Terahertz characterization of lactose

Using terahertz spectroscopy to provide supplemental information about lactose characteristics for optimization of DPI formulations

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Inhalation

A number of scientific posters presented at recent meetings, including DDL 20, have focused on novel methods for characterizing inhalable lactose used as a carrier in DPI formulations, particularly approaches for quantifying amorphous content [1, 2]. Given that lactose characteristics, including particle size distribution, surface energy, water content, and crystalline form, have potentially significant effects on the performance of DPI formulations, the ability to understand and control those variables is critical for the control of formulation quality.

To date, however, the reasons for variation in DPI formulation performance due to differences in lactose have often been difficult to pinpoint. As Derek Solomon, Laboratory Manager at Melbourn Scientific, Melbourn, UK, points out, the USP-NF monograph tests for lactose often prove ineffective in predicting lactose performance in dry powder inhaler (DPI) formulations: "There's a whole list of tests that you would perform to qualify a batch of lactose for use; so you'd perform these tests, but then you would then potentially see differences in performance of your product once formulated."

As one of the DDL posters pointed out, researchers have investigated numerous methods for determining amorphous content in lactose, including differential scanning calorimetry, dynamic mechanical analysis, dynamic vapor sorption, isothermal microcalorimetry, IR spectroscopy, powder X-ray diffraction spectroscopy, and Raman spectroscopy [1], all of which have limitations. One relatively new method that has attracted attention recently involves terahertz spectroscopy, which covers the spectral range between microwave and infrared, 40 Ghz to 4 Thz.

Terahertz technology

Alessia Portieri, Senior Scientist at Teraview, Cambridge, UK, which markets terahertz spectrometers and terahertz imaging systems, reports that pharmaceutical companies began using terahertz systems about 4 to 5 years ago. As prices for the systems have moderated, several universities and pharmaceutical companies have acquired the technology and have been developing new applications over the past few years.

To date, the pharmaceutical industry has used terahertz technology primarily for the imaging of solid dosage forms, Portieri says. In fact, Teraview markets an imaging system specifically for pharmaceutical tablet analysis and has developed methods using

terahertz imaging to analyze solid dosage form variables including coating thickness and uniformity, interaction between tablet layers, and crack propagation within tablets.

Terahertz imaging, which combines terahertz spectroscopy with time domain measurement, can be used for non-destructive testing of most materials, except for metals. The system also has the ability to penetrate to depths of at least 3 mm, making it useful for imaging plastic parts such as inhaler components, and one recent project at Melbourn Scientific involved the investigation of valve failures in a particular device, according to the company's CEO, Mark Hammond.

Terahertz spectroscopy for formulation development

The use of terahertz imaging of lactose used in inhalation powders, which is relatively recent, could prove useful for manufacturers of both lactose and DPI formulations. While Portieri does not know of any lactose manufacturers currently using the technology, Solomon and Hammond point out that fiber optic probes could allow lactose manufacturers to perform in-line quality analyses, potentially monitoring moisture content, particle size, and/or amorphous content. For DPI developers and manufacturers, the primary benefit lies in understanding raw material characteristics in line with Quality by Design (QbD) principles.

To understand the potential of terahertz spectroscopy for the characterization of lactose, Portieri, Solomon, and Hammond all point to research conducted at Schering-Plough (now Merck) and presented in 3 posters at the 2009 AAPS annual meeting in Los Angeles [3, 4, 5]. The researchers demonstrated the ability of terahertz spectroscopy to quantify the amount of lactose monohydrate in a sample of lactose anhydrous NF and found significant differences in the amount of lactose monohydrate present in samples from different vendors, with amounts of lactose monohydrate ranging from 2-10% [3].

The same researchers used terahertz spectroscopy to differentiate between solid state forms of lactose synthesized from alpha lactose monohydrate [4]. The resulting spectral "fingerprint" of a particular batch, suggest Solomon and Hammond, could provide developers with additional data for understanding factors affecting DPI formulation performance. In addition, the Schering-Plough research showed the ability of terahertz spectroscopy to monitor in real time the transformation of α-lactose anhydrous unstable to α-lactose monohydrate, which occurs on exposure to humidity [5].

Because terahertz spectroscopy can penetrate capsules and the non-metal portions of blisters, the system also allows for evaluation of the moisture protection they provide. Theoretically, the system should be able to evaluate performance of the lactose after blending since the scan can differentiate between formulation components, though Melbourn has not yet tried that type of analysis.

The additional information provided by terahertz spectroscopy can to help define a design space for the lactose carrier, notes Solomon. Determining the amount of acceptable variability in the level of α-lactose monohydrate that will give acceptable performance allows manufacturers to evaluate specific batches of lactose to determine whether they are within the amount of tolerance to produce a formulation that will perform within specifications, allowing for more consistent product.

Although the cost of the instruments remains high—one of Teraview's basic terahertz spectrometers costs about £180,000 (~$288,000) before the addition of optional modules—several laboratories, including both Teraview and Melbourn, offer terahertz analysis for fees in the range of £1,000-1,500 ($1,600-2,400) per day. Formulation developers who would like to better understand how variation in a lactose carrier will affect their product may want to send samples to a lab with drug development experience for terahertz analysis.

References

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