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Factors Affecting Defining the Quality and Functionality of Excipients Used in the Manufacture of Dry Powder Inhaler Products

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The successful manufacture of a regulatory approved dry powder inhaler (DPI) product is only achievable by applying robust control systems to all aspects of analytical, engineering, and material based processes. Whilst many aspects of DPI drug product manufacturing can be adequately controlled, it is often the control of materials, that is, drug substance and excipients, which can lead to variation in the quality of the final drug product. This article gives an overview of DPI excipients and highlights the challenges of defining and, importantly, understanding the relationships between quality and functionality for excipient components in DPI formulations.

Keywords excipient; dry powder inhaler; functionality; quality; lactose

INTRODUCTION

The goal of pharmaceutical manufacturing is the reproducible manufacture of a safe drug product and is achieved by the controlled "assembly" and "processing" of "components." For example, dry powder inhaler (DPI) products are manufactured by blending excipients and drug substances and filling into dosing units, for example, capsules, blisters, or devices, and the industry has considerable experience of formulating and manufacturing such products. However, and importantly, to ensure that the final drug product conforms to an acceptable specification, there must be robust quality assurance procedures in place for the components and processes.

Most marketed solid dosage forms contain excipients, and it can be argued that without these materials, the present-day pharmaceutical industry would not exist. Excipients are a group of materials which exhibit unique properties and are used to aid all aspects of the pharmaceutical development process, from being simple diluents and lubricants, to controlled release agents, to carriers and propellants in inhalation products (Rowe, Sheskey, & Owen, 2005). It has been estimated that there are more than 1,200 such materials in use, of which less than half have official compendial monographs. Importantly, they are accepted for use based on pharmacopoeial and regulatory requirements rather than meeting specific purity specifications. This is an important point, since while the pharmaceutical industry strives to prepare pure drug substances, many excipients are, what analytical scientists would describe as, "mixtures," "composites," "blends," "copolymers," etc. Consequently, from a scientific standpoint, excipients offer the pharmaceutical scientist challenges in terms of material and bulk properties characterization and inter and intra brand, supplier, and supply chain consistency, with obvious implications for functionality and, importantly, quality.

DRY POWDER INHALER EXCIPIENTS

Compared to conventional solid dosage forms, the number of excipients in marketed DPI products, and indeed those in development, is somewhat limited (Table 1).

The vast majority of marketed DPI products contain "carrier" based formulations which consist of a drug and a single excipient, lactose monohydrate (Telko & Hickey, 2005). These complex, so-called interactive or adhesive mixtures, consist of micronized drug particulates that are blended with larger inert excipient carrier particles. In comparison to other solid dosage forms, such carrier-based DPI formulations are relatively low-dose products with drug contents as low as, for example, approximately 0.05% for Foradil® Aerolizer®, with obvious formulation challenges. The complex interfacial interactions that occur between the drug and the excipient particles in DPI formulations impact the overall performance and efficacy of

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TABLE 1
Examples of Excipients Used in Dry Powder Inhalers (DPIs)

No. of Excipients	Excipient(s)	Formulation System	Brand/Example	Company
0	None	Agglomerate	Bricanyl® Turbohaler®	AstraZeneca
1	Lactose, monohydrate	Carrier/agglomerate	Seretide® Accuhaler® Foradil® Aerolizer®	GSK Novartis
	Lactose, anhydrous	Agglomerate	Asmanex® Twisthaler®	Schering Corp.
	Glucose, anhydrous	Carrier/agglomerate	Atrovent® Aerocaps®	Boehringer Ingelheim
	Myo-inositol	Matrix	Puffhaler®[a]	Activ-Dry
2	Lactose, monohydrate, and magnesium stearate	Carrier/agglomerate	Pulvinal® BDP Powderhale®[a]	Chiesi Vectura
Multiple	Mannitol, sodium citrate dihydrate, glycine, sodium hydroxide	Matrix	Exubera®[b]	Pfizer

