Engineering combination particles

Ultrasound-assisted particle engineering of microcrystals as a combination of two or more active pharmaceutical ingredients for treating chronic obstructive pulmonary disease (COPD)

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One of the most significant goals in particle engineering for inhaled medicines involves the creation of combination particles with two or more active ingredients that would allow consistent delivery of all of the drugs and would therefore improve patient outcomes when compared to formulations containing the actives as individual ingredients. Optimally, the particle manufacturing process would tightly control all of the parameters that influence aerosolization, deposition, and efficacy, including size, shape, surface characteristics, crystallinity, and stability.

Power ultrasound assisted particle engineering technologies such as solution atomization and crystallization with ultrasound (SAX) and its industrial variant UMAX show tremendous promise in the manufacture of particles designed for inhalation dosage forms. The SAX/UMAX technologies have the potential to revolutionize inhaled drug delivery for respiratory disorders such as chronic obstructive pulmonary disease (COPD) via the engineering of combination inhaled microcrystalline particles in which an individual particle contains two or more actives in an exact predetermined ratio.

Double therapies for COPD

Researchers project that COPD will become the third most common cause of death worldwide by 2030 [1]. Bronchodilator therapy using $ß_2$-agonists and/or anticholinergics improves lung function, symptoms, exercise tolerance, and quality of life in COPD patients [2], and therapies combining both classes of bronchodilators have greater efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator [3]. A number of pharmaceutical companies have developed such combination products, including Boehringer Ingelheim's Combivent ipatropium/albuterol product.

More commonly, clinicians recommend inhalation products combining a bronchodilator with an inhaled corticosteroid (ICS) to control the abnormal inflammatory responses central to the pathophysiology observed in COPD [3, 4]. The combination of a long-acting ß-agonist salmeterol xinafoate (SX) and the ICS fluticasone propionate (FP) marketed by GlaxoSmithKline as Seretide/Advair is currently listed amongst the top 10 best selling pharmaceutical products, with annual sales of approximately £5 billon forecasted for 2009 [5]. According to reports, the combination of SX and FP exhibits greater efficacy than monotherapy treatments with the individual components [6], as well as reduced mortality rates in COPD patients beyond the reduction achieved by individual therapies [7].

Combination inhaled drug products, which are notoriously difficult to manufacture, can exhibit significant variability in the delivery of multiple actives present in a formulation due to the complex relationship between formulation aerosolization behavior, device deaggregation properties, and patient inspiration [8]. A demand exists, therefore, for processes that enable efficient delivery of both drugs in combination inhaled products to the same site of action independent of dose variations, whether by pressurized metered dose inhaler (pMDI) or by dry powder inhaler (DPI). Particles containing both actives in the required concentration and in the respirable size range would help to achieve this goal, and a solution-to-droplet particle engineering approach has the ability to create such combination particles [9, 10].

Sonocrystallization

Not only does the SAX/UMAX technology offer superior production methods that provide better products, the process also follows guidelines speci-

fied by the FDA's quality by design (QbD) initiative aimed at improving invention, development, and commercialization of structured products to achieve superior product quality [10]. This technology shows tremendous potential to control particle size, crystallinity, and morphology of the particles, often yielding spherical particles (Fig. 1) with the optimum performance attributes for inhalation.

The SAX/UMAX process (Fig. 2) involves first forming a solution of one or more active pharmaceutical ingredients (APIs) in a suitable solvent. The next step involves generation of a fine aerosol that undergoes very careful evaporation, followed by collection of the concentrated droplets in a non-solvent for the API. Applying power ultrasound to the droplets dispersed in the non-solvent aids crystallization of the API, and a process such as spray drying or supercritical carbon dioxide drying then isolates the solids.

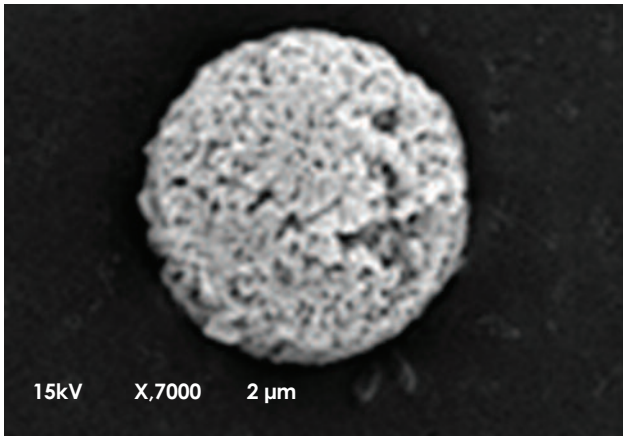
SAX-engineered combination particles of a LABA and an ICS

