Gaining new insights into pressurized metered dose inhaler (pMDI) design using synchrotron radiation

New laboratory tools use X-rays to reveal the inner workings of pMDIs, accelerating the development of new devices and formulations

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The development of new devices for the delivery of inhaled drugs depends on the ability to demonstrate equivalence with existing products. A common feature of all measures of equivalence is that they are an end result of a complex chain of events which begins with the formulation, and includes all the components of the delivery device, and environmental conditions. Analytic tools such as cascade impaction can provide valuable information on the nature of the drug particles produced, but cannot reveal the underlying processes inside the device that lead to these outcomes.

To address this challenge, new laboratory tools are required that can quickly reveal the inner workings of prototype devices and accurately measure the properties of the droplets or particles produced. A concrete example that underlines the need for such tools is the phase down of chlorofluorocarbons (CFCs) in pMDIs, which necessitated design changes in dose metering, use of different valves and seals, co-solvents and filling processes, etc. Another major transition is approaching, from hydrofluorocarbons (HFCs) to less greenhouse-intensive propellants. Detailed device and formulation modifications will be required to achieve this.

The magnitude of the challenge in developing the new tools required to produce the next generation of devices is exemplified by the operational principles of the pMDI. Vaporisation of the propellant in a pMDI results in significant variations in the quality of the spray, at scales on the order of millimeters and milliseconds. These processes, which begin inside the actuator itself, ultimately determine the nature of the final particles and the efficacy of the device. pMDI sprays are an exceptionally difficult environment in which to make accurate scientific measurements. Rapid evaporation of the propellant in the spray causes significant evaporative cooling, resulting in the formation of cold, dense clouds of vaporized propellant gas around the droplets, at temperatures below -25°C. Large temperature gradients and high droplet number densities conspire to limit the capabilities of traditional, laser-based aerosol testing tools. While they can provide useful measurements of velocity and size,[1] many other droplet properties (such as composition, temperature and drug distribution) are difficult to measure.

A response to this challenge is to move away from reliance on visible light, and instead use a synchrotron X-ray beam to reveal the inner workings of devices such as pMDIs. Synchrotron radiation is produced by turning energetic electron beams in magnetic fields. This produces bright, high resolution X-ray beams that can be tuned to specific wavelengths. Complex, specialized beamlines are required and experiments must be conducted remotely in a heavily shielded room. This article hopes to demonstrate that the benefits of using synchrotron radiation far outweigh the costs of providing this type of facility.

Depending on how they are used, synchrotron X-rays can provide valuable quantitative information on drug distribution, spray density, droplet and particle properties; metrics that are difficult or virtually impossible to obtain by other means. Unlike many traditional measurement techniques, synchrotron measurements can provide direct evidence of the effects of changes to actuator design and formulation composition on the behavior of a device, a formulation or both, rather than simply indicating a change in the end result (such as determination of fine particle fraction). This can shorten the design feedback loop and allow for more rapid develop-

ment and assessment of prototype devices. The fundamental insights gained through these measurements can facilitate the development of models to support the design of new inhaled pharmaceutical products.

X-ray techniques in pharmaceutical science

X-rays have a long history in pharmaceutical science.[2] Crystallography and powder diffraction, which reveal the structure of complex molecules, are integral to the drug discovery process. The advent of synchrotron radiation in the late 20th century enabled many new developments in pharmaceutical science that are too numerous to list here.[3]

Synchrotron beams are thousands of times brighter than traditional X-ray tube sources, thereby enabling very fast measurements. In addition, synchrotron radiation can be filtered to generate monochromatic (single-wavelength) beams while retaining high throughput. Synchrotron beams, like lasers, are also highly collimated so light remains parallel over a long distance, enabling high resolution.

