FUTURE TRENDS FOR INHALATION LACTOSE
A SUPPLIER'S PERSPECTIVE

This article looks at the current level of attention given to carrier lactose for dry powder inhalers (DPIs) and assesses how this attention may affect the future. We believe that further developments will involve closer co-operation between inhalation lactose suppliers, DPI product manufacturers and regulators. This conclusion can be supported by examples of characterization, Quality by Design (QbD) and regulatory developments

Delivering drugs to the lungs is challenging because of the body's defence mechanisms to keep particulates out of the lungs. Targeting a reliable dose of drug in a narrow particle size range is most commonly achieved by using one of two portable devices, namely the metered-dose inhaler (MDI) and increasingly the DPI.

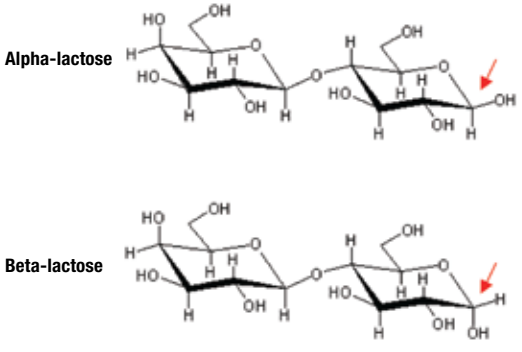
A DPI is typically filled with a homogenous blend of the micronized drug and a carrier, which is usually lactose. The carrier has to fulfil a number of roles. It has to blend homogenously with the low dose of drug (typically measured in micrograms); allow filling of the blend into a reservoir, or into single-dose capsules or blisters, which are fitted into the device; and finally to separate from the drug during inhalation so that the drug can be inhaled into the patient's lungs. The correct performance of the DPI, and hence patient's wellbeing, depends on the three-way interaction of drug, the device and the carrier. Consequently, lactose for DPI use attracts much attention from product formulators, medicines agencies, regulatory bodies and pharmacopoeia. Many DPI products contain lactose that has been developed by excipient suppliers in conjunction with pharmaceutical companies, and has been optimized for use with a particular drug and device combination.