[a]Not marketed (brand of technology platform).
[b]Recently withdrawn from the market.

the drug product. However, the performance of such systems can be improved and a common approach is via the inclusion of ternary excipient agents, such as fine lactose particles of similar geometric size as the drug particles, and the so-called force control agents (e.g., magnesium stearate). Alternatively, DPI systems employing a matrix of excipients have recently been developed to enable delivery of biological agents and conventional small chemical molecules to the lung. Although only a limited number of particle processes are employed to produce excipients and drugs for DPIs, many particle engineering approaches, such as supercritical fluid technologies, have been investigated (Chow, Tong, Chattopadhyay, & Shekunov, 2007). In all such formulation strategies, it is clear that, compared to conventional solid dosage forms, the quality and functionality of the excipient component(s) in all DPI drug products is critical and should be controlled and understood in order to manufacture a robust and efficacious drug product.

Since, in most cases, only one excipient is employed, typically lactose monohydrate, it can be argued that this would reduce any potential product functional variations due to, for example, component variations as observed in multiexcipient formulations, such as in tablet blends. Additionally, the use of a limited number of excipients should allow the focusing of resources to understand and control these materials and to develop close supplier–user relationships. However, the complex nature of DPI products limits any such potential advantages, and it can be argued that, based on the fact that only one excipient is used, the functional demands on the excipient are even greater, since the formulation performance is based on surface phenomena, posing unique quality challenges for suppliers and users.

Excipients, whether for traditional solid dosage forms or DPIs, are initially selected based on their perceived functionality. In the case of DPIs, the "functionality" of the excipient is somewhat different to conventional solid dosage forms. Indeed, DPI excipients are used to provide functionality to a formulation, and such functionality is often defined as carrier, diluent, etc. Such DPI formulation and excipient functionality is measured by performance testing, for example, evaluating the in-process fill mass of capsules and the relative amount of respirable drug liberated from the formulation via an inhalation device. However, in recent years their functional range, or rather description, has extended to "stabilizers," as in matrix systems and as processing aids, for example, to allow the possibility of low-mass powder filling of capsules and blisters (Kieckbusch et al., 2007). Consequently, it becomes more important to consider the implications of what is defined as "quality" and "functionality" since such attributes will be different than, for example, lactose for conventional pharmaceutical applications. This may have particular relevance when considering manufacturing and technological advances such as process analytical technology.

QUALITY AND THE REGULATORY ENVIRONMENT

In many industries, including the pharmaceutical industry, "components," such as excipients, are invariably supplied by "third parties." Although pharmaceutical companies exercise a very high degree of control over their drug substances and manufacturing processes, the same cannot be said for components manufactured and supplied by any third parties, such as excipients.

Pharmaceutical drug product components, that is, drug substance and excipients, are qualified for use by using specification criteria. In addition, excipients are deemed suitable for use if, along with any product-related specifications, they comply with regulatory requirements, typically, the regional pharmacopoeia.

However, many excipient monographs contain no specific purity requirements with obvious supply chain implications. The lack of compendial requirements for purity and functionality, and the specific functional requirements for DPI carrier excipients, has resulted in DPI excipients being primarily DPI product specific, that is, "customer grades," with obvious qualification challenges. Consequently, product quality is, in part, a result of the robustness of the product and component "specification chain." Therefore, when considering the development of a DPI excipient "specification" or "quality" criterion, it is important to understand the possible effect of any ranges in the specifications for product quality, from laboratory scale to full production. This is especially true for the pharmaceutical industry since it is subject to specific compendial/guidance-driven requirements, which even though in many cases, may appear to be rather broad and can often utilize "unique" testing methods, must be adhered to.

