Applications of surface analytical techniques in characterization of dry powder formulations

A brief review of advanced characterization techniques used to determine the surface chemistry of dry powder formulations

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Introduction

Production of inhalable drug particles traditionally involves milling, spray drying, spray freeze drying and supercritical fluid processes. Many of these processes expose the formulation to thermal or mechanical stresses, leading to changes in the particles' surface and physicochemical properties. Among various particle properties (particle size and size distribution, surface properties, hygroscopicity, electrostatic charge and relative humidity), surface roughness, hydrophobicity and composition have pivotal impact on the interparticle interactions, aerosolization behavior, dissolution and stability of an inhalable product [1]. For example, the hydrophobic surface of a particle reduces moisture adsorption and the formation of liquid bridges, rendering the particles less cohesive and improving their flowability [2]. Various advanced surface characterization techniques such as atomic force microscopy (AFM), X-ray photoelectron spectroscopy (XPS) and time of flight secondary ion mass spectrometry (ToF-SIMS) have been used to determine the surface chemistry of dry powder formulations and the effects of the particle surface chemical properties on the dissolution and aerosol performance of dry powder inhalers (DPIs). This article discusses surface analytical techniques and applications in dry powder formulation characterization.

Atomic force microscopy (AFM)

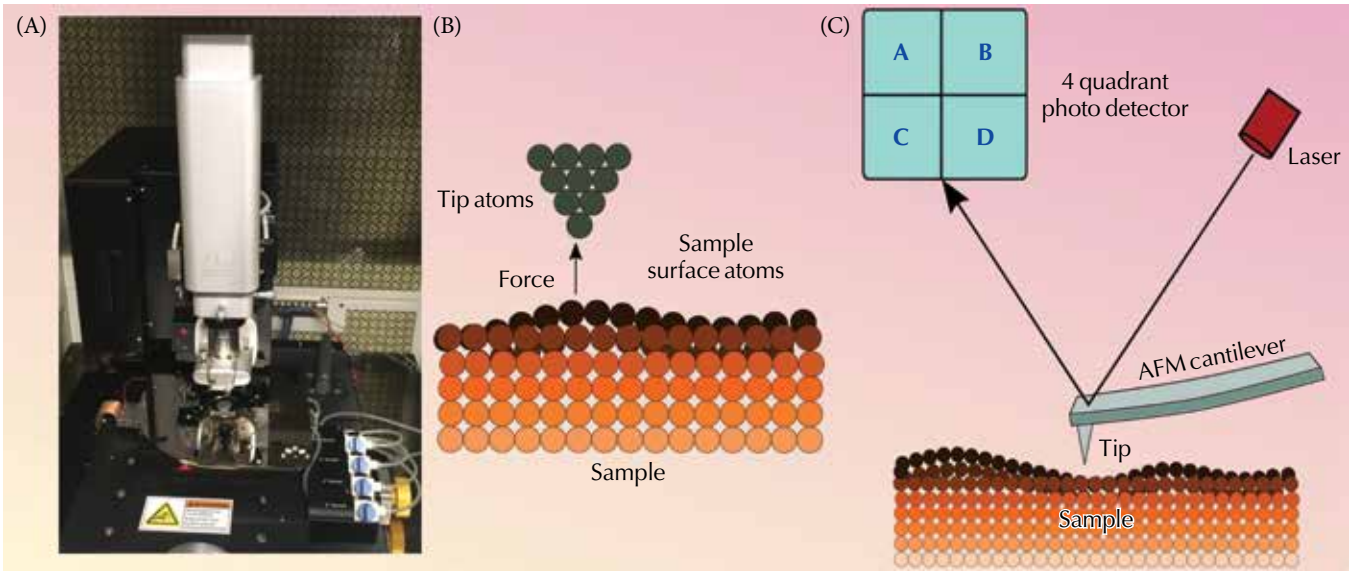
The atomic force microscope (Figure 1) is a mechanic-optical instrument that forms images of surfaces using a probe or micro-leverage, which traverses the sample by performing a line-by-line scan, i.e., it scans the sample based on position and generates an image. This technique resolves three-dimensional (3-D) topographic images, makes measurements on the order of nanometers, detects nano-newton forces, and makes measurements of visco-elasticity and hardness of the sample. The AFM tip is mounted on a micro-leverage, which is influenced by a laser. Therefore, each time the tip goes up or down due to the interaction with the surface being analyzed, the micro-leverage reflects the deviation of the laser to a photodetector and is interpreted by software, generating an image (Figure 1B) [3]. The surface roughness and interparticle forces among drug/drug particles and drug/carrier particles, as well as particle/lung surfactant interactions, can be quantified using AFM [4]. However, AFM has limitations; for instance, it only determines the properties of well-separated particles under isolated conditions and does not measure the bulk properties of a formulation as a whole [3].