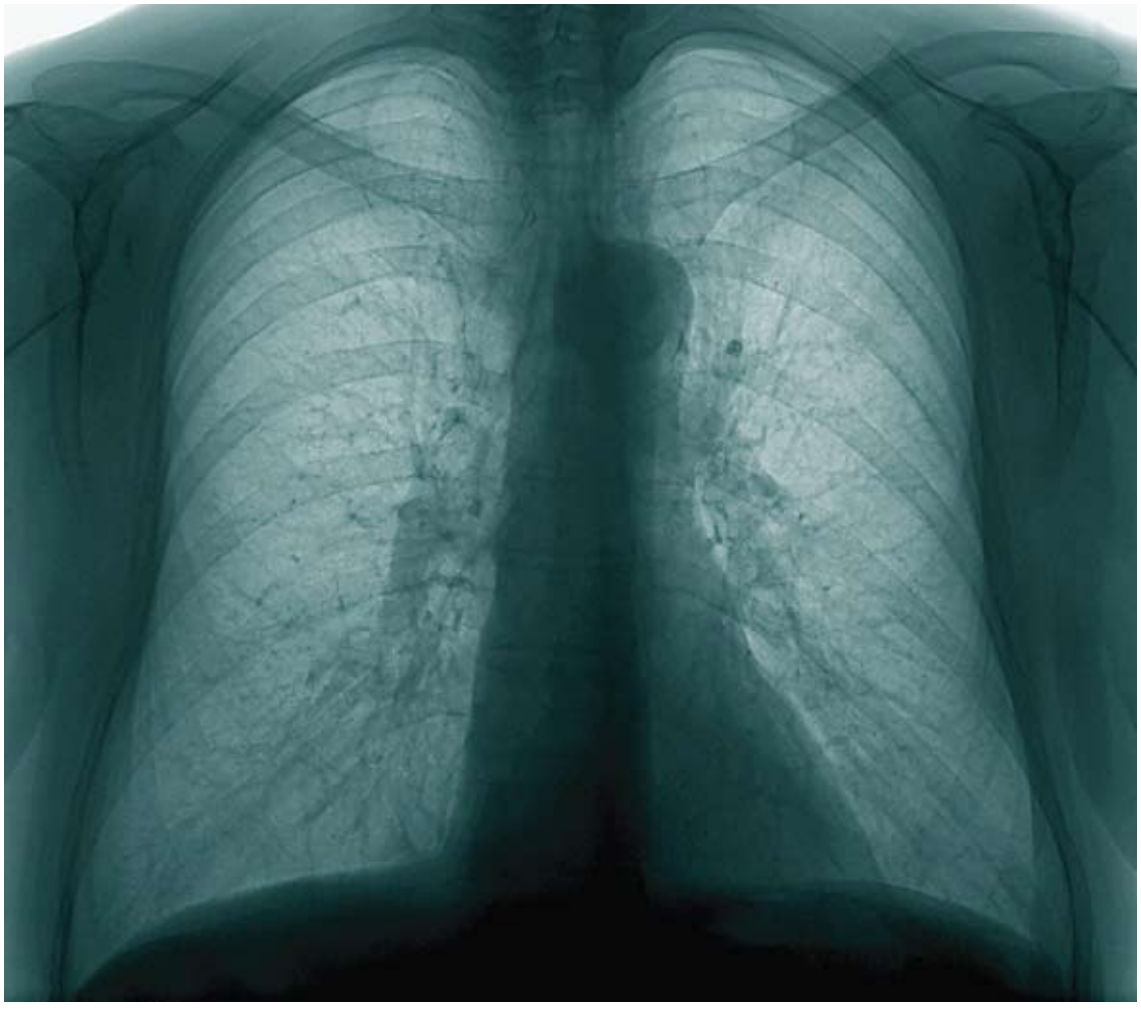
Inhalation Lactose Characterization

Development of a robust DPI product depends on knowledge and understanding of the characteristics of the inhalation carrier, and the effects of variations in these characteristics on the performance of the DPI product. In this respect, excipient suppliers build up a history of extensive inhalation lactose characteristics through the inhalation product development process. The analytical methods used to measure these characteristics, however, vary between suppliers of inhalation lactose, users and academics interested in dry powder inhalation. Progress in characterization will be greatly helped if there is common agreement on the analytical methodology used, because different methods can give very different values. Some examples will illustrate this point.

The most obvious area for characterization is chemical purity, or more accurately knowledge of impurities. Inhalation lactose is subject to a number of tests not normally applied to other lactose grades. These include tests for anomer ratio (that is, the proportions of alpha-lactose and beta-lactose — see sidebar), tests for related sugars, (glucose and galactose), tests for residual proteins or protein fragments and measurement of amorphous

Lactose exists in two different forms named alpha-lactose and beta-lactose with structures that differ only in the stereochemistry at the arrowed position. In aqueous solution, both forms exist with an equilibrium mixture of about 60% beta-lactose and 40% alpha-lactose. Depending on the conditions, lactose can be made to crystallize predominantly as either alpha-lactose monohydrate or as anhydrous beta-lactose. When a lactose solution is spray dried or freeze dried the resulting amorphous powder may contain both forms of lactose.





lactose. Each of these analyses can challenge the analytical chemist, but we will look at the last two characteristics as examples where the analytical methodology can have a profound influence on lactose characterization.

Protein

The protein content of inhalation may be an important factor for inhalation lactose because of the need to eliminate the risk of prophylaxis. In the European Pharmacopoeia monograph for lactose, a test for "Protein and Light Absorbing Impurities" is included with the test specifying measurement of the ultraviolet (UV) absorbance of an aqueous solution in the 210–300 nm, but it is clear that this provides no useful quantitative information about protein content. One reported study showed that there was no relationship between the absorbance of a lactose solution at 400 nm and protein measured by Kjeldahl.[1] But this is not surprising because absorbance at 400 nm measures the 'yellowness' of a solution. Such yellowness arises from a number of factors including the potential reaction of residual proteins with reducing sugars, whereas Kjeldahl's method measures total nitrogen and multiplies by a factor (6.38 in the case of milk proteins) to estimate protein content. Neither of these crude measures of protein content provides any real indication of the protein content of inhalation lactose.

