



INGREDIENT-SPECIFIC PARTICLE SIZING: REDUCING RISK, CUTTING COST AND SAVING TIME IN PRECLINICAL INHALABLE FORMULATION DEVELOPMENT

In today's fast-growing inhalables market, the availability of suitable, efficient and cost-effective means of gathering particle analysis data for pulmonary formulation is clear. In this article, Dr Oksana Olkhovyk, Senior Scientist, and Linda Batykefer, Marketing Manager, both of ChemImage Corporation, provide the latest about cutting-edge imaging tools for ingredient-specific particle sizing that ChemImage is putting at the disposal of the global pharmaceutical industry.

INTRODUCTION

There is an abundance of evidence supporting the fact that the markets both for respiratory drugs and respiratory drug delivery technologies are healthy, vibrant and growing. In recent years, whilst pharmaceutical company product pipelines overall have been reduced, along with the number

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of new drug approval applications submitted to regulatory authorities, pharmaceutical companies are continuing to pursue new delivery methods for their drug products. The inhalation and nasal products had combined sales exceeding US\$22 billion in 2007 for treatment of asthma, COPD, allergic rhinitis, influenza, migraine and osteoporosis, and for use in general anaesthesia.¹

One common trend is to develop respiratory delivery technologies for drugs currently administered via injection. Despite some initial problems, such as the failure of Pfizer's Exubera (inhaled insulin), the concept of systemic

delivery via the lung is by no means dead, and many companies continue to develop inhaled drug products.²

While the indications for many inhalable and nasal drug delivery products have been somewhat limited to diseases such as allergic rhinitis and asthma, this is likely to change soon. Continuous research and development activities are gradually opening up opportunities in new therapeutic areas.

Nasal drug delivery is becoming more common due to the potential for increased drug uptake rates, improved bioavailability for certain drugs (relative to oral dosing), and convenient administration. A growing number of nasally delivered, systemically acting drugs for a number of therapeutic areas are reaching the market or are in the pipeline.³

Other areas where new nasal and inhalation drug delivery approaches could provide an alternative to current dosage forms (such as intravenous administration) are crisis situations (seizure and heart attack), motion sickness and psychotropic drugs.³

WHY PARTICLE SIZE MATTERS

For nasal sprays and aerosolised products, there are two important measures of particle



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size. The first measurement is that of the aerodynamic particle size, which is traditionally measured via cascade impaction, and is the key method of predicting where particles will deposit in the nose, oesophagus or lungs.

The second measure, the drug particle size, is an important determinant of the rate of dissolution and availability to sites of action within the nose (optimally approximately 10µm) or the lungs (<5µm). Therefore drug, or drug aggregate, particle size distribution (PSD) should be characterised in the formulation both within the primary container and within the aerosolised droplets.⁴

INGREDIENT-SPECIFIC PARTICLE SIZING

The ability to gather general, basic information for a given formulation about aerodynamic particle size and particle size distribution is of course an essential starting point in successful product development. However, traditional methods only provide the most rudimentary, purely physical data and cannot differentiate as to what a given particle comprises chemically.

There is so much more useful information to unlock. In reality, inhaled formulations are rarely, if ever, comprised of just one ingredient. There will usually be at least two components; the active pharmaceutical ingredient (API) and an excipient. Furthermore, the presence of more than two ingredients is becoming more commonplace as combination products – containing two APIs plus an excipient – are developed.

It cannot be assumed that all ingredients have similar physical characteristics, exhibit uniform particle size distribution nor that they behave in the same way. Thus, information pertaining to the particle size of specific ingredients represents a significant advancement and holds many advantages.

Ingredient-specific particle sizing (ISPS) is the technique offered by ChemImage which fulfils precisely this requirement for particle size data.

The technique uses ChemImage's unique technology combination of Raman chemical imaging, optical microscopy, and automated data gathering software to identify particles based on a unique chemistry (for example API versus excipient) and physical size information. Chemical information is based on the component chemistry identified by the unique Raman scattering.

