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From Single Excipients to Dual Excipient Platforms in Dry Powder Inhaler Products

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Abstract

Recent years have seen a marked diversification of excipient based formulation strategies used for the development and commercialisation of dry powder inhaler (DPI) products. These innovative approaches not only provide benefits to patients and health care professionals through the availability of a wider range of therapeutic DPI products, but, importantly, also allow formulators to exploit the potential opportunities that excipients provide for the development of DPIs. Whilst many DPI products have, and continue to be developed using a single formulation excipient, the commercialisation of DPI products which contain the two excipients lactose monohydrate and magnesium stearate, namely the 'dual excipient platform' has recently been achieved. This article provides an overview of the background and current status of the development of such 'dual excipient platform' based DPI products.

Keywords: Dry powder inhaler, excipients, formulation, inhalation

1. Introduction

Medicaments have been delivered to the respiratory tract for thousands of years with this route of administration now established as a standard and valuable drug delivery tool in the physician's armoury. Throughout history, the fundamental goal of drug delivery to the lungs has essentially remained unchanged, namely to generate and deliver a targeted efficacious dose of active ingredient to the patient. This is equally true in the modern respiratory era where many approved drugs are now routinely delivered to the patient using the very different, but well understood delivery devices including pressurised metered dose inhalers (pMDIs), nebulisers and DPI delivery platforms. As with early forms of drug delivery to the respiratory tract, such modern delivery systems also contain formulation ingredients other than the drug substance. Whilst ancient texts, such as the Ebers papyrus, and apothecaries

may not have defined them, most ancient formulas, and indeed formulas until the end of the 19th century, contained additional materials; what we would in the present day refer to as, 'excipients' (Anderson, 2005; Sanders, 2007). Excipients now form one of the key cornerstones for the development of a vast majority of medicines. Pharmaceutical development strategies are often progressed based on understanding the functionality of excipients, and, importantly, their relationships to the processability and properties of any final dosage form. Since the primary task of development is to achieve the commercialisation of pharmaceutical drug products which can be manufactured consistently to meet defined quality attribute specifications, improvements that can be gained from any aspects of the drug product manufacturing processes would be beneficial for patient outcomes. This is true for excipients, which often form the major component of drug products, where their unique, and importantly, multi-functional properties have allowed their use as drug delivery vehicles in a wide range of dosage forms, including respiratory products, including DPIs.

2. Respiratory therapy: The modern era and the dawn of the excipient age

The modern era of drug delivery to the lungs using DPIs essentially began in the 1940's with the appearance of the first approved commercial DPI product, namely the Abbott Aerohaler[®], from Abbott Laboratories, USA. This product was used to deliver penicillin and norethisterone and contains many features which would be recognisable today, in that it uses a small capsule reservoir (also described as a 'sifter') containing a lactose based formulation, designed to be used in a device which utilises the patient generated inspiratory airflow to disperse the therapeutic particles in an airstream (Fields, 1949; Sanders, 2007). It is particularly interesting to note that in the original 1949 Abbott Laboratories patent for this product, the inventor, Mack Fields, described the rather insightful claim that 'smoother

and more accurate mechanical action can be secured by mixing the penicillin with at least a little other material intended to function as a diluent or vehicle', an early reference to the functionality, and importance, of an additional 'material'; *i.e.* the 'excipient'.

Whilst many attributes, and concepts, of the Abbott Aerohaler® are common in the current DPI arena, it was only in the 1960's with the development of the single unit dose gelatin capsule based product, the Intal®Spinhaler®, that researchers began to investigate the potential applications and functionality of excipients in DPIs. For example, as early as 1971 the importance of particle size distribution characteristics for the dispersion of lactose and formulations of (di)sodium cromoglycate and lactose from a Spinhaler® was described by Bell et al. (1971). The Intal®Spinhaler® proved to be the forerunner to the development and commercialisation of many 'drug only' and excipient based DPI products (Healy et al., 2014; Yang et al., 2014). Whilst the formulation approaches to DPIs during this era of expansion remained relatively unchanged, essentially using a 'single excipient platform' (SEP) based on micronised drug substance and a single excipient, lactose monohydrate, this period also saw further advances in the scientific understanding of the interactions between the components of DPI products, namely the drug substance, excipient, container system and device. These scientific advances have enabled the successful development of a technologically diverse and elaborate range of excipient based reservoir, capsule and blister formulation container closure systems for the delivery of mono and combination drug therapies.