Applications of AFM in surface analysis of inhalable dry powder particles

This technique is widely used for the analysis of nanomaterials and micromaterials and offers advantages. Unlike electron microscopy, it does not require a vacuum to operate. It also does not require a conductive surface for analysis, which broadens the range of samples that can be analyzed. These can include biological samples (e.g., proteins, human cells and microbes), solid samples and polymer films [5].

Figure 1

Atomic force microscopy (AFM) system (A). Schematic diagram of the basic principle (B) of atomic force microscopy (AFM) and instrument (C).



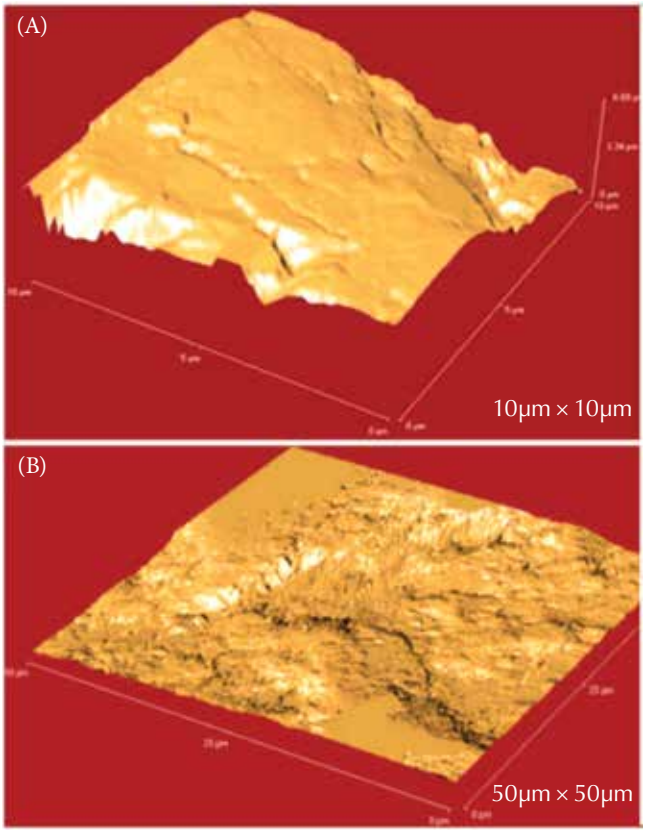
Drug delivery by inhalation and effective distribution of active pharmaceutical ingredients (APIs) can be affected by particle morphology, size and particle surface properties such as texture and free energy. Surface properties of each drug and carrier particle are known to have important effects on dissolution, cohesion, surface area, interparticulate forces, crystallization and DPI performance [6]. AFM has been used to study the correlation between aerosolization performance and particle surface texture [7-9].

Utilizing AFM, Huang, et al. [10] investigated the correlation between nanometer surface roughness and aerosolization performance of chitosan-based dry powder formulations. They found that the fine particle fraction of the formulations positively correlated with the degree of nanometer roughness. In a study by Hickey, et al. [11], the surface roughness of sieved and milled α-lactose was evaluated using AFM (Figure 2). The particle surface of sieved lactose (Figure 2A) was relatively smooth with few nanocrevices. However, the particle surface of milled lactose showed highly irregular surface morphology with many nanocrevices (Figure 2B).