An example of ingredient-specific particle size distribution data for a sample formulation containing two APIs is shown in figure 1. The

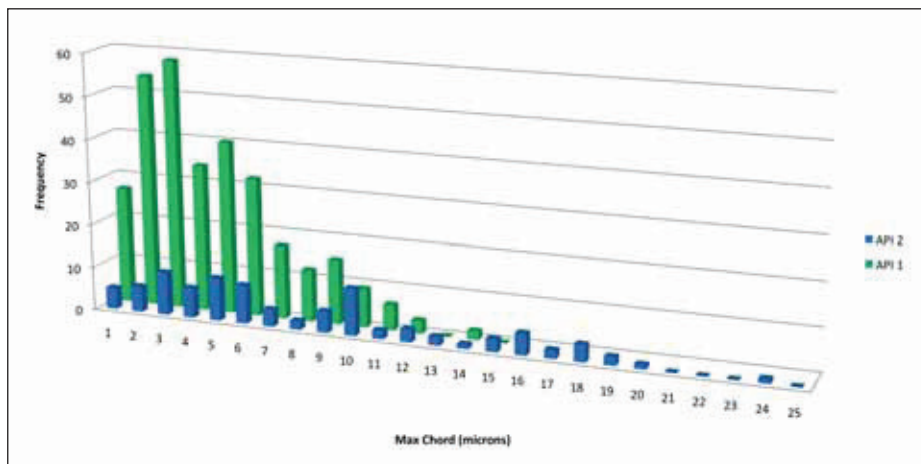


Figure 1: Example particle size distribution (PSD) chart showing ingredient-specific PSD of two APIs.

data is obtained from the combined information of the optical and Raman chemical image.

See boxed text on page 8 for more information on Raman chemical imaging and Raman spectroscopy.

Raman spectroscopy is a very selective vibrational technique and is often used in the pharmaceutical industry to identify drug polymorphs (different crystalline structures that are made of the same molecules, but exhibit various crystal habits or packing). With the ability to detect such small spectral differences, Raman spectroscopy is very comfortably able to differentiate between various materials in a pharmaceutical formulation, including the drug substance and various excipients (see figure 2).

Ingredient-specific particle sizing is especially useful for drug-specific particle sizing of both metered dose inhalers (MDIs) and nasal spray suspensions. The method was initially investigated in collaboration with the US FDA to achieve drug particle size distribution

measurements for nasal spray suspensions.⁵ In addition to investigating formulations for API particle size distribution, ISPS has been found to be useful for the study of drug/drug and drug/excipient aggregates.

Particle size is directly related to deposition location in the body as well as bioavailability. Aggregates, which in effect bring about an increase in overall particle size, cause a number of problems including:

- clogging of the medical device
- deposition in the wrong or unwanted part of the body
- changes in bioavailability

Readily available, high quality drug particle size data could provide the necessary information for conclusive in vitro bioequivalence (BE) comparisons of drug PSD, including PSD of dispersed and agglomerated API particles, as well as the extent of agglomeration in the product.⁵

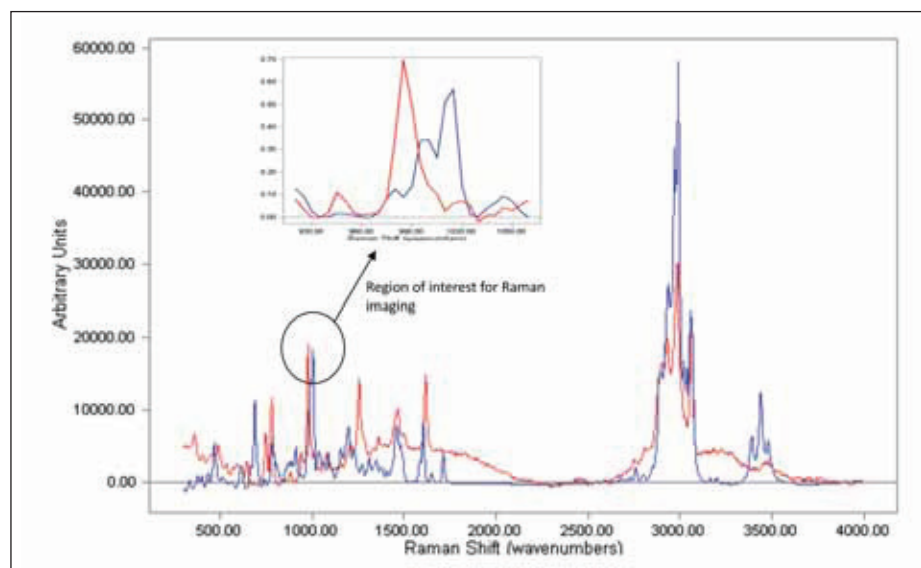


Figure 2: Raman Spectra of API components showing the ability of the Raman method to be used to distinguish the two API materials from one another.