Like other manufacturing sectors, the pharmaceutical industry, including the excipient segment, is challenged by changing regulatory environments. For example, excipient monographs are being reassessed and in some cases harmonized. The globalization of the pharmaceutical industry, and advances in technology, is also allowing materials, including excipients, to come under greater analytical scrutiny. Additionally, general guidance frameworks for pharmaceutical development, such as those based on the International Conference on Harmonization, are available. In terms of DPIs, and DPI excipients, more specific guidance for inhalation products recognize the need to control DPI excipients, such as lactose monohydrate, and that monograph tests are not adequate for controlling the functional and material characteristics of such excipients when used for DPI applications (CDER, 1998; EMEA, 2006). Such specific guidance suggests that pharmaceutical development studies should include the characterization of excipients, where relevant to the functionality of the drug product. Indeed, such recent developments together with any changes to excipient monographs are likely to indirectly impact pharmaceutical development and may have implications for drug product performance. Therefore, it is vital that pharmaceutical companies have a true understanding of the robustness of their excipient supply chain from the supplier to the final drug product. The following sections discuss the possible impact of such developments on DPI product development, and excipient quality and functionality definitions.

Excipient Monographs

Compendial excipient monographs form the cornerstone of excipient qualification. The development of excipient monographs since the introduction of "official" compendia in the 19th century is an interesting subject. Excipients, in view of their development history, have quite unique qualification controls, and their regulatory acceptance is generally based on the products fulfilling the requirements of the relevant current monograph in the "main" regional pharmacopoeia, namely the *European Pharmacopoeia* (EP), the *United States Pharmacopoeia and The National Formulary* (USPNF), and the *Japanese Pharmacopoeia* (JP). Since many excipient monographs do not contain what analytical scientists would consider as purity specifications, the acceptance qualification system is based on compendial acceptance rather than purity or functional performance. For example, there is no specific assay test for lactose in the lactose monographs. Many of the tests in such monographs have remained essentially unchanged for decades. In many ways, the excipients lactose, both monohydrate and anhydrous, and magnesium stearate, which are used in DPI products, are good examples of the somewhat anachronistic position of excipients in the pharmaceutical industry. For example, the USPNF compendial descriptions of these materials are presented in Table 2. It can be seen that the descriptions can be interpreted as "broad" and yet they are components of official monographs which essentially means that any purity criteria is based on testing rather than descriptions. In many cases, the purity of an excipient used in the pharmaceutical industry is often obtained as an indirect result of individual

TABLE 2
Example of the Compendial Descriptions of Dry Powder Inhaler (DPI) Excipients (*United States Pharmacopoeia, The National Formulary*, 2008)

Excipient	Description (USP31NF26)
Lactose monohydrate	"is a natural disaccharide, obtained from milk, which consists of one glucose and one galactose moiety. [Note—Lactose Monohydrate may be modified as to its physical characteristics. It may contain varying proportions of amorphous lactose.]"[a]
Lactose anhydrous	"Anhydrous lactose is O-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose (β-lactose) or a mixture of O-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose and O-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose (α-lactose)."
Magnesium stearate	"Magnesium stearate is a compound of magnesium with a mixture of solid organic acids and consists chiefly of variable proportions of magnesium stearate and magnesium palmitate. The fatty acids are derived from edible sources. It contains not less than 4.0% and not more than 5.0% of Mg, calculated on the dried basis."

[a]This descriptive allowance for amorphous components was removed from the *European Pharmacopoeia*, 4.6.

tests within the monograph, and it should be mentioned that many excipients' functionality is, in part, due to the fact they are "impure."

It is important to realize that even though monographs for excipients may not guarantee a consistently functional material, they do form the basic pharmaceutical quality requirement. This is especially true for DPI excipients, such as lactose monohydrate, where it is difficult to relate product performance to compendial testing due to the complexity of the pharmaceutical performance of DPI formulations.