In addition, AFM has the power to discriminate between polymorphic domains, such as crystal and amorphous faces [12-13]. Physical forces, such as van der Waals, electrostatic and capillary, increase cohesion/adhesion forces among micrometer-sized particles (drug/drug, drug/carrier) and with other surfaces, which can affect aerosolization [3]. These cohesion/adhesion forces can be quantified using colloid-probe AFM. This generates a force-distance

Figure 2

Atomic force micrograph of the surface of a lactose particle: sieved lactose (A); and milled lactose (B). Adapted with permission from reference 11. (Copyright Elsevier 2007.)



curve that can be acquired by engaging and withdrawing the probe from the sample. The curve is produced by the difference in magnitude of the types of forces acting between surfaces and is quantified by the cantilever deflection during approach and retraction [14]. Li, et al. [15] used AFM to study particle/particle cohesion/adhesion forces between paenol-γ-cyclodextrin metal-organic frameworks (PAE-CD-MOFs) and lactose (Inhalac®, Meggle, Wasserburg am Inn, Germany) particles for inhalation formulations. A PAE-CD-MOFs single particle was fixed on the tipless AFM probe, then the DPI formulation or lactose was dispersed in a glass substrate for modulus measurements. The authors observed that adhesive forces between PAE-CD-MOFs and lactose (Inhalac 400) particles were stronger than PAE-CD-MOFs cohesive forces.

AFM in combination with other techniques

As discussed, interparticulate forces between drug particles and carriers will determine detachment of drugs from carriers and influence lung deposition. Quantification of drug distribution in a formulation or at a single-particle level remains challenging, yet important, due to the need for consistency in inhaled drug dispersion and delivered dose uniformity. The most common techniques used to test drug distribution are Fourier transform infrared spectroscopy (FTIR), Raman spectroscopy and X-ray photoelectron spectroscopy (XPS), but those instruments have some drawbacks as they only allow surface characterization at macro/micro levels with limited characterization of nanochemical domains. FTIR acquires a spectrum from a bulk powder and may not provide a representative fingerprint of a single particle. However, the novel AFM-IR technique has the potential to overcome these limitations, as it provides ultrahigh resolution of a single particle by combining the high spatial resolution of AFM with conventional IR spectroscopy [16-18]. AFM-IR absorption maps are obtained by illuminating the sample at a fixed wavelength while scanning the AFM tip over the sample [19].

Another parameter that has received limited attention is the measurement of interactions between lung surfactants and aerosolized drug formulations. However, because lung surfactants play a vital role in the dissolution process following deposition, studying these interactions is very important. In combination with a Langmuir-Blodgett trough, AFM can provide quantitative measurements using a single-particle probe between drugs and phospholipids films. Arora, et al. [20] studied the interaction of L-leucine-stabilized voriconazole dry powder formulations with a simulated pulmonary surfactant and showed a decrease in adhesion of particles with higher L-leucine concentration (% w/w), due to increased hydrophilic surface.

X-ray photoelectron spectroscopy (XPS)

X-ray photoelectron spectroscopy (XPS), also known as electron spectroscopy for chemical analysis (ESCA), is a surface-sensitive spectroscopic technique that is used to determine the quantitative atomic composition of thin-surface films to a depth of approximately 5-10 nm [21]. XPS involves the bombardment of a high-energy X-ray beam on the surface of a sample and emission of electrons (photoelectrons) from the atoms (Figure 3). The photoelectron kinetic energy (E_k) of the emitted electrons is given by equation 1:

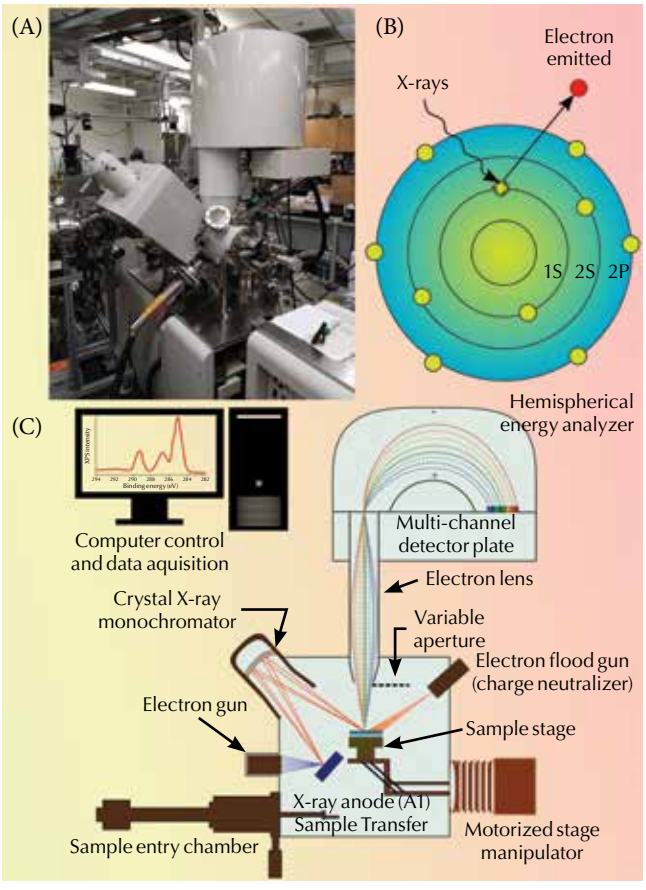
$$E_k = h\nu - E_b \qquad (1)$$

where $h\nu$ is the energy of the incident radiation and E_b is the electron's binding energy at a particular level [21-22].

The XPS technique produces quantitative and qualitative information; quantitative information arises from the element's specific binding energies and

Figure 3

X-ray photoelectron spectroscopy (XPS) system (A). Schematic diagram of the basic principle (B) of X-ray photoelectron spectroscopy (XPS) and instrument (C).



the relationship between the photoelectron peaks' intensity and the element concentration. Because each element has unique binding energies, XPS can identify and determine the elements' concentration on the surface. Variations in the elemental binding energies (the chemical shifts) arise from differences in the polarizability and chemical potential of compounds; these chemical shifts can be used to qualitatively identify the chemical state of the materials being analyzed [21-22]. The peak shape and binding energy can be slightly varied by the chemical state of the emitting atom. Therefore, XPS can also provide chemical bonding information and enables quantification of surface compositions of compounds with the same elements. However, the XPS technique has drawbacks/limitations such as reproducibility error (~10%), a high vacuum environment (10^{-8} to 10^{-11} torr) that is not suitable for all materials and poor lateral resolution (~10 μm); in addition, the charging effect may result in shifting of photoelectron peaks from insulating samples to higher binding energies. The process also can be time-consuming (0.5 to 8 hr/sample) [23].

A typical XPS (Figure 3) consists of an X-ray source, sample stage, extraction lenses, an electron energy analyzer and an electron detector housed in an ultra-high vacuum environment. The X-ray source uses a heated tungsten or lanthanum hexaboride (LaB_6) filament, which produces electrons that are accelerated towards a high-voltage anode (magnesium or aluminum), and a narrow range of X-rays are focused onto the sample by a monochromator (Al Kα). The electrons ejected from the sample surface pass through the extraction lenses, which define the acceptance angle for collecting electrons emitted from the sample to the concentric hemispherical analyzer. The electrons with the correct kinetic energy or pass energy (E_{pass}) enter through the analyzer, strike the detector and produce an energy spectrum.

Applications of XPS in surface composition analysis of inhalable dry powder particles

Many reported studies use XPS as a sophisticated surface-characterization tool. For example, in a study by Mangal, et al. [24], ciprofloxacin antibiotic was co-jet-milled with different lubricants of magnesium stearate (MgSt) and L-leucine under various process conditions. XPS determined the effect of lubricant concentration and lubricant materials on the surface coverage of the co-jet-milled ciprofloxacin powders. The researchers also used XPS to quantify the surface lubricant coverage and correlated it with the co-jet-milled powders' aerosolization for a better fundamental understanding of dry powder inhaler formulations. The results showed that MgSt achieved greater lubricant surface coverage than L-leucine at the 5% and 10% lubricant levels [24].