Obtaining drug particle size information is important from a cost perspective. Prior to entering clinical trials, this additional information can prove to be valuable, raising confidence and lowering risk of failure for *in vivo* biostudies.

The value and importance of gaining this information before taking the expensive step of beginning clinical trials cannot be emphasised enough.

To give another example, in generic product development, if drug PSD of the generic is found to be not equivalent to (or outside of acceptable variability thresholds of) the innovative product's PSD, clinical trials can be postponed until the acceptable drug PSD is reached – saving significant time and money for generic companies.

Ingredient-specific particle sizing technology and service helps innovative drug developers to characterise and design their formulations better and, further on in development, as part of batch release testing.

With the increase in interest from innovative drug developers in inhalation and nasal drug delivery, methods that characterise formulations without destroying the sample are increasingly needed.

With additional information related to drug particle size and material composition at their disposal – information which was not easily accessible in the past – innovators are even better equipped to design unique, hard-to-duplicate formulations.

ISPS has proven especially useful for innovative drug developers who are interested in combining multiple drug substances in one formulation. While cascade impaction is useful for MDIs and DPIs when only one active ingredient is present, the situation becomes more complicated when two APIs are present. Raman chemical imaging has been evaluated as a possible candidate to replace cascade impaction as a tool to determine chemical identity PSD. An example of such an application of ISPS technology follows.

RAMAN CHEMICAL IMAGING FOR PSD OF TWO APIS IN COMBIVENT™ MDI

The MDI is the most common device for therapeutic aerosol delivery, second only to tablets among self-medicated dosage forms.⁶ The PSD of the drug substance in the aerosol plume is a very important parameter and, in

regulatory terms, is a required measurement for *in vitro* testing of MDIs.⁶ A typical MDI formulation contains API, propellants and surfactants. Although PSD of the drug can be easily determined prior to the formulation, it is a challenge to establish it in the finished product.

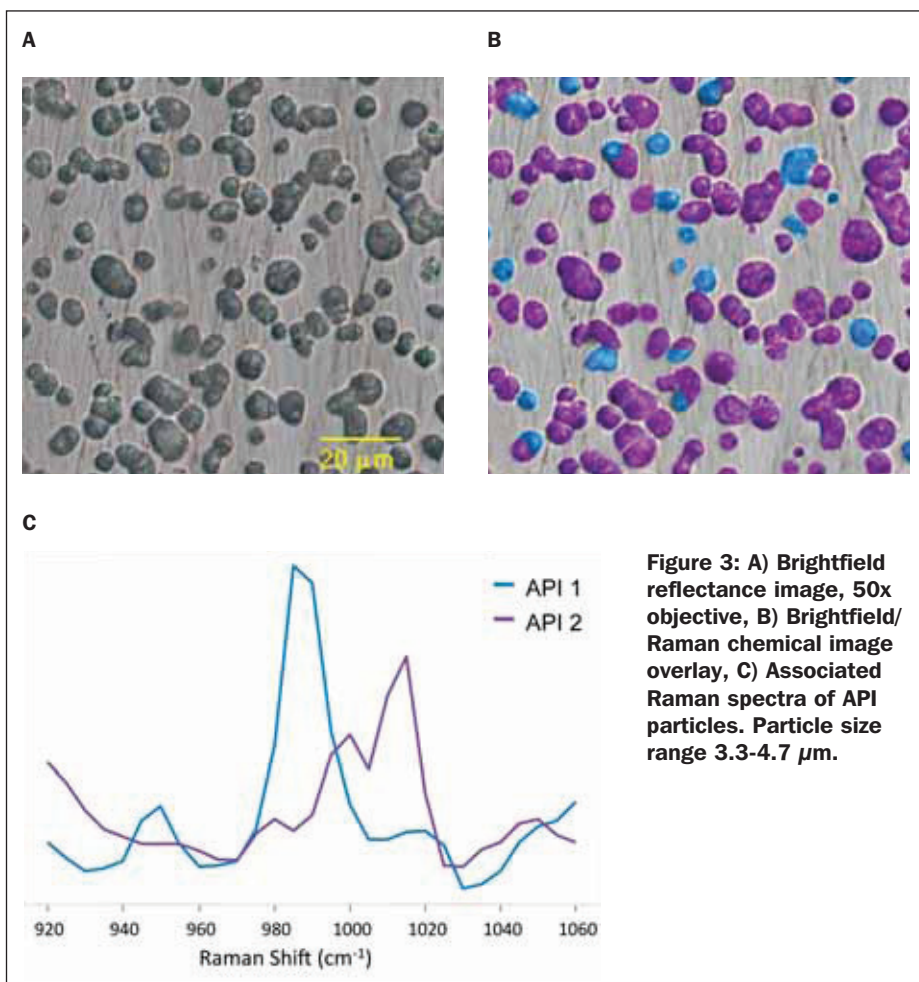
The standard traditional apparatus for the *in vitro* determination of PSD information is the Anderson cascade impactor (ACI). A complete ACI analysis includes introduction of the sample into the ACI where particles are separated on the basis of their aerodynamic size, this is followed by extraction of the drug substances from the ACI plates, final filter, USP throat and mouthpiece adaptor, and finally performing quantitative chemical analysis by either HPLC or spectroscopy methods.