In view of the many, often subtle, differences in requirements in regional monographs and the increasing globalization of the pharmaceutical industry, efforts in recent years have been undertaken to harmonize excipient monographs through the activities of various pharmacopoeias and organizations, such as the International Pharmaceutical Excipient Council and the Pharmacopoeial Discussion Group. This has achieved some success with the harmonization of some excipient monographs, including lactose. However, even though many components of monographs can be harmonized, there can be some points where the regions do not appear harmonized. For example, even though the USPNF description of anhydrous lactose was expanded to become more aligned with the EP, there is still no requirement in the EP for loss on drying for lactose monohydrate, which is a requirement for the USPNF (*European Pharmacopoeia*, 2008; *United States Pharmacopoeia*, *The National Formulary*, 2008). Such vagaries allow lactose products such as spray-dried lactose and agglomerated lactose, which are essentially composite or co-processed materials to be used since they conform to lactose monohydrate monographs, highlighting the relationships between monographs and purity. It is such nuances in compendial tests and, importantly, changes to such tests, which may have implications for the quality for drug products and, in particular, DPIs, where the quality requirements for the excipients may be greater. This is exemplified by the fact that the possibility of producing specific inhalation lactose monographs has been discussed.

Compendial Functionality Testing

The issue of how monographs relate to functionality and the possible impact on pharmaceutical development process is being considered. The EP has recently attempted to address the issue of the relationship between monographs and functionality by including the so-called functionality-related characteristics which "can however contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use" as "non-mandatory" sections of some excipient monographs, as shown for lactose in Table 3, together with a general chapter describing their relevance to monographs (*European Pharmacopoeia*, 2008).

However, the question has to be asked whether such "functionality-related characteristics" are indeed "key performance indicators" for pharmaceutical development, and it should be recognized that any monograph-related functionality testing of excipients, especially widely used excipients such as lactose monohydrate, may not be relevant for every pharmaceutical application, including for DPIs. For example, having particle-size data of lactose, albeit as a "non-mandatory" part of a lactose monograph, does not necessarily afford any functionality information since the functionality will depend on the application (e.g., tablet filler or DPI carrier) even though it is generally accepted that larger particle-sized excipients exhibit relatively improved flow. Indeed, the question of "non-mandatory" components may be academic as users will simply begin to request the inclusion of all the components of a monograph, "non-mandatory" or otherwise. Suppliers of DPI excipients already provide additional testing of their products for their customers to ensure product acceptability, reflecting the functional demands on such excipients. Interestingly, the USP has proposed to include a general excipient performance chapter (Amidon et al., 2007). The proposed USP excipients chapter does not include, at present, a specific inhalation excipient section. It is not as yet clear how these two approaches will affect the gains of many years of harmonization discussions and achievements. This situation is again highlighted by the fact that there is a test and specification for loss on drying for anhydrous lactose in the USPNF; however, in the EP, the test is deemed a "functionality-related characteristic" and "non-mandatory" test, with no specification. This compendial situation may be further clouded since the possibility of producing specific pharmacopoeial inhalation lactose monographs, with the tightening of some specifications, is under consideration. Although any such developments may improve quality, the impact of any compendia-driven specification changes should be fully evaluated to ensure

TABLE 3
Functionality-Related Characteristics of Lactoses as Defined by the *European Pharmacopoeia* (2008)

Excipient	Functionality-Related Characteristics	Definition
Lactose monohydrate	Particle-size distribution; bulk and tapped density; and "other methods can be used"	"…a controllable physical or chemical characteristic of an excipient that is shown to impact on its functionality"
Lactose anhydrous	Particle-size distribution; bulk and tapped density; alpha and beta lactose content; loss on drying; and "other methods can be used"	

continuing supplier and user compliance and, importantly, their relevance to patient safety.