Although X-rays have been used for many decades in pharmaceutical science, their use in aerosol and spray science is relatively new. Over the last 15 years, a significant effort has been invested in the development of techniques to study optically dense sprays in harsh environments, such as fuel sprays for internal combustion engines.[4] A benefit of X-rays is that they scatter weakly, compared to visible light. This means they are relatively unaffected by the high density, composition and temperature changes in sprays that confound traditional measurement techniques. Over the last few years, these tools have been adapted for use in pMDIs, and are now starting to be used by several research and development teams around the world[5] to aid in the design of a variety of pMDI products.

This article presents an overview of some of the most commonly used synchrotron techniques for sprays, describes recent work in applying these techniques to pMDIs, and gives examples of the insights that can be gained through their use.

Phase contrast imaging

X-ray phase contrast imaging techniques exploit the intense, collimated nature of synchrotron light to produce detailed images of the internal structure of objects.[3] X-rays reveal fluid motion inside opaque objects such as pMDI actuators, without the need for any modifications or contrast agents. The short wavelengths of X-rays give rise to sharp images with micrometer resolution. The short pulses produced by synchrotrons allow moving features like droplets to be imaged with great clarity.

An example experiment in a pMDI nozzle[6] is shown in Figure 1. An X-ray beam is allowed to enter the test section through a shutter. The beam power can be on the order of kilowatts, so exposure times are limited to milliseconds in order to avoid damaging the system.

When X-rays pass through the actuator, the liquid formulation will absorb some of the X-rays while the vapor permits the beam to pass through relatively unimpeded. The surfaces of droplets and bubbles also deflect some X-rays, which interfere with parallel rays, resulting in diffraction patterns. These are recorded on a scintillator screen some distance from the actuator. The visible light emitted by the scintillator is captured with a microscope and high-speed camera.

An example of some X-ray phase contrast images in placebo pMDIs are shown in Figure 2. These experiments were conducted at the 7-ID beamline of the Advanced Photon Source at Argonne National Laboratory (Lemont, Illinois, US). The expansion chamber and nozzle region of a conventional pMDI are shown in false color. Dark regions represent strong absorption while bright regions indicate that the beam has passed through unimpeded. The fluid enters the expansion chamber from the top and exits through the nozzle at center-right (top left panel). Three snapshots at the start, middle and end of a spray event are shown from top to bottom. In the left column, an HFA-134a placebo formulation with 15% ethanol co-solvent is imaged. In the right column, a pure HFA-134a formulation is imaged.

The images reveal strong swirling motions as the fluid first enters the chamber (top row). Later, significant differences between the two formulations appear. The solvent-containing formulation forms a fine foam, while the pure propellant formulation forms large bubbles. These two scenarios result in different inlet conditions for the nozzle. In both cases, the bubbles grow over time as the actuator empties. This indicates decreasing chamber pressure and rate of delivery over time. When an active pharmaceutical ingredient (API) is introduced, settling in the bottom of the chamber can occur. Clogging of the nozzle between actuations can be directly observed when it occurs.

Figure 1

Schematic diagram of the X-ray phase contrast imaging technique.