The procedure is time consuming, labour intensive and destructive. Presence of non-volatile excipients in the formulation or a second API may complicate particle size characterisation even further. Analysis of the deposition profiles may indicate formulation issues such as agglomeration of APIs or physicochemical stability (polymorphism, hydration) after actuation. Furthermore, a large variability in results has been observed between different operators and different ACI units. As a consequence, there is a high demand for the replacement of the ACI with an alternative technique capable of concurrently performing PSD determination and chemical identification.⁶

In a previous study, Raman chemical imaging (RCI) was evaluated as a method for identifying two API species on cascade impaction plates and characterising drug interaction in Combivent® Inhalation Aerosol (Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT, United States), an MDI sample containing two APIs. RCI successfully identified each API particle and the total number of particles and PSD for each API and PSD of aggregated API particles were reported.⁶

ChemImage had successfully applied RCI to measure ingredient-specific size distribution in formulated nasal sprays and aerosols. This investigation was initially reported in 2005; significant progress has been made since to optimise the technique and enhance the capabilities of RCI for the pharmaceutical industry. Issues have been addressed related to automation, image processing, and particle size analysis by applying an automated method of data collection and analysis of fused RCI and brightfield imaging.^{7,8} A new, patent-pending image processing method has been developed to evaluate each particle in the field of view individually, rather than collectively.⁹

Using this image processing technique, the original Combivent RCI data reported by Guo *et*



al was revisited. API 1 (albuterol sulfate) and API 2 (ipratropium bromide) are presented as purple and blue in the brightfield / Raman binary image overlay (figure 3). Intensity maps were developed for each API using an iterative threshold process. Once the particle map is produced, a feedback loop is initiated which confirms the chemical identity against the Raman spectrum and validates the particle size against the brightfield optical image. This individual particle identification approach allows for a more accurate and reliable drug PSD measurement, effectively addressing concerns of accurate size measurements in the previous publications.⁵ This combined image analysis approach helps to avoid the issue of over- or under-sizing particles due to Raman signal intensity – which is related to size of the particle.

CHEMIMAGE'S SERVICES: HOW AND WHEN?

The ISPS services offered by ChemImage and described here represent a material advance in the speed, cost and level of detail at which companies developing inhalable formulations can investigate their products' properties and behaviour.

The major advantage of utilising these contract services is the ability to understand

the drug properties within the formulation. RCI provides drug particle sizing and distribution information and also provides information about aggregates. What is the drug PDS for each API? What particles are aggregating? Are drug particles aggregating or are drug and excipient particles aggregating to one another? Is this related to the device delivery or does this happen in the bulk formulation?

ISPS can be used during product development, specifically formulation development, as well as R&D for novel or existing formulations and during manufacturing for batch release testing. Possessing this information could ultimately result in, for example, faster ANDA filing, or more efficient and successful clinical trials. With a better understanding of the formulation, companies can mitigate risk in a number of steps during development for approval.