International Conference on Harmonization

Even though the previously mentioned recent US and European specific inhalation guidance emphasize the importance of controlling excipients (and drug substances) (CDER, 1998; EMEA, 2006), the question of defining and understanding quality and functionality and how they relate to general pharmaceutical processes and product robustness is finally being discussed by, for example, the pharmacopoeias and, importantly, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). For example, developments such as ICH Q8 (ICH, 2006) have led to the increasing use of concepts such as "quality by design" (QbD) and "design space" for pharmaceutical processes. One aspect, amongst others, of these developments is that "those aspects of drug substances, excipients and manufacturing processes that are critical and that present a significant risk to product quality, and therefore should be monitored or otherwise controlled, should be identified and discussed." This rather broad guidance may be again particularly challenging for DPI excipients because of their unique functional role, their natural source, and their route of delivery to the body. Importantly, the ICH Q8 guidance, together with the more specific US and European inhalation guidance, demonstrates that regulatory agencies are focusing on improving the quality of pharmaceutical drug products and the robustness of pharmaceutical processes.

THE IMPACT OF CHARACTERIZATION STUDIES

There have been significant advances in analytical technologies in recent years allowing in-depth analysis of pharmaceutical materials, including excipients, and there are an increasing number of articles in the literature reporting excipient studies. Although such studies may be academically interesting, they do illustrate the "analytical" differences between some compendial tests and what is "measured" through modern instrumentation, and, importantly, allow a discussion concerning the relevance of any such observations for functionality, quality, and safety. Typical questions surrounding such analysis concern the level, and relevance, of "impurities" or "minor" components and the identification and understanding of any inter batch or supplier variations. This is particularly of interest for DPI excipients in view of their pulmonary route of delivery and the importance of surface interactions.

Impurities or Minor Components

As previously stated, many commercially available pharmaceutical excipients consist of two or more components. Such materials can be said to contain "minor components," "concomitant components," "residuals," "impurities," "additives," etc, posing interesting "definition" and characterization challenges. However, and particularly for DPI excipients, it should be emphasized that even if a material is used in a highly pure form, the surface will invariably consist of two components, the material, in any appropriate orientation, and water. In terms of DPI carrier excipients, namely lactose monohydrate, it is the interactions of the drug and the surface which can affect the performance and stability of a formulation, and such interactions can be affected by water activity (Price, Young, Edge, & Staniforth, 2002; Rowley & Mackin, 2003). Since lactose monohydrate is typically greater than 98% of a carrier-based formulation, the water activity at which materials are produced, stored, and processed should always be considered when evaluating the performance of a DPI formulation.

In recent years, excipients have come under the increasing scrutiny of analytical chemists. This is especially true for DPI excipients, such as lactose monohydrate. Analytical instrumentation can be used to characterize such materials in terms of their bulk and surface characteristics. The level of scale of scrutiny now allows the routine determination of material descriptors such as surface energy and the investigation of the adhesive and cohesive interactions between DPI particulate components using atomic force microscopy (Begat, Morton, Staniforth, & Price, 2004). However, some investigations have focused on evaluating various aspects of compendial testing. For example, one such area of interest is the level of proteins and peptides in inhalation grade lactose. In recent years, there have been several reports of the contamination of milk proteins in lactose-containing DPIs, which can cause anaphylaxis in cases of severe allergy to cow's milk (Morisset, Moneret-Vautrin, Commun, Schuller, & Kanny, 2006; Nowak-Wegrzyn, Shapiro, Beyer, Ludmila Bardina, & Sampson, 2004). The presence of proteins and peptides may also have implications for product stability if, for example, the pharmaceutically active material is capable of interacting with such molecules. Lactose is obviously a natural product which is derived from milk. The early development of lactose monographs recognized that proteins and peptides may be present in lactose. This is especially important for pharmaceutical applications and tests based on solution UV absorbance were developed. One of these, the absorbance at 400 nm is related to any visible "discoloration" of lactose which may, in part, be due to the reaction of an amine (proteins and peptides) with a reducing sugar, the so-called Maillard reaction. However, in terms of other test methods, it is not clear what the value of the absorbance at 400 nm really means, for example, if the protein level in lactose is determined using the Kjeldahl method, then there is no apparent relationship between these data and the absorbance at 400 nm data, as shown in Figure 1.