Shetty, et al. [25] investigated the influence of excipients on the physical and aerosolization stability of spray-dried ciprofloxacin dry powder inhaler formulations. In this study, ciprofloxacin hydrochloride was co-spray-dried with different excipients such as mannitol, L-leucine and disaccharides (sucrose, lactose, trehalose). XPS was used to characterize the surface of the produced powders. The data showed that L-leucine demonstrated aerosolization stability by alleviating the crystallization of ciprofloxacin to some extent and preventing a significant change in particle morphology. Furthermore, the data demonstrated the enrichment of L-leucine on the particle surface, which led to a corrugated particle shape and improved aerosol performance compared with the spray-dried ciprofloxacin alone [25].

In another study, Bosquillon, et al. [26] used XPS to characterize the surface composition of dry powder aerosols prepared by spray drying. The powder aerosols were made of albumin, 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine (DPPC) and a protein stabilizer (lactose, trehalose or mannitol). Surface composition analysis by XPS revealed the migration and enrichment of DPPC on the spray-dried particle surface relative to albumin [26]. Bhujbal, et al. [27] presented an advanced platform for surface characterization utilizing two complementary techniques, XPS and ToF-SIMS. This platform enables qualitative and quantitative surface composition measurements for fine spray-dried amorphous solid dispersion (ASD) particles. The ASD particles consisted of naproxen (drug) and Kollidon VA 64 PVPVA (i.e., a copolymer composed of 1-vinyl-2-pyrrolidone and vinyl acetate in a 6:4 mass ratio) with ultra-surface-sensitivity (i.e., < 10 nm from the surface) and superior spatial resolution. XPS (Figure 4) and ToF-SIMS demonstrated that PVPVA was predominantly enriched on the surface of the spray-dried naproxen-PVPVA ASD particles. The XPS technique could differentiate between two batches of spray-dried ASD particles that had a small difference in surface composition produced by changing feed solution solvents (Figure 4) [27].

Time-of-flight secondary ion mass spectrometry (ToF-SIMS)

ToF-SIMS, a variant of static secondary ion mass spectrometry (SIMS), is a highly sensitive surface analytical technique with an average analysis depth of ~1 nm. It evaluates the chemical composition of the surface of a solid sample without causing significant damage to the sample's surface [28]. The fundamental principle of ToF-SIMS (Figure 5A) involves the bombardment of a solid surface by a high-energy primary ion pulse, which results in emission of secondary ions. Then the secondary ions are separated, according to the mass-to-charge ratio in the time-of-flight region, and their mass is deter-

mined by measuring the time required for the ions to reach the detector (i.e., time-of-flight) [29].

A typical ToF-SIMS instrument (Figure 5) consists of an ultrahigh vacuum chamber, a pulsed ion gun, extraction and focusing optics, a flight tube (approximately 2 m in length) and a detector. The pulsed ion gun utilizes mono-atomic primary ion beams such as Ga^+, Cs^+, In^+ and Au^+, and polyatomic primary ion beams such as $SF5^+$ (reactive beams), and Au_n^+, Bi_n^+, and C_{60}^+ (cluster beams) [29]. Other components include an electron neutralizer for charge compensation, a sample stage and a computer for instrument control and data collection. Similar to the XPS technique, the sample preparation is simple and does not require a conductive surface for analysis [28]. ToF-SIMS can be used in three modes of operation, including surface spectroscopy, surface imaging and depth profiling, and gathers data on chemical composition, localization and quantification [28].

ToF-SIMS is a highly sensitive analytical technique that evaluates the surface composition of the upper one to two monolayers. It can provide information about composition that is difficult to obtain with conventional techniques. However, ToF-SIMS has several drawbacks such as causing more surface damage than XPS, difficulty in data interpretation and the requirement of standards for quantification of mass spectra [30-31]. ToF-SIMS has been used for surface composition analysis of multilayer drug-loaded beads, drug-eluting implantable stents, porous microspheres and spray-dried microparticles.