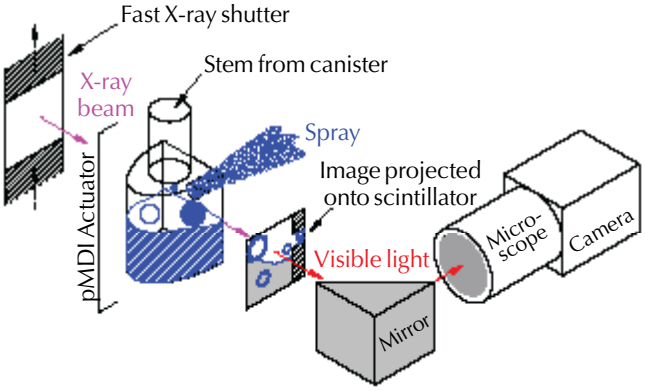
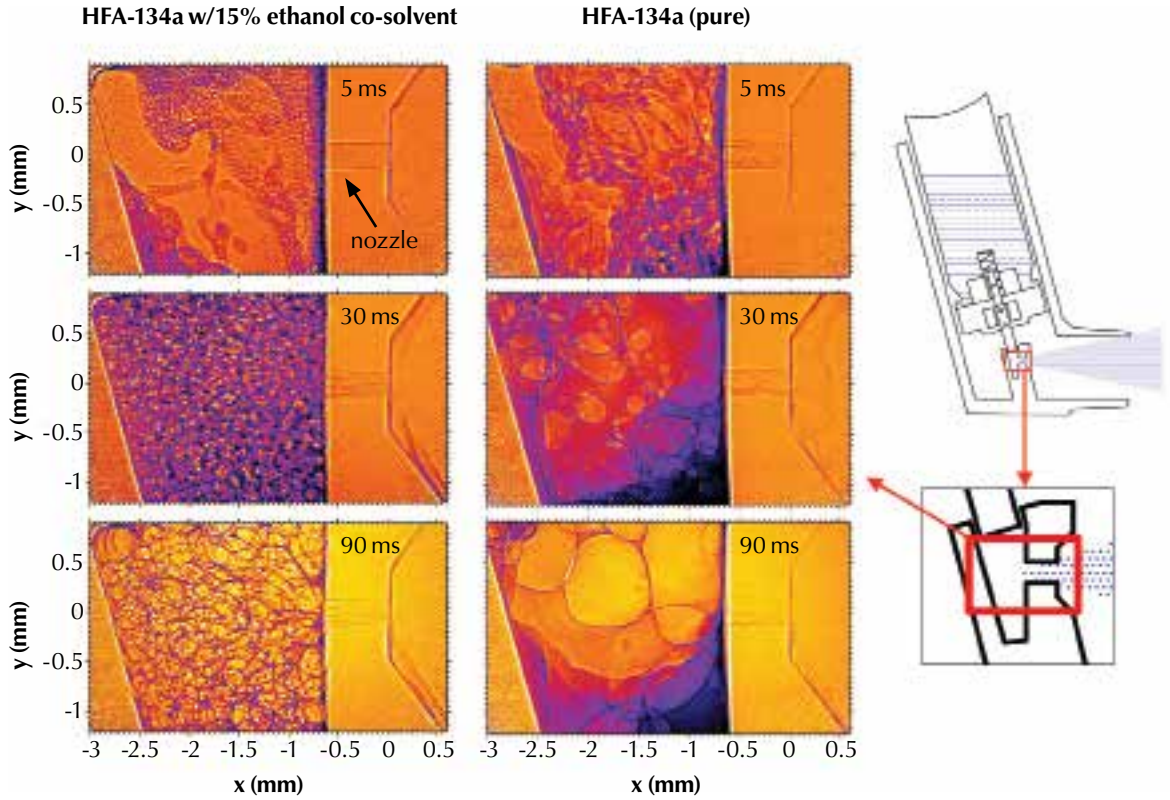


Figure 2

Sample false-color phase contrast images inside a placebo pMDI with 15% ethanol co-solvent (left column) and pure HFA-134a propellant (right column).



X-ray phase contrast images can be difficult to interpret, as complex three-dimensional features are flattened into a single image. However, it can provide valuable insight into the structure of the flow inside the pMDI and gives instant feedback on the effects of changing the actuator or formulation. For example, one can observe that the vaporization process begins inside the metering valve, well before the fluid reaches the nozzle. In addition, formation of droplets begins, not in the spray or at the exit of the nozzle orifice, but at the entry to the nozzle orifice. These insights are now enabling the development of more physically representative models for pMDI droplet formation.

Focused-beam techniques: Radiography, elastic scattering and fluorescence spectroscopy

While powerful, X-ray imaging is not well suited to studying the structure of the spray outside the actuator. This task is made easier through the use of focused, monochromatic X-ray beams.[4] These beams can provide high temporal and spatial resolution, at the cost of only being able to analyze a small region of space. The beam focus is typically 5-10 µm wide. The temporal resolution can be as fast as 150 ns. Different wavelengths and detectors enable a range of techniques, three of which are discussed here.