3. Excipient platforms in commercialised DPIs

Even though the development of DPI products requires a somewhat different, and unique, set of considerations compared to more standard oral solid dosage forms, it is important to

remember that the general role of excipients in DPI products is essentially the same as for all pharmaceutical products, namely to impart functionality to the formulation so as to enable the manufacture of a robust, stable and reproducible drug product which maintains its potency over its entire shelf-life. The establishment of a dose range and dosing regimen provides an efficacious and safe medicine for the patient and development studies based on identifying critical quality attributes using quality by design can elucidate the approaches available to develop a commercial product, thereby allowing appropriate product specifications to be developed, and achieved. The tailoring of any such development strategies can impact the development timelines and the product performance and stability profiles and hence any achievable product efficacy and shelf-life. The solution of these often conflicting challenges is the conundrum of pharmaceutical development, for which excipients can play a key role. This is especially true for DPI products, not only in view of their route of administration, but also in that they are typically very low dose products compared to standard oral solid dosage forms. Consequently, robust and often specialised analytical methodologies and techniques are required to control the qualities of the final drug product and its components during development and, importantly, commercialisation.

The successful commercialisation of many mono and combination DPI drug therapies demonstrates that such development challenges can be readily surmountable for micronised drug substances in SEPs. However, the turn of the 21st century has seen a sea change in how users, and regulators, consider the wider potential, applicability and control of excipients in DPI products. For example, the importance of excipient quality, characteristics and functionality is reflected not only in the increasingly demanding regulatory and GMP frameworks for excipients, but also by their inclusion in sections of the

European and US regulatory guidance for inhaled products, which form part of the global regulatory environment for the submission of DPI product dossiers to health authorities for obtaining marketing authorisations.

4. The single excipient platform

The SEP has been the most prevalent excipient strategy used in modern commercial DPI products and is defined as a final formulation, which consists of one or more active pharmaceutical ingredients (APIs) and a single excipient, regardless of any blending, mixing and particle manipulation steps. The majority of approved SEP DPI products have been developed based on the well-known 'carrier' approach, however, the use of a single excipient in DPI formulations now also encompasses systems based on elaborate particle engineering technologies.

5. 'Carrier' based DPI formulations and products

As previously stated, many commercialised DPI products have been developed based on using a single excipient in the formulation. The vast majority of these products contain lactose monohydrate as the excipient in so called 'carrier' and 'agglomerate' based formulations where the excipient is used to aid the dosing of the drug and to modify the cohesive nature of micronised drug substances which directly influences DPI characteristics such as blend uniformity, content uniformity, manufacturability and ultimately, aerosol dose delivery performance characteristics. Indeed, there is perhaps no other solid dosage form where so many aspects of the final drug product manufacturing and performance are dependent on the multi-functional properties of a single excipient. However, it should be emphasized that while these SEP excipients are described as 'carriers' for DPI products, their actual functionality extends far further. For example, drug product expiry dates of 18 to 24 months at 25 degrees Centigrade storage conditions are readily achievable, suggesting that

a stable product can be commercialised without any additional, and unnecessary and costly, formulation/excipient manipulation. In such cases, the excipient may be providing stability to the formulation and drug product, however, when the target acceptable expiry date is achieved, any 'stabilising' functionality is often not in evidence, or 'claimed'.

5.1 The functionality of the 'carrier' excipient in SEP DPI formulations and products

The role, or functionality, of the single excipient in SEP based DPI products has traditionally been described as a 'dispersant', 'filler', 'diluent' or 'carrier'. In particular, the latter term is somewhat unique to DPI's and was used as early as the 1970's by Hartley and Gunning (1976) to describe the role of lactose in DPI formulations of sodium chromoglycate. Investigations into the physical properties of pharmaceutical powder mixtures began in earnest in the 1970's and 1980's where researchers including Travers, Hersey, and Staniforth, and their co-workers, published a series of articles relating to the interactions between particles in powder beds in what were then described as so-called 'ordered mixtures' or 'adhesive mixtures' (Travers, 1971; Hersey, 1975; Lai et al., 1981; Staniforth et al., 1982). The importance of this growing area of scientific interest was recognised in the British Pharmaceutical Conference Science Award Lecture 'Order out of Chaos', presented by John Staniforth in 1986 (Staniforth, 1987).