Applications of ToF-SIMS in surface composition analysis of inhalable dry powder particles

API and excipient distributions on the solid surface of a dry powder particle are critical for controlling pharmaceutical performance properties, such as shelf life and dispersion characteristics. Several studies have used ToF-SIMS to map the distribution of API and excipients on a particle surface [24, 32-35]. In a study, the composite dry powder formulations of kanamycin (a hygroscopic drug) and rifampicin (a hydrophobic drug) were produced using spray drying and the surface distribution of the drugs was characterized using ToF-SIMS [32]. The study reported hydrophobic rifampicin enrichment on the surface of the composite dry powder particles. The study further investigated the effect of hydrophobic surface enrichment on aerosolization of kanamycin. The rifampicin surface enrichment significantly improved aerosolization (fine particle fraction (FPF) of 77.4%) compared to the kanamycin-only powder (FPF < 28%).

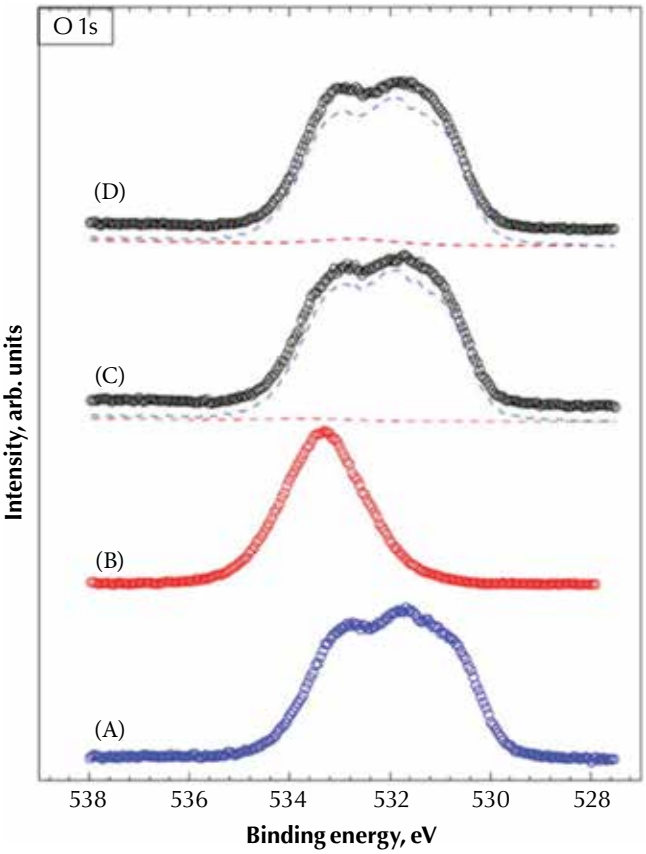
ToF-SIMS has been used to map the distribution of surface-active excipients, L-leucine and DPPC in co-spray-dried powders containing the antitubercular drugs, pyrazinamide and moxifloxacin (Figure 6) [34]. The co-spray-dried powder composed of pyrazinamide and moxifloxacin without surface active excipients showed the surface composition of moxifloxacin with negligible amounts of pyrazinamide. The addition of L-leucine (10% w/w) and DPPC (10% w/w) along with pyrazinamide and moxifloxacin produced composite particles with a surface coat composed of excipients (L-leucine and DPPC) with a small amount of moxifloxacin and showed improved aerosolization.

In another study, the spatial distribution of lubricants such as magnesium stearate (MgSt) and L-leucine on the surface of co-jet-milled ciprofloxacin particles was examined using ToF-SIMS [24]. This study reported higher surface coverage of MgSt on the ciprofloxacin particles, which reduced surface energy and friction between the particles, compared with the same concentration of L-leucine.