The preparation of combination particles by SAX technology enables the crystallization of both APIs in a single particle, as well as control over the morphology. The processing of SX and FP by SAX in a ratio of 1:10, respectively, for example, produces spherical combination particles with a defined corrugated morphology (Fig. 3). The SX/FP particles produced by this method possess a volume-weighted median diameter of 3.56 µm. X-ray powder diffraction (XRPD) patterns show sharp diffraction peaks associated with micronized FP, micronized SX, and SAX-produced FP/SX (Fig. 4), suggesting that the materials are predominately crystalline.

The combination particles have a particular advantage in the inhibition of the pro-inflammatory protein interleukin-8 (IL-8). IL-8 plays a key role in the

Figure 1

SEM and atomic force images for SAX/UMAX particles of a well established asthma product showing morphology and nanotopology



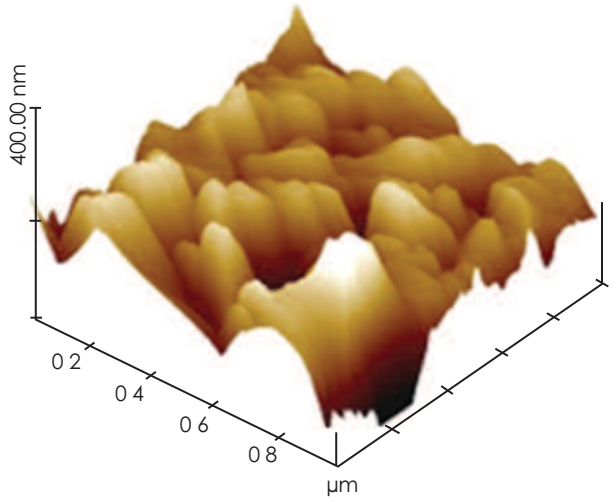


Figure 2

The SAX/UMAX process concept

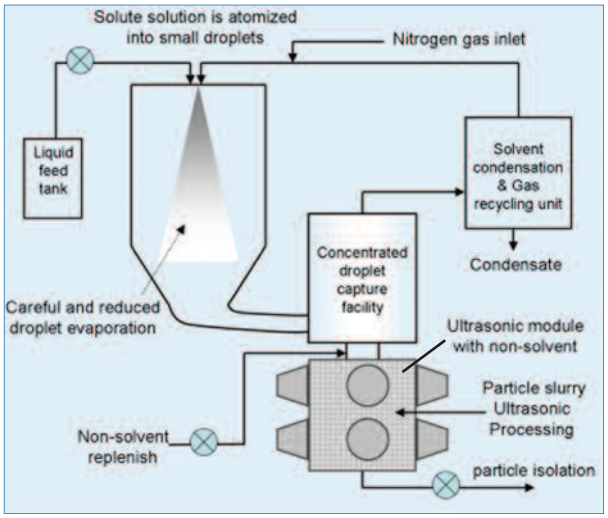


Figure 3

Scanning electron micrograph of combination SX/FP SAX particles

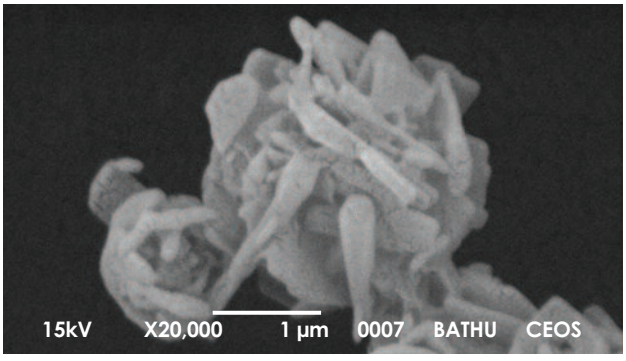
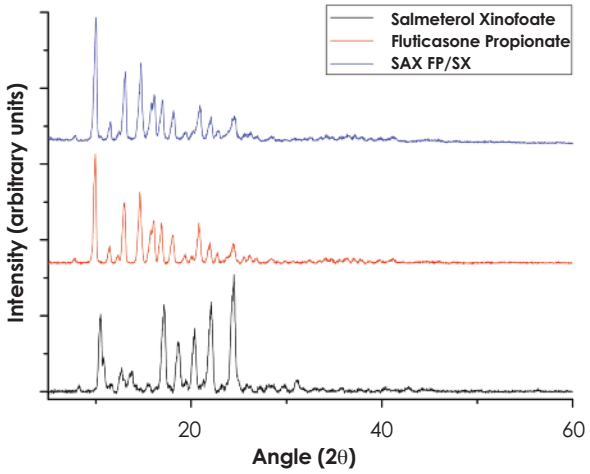