Even though many of these early reports used the phrase 'carrier' to describe the larger particle sized component in binary powder mixtures, these studies were primarily focused on the evaluation of the properties of the powders in relation to standard tablet and capsule based solid dosage forms, for example, segregation and homogeneity, and not their role in inhaled products. Since these early fundamental studies a plethora of scientific literature, reviews and patents has appeared describing the interactions of particles in

powder mixtures, including various aspects of 'carrier' based DPI's and researchers are continuing to elucidate the relationships between the properties of 'carrier' excipients and drug substances, and their impact on pharmaceutical performance. For example, for such formulations, it is now accepted that particle size distribution of the 'carrier' excipient is critical for product performance, and requires appropriate controls.

Additionally, the increasingly universal use of terms such as 'adhesive mixture' and 'carrier' to describe formulations and excipients in DPI's has led to their appearance in regulatory relevant documents. For example, in 2012, the description 'adhesive mixture' was used in the public European Committee for Medicinal Products for Human Use (CHMP) assessment documentation (EMA/CHMP/303918/2012) to describe the micronised acridinium bromide and lactose monohydrate formulation in the DPI product, Bretaris®Genuair®. Moreover, the 'carrier' description is now so commonplace in academic, industrial and regulatory circles that in 2014 it was incorporated into the updated respiratory section of the United States Pharmacopoeia general chapter <1059> Excipient Performance (United States Pharmacopoeia, 2016) and also appears in the public CHMP assessment documentation of several recently approved DPI products, for example, EMA/659981/2009 for Onbrez®Breezhaler®, approved in 2009. Such 'carrier' excipients, often of a small particle size, are also used in what are described as 'agglomerate' formulations, where the functionality of the excipient is similar to the 'carrier' based systems, for example in Symbicort®Turbohaler®.

Developing such SEP based products is a challenging and often a semi-empirically driven process. However, pathways for the development of lactose monohydrate based 'carrier'

and 'agglomerate' formulations containing micronised drug substances presently consist primarily of standard robust unit process operations, such as micronisation, blending, filling and packaging. Even though the use of such processes in DPI products is somewhat unique to this sector of the pharmaceutical industry, their impact on the final drug product is well understood. These processes have been successfully used to commercialise many originator, and more recently, generic DPI products. Even though the vast majority of marketed SEP 'carrier' based DPI products contain lactose monohydrate, single excipient 'carrier'/'agglomerate' based DPI products have also historically been commercialised utilising anhydrous glucose (Atrovent®Aerocaps®) and anhydrous lactose (Asmanex®Twisthaler®) in single dose capsule and reservoir devices, respectively. Even though such 'anhydroglucose' containing excipients exhibit similar physicochemical characteristics to lactose monohydrate, the development of DPI products using these alternative excipients is not without risk, and represents the first signs of a willingness to investigate and innovate new excipient delivery platforms, an interesting indication of future development scenarios.

6. Particle engineered single excipient based DPI formulations and products

The use of excipients in SEP DPI products beyond the traditional functional role of 'carrier' has also been realised with the approval of Bronchitol®, approved in Europe in 2012 (EMA/CHMP/121817/2012), and Afrezza®, approved in the US in 2014. The approval of these two products not only represents advances in innovation in the respiratory sector, but also a step change in the technological and regulatory approaches to the so-called SEP, which should not be underestimated in terms of their achievement. From the publically available regulatory product reviews, patient information and literature, both of these products not only contain elaborately engineered particles but also novel DPI excipients,

with the former, developed by Pharmaxis, containing spray-dried engineered mannitol, see Figure 1 which is the actual efficacious agent (atypical active) (Hurt and Bilton, 2012), and the latter, fumaryl diketopiperazine, see Figure 2. Afrezza® was originally developed by MannKind Corporation as Technosphere® for delivery of insulin to the systemic circulation *via* the lungs and this delivery platform is based on the elaborate self-assembly properties of the propriety excipient, fumaryl diketopiperazine, a substituted diketopiperazine (Leone-Bay and Grant, 2006). Mannitol is also marketed in several countries as Aridol®/Osmohale®, a capsule based DPI indirect diagnostic osmotic bronchial challenge test that can be used to identify bronchial hyper-responsiveness. Additionally, other sophisticated SEP particle engineering technologies are also being developed for the respiratory sector by companies such as Liquidia (Garcia et al., 2012).

