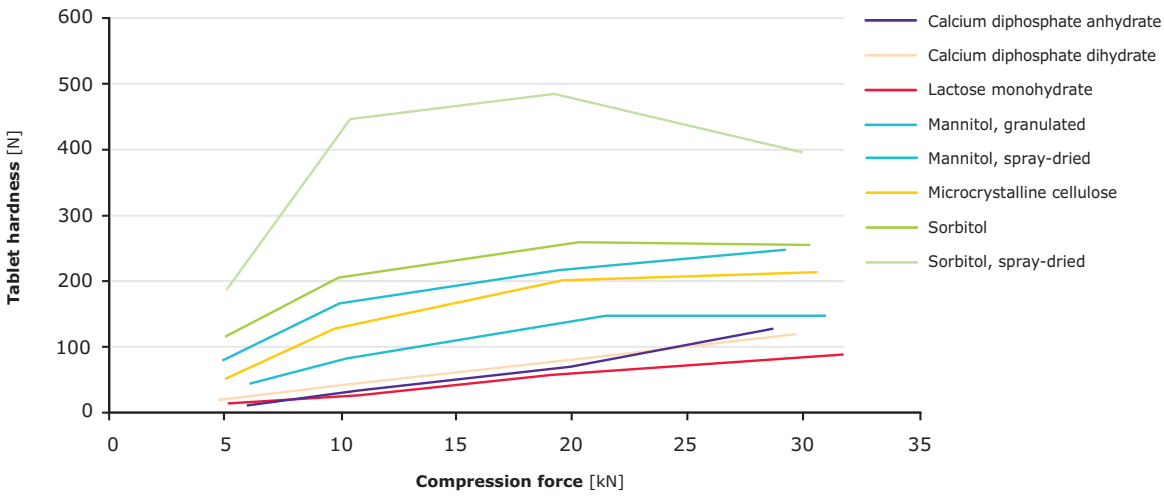
	Old formulation	New formulation
Filler/binder	Mannitol C	Mannitol B
Compression force	18 kN	2 kN
Tablet hardness	40 N	55 N

Figure 7 shows an overview of compressibilities of different directly compressible fillers. The upper two curves both represent sorbitol, with the higher curve representing the spray-dried form, and the lower curve representing the crystallized form. The difference in performance between these two forms is explained by the larger surface areas of sorbitol in its spray-dried form. The larger surface area created by the spray-drying process leads to a higher compressibility or higher hardness in the tablet. In other words, the particles are actually engineered towards better compressibility.

It is also important to note here that sorbitol is much more compressible than, for example, MCC, lactose, phosphates, and other alternatives. This is because, with a melting temperature of 95 °C sorbitol melts to a certain degree during the tableting process, as described above. When the increased temperature dissipates, the recrystallisation of slightly molten particles, creates a much stronger binding when compared with the mechanical binding of particles within MCC. This binding process is a reason for sorbitol's good compressibility.

Figure 7:

Comparison of tablet hardnesses manufactured at different compression forces using a variety of commonly applied directly compressible fillers.



Granulation: The granulation process can also affect API stability. This is why direct compression is usually preferred to wet granulation not only because of cost concerns, but also in terms of sensitive APIs, as no water and heat is applied in direct compression processes.

These advantages often outweigh the fact that direct compression can present challenges in relation to content uniformity, compressibility and flow in some instances.

Content uniformity is important because in a statistical mixture where API and excipient particle sizes differ significantly, segregation can occur. This is critical in direct compression or any tableting process, because it can affect the content uniformity of the final dosage forms.

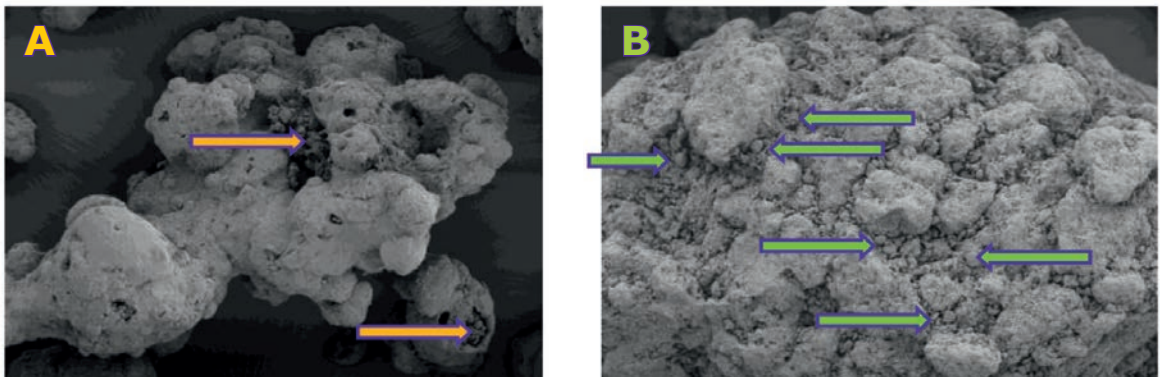
Figure 8 illustrates an alternative – an ordered mixture in which API particles, typically micronized, are adsorbed on the excipient particles' surface. It shows two different spray-dried mannitols, both mixed with model API ascorbic acid.