If absolute determination of proteins is required, then sensitive surface analytical techniques are available. For example, using X-ray photoelectron spectroscopy (XPS), the content of nitrogen, and hence proteins/peptides, can be determined. For example, a typical XPS analysis for an inhalation grade lactose

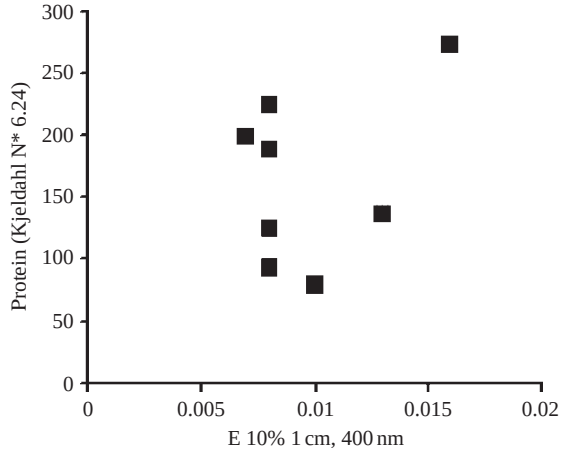

FIGURE 1. Relationship between protein content as determined using the Kjeldahl method and the absorbance in solution at 400 nm compendial test (adapted from Hickey et al. (2007)).

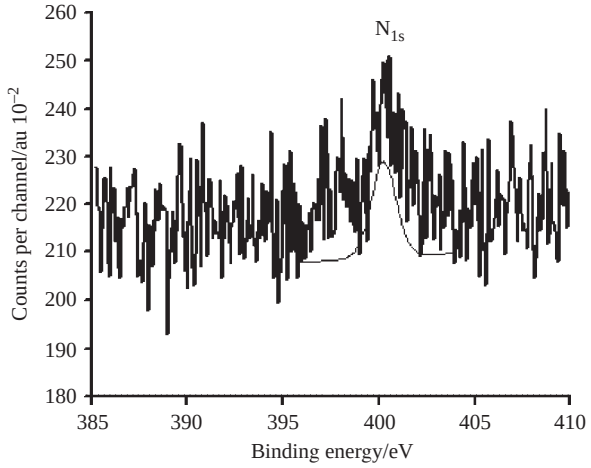

FIGURE 2. Typical X-ray photoelectron spectroscopy (XPS) data for inhalation grade lactose.

as shown in Figure 2, and the nitrogen content in several inhalation grades of lactose are presented in Table 4. It can be seen from Figure 2 and Table 4 that the XPS technique is clearly capable of detecting nitrogen in the surface of the lactose grades studied. Additionally, it has been reported that inhalation grade lactose can contain up to 10% surface peptide (Kaerger, Price, Young, Edge, & Tobyn, 2006). However, the key question surrounding such data is how they relate to pharmacopoeial monographs, and, importantly, how they can enable pharmaceutical regulators to assess any potential impact or relevance for current compendial specifications and patient safety.

Batch Variations

The robustness of typical carrier-based DPI formulations is, in part, dependent on the interparticulate forces that act between excipient and drug particles. Such formulations consist of a range of particles and particulate assemblies, the properties of which will be dependent on, amongst other things, the physicochemical properties of the formulation components (Hickey et al., 2007). In terms of formulation, it is obviously desirable to have a consistent quality of excipient (and drug substance). Clearly, there are many powder characterization techniques available to try to ensure that this is achieved, and DPI excipient suppliers now regularly use techniques such as differential scanning calorimetry and laser light diffraction for their lactose products. However, modern analytical techniques have been used to try to identify inter batch or supplier differences. For example, one such, now commonplace, technique is inverse gas chromatography. This technique uses molecular probes to determine the surface energies of materials and has been widely used to study pharmaceutical materials, including excipients, such as lactose. In brief, the technique is based on the interactions of gaseous probe molecules with stationary phase in a packed column, which give rise to a characteristic net retention volume, VN, which can be related to free energy of adsorption and used to calculate various other thermodynamic parameters. Some typically reported dispersive surface energies of lactoses and magnesium stearate are shown in Table 5.