Even though both the ‘carrier’ and, more recently, particle engineering, SEP strategies continue to be successful and widely used in commercialized DPIs, this does not mean that other, multiple excipient based platforms, have not been explored by the respiratory sector and DPI products based on using two or more excipients indeed, have been commercialised. For example, the use of multiple excipients in DPI products has been realised with the approval of Exubera™, and more recently, TOBI®Podhaler®, but perhaps the most notable and more broadly applied new excipient platform strategy for the development of DPI’s used to date is the ‘dual excipient platform’ (DEP) where lactose monohydrate is used in conjunction with a second, ternary, excipient, namely magnesium stearate.

7. The dual excipient platform

Whilst the 'carrier' based SEP approach has been demonstrated to be more than capable of supporting the development and commercialisation of many originator, and to a lesser extent, generic DPI products, there may be instances where the use of such historical 'single excipient' approaches may not be appropriate for the development of some DPI products, especially in standard capsule and/or blister container systems. For example, the use of a SEP may not be capable of achieving the required performance efficiency, manufacturability and scale or commercial shelf-life using well understood product and company specific 'carrier' excipient based processing steps. Additionally, the SEP may not be readily adaptable for intellectual property reasons or for the matching of generic DPI's to their originator products.

In terms of new approaches for the commercialisation of DPI products, recent development strategies have focused on maintaining a well understood and established inhaler device, container systems and manufacturing processes, whilst modifying the functionality of the formulation by the addition of a single ternary material, and in particular, an excipient, and most notably, magnesium stearate; creating a 'dual excipient platform'. Such a DEP can be considered as a highly functional excipient system in which a second (ternary) excipient is added during one or more of the manufacturing unit operation(s) at a certain final level to impart a required property to the final formulation and drug product rather than any simple blending, mixing or manipulation of the same single excipient. However, it should be considered that any added material may also inadvertently impart functionality to another aspect of the drug product in addition to modifying the targeted functional characteristic, which is important for any intellectual property considerations.

7.1 The dual excipient platform in commercial DPI products

Whilst there has been a considerable number of academic publications and patents concerning the use of additional (ternary) excipients as functional additives for DPI's, their use in approved products has expanded since 2010 with no less than 6 product approvals by 3 sponsors in global regional markets between 2010 and 2015, all of which contain lactose monohydrate and magnesium stearate, see Table 1.

The approval of these products also demonstrates the applicability of the ternary excipient, magnesium stearate, in different lactose monohydrate based DPI delivery platforms, namely, capsule, blister and reservoir. One interesting additional aspect of such approvals is that the sponsors of these products appear to be also adopting internal flexible development approaches in that they have commercialised products which contain both a single excipient, lactose monohydrate, and products which contain two excipients, namely, lactose monohydrate together with the ternary, additional, excipient, magnesium stearate. In view of the number of successful capsule, blister and reservoir based DPI product approvals which contain magnesium stearate it can be argued that such a development strategy is now becoming an industry and regulatory 'standard'. However, the successful development of any new excipient platform in DPIs represents real scientific and technological innovation by the industry.

7.2 The functionality of magnesium stearate in DEP DPI formulations and products

Magnesium stearate is produced from animal and vegetable sources and is a well-known excipient, which is widely used a lubricant in solid dosage forms. However, as with many excipients, magnesium stearate is not a single pure chemical entity, and in this case, the commercial excipient exists as a composite/mixture of magnesium salts of stearic acid and

palmitic acid (Allen and Luner, 2009). The traditional role of magnesium stearate in solid dosage forms has also been expanded to DPIs where its functionality in DEP formulations has been described in the literature as a ‘lubricant’, ‘force control agent’, ‘water barrier’, ‘stabiliser’ and ‘chemical stabiliser’, which are discussed in the following Sections, suggesting multi-functional properties of this excipient in this solid dosage form.

7.3 Magnesium stearate as a lubricant in DEP DPI formulations and products

The pre-cursor to what we now recognise as the DEP really began in the 1980’s. One of the first roles for a ternary additional material in a DPI product was described by Chiesi and Pavesi in 1987 for the alleviation of potential issues with the mechanical dosing mechanism in a reservoir type DPI device. The functional property of the ternary materials described, including magnesium stearate and sodium benzoate, was described as a ‘lubricant’, which is the widely accepted pharmaceutical functionality of such excipients (Chiesi and Pavesi, 1987). The first modern era DEP DPI product, Pulvinal®Beclometasone® (Chiesi), see Figure 3, a lactose monohydrate based reservoir device product, available in three dose strengths of beclometasone dipropionate, which, according to the patient information leaflet also, importantly, contained magnesium stearate, was approved in the UK in 2001. This was followed in 2004 by the approval of the Novartis reservoir based multi-dose DPI product, Foradil®Certihaler®, which also used a DEP of lactose and magnesium stearate. The approval of these two products represents innovative and novel formulation approaches for the commercialisation of DPI products.