X-ray radiography measures the fraction of X-rays transmitted through a spray.[4] An example is shown in Figure 3. If the composition of the spray and the surrounding gas are known, the total mass inside the beam at a given point in space and time can be easily determined.[7] Radiography reveals the complex, rapid variations that occur throughout the duration of pMDI sprays and how they are affected by the actuator and formulation. A limitation is that radiography cannot distinguish the effects of the API from the propellant; fluorescence techniques are required to achieve this and these are discussed in more detail later.

By their nature, sprays of small droplets tend to be dilute so the fraction of the beam absorbed is less than 1%. This limits the quality of the data that can be obtained for a given sample size. However, when X-rays are absorbed by the spray, they are also weakly scattered. A small fraction of these can be detected by a scattering detector,[8] as shown in Figure 3. An example time-resolved, elastic scattering measurement is shown in Figure 4 (blue line, top right). Here, an HFA-134a formulation with 15% ethanol co-solvent and 3.38 µg/µL ipratropium bromide (API) is shown. The measurement is 1.5 diameters from the nozzle, in the center of the spray. The measurement reveals the unsteadiness of the spray core.

When X-rays interact with the API, X-ray fluorescence can also occur. X-ray fluorescence enables tracking of a suspended or dissolved API, independently of any co-solvent, excipient or propellant.[9] The API must contain a suitable element that is not contained by any

Figure 3

Schematic diagram of focused-beam techniques for pMDI sprays; radiography, elastic scattering and fluorescence.

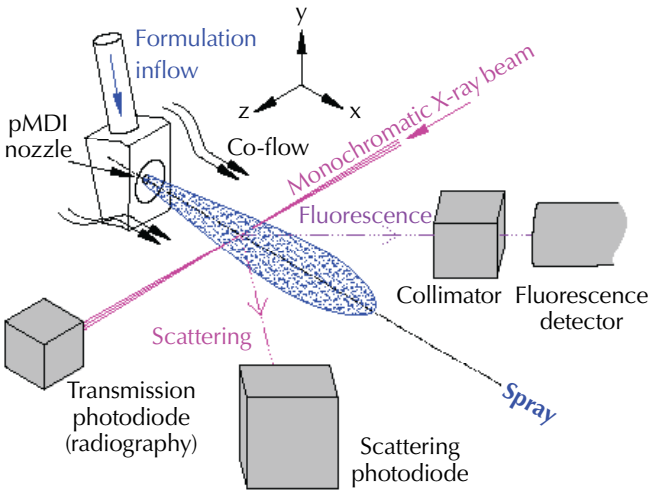
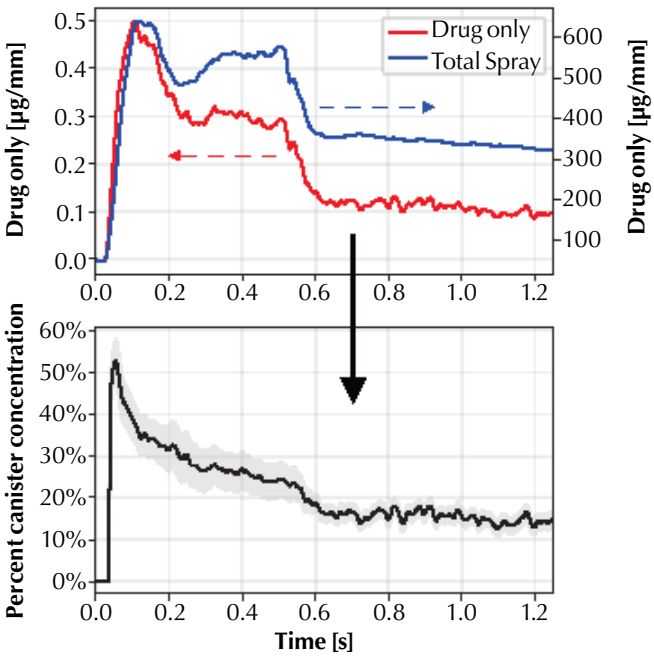