Figure 4

XRPD diffractograms of micronized fluticasone propionate and salmeterol and combination SAX particles of fluticasone propionate and salmeterol

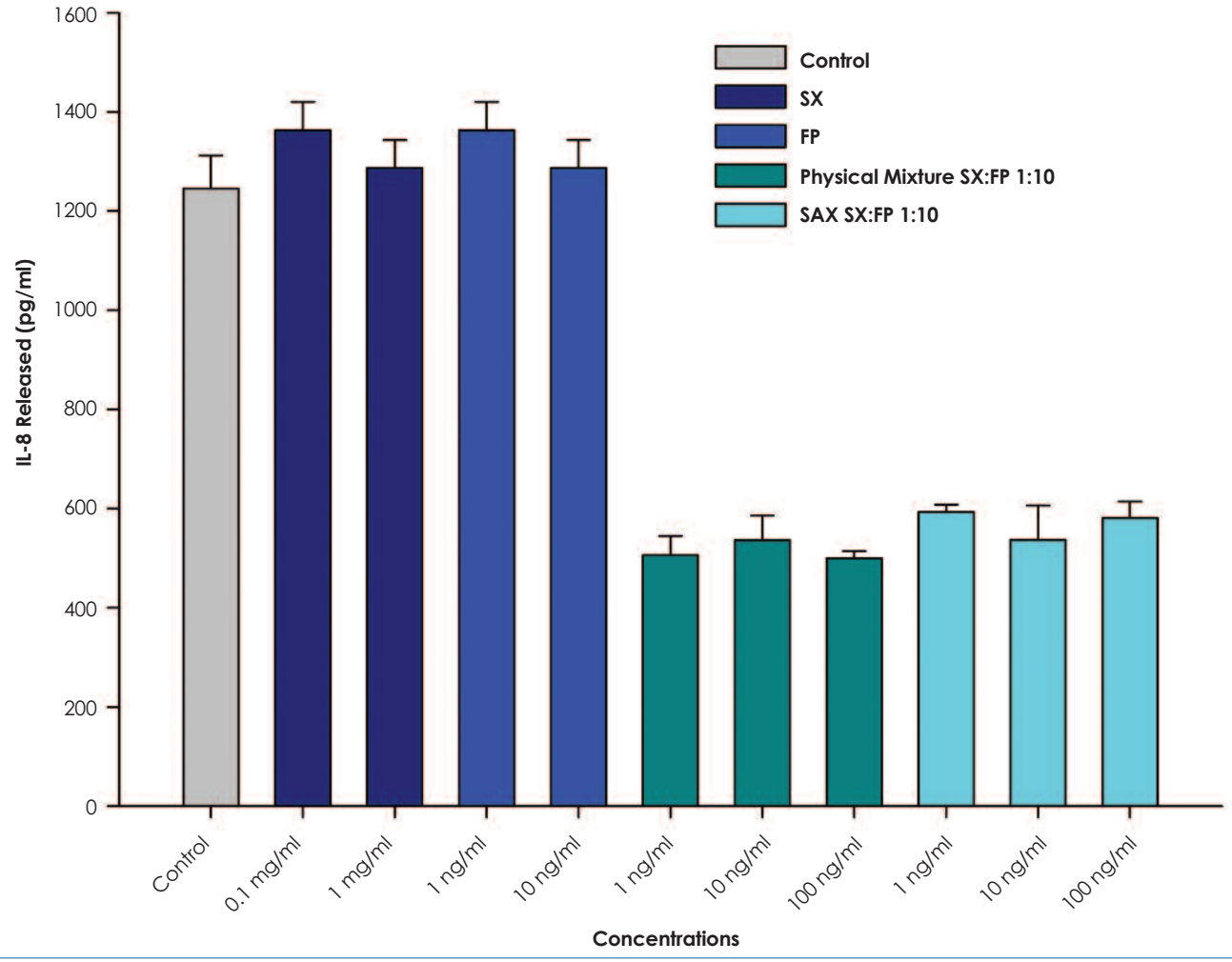


inflammatory processes involved in COPD as increased production of IL-8 in response to inflammatory stimuli such as cigarette smoke or bacteria attracts neutrophils, immune cells that can ultimately damage lung tissue [11]. Previous studies have reported synergistic interactions between SX and FP at the receptor, molecular, and cellular level that inhibit the release of IL-8, resulting in improved health status and reduced symptoms in patients [12-14]. A study of the SAX combination particles containing SX and FP in a ratio of 1:10 has shown their ability to inhibit the release of IL-8 from epithelial cells compared to that of micronized SX and FP alone (Fig. 5).