However, even though the earlier Pulvinal®Beclometasone® product was successfully developed and received a marketing authorisation, there were no initial reports of any other

potential functionality advantages that such ternary materials may offer in terms of DPI product performance.

7.4 Magnesium stearate as a performance enhancer in DEP DPI formulations and products

It did not take long, however, before investigators began to study the effect of ternary materials on the properties of powders and DPI product performance. In terms of the use of magnesium stearate, reports by workers such as Staniforth and co-workers had already described the influence of a ternary component, magnesium stearate, on the adhesion of salicylic acid to sucrose (Staniforth et al., 1982). Such observations were further elaborated for the potential advantages of ternary materials for DPI product performance and patents and scientific literature began to appear at the turn of the 21st century, claiming that the addition of ternary materials, such as magnesium stearate, could improve the fine particle dose performance characteristics of DPI formulations (Brambilla et al., 2003; Chiesi et al., 2001; Musa et al., 2003; Staniforth, 1997; Zhou and Moreton, 2012). Since this time many patents have appeared describing the use of excipient ‘combinations’, with these patents typically describing formulations containing dual excipient ‘mixtures’ of lactose monohydrate and a ternary material, including magnesium stearate. The use of lactose monohydrate and magnesium stearate as an excipient template for DPI development was further expanded with technology platforms such as Powderhale® (Vectura) and SkyeProtect® (SkyePharma) appearing.

7.5 Magnesium stearate as a force control agent in DEP DPI formulations and products

Whilst the use of such ternary materials in DEP DPI products may now be considered to be a somewhat standard approach, it should not be underestimated what this technological achievement represented in terms of modern DPI development and, importantly, regulatory

approval. With the increased understanding of the surface and particulate interactions in DPI's (Price et al., 2002; Begat et al., 2004; de Boer et al., 2012), the use of such ternary materials in modern DPI development has led to the functionality of such a performance enhancer to also now being widely referred to as a 'force control agent' (Begat et al., 2005; Begat et al., 2009). Where such additives were added to DPI's their function was invariably to modify the characteristics of the powder formulation by impacting the inter-particulate interactions, or 'cohesive-adhesive balance' resulting in improved powder properties and aerosolisation performance.

7.6 Magnesium stearate as a water barrier in DEP DPI formulations and products

It has been reported that the presence of magnesium stearate in DPI lactose monohydrate formulations results in not only the generation of a higher, but more stable fine particle mass, which was explained in terms of the functional ability of magnesium stearate to protect the formulation from moisture, representing yet another possible functional 'stabilising' role for ternary materials in DPI products (Guchardi et al., 2008; Keller and Müller-Walz, 2001).

7.7 Magnesium stearate as a stabiliser in DEP DPI products

The previous sections described the functionality of the ternary material magnesium stearate in DEP formulations and products. It is clear that the presence of magnesium stearate can, in some cases, impart beneficial properties to DPI DEP formulation products and it can be argued that any such improvements can be described, to some degree, as stabilising effects. However, the true benefit of any possible improvements to any DPI performance characteristic can only be fully elucidated after the evaluation of their performance during stability assessment over a commercially acceptable shelf-life.

Any decisions for pharmaceutical product development strategies are based on both commercial and development considerations. This is equally true for DPI products where the fundamental goal of pharmaceutical development remains the same: to develop the required marketed form of a drug product, whether this be for an originator or generic product, in an appropriate timeframe. Whilst this naturally focusses on the needs of patients in terms of disease state, therapy, outcomes, compliance etc., the achievement of an acceptable product shelf-life is a pre-requisite for the commercialisation of a drug product and this is often a major challenge during development and the subsequent defining of the product specifications (Capen et al., 2012). Whilst early development stability studies can provide indications of DPI product performance and allow the assignment of a shelf-life in the various global climate temperature and humidity zones there may be situations where the expected stability profile for commercialisation may not be achievable using standard and well understood materials and processes, especially in SEP products. Clearly, in such instances simple modifications of the manufacturing processes or levels, and ranges, of functionality provided by the device/container system, packaging, storage conditions, drug substance or the single excipient may not be sufficient to achieve, or maintain, an acceptable level of a particular critical drug product quality attribute.