The earlier in formulation development this technique is employed, the better the chances of identifying incorrect drug particle size distribution, or aggregation issues.

If being used as part of a BE study, this method can also be used to gain an understanding of the innovator drug product. This testing can be done early on before the innovator or generic product is even in development, or it can be done in parallel.

TO OUTSOURCE RESEARCH OR PURCHASE EQUIPMENT?

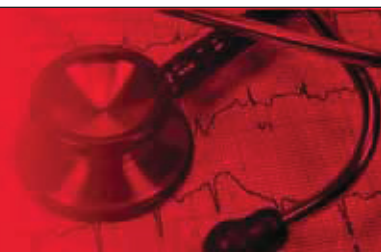
ChemImage typically offers its ISPS services on a contract research basis. However, it is also possible to purchase the equipment necessary to do this work from ChemImage. This is especially useful for organisations which plan to do a significant amount of drug PSD testing in the future. Larger volumes of sample testing may make purchase of the equipment more cost effective. Purchase of the equipment is a capital expense, but also offers customised options for multiple imaging platforms including microscopic Raman and Near-IR or Fluorescence chemical imaging capabilities in addition to basic optical microscopy and Raman spectroscopy.

ABOUT CHEMIMAGE:

Founded in 1994 and headquartered in Pittsburgh, PA, US, ChemImage provides revolutionary Raman, Near-Infrared and Fluorescence chemical imaging technologies for chemical and biological applications in numerous global industries including



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Q: What is Raman Chemical Imaging?

A: Raman chemical imaging builds on the ability of spectroscopy by adding a spatial context to the chemical information provided. Raman Chemical Imaging (RCI), a method that combines the capabilities of molecular spectroscopy and advanced digital imaging, details material morphology and composition with a high degree of specificity in a non-contact, non-destructive manner.

A Raman chemical image provides a Raman spectrum at each pixel in the image, providing spatially resolved Raman spectroscopic information. Interrogation of individual pixels assists in the interpretation of the data. Presence or absence of API within a field of view is determined by whether or not the Raman spectral features characteristic of the drug are present. Imaging allows one to understand size, shape, and spatial distribution of chemical components which provides a number of advantages of simple Raman spectroscopy, and in particular drug particle sizing for nasal and pulmonary drug products.

In the wide-field RCI approach, digital images are acquired at pre-defined Raman spectral regions, by imaging an area through an electro-optically controlled, liquid crystal tunable filter (LCTF) which serves as an imaging spectrometer. The RCI microscope simultaneously provides diffraction-limited spatial resolution

(approaching 350 nm for high signal-to-noise images) and high Raman spectral resolution. The no-moving-parts approach employed to construct Raman chemical images enables fusion of optical and Raman chemical imaging data. Fused optical/Raman images are used to guide the size measurements, differentiation between drug aggregates and individual particles. This approach helps eliminate problems often seen with morphologically-directed, confocal Raman spectroscopy, which requires precise, repeatable stage translation.

Q: What is Raman spectroscopy?

A: This is a spectroscopic technique used to study vibrational, rotational, and other low-frequency modes in a sample system. It relies on inelastic scattering, or Raman scattering, of monochromatic light, usually from a laser in the visible, near infrared, or near ultraviolet range. The laser light interacts with phonons or other excitations in the sample system, resulting in the energy of the laser photons being shifted up or down in energy. The shift in energy gives information about the phonon modes in the system.

Scattered photons from the illuminated sample spot are collected with a lens and sent through a monochromator – or in the case of imaging an imaging spectrometer. Wavelengths close to the laser line, due to elastic Rayleigh scattering, are filtered out while the rest of the collected light is dispersed onto a detector.

pharmaceutical, anatomic pathology, forensics and threat detection.

The ChemImage workforce of researchers, software designers, hardware developers, scientists, business analysts and administrative support has tripled in the new Millennium, as more and more industries begin to understand and integrate the power of chemical imaging as a tool for realising their vision.

ChemImage currently has an extensive patent portfolio including 75 issued US patents, 12 allowed patents and has over 100 US and foreign patents for technology and methodology advancements across all of our lines of business.

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