An improved method for protein measurement may be Bradford's method, which measures the shift in absorbance of the dye Coomassie when it binds to protein. When batches of inhalation lactose are measured by Kjeldahl's method and Bradford's method (Figure 1), however, it is clear that there is no correlation between the values measured by the two techniques and there is a discrepancy of about one order of magnitude between the data ranges. The range of values measured by Kjeldahl's method is approximately ten times higher than the data range of Bradford's method. Thus, available techniques for the measurements of protein in inhalation lactose lack the specificity to make accurate determinations, which give rise to very different estimates of protein content.

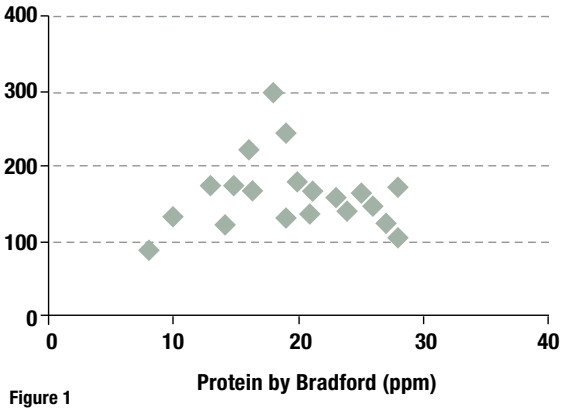


Figure 1: Lack of relationship between protein content of inhalation lactose measured by two techniques in 21 batches of inhalation lactose.

Figure 1

The amorphous content of inhalation lactose is the subject of much interest. It is unclear whether the presence of amorphous lactose in a DPI device is itself deleterious, but amorphous lactose is by its nature unstable and tends to convert to more stable crystalline forms when the atmospheric relative humidity exceeds 58%.[2] Crystallization of amorphous lactose in a DPI device, however, may change the performance of the formulation and the amount of active delivered to a patient's lung may, therefore, change. Thus, it is important to be able to analyse amorphous lactose with accuracy and precision at the low levels found in most grades of inhalation lactose.

Amorphous lactose mainly results from crystal damage of lactose monohydrate after drying. This damage is most pronounced when lactose is milled, and the higher the degree of milling then the finer the lactose and the higher the amorphous content. At the extreme of micronized lactose with median particle size of about 3 µm then the amorphous lactose content has been reported to be as high as 11%, whereas for sieved lactose, which should have the least damaged crystals, values of <1% have been reported.[3] But such statements require an understanding of the means of measurement of this property and the transformations that lactose undergoes during the measurement.

Spectroscopic techniques have been applied to this measurement, but they generally lack the sensitivity to measure the amorphous content of inhalation lactose, and sufficiently sensitive techniques may be classified as either calorimetric (for example, DSC or isothermal calorimetry) or gravimetric (DVS).[3–5] All calorimetric and gravimetric techniques, however, suffer from the same general drawback — the lactose transformations that take place during the measurement are complex and sometimes difficult to rationalize. It is, therefore, sometimes unclear exactly what is being measured by the analysis. For example, the isothermal microcalorimetry technique reported by Dilworth is the summation of the net heat change of five possibly overlapping regions of the total calorimeter trace. Similarly, the gravimetric method reported by Buckton and Darcy, in which the total weight gain was assumed to be a result of the crystallization of amorphous lactose to alpha-lactose monohydrate, involves other transformations that serve to underestimate the amorphous lactose content.[6]

Finally, there is the question of which standard should be adopted to translate the machine output (heat flow or weight change) into actual amorphous content. A standard of amorphous lactose can be made by either freeze drying or spray drying an aqueous solution of lactose, but is it reasonable to equate amorphous lactose formed by milling alpha-lactose monohydrate to a standard made by drying a solution that contains approximately 60% of beta-lactose?