In general, two types of stability profiles are exhibited by pharmaceutical drug products during storage time namely, constant and non-constant. The constant stability profiles consist of quality attributes stability indicators which have little or no variability during time when stored at the long term storage condition, with any apparent changes being a consequence of product or method variability. The non-constant stability profiles contain quality attributes which either increase or decay during storage at the long term storage

condition. It is the products which exhibit non-constant stability profiles which pose the greatest challenge for the commercialisation of a product since an acceptable shelf-life may not be achievable due to, for example, the early occurrence of out of specification events. Whilst out of specification results may not impact toxicity (e.g. not associated with increased levels of impurities), they can sometime impact the efficacy of the drug product. In many cases, any well understood decaying or increasing specification stability indicating parameter can be controlled to exhibit an acceptable sustained stability profile, allowing an acceptable shelf-life to be achieved, represented for decaying stability profiles in Figure 4. For example, the rate of any detrimental physico-chemical interactions in the product may be reduced by refrigeration, API salt form and hydration state, formulation and device design and processing and packaging configurations. However, such control measures may not always readily achieve the required outcomes for some development programs or be commercially viable and alternative strategies need to be considered. This is especially true for capsule and blister based DPI products, where, for example, any moisture ingress occurring during storage may influence the long term performance of the product, see Figure 5.

7.8 The use of magnesium stearate as a stabiliser in DEP blister based DPI products

From a development, scientific and innovation perspective, perhaps the most interesting of the DEP approved products are the GSK blister based products Relvar®Ellipta®/Breo™Ellipta™ and Anoro®Ellipta®/Anoro™Ellipta™, not only for their use of the 'dual excipient platform' but that they also utilise new device delivery systems, albeit still blister based, compared to the previous generation of products. These two products are combination products, but in contrast to the precursor combination product, Seretide®Accuhaler®/Advair™Diskus™, where the 2 APIs, salmeterol xinafoate and

fluticasone propionate, are 'co-formulated' into a single blister in a single blister strip, the two APIs in Relvar[®]Ellipta[®]/Breo[™]Ellipta[™], namely vilanterol trifenate and fluticasone furoate, and Anoro[®]Ellipta[®]/Anoro[™]Ellipta[™], namely vilanterol trifenate and umeclidinium bromide, are each separately formulated into single mono therapy blisters in two individual blister strips, within their respective dual blister devices. This packaging strategy may be useful to avoid drug-drug incompatibility or formulation quality changes during storage.

The public US prescribing information for the two new GSK combination products suggest that the four mono drug formulations in each of the two blisters in the two products contain approximately 12.3 - 12.4 mg of lactose monohydrate so that the total single formulation masses are 12.5 mg, with the public European product characteristics information stating that the delivered dose from the two products is approximately 25 mg of lactose monohydrate. This single blister formulation fill mass of 12.5 mg is similar to the formulation mass in the single blisters in the Seretide[®]Accuhaler[®]/Advair[™]Diskus[™] co-formulated combination product. Additionally, the public US prescribing information also states that the vilanterol trifenate and umeclidinium bromide formulations also contain magnesium stearate, at the levels of 125 µg and 75 µg, respectively, see Table 2 for the formulation compositions of Anoro[®]Ellipta[®]/Anoro[™]Ellipta[™]. These differences suggest that the magnesium stearate levels may require adjusting in different formulations to optimise and achieve the desired functional benefits. Typical scanning electron microscopy images of the umeclidinium bromide and vilanterol trifenate formulations in Anoro[®]Ellipta[®] are shown in Figure 6. It can be seen from Figure 6 that the formulations exhibit particle characteristics, which are typical for lactose based DPI formulations, suggesting that the use of magnesium

stearate in these DEP products has not modified the macroscopic particle characteristics of the formulations.

In contrast, from the public US prescribing information, the related approved GSK mono therapy product Arnuity®Ellipta® (fluticasone furoate), the second drug component in Relvar®Ellipta®/Breo™Ellipta™, only contains the excipient lactose monohydrate in the formulation, suggesting that in this case, the functional properties of the formulation are sufficient without the addition of the ternary excipient, magnesium stearate. However, the mono therapy of umeclidinium bromide, Incruse™Ellipta™, contains magnesium stearate at similar levels to the umeclidinium bromide formulation in the combination product, Anoro®Ellipta®/Anoro™Ellipta™. This again demonstrates the continuing flexible, and innovative, development approaches used during product development.