Figure 4

Sample results from scattering (blue) and fluorescence (red) measurements in a solution-based pMDI spray at x/D =1.5.



other molecule in the formulation. In practice, these elements are chlorine (17) through cerium (58). Unlike visible fluorescence, the X-ray photons can escape the dense core of the spray. A detector that can discriminate photons based on their energy is used to capture them, as shown in Figure 3. These experiments were conducted at the 7-BM beamline of the Advanced Photon Source at Argonne National Laboratory. A sample result for an HFA-134a formulation with 15% co-solvent and 3.38 µg/µL ipratropium bromide is shown in Figure 4 (red line, top right). The fluorescent tracer is the bromine atom in the ipratropium bromide molecule; no dopant is required.

An advantage of focused-beam techniques is that they can be made simultaneously. By measuring the total mass of spray and the amount of drug present in the spray at the same time, the instantaneous mass fraction of drug inside the spray is revealed. This is shown in Figure 4 (black line, lower right) with the shaded region indicating uncertainty. This measurement is effectively independent of the number density of droplets in the spray and reveals that the underlying concentration of the drug inside the droplets decays during the spray. This can be compared to the expected concentration of the drug in the formulation. As has been known for some time, a significant portion of the drug remains in the canister and actuator after use. Focused-beam measurements allow determination of exactly why, when and how this is occurring.[9] This insight is now being used to inform the design of improved actuators.

Ultra-small-angle X-ray scattering (USAXS)

One of the complicating factors in predicting the behavior of pMDIs is that the formulation is a multi-component mixture. For solution pMDIs, in particular, differences in volatilities between propellants and co-solvents make predicting droplet composition difficult, even if the formulation is well defined. Phase-contrast imaging (Figure 2) reveals that the propellant begins to boil inside the actuator so the composition is likely different at every stage of the spray formation process. The composition and evaporation rates of the droplets are intricately connected to particle formation. Temperature and solubility changes can have drastic effects on the shape of the particles. Variations in particle shape alter their aerodynamic properties and surface area, affecting deposition in the airway and rate of absorption. To understand how the actuator drives these changes, a means of measuring the local composition of the droplets and particles where they are first created is required.

The elastic scattering of X-rays from droplets and particles at small angles depends on their surface area, volume fraction and composition. If the composition is known, ultra-small-angle X-ray scattering (USAXS) can be used to measure surface area and size of droplets in environments that are too optically dense to permit laser scattering.[10] In pMDIs, however, the spray plume is sufficiently dilute to allow size distribution measurement using laser diffraction. This opens up the possibility of using USAXS and laser diffraction together to determine droplet composition. In solutions of fluori-

nated propellants, droplet electron density can vary by up to 40% as the propellant evaporates, causing significant changes in scattering intensity. Since both techniques are volumetrically averaged, the spray need not be monodisperse. Due to the short wavelengths of X-rays, the droplet size must be small enough so the scattering angle is sufficiently large. For benchtop X-ray scattering instruments, this limits the droplet size to less than 1µm, which is too small. However, the USAXS instrument at the 9-ID beamline of the Advanced Photon Source at Argonne National Laboratory[11] can achieve much smaller scattering angles, increasing the maximum droplet size above 10 µm.

An example USAXS experiment is shown in Figure 5. X-rays scattered from the spray are only permitted to reach the detector within a narrow range of angles. The analyzer crystals are rotated to obtain a rocking curve over a range of angles. A large number of sprays must be repeated to build a complete set of measurements. Using focused-beam mass distribution and laser diffraction sizing, the electron density contrast at a given location is determined. From this, the composition of the droplets can be calculated.