Although ToF-SIMS is recognized as a qualitative or semi-quantitative method, a recent study [36]

Figure 4

Example of the O 1s peak curve-fit: PVPVA (reference spectrum) (A); Naproxen (reference spectrum) (B); Batch 1 (PVPVA component is blue; naproxen component is red) (C); Batch 2 (PVPVA component is blue; naproxen component is red) (D). Adapted with permission from reference 27. (Copyright American Chemical Society 2018.)



developed a multivariate ToF-SIMS methodology to quantify surface composition and chemical distribution for dry powder blends. In the study, ToF-SIMS coupled with multivariate image analysis was used to quantify the surface composition of two types of dry powders, such as binary blends of lactose with coating agents (magnesium stearate, sodium stearyl fumarate and leucine) and adhesive mixtures of inhalation drugs (salbutamol sulfate, beclomethasone dipropionate and budesonide) with carrier lactose. The mass spectrum at each pixel was fit to a linear combination of reference spectra. From the pixel compositions, average surface coverage and other differentiating image features were calculated. In comparison to XPS, the surface coverage data collected using ToF-SIMS with multivariate analysis provided more surface information, for instance, on the thickness of the coated layer.

Conclusions

The surface composition and interfacial properties of dry powder particles play a significant role in the processing, structure and functionality of orally inhaled dry powders. Therefore, surface characterization techniques are critical to better understanding powder behavior in the early stages of DPI formulation, which may help avoid stability issues later in development. This article describes advanced surface characterization techniques, such as AFM, XPS and ToF-SIMS, which can be used to determine surface chemistry and interparticle properties of inhalable dry powder particles and help facilitate optimization of formulations.

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Figure 5

Schematic diagram of the basic principle (A) of time-of-flight secondary ion mass spectrometry (ToF-SIMS) and the instrument (B).