The study involved treating human bronchial epithelial cells with both the individual drugs and with the combination particles following activation of the cells with lipopolysaccharide (LPS). Neither SX nor FP alone inhibited IL-8 release. However, SAX particles containing the combination of SX and FP in concentrations as low as 1 ng/ml significantly reduced IL-8

Figure 5

Anti-inflammatory effects of binary treatment with salmeterol (SX) and fluticasone propionate (FP) and combined treatments prepared using physical mixtures and combined SAX particles of salmeterol and fluticasone propionate (SX:FP) on human bronchial epithelial cells in culture



release after LPS challenge, as did a physical mixture of both drugs.

Engineering both actives into one particle using the SAX/UMAX approach may enhance synergistic action because the combination particle enhances the likelihood of co-deposition of the drugs at the same site of action, while data suggest that aerosolization of a formulation containing separately micronized FP and SX may deliver the actives non-uniformly within the respiratory tract, limiting the possibilities for synergy. Cascade impaction of carrier-based DPI formulations of combined SAX engineered SX/FP and of separately micronized SX and FP show that aerosolized SAX combination particles deposit consistently across the stages of the impactor. The DPI formulations containing micronized forms of the separate drugs, however, showed non-uniform delivery of both actives across stages 2-5 of the impactor, with significantly more FP being delivered than SX (Fig. 6).

Triple therapy for COPD

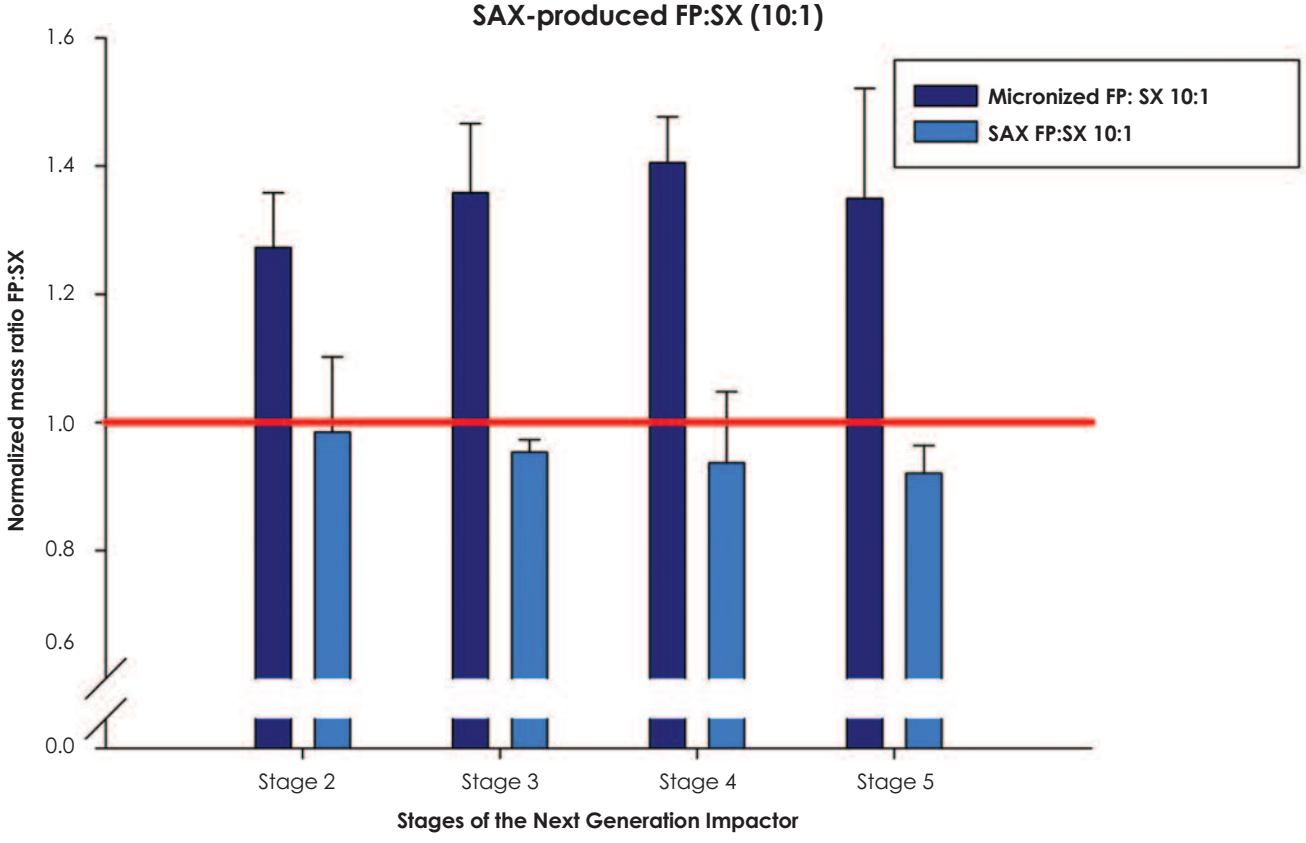
In order to address all of the processes that contribute to COPD, clinicians often employ a triple therapy using anticholinergics, LABAs, and ICS to maximize control of patient symptoms. A recent study investigating such a triple therapy with salmeterol, fluitcasone propionate, and tiotropium bromide in COPD patients found that it proved significantly more effective in controlling pulmonary lung function than treatment with a double therapy of salmeterol and fluticasone propionate [15]. Combination inhalation dosage forms containing these three classes of therapeutics, however, pose significant challenges to formulators, and as of now, no pharmaceutical manufacturer markets a regulated triple API product for COPD.