A result of such a measurement is shown in Figure 6. As in the previous examples, an HFA-134a formulation with 15% ethanol co-solvent and 3.38 µg/µL ipratropium bromide was investigated. The measurements were made along the centerline of the spray (horizontal axis). The blue bars indicate the Sauter mean diameter of the droplets, as measured by laser diffraction. The orange bars indicate the volume fraction of co-solvent in the droplets as determined by USAXS composition measurement. At 7.5 mm from the nozzle, all the propellant has evaporated and the droplet is pure co-solvent. Any further decrease in electron density beyond this point is entirely due to ethanol evaporation, at which point precipitation of the API inside the droplets can begin. These data reveal the regions of the spray in which co-solvent evaporation (and precipitation processes) are occurring. Evaporation affects the precipitation rates of particles, and thus their size, shape, and surface area. All these parameters affect the clinical efficacy of the formulation. These insights enable the development of precipitation models for new formulations. USAXS techniques are also capable of similar measurements in suspension pMDI sprays and in the future may also be applied to DPIs.

Supporting the development of new inhalers

Table 1 lists synchrotron radiation techniques, their purposes, benefits and disadvantages. Depending on the research question being asked, one or more techniques would be used. Some techniques, such as radiography and fluorescence, necessarily go hand-in-hand. Others such as phase-contrast and USAXS can be performed, when necessary, to address specific questions. Research to date has been exclusively on pMDIs but these techniques may also be used in the future to evaluate other types of inhalers, such as DPIs or nebulizers.

Synchrotron radiation offers a means for investigating the behavior of complex fluid mixtures inside small devices such as pMDIs. Synchrotron X-rays can provide valuable quantitative information on drug distribution, spray density, and droplet and particle properties; metrics difficult to obtain by other means. Synchrotron measurements also can provide direct evidence of the effects of changes to actuator design and formulation composition on the behavior of a device, a formulation or both. This can shorten the design feedback loop and allow for more rapid development and assessment of prototype devices to facilitate the intro-

Figure 5

Schematic of an ultra-small-angle X-ray scattering (USAXS) experiment.

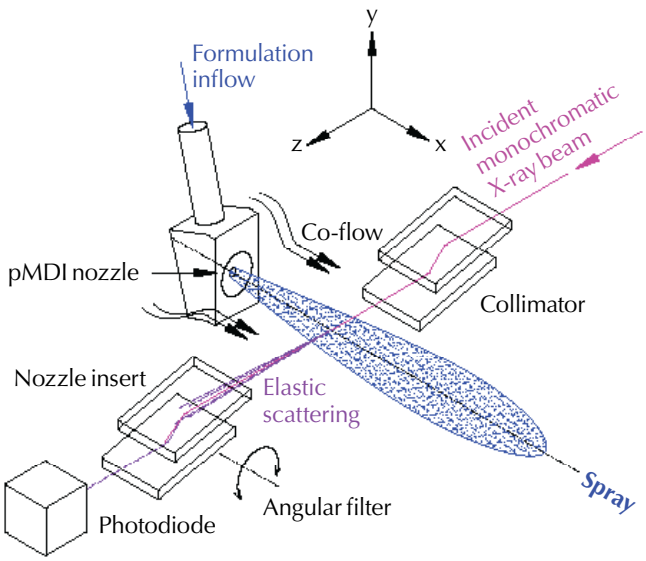
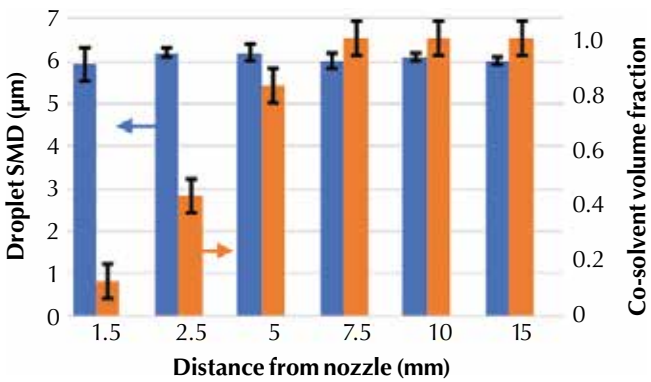