TABLE 4
X-ray Photoelectron Spectroscopy (XPS) Surface Nitrogen Content of Typical Inhalation Grade Lactoses

Inhalation Grade Lactose Monohydrate (Sample Number)	N% XPS
1	0.6
2	1.0
3	1.1
4	0.6
5	0.9

It can be seen from Table 5 that the reported dispersive surface energy values for lactose monohydrate, including some milled samples, are similar. Indeed a cursory view of the data suggests that the standard use of the technique is apparently incapable of differentiating between materials as diverse as magnesium stearate and lactose. The applicability of this technique for excipients, such as lactose monohydrate, has recently been addressed where the dispersive surface energies of inhalation grades of sieved lactose and milled lactose were reported as 42 and 41.7 mJm^{-2}, respectively, at 30°C. However, the authors suggested that more thorough evaluation of IGC would be required to investigate and identify batch to batch variations (Telko & Hickey, 2007). These studies demonstrate that even though modern analytical techniques can be used to study pharmaceutical materials, such as excipients, the interpretation of observations, especially relating to functionality, should not

TABLE 5
Literature Values of Dispersive Surface Energies for Lactose and Magnesium Stearate

	Dispersive Surface Energy (mJ/m^2)	Reference
Lactose monohydrate	40.6	Swaminathan, Cobb, and Saracovan (2006)
	40–42	Ticehurst, York, Rowe, and Dwivedi (1996)
	31.2	Newell, Buckton, Butler, Thielmann, and Williams (2001)
	41.4	Planinšek, Trojak, and Srčič (2001)
	41, 39	Sethuraman and Hickey (2002)
	42, 42, 41.7	Telko and Hickey (2007)
Magnesium stearate	41.4	Swaminathan, Cobb, and Saracovan (2006)

only be related to material physicochemical characteristics but also take into account the nature of the sample in terms of, for example, source, any particulate distributions, purity, etc.

CONCLUSIONS

The advent of regulatory guidance, such as ICH Q8, Q9, and Q10, specific US and European inhalation guidance, pharmacopoeial monograph modifications, and continuing advances in analytical capabilities means that pharmaceutical development, processes, and materials will inevitably come under greater scrutiny and consequently require greater awareness by the pharmaceutical industry. This is especially true for DPI excipients where, in view of the importance of surface interactions, relationships between compendial testing, specifications, functionality, and quality may need further evaluation. In terms of DPI excipients, such as lactose monohydrate, such advances, together with any excipient company mergers and joint ventures, product withdrawals, manufacturing modifications, and changes in the perceptions of excipients by users, demonstrate the current fluid nature of current trends in the DPI excipient regulatory and business environment. How these current and proposed regulatory regimes and concepts, and issues and proposals will impact the pharmaceutical industry and, importantly, suppliers and users is unclear. However, due to the up to now very limited number of approved matrix-based inhalation products, it is likely that DPI carrier excipients will enhance their position and remain as niche, low volume, relatively high cost, specialized products requiring increased supplier support. This, together with the unique and high functionality of DPI excipients, and the fact that they tend to be produced as customer grades require that users develop and maintain close collaboration with suppliers. The unique position of DPI excipients is also further evident by the proposed introduction of specific monographs for inhalation lactose, both anhydrous and monohydrate. However, whilst further characterization and regulatory scrutiny of DPI excipients is inevitable, and welcome, the relevance to quality, functionality, and, importantly, patient safety should be addressed when considering modifications to any regulatory DPI excipient frameworks.

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