Recently, however, the SAX process has successfully produced engineered particles containing salmeterol, fluticasone propionate, and ipatropium bromide. Scanning electron micrographs show spherical particles with defined morphology and a volume-weighted median diameter of 3.06 μm, in which each particle appears to contain all three molecules (Fig. 7). Furthermore, X-ray powder diffractograms of the material suggests that the "triple" combination SAX particles are predominately crystalline (Fig. 8).

Comparison of a triple combination particle formulation with a formulation containing the micronized forms of the individual components in drug-only pMDI suspensions demonstrates that aerosolization of the SAX preparation resulted in significantly more consistent aerodynamic particle size distribution of all

Figure 6

Ratio of FP:SX from mean normalized data of stages 2-5 of micronized FP:SX (10:1) compared with SAX-produced FP:SX (10:1)



three actives than the preparation containing the individual components. These data suggest that the SAX/UMAX processing technologies have the ability to successfully generate particles for triple therapy, potentially providing a revolutionary treatment for COPD patient (Fig. 9).

Figure 7

Scanning electron micrograph of triple therapy SAX particles containing salmeterol, fluticasone propionate, and ipatropium bromide

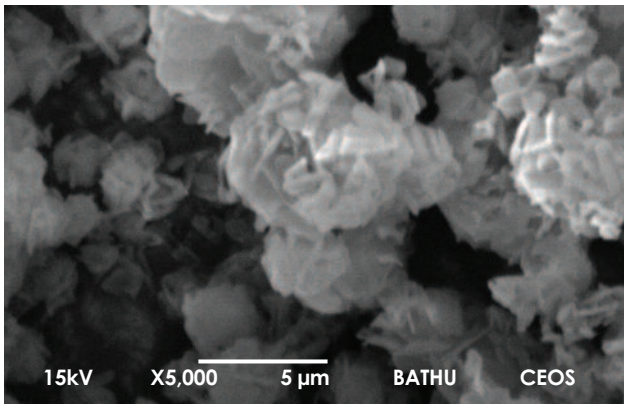


Figure 8

XRPD diffractograms of micronized fluticasone propionate, salmeterol, and ipatropium and triple therapy SAX particles containing salmeterol, fluticasone propionate and ipatropium bromide

