Similarly, excipients have a critical role to play in both de-stabilising (i.e., known incompatibilities\(^3\)) and stabilising dosage forms\(^1,4\). In the latter case, purer grades of certain poly(oxyethylene) excipients, such as polyethylene glycol and polyethylene oxide can be used to stabilise drug substances known to be susceptible to oxidative instability, as can antioxidants, such as butylated hydroxy anisole and propyl gallate, among others. In addition, low moisture grades of common diluents, e.g., Avicel\(^\circledR\) PH 103 and Avicel\(^\circledR\) PH 112, can help to address hydrolytic instability. The functional role of an excipient is often dictated by its concentration in the formulation. For example, microcrystalline cellulose – such as Avicel\(^\circledR\) PH, Emocel\(^\circledR\), Fibrocel\(^\circledR\), Pharmacel\(^\circledR\), Tabulose\(^\circledR\) and Vivapur\(^\circledR\) – can be used as a binder/diluent, lubricant or disintegrant in a solid oral dosage form\(^4\).
Historically, excipients were viewed as being inert or inactive components of the formulation. This view is, however, rather inaccurate given what is known today about their different biological effects. Pharmaceutical additives can, for example, influence efflux- or absorptive transporters and others may affect drug metabolism\(^5\). Thus, the in vivo properties of a drug product, i.e., its bioavailability, can be intrinsically linked with the selection, grade, quantity and quality of the excipients present. For instance, disintegrants and wetting agents may play key roles in the solubilisation process of poorly soluble drugs. Similarly, excipients can significantly impact on both drug substance solubility and permeability\(^4\), which are key variables ultimately affecting drug absorption\(^7\). Finally, excipients can affect the aesthetic properties of the product, as seen with aqueous film coats, and organoleptic properties, including sweeteners and flavourings\(^4\).

**Excipient quality**

One of the conundrums facing the pharmaceutical industry is that excipients are typically not commodity products, nor are pharmaceutical companies generally major customers. Excipients are usually high volume, low-value products used by a broad range of industries besides pharmaceuticals, including cosmetics, hygiene, food and drink. As a consequence, the pharmaceutical industry has limited influence over the overall quality of excipients. Indeed, it is not uncommon for an excipient manufacturer to change its manufacturing process (and thereby its overall quality profile) to make production more cost effective, without consulting the customer\(^4\). As a consequence these changes may, in turn, adversely affect the quality of the drug product, thereby necessitating changing the excipient supplier, to ensure it meets its pre-determined quality criteria. Unfortunately, this cannot be undertaken without prior approval from the appropriate regulatory authorities or generating adequate data in support of any change(s) – it takes time and money to implement these modifications.

It is the pharmaceutical company’s responsibility under good manufacturing practice (GMP) to ensure that the final product is of the required quality, and this includes adequate quality of the input materials, including the excipients. To facilitate this, the United States Pharmacopoeia has issued GMP guidance for excipient manufacturers\(^9\). In parallel, the European Union has issued GMP guidance for excipients\(^9\), which, in common with many recent regulatory guidance documents, is risk-based in nature. The EU guidance is sub-divided into four chapters comprising scope; the determination of the overall level of GMP based on the type and use of the excipient; a determination of the risk profile of the designated excipient manufacturer; and confirmation of the application of the appropriate level of GMP. In addition, IPEC/PQG (International Pharmaceutical Excipients Council/Product Quality Group) has issued an implementation guidance\(^10\).

**Pharmacopoeial monographs**

The pharmacopoeias have been the bastion of quality standards for excipients for many decades and these standards are enshrined in the individual excipient monographs. The United States Pharmacopoeia states; “Every compendia article in commerce shall be so constituted that when examined in accordance with these assay and test procedures, it meets all of the requirements in the monograph defining it.” Similar requirements are articulated in the Japanese Pharmacopoeia and European Pharmacopoeia. Thus, any excipient monograph provides a listing of all relevant quality attributes, appropriate tests and designated limits, which defines its overall quality. Essentially, the monograph is a quality specification.

Each monograph includes a series of universal tests, such as appearance, identity, assay and impurities\(^11\), together with specific tests, as appropriate. The latter tests are typically only included when they could have an “impact on the quality of the excipient for release and/or compendial testing and/or when needed to allow differentiation of the available commercial physical grades of the excipient”. Furthermore, additional tests can be included to fully evaluate and control the quality of the designated excipient. Accordingly, functionality tests have been added to certain excipient

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monographs over recent years on a case-by-case basis; for example, magnesium stearate has a specific surface area test. These functionality tests relate to any prerequisite performance criteria, including flow, compaction, compression, etc., that facilitate processability and/or manufacturability during the manufacturing process and thereby improve the performance and overall quality of the resultant product.