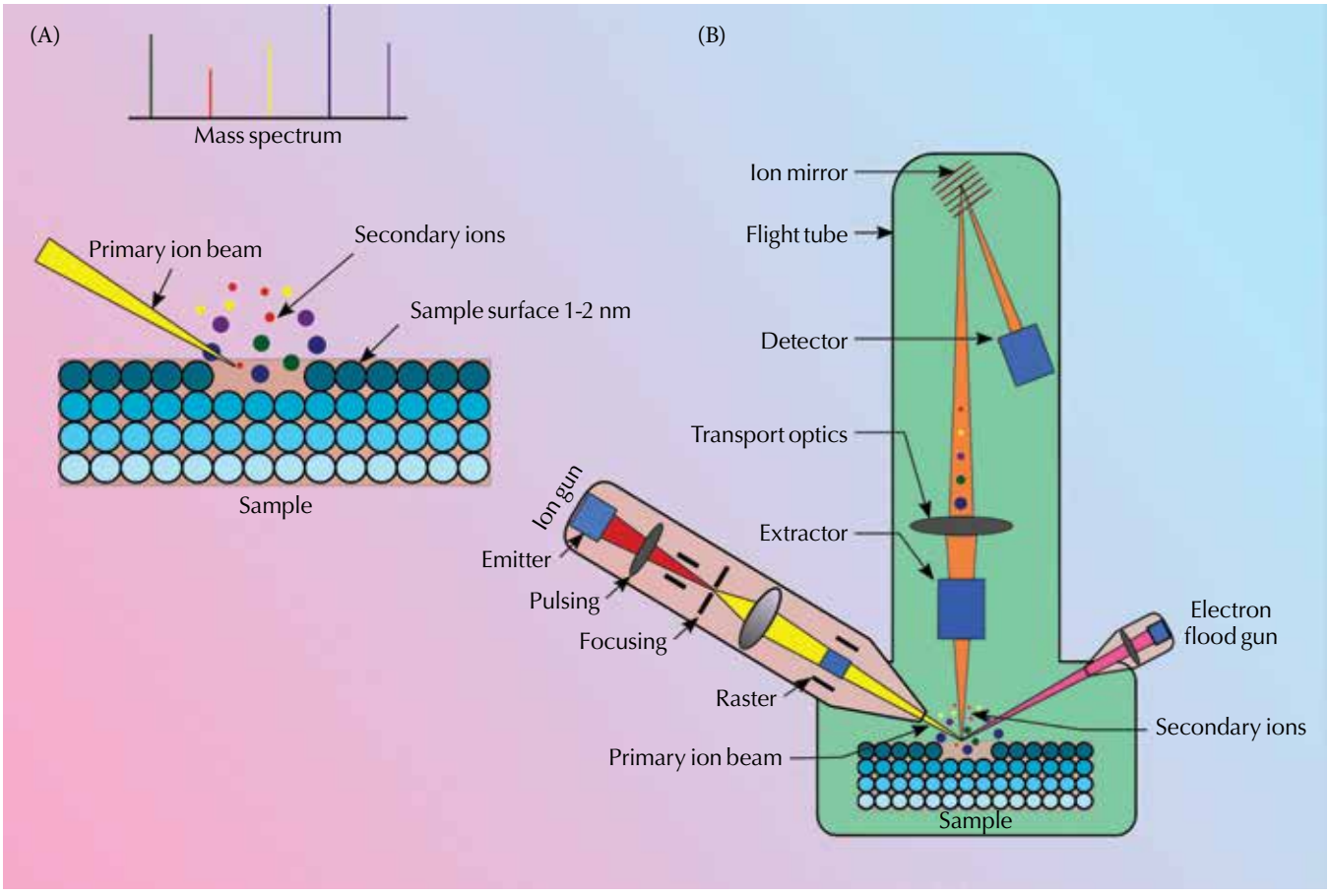

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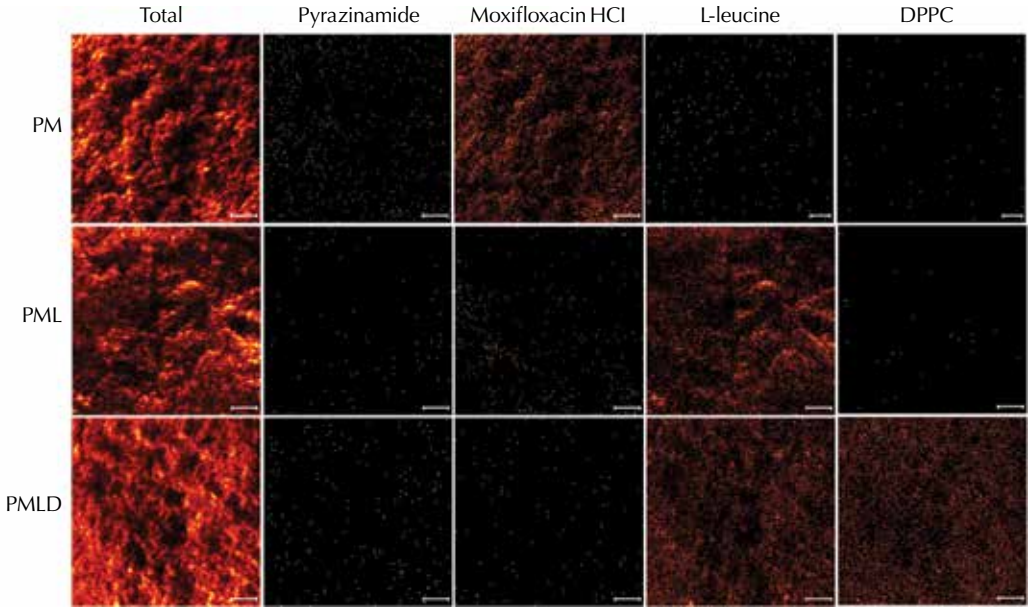
Figure 6

Time-of-flight secondary ion mass spectrometry (ToF-SIMS) micrograph images of spray-dried formulations PM, PML and PMLD at scanning area of 100 × 100 µm. The scale bars represent 10 µm. The formulation codes PM, PML and PMLD indicate: P, pyrazinamide; M, moxifloxacin HCl; L, L-leucine; D, 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine (DPPC). Adapted with permission from reference 33. (Copyright Elsevier 2018).



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