At the present stage of development, it is dangerous to quote a value for the amorphous content of inhalation lactose as though it is an absolute quantity that can be measured with the accuracy of many other analytical techniques. The way forward in this important area must be for suppliers of inhalation lactose, developers of DPI products and regulators to agree which analytical methods and standards are the most appropriate such that discussion of amorphous lactose can be focussed on the role of amorphous lactose in DPI performance.

Quality by Design

The QbD initiative will inevitably forge a closer relationship between excipient suppliers and pharmaceutical manufacturers. Identification of key excipients and their most relevant properties can be built into formulation experiments that define knowledge, design and control spaces. In many formulation examples, the excipient company can routinely supply an excipient that falls within the required control space. The relationship between excipient supplier and user reverts to one of buying to specification and the excipient manufacturer's target of 'right down the middle of the spec' is sufficient. But inhalation lactose suppliers see a very different trend, and it is a trend that challenges this manufacturing paradigm.

The apparently simple three component formulation model of drug + device + lactose is deceptive because the finished product has to deliver a consistent amount of active every time a patient inhales. This is measured typically as the 'respirable fraction' and is defined by the amount of drug delivered in a certain

particle size range, which may be substantially lower than the amount of drug in an individual dosage unit. The respirable fraction can depend on a great number of variables.

A typical project to develop an inhalation carrier in conjunction with a DPI manufacturer may begin with a range of lactose samples that provide, as far as possible, a spread of properties so that the customer can start to build up knowledge space related to lactose. The DPI developer may use these measurements, together with knowledge of various drug and device properties, to build a multivariate model that relates these input properties to the respirable fraction (or other measure of product performance). The key inputs can then be teased out of the data. At this stage, it is important that the inhalation lactose supplier and the DPI producer are in close contact so that there is a common understanding of the key input variables and the extent of control that can be exerted by the lactose manufacturer. Such understanding can become vital to the eventual supply of commercial material.

For a sophisticated DPI producer, the multivariate model is not just a development device — it is a tool that is developed through the commercial lifetime of the DPI product and may be used to match a set of key inputs to minimize the variation in the respirable fraction. For the supplier of inhalation lactose, this can mean requests for commercial batches of product that are targeted to specific parts of the lactose specification. This can represent quite a challenge for the lactose manufacturer and can generally only be met if there is the high level of interaction during development so that both supplier and user can agree on the key variables and the ability to control them at the commercial production scale. Thus, QbD, or this more sophisticated approach, requires increasing co-operation between supplier and user.

Regulatory Developments

The importance of inhalation lactose in DPI performance has attracted a great deal of regulatory attention. In addition to the general requirements, such as QbD described above, two monographs covering Lactose for Inhalation and Anhydrous Lactose for Inhalation are under construction and review by the US and the European Pharmacopoeias. These are important and eagerly awaited developments, but questions are immediately raised about those lactose properties that should be included in pharmacopoeial monographs and those that are better dealt with for a specific medicinal product in the product license application.

For example, there can be no question that aspects related to improved microbiological control represent improvement in patient safety. Conversely, one could question whether general controls on

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"Functionality Related Parameters" will benefit patients. If control over anomeric purity becomes a pharmacopoeial requirement, with a specified limit for the content of beta-lactose in alpha-lactose monohydrate, then it is possible that one particular form of lactose monohydrate will automatically fall out of the scope of the monograph and may not be labelled as lactose for inhalation. This is because granulated forms of lactose are made by granulating crystalline lactose monohydrate with a solution of lactose. The dissolved lactose contains about 60% beta-lactose, which results in elevated levels of this anomer in the granulated product. Does this mean that DPI products will no longer be developed using granulated lactose, even though it is the best carrier for some drug–device combinations?

Again, this is an area of development where inhalation lactose suppliers and DPI developers can work together with regulators to ensure that the right balance is found between the general requirements of a pharmacopoeial monograph and the interests of the ultimate end user, namely the patient.

Conclusions

Inhalation lactose is an excipient of very high functionality that contributes greatly to the consistent performance of DPIs and, therefore, ultimately to patient well being. Suppliers, users and regulators need to work increasingly closely to develop deeper understanding of characterization, to adopt a different manufacturing strategy based on statistical models and to provide the right regulatory framework for future developments. **Pharma**

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