However, these tests cannot be overly prescriptive as any given excipient in any given formulation (even at the same quantitative level) may produce widely different outcomes. Thus, 0.5%w/w of magnesium stearate may adequately lubricate a compression blend with lactose as the principal diluent; in contrast, this same level would be inappropriate for a blend containing an abrasive diluent such as calcium phosphate. As a consequence, any significant and reliable assessment of a functionality test is only possible within the framework of the specified formulation. Therefore, whereas functionality tests could be perceived as highly relevant material attributes for any specific excipient, their use is somewhat limited by the nature of their usage in the designated formulation (quantity, quality, grade, supplier, etc.). For several years there has been a trend towards better understanding of excipient effects on dosage form performance for a given formulation. While a mechanistic understanding is not always easy to achieve and may require substantial resource investment, formulators should at least conduct experiments to obtain a correlational basis that links experimental properties with processability and final drug product attributes.

The role of excipient quality in a QbD world

The ICH Quality by Design (QbD) guidance documents, particularly ICH Q8, state that the sponsor should identify any critical material attributes for the drug substance and key excipients. The minimum expectation is that ‘those aspects of drug substance, excipients, container closure systems and manufacturing processes that are critical to product quality should be determined and control strategies justified’™. ‘Critical’ is defined as the time when the intrinsic variability may affect drug product quality. The assessment of the likely variations in performance of key excipient attributes; for example, specific surface area, have therefore become an essential part of the QbD paradigm.

It is well established that the use of different suppliers of the same excipient grade can result in different product performance. For example, the lubrication or dissolution performance of magnesium stearate from different suppliers may not necessarily be the same. Similarly, it has been reported that changing from animal- to vegetable-sourced magnesium stearate can affect the blends’ lubrication efficiency, which results in lower ejection forces for the tablet. Additionally, there are reported effects on increased granule size of the resultant formulation when changing from animal to vegetable grades of magnesium stearate.

It is also interesting to compare different polymer grades. When the compression characteristics of Avicel® 101 (FMC Biopolymer) and Vivapur® 101 (JRS Pharma) were evaluated using multi-variate analysis, the data demonstrated significant supplier variability in terms of compression characteristics. Similarly relevant quality differences were further evidenced with using Avicel® RC-591 or Vivapur® MCG591 in alternative suspension vehicles.

Several excipient suppliers are offering specialised QbD packages, i.e., different batches of a specified excipient that meet pharmacopoeial specifications, but with physicochemical properties that are at the extremes of the allowable specification range. FMC Biopolymer is one such company, which offers stretch samples on certain designated excipients, together with process data and technical services to accommodate clients that wish to perform ‘Design of Experiments’ to generate a design space.

Dual sourcing of key excipients

It is clear that introducing a second excipient vendor into the manufacturing supply chain presents significant challenges. However, the consequences of not having supply chain flexibility for these key excipients, such as release-controlling excipients in controlled-release products or structure-forming excipients in semi-solid products (creams, lotions, ointments, etc.), can be severe. This was exemplified...
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by an explosion at Shin-Etsu’s methylcellulose plant in Japan in 2007, which had global impacts on hydroxypropyl methylcellulose (HPMC) supply, particularly for controlled-release products*. Many companies were faced with supply chain issues for this key excipient and were forced to either stockpile existing materials and/or assess equivalent grades from other suppliers, such as Dow. This had a subsequent knock-on effect on supplies of Dow HPMC. Additionally, some customers encountered difficulties with the inter-changeability of these ‘equivalent’ grades, which adversely affected the dissolution profiles of their registered products, and thus the changes affected product quality.

Conclusions
Excipients represent an essential part of any formulation and they generally exhibit a range of different functionalities. The quality of excipients is specified in the different Pharmacopoeial Monographs and, through analytical testing, assures that the raw materials comply with general quality standards. However, this does not directly mean that for a specific formulation adequate processability is obtained and final product specifications are met. Using a thorough QbD development approach is a way to properly identify which material factors are important for critical quality attributes so that additional analytics and functionality testing of excipients has become quite common in modern pharmaceuticals.

Since a dual sourcing strategy is important for supply chain management, alternative excipient suppliers must be evaluated as part of formulation development. Pharmaceutical companies will increasingly learn about the specific performance differences of different excipient grades and suppliers by making use of modern analytical tools. The possibility to replace an excipient will become even more important in the future because excipient suppliers are constantly streamlining their portfolio to reject less profitable excipient grades. For older products, it is essential that the manufacturing and science groups of companies are in close contact with relevant excipient suppliers to initiate retrospective QbD activities early on, so that any necessary excipient replacement process will run smoothly and without issues of processability or quality defects.

References
8. USP. 2016. Good manufacturing practices for bulk pharmaceutical excipients. <1078>
11. ICH Q6A
14. ICH Q8 (R2)
Accessed on 27 July 2016

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