In terms of the functional development of ternary excipients in such DEPs it is equally interesting to note that the public CHMP assessments of Anoro®Ellipta® and Relvar®Ellipta® describes the functionality of the magnesium stearate in the vilanterol trifenate formulation as both a 'stabiliser' and 'chemical stabiliser', and in the umeclidinium bromide formulation as a 'stabiliser', with the functionality of lactose being described as a 'carrier/diluent', see Table 2. This 'stabilising' functionality description is a widening of the accepted role and functionality of such ternary agents and 'force control agents', and should not be over-emphasised in terms of the implications for DPI development, for both originator and generic products.

In terms of stabilising ternary excipients used in DPIs, the use of sugar esters, such as cellulose acetate, to inhibit or reduce the chemical interactions between an API and a carrier, and thereby reducing chemical degradation, was described by Monteith and co-workers (Monteith et al., 2006a; Monteith et al., 2006b). The use of ternary derivatised carbohydrates was also reported to eliminate, or reduce, the detrimental effects of storage conditions on the fine particle dose of DPI formulations (Bulsara and Roche, 2005). Similar observations were reported by Monteith and Thomas (2006), who described the use of magnesium stearate as a ternary agent to inhibit or reduce chemical interaction between an API and a carrier in a solid pharmaceutical formulation, wherein the API is susceptible to chemical interactions with the carrier. It was suggested that the role of magnesium stearate, and sugar esters such as cellulose acetate, as inhibitors of chemical interactions may be related to the findings that, under accelerated stability conditions, certain inhalable APIs undergo degradation in the presence of lactose. It was proposed that this type of chemical reaction may proceed via the Maillard reaction, as suggested by Wirth et. al. (1998) for the drug Prozac®, who reported that drug substances, which have secondary or primary amine moieties, as have many small molecule respiratory drug substances, can undergo the Maillard reaction with lactose under pharmaceutically relevant conditions. However, many long acting beta agonist respiratory drug substances in approved products, contain such a similar N-substituted aminohydroxyethylbenzene type secondary amine structures to vilanterol, for example, formoterol, indacaterol and salmeterol, see Figure 7. Moreover, commercialisation of the latter 3 compounds in DPI products has been achieved without the incorporation of any ternary excipient suggesting that, as expected, the relationships between chemical interactions and delivery systems and shelf-life in DPI products are complex.

7.9 The use of magnesium stearate in DEP capsule based DPI products

The role of such DEPs based on lactose monohydrate and magnesium stearate has also been demonstrated to be equally applicable to other DPI platforms beyond blister based products. Indeed, the public European product information and US prescribing information for the two recently approved capsule based products, the mono therapy Seebri®Breezhaler®/Seebri™Neohaler® (glycopyrronium bromide), and the combination therapy Ultibro®Breezhaler®/Utibron™Neohaler® (glycopyrronium bromide and indacaterol maleate), both developed by Novartis, show that both the products also contain the two excipients magnesium stearate and lactose monohydrate, see Figure 8 and Table 3.

It is interesting to note that the indacaterol maleate component in the co-formulated combination product Ultibro®Breezhaler®/Utibron™Neohaler® is also approved as the mono therapies, Onbrez®Breezhaler®/Arcapta™Neohaler™ in Europe and US, respectively, but this product only contains lactose monohydrate. This is similar to the excipient strategy diversity situation with the previously discussed GSK mono and combination products and again suggests that the functional properties of the indacaterol maleate formulations in the mono therapies are sufficient without any additional magnesium stearate, further demonstrating the continuing flexible development approaches used during DPI product development.

The public US prescribing information and European product information also suggest that the two Novartis DEP products contain similar masses of lactose monohydrate to the Novartis SEP product, Onbrez®Breezhaler®/Arcapta™Neohaler™, approximately 25 mg. Additionally, the public US prescribing information for Seebri™Neohaler® and Utibron™Neohaler® also states that the glycopyrronium bromide and glycopyrronium

bromide/indacaterol maleate formulations also contain magnesium stearate, at concentrations of 0.16% and 0.12%, respectively, see Table 3. This small apparent difference in magnesium stearate levels for similar mass formulations suggests that the functional benefits of magnesium stearate can vary between formulations. However, it should be noted that the levels of magnesium stearate in the Novartis DEP products are almost an order of magnitude lower than the magnesium stearate levels in the GSK DEP products, suggesting that the functional benefits of a ternary material are drug substance, formulation and product specific. Indeed it was suggested by Monteith and Thomas (2006) that the optimal amount of magnesium stearate in a DEP formulation would vary depending on, for example, the API, and the particle size.