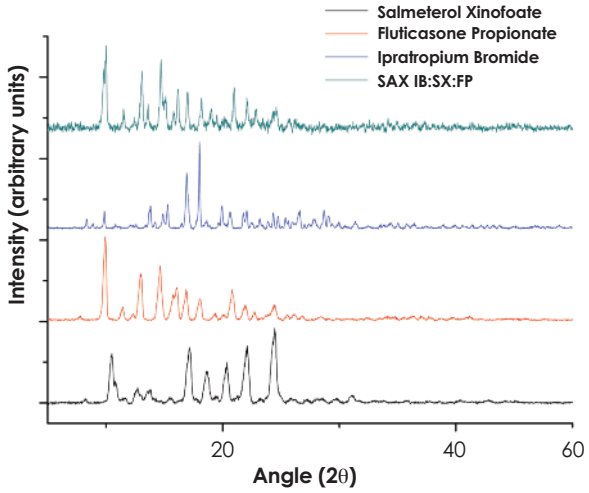
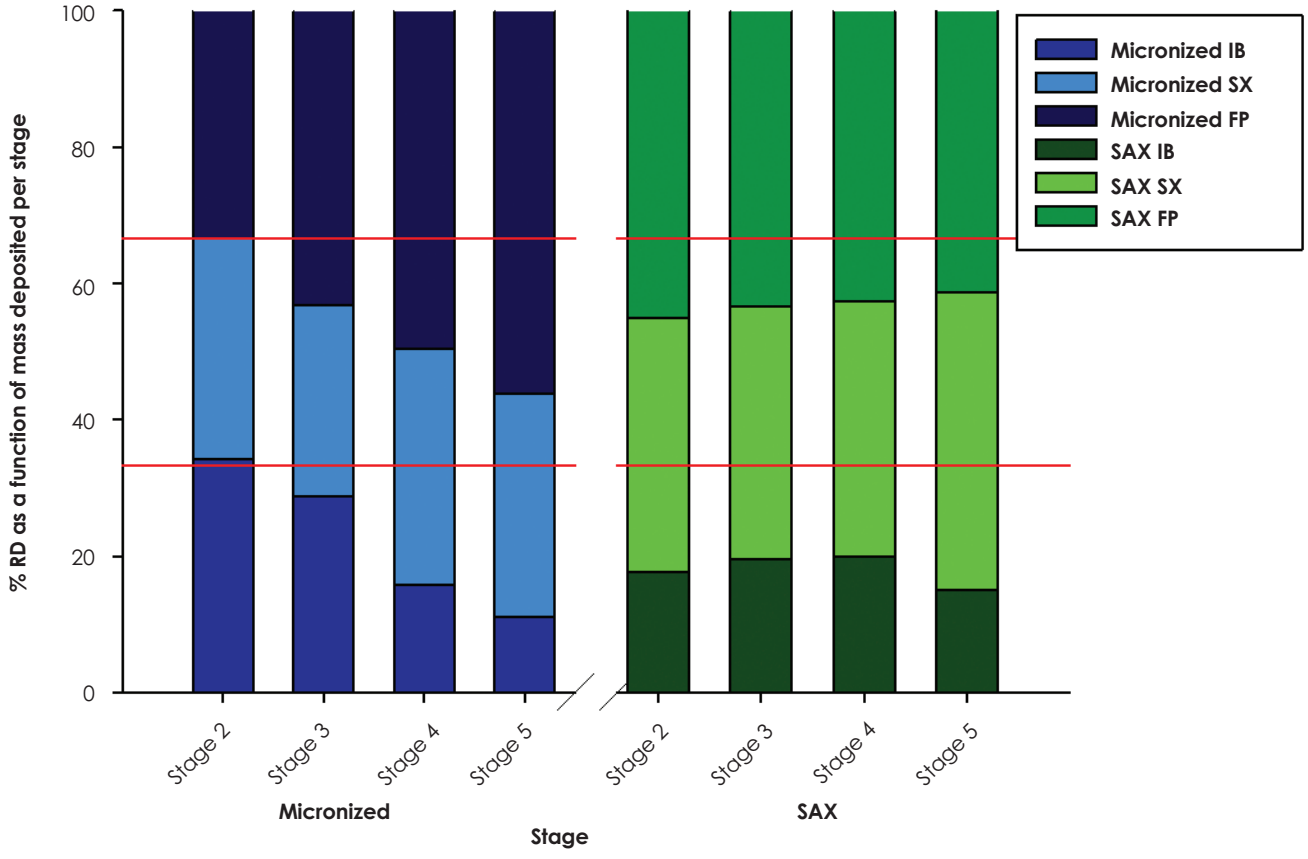


Figure 9

Percentage mass of each drug deposited on stages 2-5 of an Anderson cascade impactor following aerosolization of suspension pMDI containing micronized ipatropium bromide, salmeterol, and fluticasone propionate and triple combination SAX particles containing all three molecules



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