The excipient particle in Figure 8 A has a smaller, smoother surface area with limited regions where the API is located in an adsorbed form. Figure 8 B shows a mannitol with a larger, more structured surface area which can clearly be seen to adsorb the API, especially in micronized form, more easily.

Figure 8:

Scanning electron microscopy (SEM) images comparing the API adsorption on the surface area of two different types of spray-dried mannitol.

In both cases, the mannitol was mixed with 1% of ascorbic acid (particle size < 10 µm)



The potential suitability of direct compression for formulations must be considered on a case-by-case basis.

Some examples are illustrated through the following case studies.

API Stability: Case Study 1

In a formulation with a very low dose of API of 0.5 mg in a 120 mg tablet (0.4% w/w), the API must be distributed very effectively to ensure good content uniformity of the final solid dosage forms. Direct compression would not usually be selected in this instance, due to concerns about keeping content uniformity within the target parameters.

However, as the API in this case is moisture sensitive, the traditional wet granulation process using water and heat is unsuitable. Putting the mixture on a rotary press with Parteck® M mannitol at two different speeds yields very consistent results with a content uniformity of ± 1.8%. This is a direct result of the large surface area effect which was explained for sorbitol in more detail on previous pages and applies also for the present case study.

Figure 9 shows clearly that the particle-engineered excipient Parteck® M (Figure 9 B) has a larger surface area than conventional direct compressible mannitol (Figure 9 A). As a consequence, it is better compressible and especially suitable for direct compression processes when low amounts of API are used.

API Stability: Case Study 2

Atorvastatin is well-known as an API that is sensitive to heat, moisture, oxidation, light and acids, and which is unstable in its amorphous form.

To address the moisture and heat sensitivity, direct compression should be used instead of wet granulation.

Low compression force is required to negate the heat sensitivity and amorphous instability. To prevent oxidation, the use of peroxides contained in excipients like povidone or crospovidone should be avoided. Acid sensitivity can be addressed via the addition of an alkalizer such as meglumine or calcium carbonate. Light sensitivity is not a significant issue when choosing appropriate excipients because most of the API material is hidden within the tablet or can be addressed by coating the tablet or using an appropriate packaging.

One possible approach for an atorvastatin formulation could involve the use of a mannitol with a low moisture content, together with an alkalizer in a low-force direct compression process.

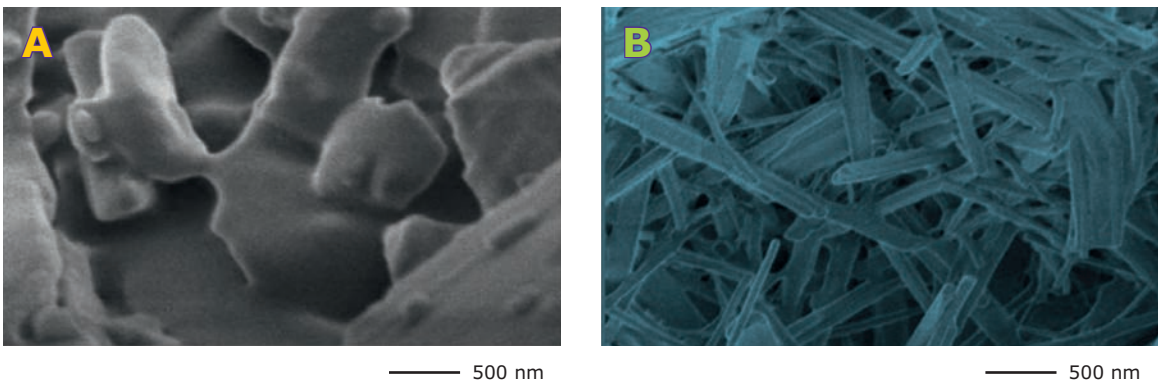


Figure 9:

SEM images comparing the particle structures of conventional directly compressible mannitol (A) and particle-engineered Parteck® M mannitol (B)

Conclusion

This white paper demonstrates that excipients are not really inert ingredients within solid dosage formulations and can either improve API stability by preventing instabilities, or induce instabilities thereby negatively impacting stability. It also shows that ensuring formulations are as simple as possible is generally a sound strategy when seeking to avoid or address potential API instability: generally speaking, a consequence of increasing formulation complexity with several different APIs and excipients is that the probability of component interactions also increases and, therefore, it is good practice to try to keep a formulation as simple as possible. Also, when choosing a formulation technology, possible API instabilities resulting e.g. from exposure to heat and/or moisture must be considered.

In conclusion, direct compression, used in conjunction with excipients that exhibit low moisture content and a low impurity profile, is often an optimal approach to solid dose drug production, especially when formulating APIs prone to instabilities.

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