In terms of the functional development of ternary excipients in the Novartis DEP products, the public CHMP assessments of Seebri®Breezhaler® and Ultibro®Breezhaler® also describe the functionality of the lactose monohydrate in both formulations as a 'carrier', see Table 3. Whilst there is no information concerning the functionality of the magnesium stearate, the public CHMP assessment of Seebri®Breezhaler® describes some interesting insights into the functionality of the excipients in this DEP product in that that the micronised active substance is described as being 'stabilised by an added excipient'; another reference to the stabilising functionality of excipients in DPI products. Additionally, in contrast to the 2 DEP GSK products, where the public CHMP assessments simply describe 'blending' manufacturing processes, the public CHMP assessment of Seebri®Breezhaler® describes the manufacturing process of the finished product which involves the preparation of a 'pharmaceutical intermediate which is then blended with excipients and filled into hard capsules'. The limited availability of information concerning the manufacturing of the blister

and capsule based DEP products does indicate that different process strategies may be being used to achieve the desired outcomes, again reflecting the flexible and innovative approaches made during development.

Equally of interest is that for the 3 Novartis commercialised products, Onbrez®Breezhaler®/Arcapta™Neohaler™, Seebri®Breezhaler®/Seebri™Neohaler® and Ultibro®Breezhaler®/Utibron™Neohaler® the public CHMP assessments and US prescribing information suggest two different capsule types have been used with hypromellose being used in the DEP products Seebri®Breezhaler®/Seebri™Neohaler®, and Ultibro®Breezhaler®/Utibron™Neohaler®, and gelatin in the SEP product, Onbrez®Breezhaler®/Arcapta™Neohaler™. Since the hypromellose and gelatin capsules have different characteristics, such as water content, the use of different capsule materials offers another formulation option when considering development strategies for DPIs (Richardson, 2011).

7.10 The use of magnesium stearate in DEP reservoir based DPI products

The universality of the DEP would not be complete without its use in reservoir based DPI products, which has, indeed, been achieved. As previously mentioned, the first modern commercial DEP DPI product, Pulvinal®Beclometasone®, was developed by Chiesi as a multi-dose reservoir based product, followed by the Novartis multi-dose reservoir product Foradil®Certihaler®. Chiesi have followed the same 'reservoir' based strategy with the approval in 2012 of the DEP beclometasone dipropionate/formoterol fumarate co-formulated combination reservoir DPI product, Foster®NEXThaler®, see Figure 9. This again suggests that the development strategies of pharmaceutical companies tend to be based on attempting to minimise development risks by manipulating formulations and using well

understood, albeit internal and often proprietary, processing operations. The public summary of product characteristics of Fostair[®]NEXThaler[®] (the UK brand of Foster[®]NEXThaler[®]), from 2014, states that the product contains the two excipients, lactose monohydrate and magnesium stearate, which is similar to the two excipients used in the previously discussed commercial blister and capsule based DEP DPI products.

8. Conclusions

For many decades DPI products have been successfully developed using a variety of formulation strategies including drug only or powder mixture approaches containing a single excipient, typically lactose monohydrate. Single excipient based formulations continue to be used in approved commercial DPI products today. However, since 2010 there has been a major diversification in the formulation strategies successfully used and implemented in approved DPI products. The early fundamental studies and pharmaceutical innovations of Hersey, Monteith, Thomas, Staniforth, Chiesi etc., and their co-workers, has finally resulted in the successful development, understanding and implementation of novel DEP strategies in commercialised DPI products. These innovations have not only allowed the expansion of DPI development options for pharmaceutical companies but, importantly, also the availability of an increasing range of medicines that are beneficial to patients.

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Figure 1. Scanning electron microscope image of spray-dried mannitol in Bronchitol[®], mag. x4000. Image with permission of University of Sydney.

Figure 2. Chemical structure of fumaryl diketopiperazine (FDKP).

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Figure 9. Foster[®]NEXThaler[®] commercial lactose monohydrate/magnesium stearate DEP product. Image with permission from Chiesi.

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