Figure 6

Sample results from a USAXS experiment in a solution-based pMDI spray of 85% HFA-134a, 15% ethanol, and 3.38 µg/µL ipratropium bromide. Average droplet diameter (blue) and droplet composition (orange) are shown against distance from the nozzle.



duction of new inhaled pharmaceutical products. While synchrotron facilities are not widely available, it is hoped they will benefit the development of a wide range of inhaled pharmaceutical products.

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Table 1

Summary of X-ray measurement techniques and their purposes, benefits and disadvantages

Technique	Evaluates/Determines Purpose	Benefits	Disadvantages
X-ray Phase Contrast	Evaluates/Determines: Internal structure of liquid flow inside devices Purpose: Rapid assessment of flow in prototypes	• Correlates internal geometry to changes in spray properties • Does not require modification to device • Suitable for all liquid-based delivery devices • Investigate causes of clogging and deposition	• Difficult to determine quantitative properties, such as liquid density or droplet size • Requires specialized synchrotron facility • Not suitable for DPIs
X-ray Radiography	Evaluates/Determines: Accurate measurements of local spray density at high speed Purpose: Link changes in impactor measurements to changes in spray, due to formulation and/or device	• Does not require a synchrotron source; a lab-scale X-ray source fitted with a polycapillary optic could also be used • High temporal resolution, enabling observation of fast-moving droplets and particles • Suitable for all liquid-based delivery devices • Enables assessment of effects of formulation changes in regions where environmental and patient-use factors are not yet influential	• Weak absorption of X-rays limits precision of data • Requires a specific range of X-ray energies (6-8 keV) • Requires many repeated sprays • Not well-suited to DPIs • Cannot be conducted simultaneously with X-ray fluorescence unless X-ray beam is polychromatic
X-ray Elastic Scattering	Evaluates/Determines: Accurate and precise measurements of spray density Purpose: Demonstrate equivalence of spray between devices and formulations, independent of environmental factors	• Does not require a synchrotron source; a lab-scale X-ray source could also be used • Better signal quality than radiography and can be performed simultaneously with X-ray fluorescence • With X-ray fluorescence, enables drug mass loading in droplets to be quantitatively assessed inside the spray; this is not possible using conventional measurement tools	• Requires complex calibration procedure • Limited time resolution compared to radiography; can only observe average densities, not individual particles or droplets
X-ray Fluorescence	Evaluates/Determines: Local drug concentration in droplets and particles Purpose: An unequivocal means of demonstrating equivalence of drug delivery capacity of new devices and formulations, independent of environmental factors	• Combined with elastic scattering, enables drug mass loading in droplets to be quantitatively assessed inside the spray; this is not possible using conventional measurement tools • Unaffected by co-solvent, propellant and ambient conditions • Suitable for liquid sprays, nebulizers and dry powders	• Requires careful calibration • Requires specialized detector equipment
Ultra-Small Angle X-ray Scattering	Evaluates/Determines: Droplet composition and evaporation rates Purpose: Determine in situ evaporation and precipitation rates for the prediction of particle structure and translation of single-droplet measurements	• With radiography, enables evaporation rates and composition of droplets to be determined inside the spray; this is not possible using conventional measurement tools • Unaffected by co-solvent, propellant and ambient conditions • Suitable for liquid sprays, nebulizers and dry powders	• Requires a specialized synchrotron beamline • Requires careful calibration • Not stand-alone; must be supported by other measurements (i.e., radiography) to obtain quantitative results

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