Improved Localised Lung Delivery Using Smart Combination Respiratory Medicines

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Abstract

Combination therapies for the treatment of chronic obstructive pulmonary disease (COPD) have long been used to provide improved disease management. Current therapies aim to provide bronchodilatation and most of them are based on β-agonists or anticholinergics/muscarinics. A widely used combination is an inhaled corticosteroid (ICS) plus a long-acting β-agonist (LABA), which have shown an additive improvement in lung function. However, for inhalation combination products, the most significant pharmaceutical challenge is to maintain a constant ratio of drug components during various stages of drug formulation and drug delivery. Drug delivery to lungs with a consistent and predesigned ratio of co-associated active components can help maximise the chance of co-location at the active site and hence increases the potential of synergistic action from the solid. Newer particle engineering-led approaches, such as constructive sonocrystallisation particle engineering, can help design these smart medicines that can help achieve consistent localised delivery.

Keywords

Particle engineering, combination, budesonide, fluticasone, formoterol, salmeterol, synergy

Over the past 20 years, chronic obstructive pulmonary disease (COPD) has emerged as a major public health problem and is a major cause of chronic morbidity and mortality worldwide. The disease severity is also known to increase with age. The key objectives with reference to disease management are to prevent disease progression, provide symptomatic relief and improve quality of life by providing treatment for complications and exacerbations.

Current Practices and Development Pipeline

Bronchodilators (relievers) are normally used as first-line agents for the symptomatic treatment of patients with COPD, whereas inhaled glucocorticoids are the mainstay of long-term control therapy for persistent disease.1 However, patients show variable responses to inhaled glucocorticoids and some exhibit resistance to this drug class.2 Although long-acting bronchodilators have been an important advance in the management of COPD, these drugs do not interfere with the underlying inflammatory process. However, the significance of treatment is mainly judged by the adverse effects of the medication and how these are prevented or minimised. No currently available treatments reduce the progression of COPD or suppress the inflammation in small airways and lung parenchyma.3 Towards this end, guidelines provided by the UK National Institute for Health and Clinical Excellence (NICE) for the use of inhaled therapies give better understanding of the disease stage and suggested treatment.4 As indicated by the NICE guidelines (see Figure 1), with disease progression, the treatment option requires incorporating a progressive increase in the number of pharmaceutical agents, often in combination, to provide the desired effect of symptomatic relief.

Two combination schemes widely used for the treatment of COPD are a short-acting anticholinergic plus a short-acting β2-agonist (SABA) and an inhaled corticosteroid (ICS) plus a long-acting β2-agonist (LABA). Among these, the use of the ICS plus LABA combination has shown an additive improvement in lung function. For example, since its launch in 2001 the Advair®/Seretide® (GSK) combination product inhaler has been used as a very effective treatment of asthma. The concurrent delivery of the ICS fluticasone propionate (FP) and the LABA salmeterol xinafoate (SX) is required for respective treatment of the inflammatory and bronchoconstrictive elements of asthma.5 The use of this combination and an extensive review of its role in asthma management are provided elsewhere.6

Symbicort® (AstraZeneca), a combination product containing the ICS budesonide (BDS) and the LABA formoterol fumarate was launched
several years later and is another mainstay treatment for asthma and COPD. Formoterol has a rapid onset of bronchodilator action which is mediated mainly by a relaxing effect on contracted airway smooth muscle and, as a reliever, gives rapid and sustained relief of symptoms during an exacerbation. 7 A review of the use of BDS and formoterol in asthma is provided elsewhere. 6 Depending upon specific country requirements and marketing/regulatory approval, both Advair/Seretide and Symbicort combination drug products are available as dry powder inhalation (DPI) or metered dose inhalation (MDI) formulations in various ratios, with the ICS being present in a five- to ~30-fold mass excess compared with the LABA.

While anticholinergics and β-agonists reduce bronchoconstriction through different mechanisms, there is also a long history of combination therapy with these drug classes. The first inhaled combination therapy introduced in the US was Combivent® (Boehringer-Ingelheim, Ridgefield, CT), the combination of ipratropium and albuterol. 9 In a crossover study, combining the standard doses of ipratropium and albuterol (40 μg and 200 μg, respectively) produced greater bronchodilatation in 26 patients with stable COPD than did doubling the standard dose of ipratropium. 10

Based on these combination products, it is very clear that the current therapies aim to provide bronchodilatation; most of them are based on β-agonists or anticholinergics/muscarinics and are given by inhalation. Theophylline (phosphodiesterase inhibitor) is the exception and can be given orally. Combinations of bronchodilators improve effectiveness, improve compliance and reduce costs without increasing adverse effects. 11 The use of combination therapy for the treatment of asthma and chronic inflammatory disease is now very topical, with many new combinations of drugs either launched or close to launch (see Table 1).

Combination Respiratory Medicines and Mutual Synergy

Whilst corticosteroid therapy is an effective treatment for airway inflammation, the use of an ICS and an LABA together provides greater asthma control along with a reduction in the frequency and severity of exacerbations. 12 This superior control is attributed to the complementary actions of the drugs when taken together, including the activation of the glucocorticosteroid receptor (GR) by salmeterol, and the effects of the LABA on other cellular functions related to inflammation in principle, each drug enhances inflammation and bronchodilatation. In practice, each drug enhances the biochemical and pharmacological effects of the other. It is postulated that, mechanistically, the synergy is related to the effects of the LABA on the GR function by priming the GR for subsequent corticosteroid binding. 13 In a similar approach, product synergy has also been demonstrated by using the long-acting muscarinic antagonist, R-glycopyrrolate combined with the phosphodiesterase-4 inhibitor rolipram, the antihistamine azelastine and the corticosteroid BOS on the release of tumour necrosis factor-α in lipopolysaccharide-stimulated monocytes. 14 Interestingly, the use of theophylline in combination with an ICS has been reported to provide potent anti-inflammatory activity without side effects associated with existing therapies. 15

Figure 1: National Institute for Health and Clinical Excellence Guidelines on Chronic Obstructive Pulmonary Disease Management According to Disease Severity

Table 1: A Selection of Combination Products for Asthma and Chronic Obstructive Pulmonary Disease, either Marketed or in Clinical Development

<table>
<thead>
<tr>
<th>Company</th>
<th>Product Type</th>
<th>Product type</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK</td>
<td>Fluticasone propionate/ salmeterol xinafoate; Advair/Seretide®</td>
<td>ICS/LABA</td>
<td>Marketed</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Budesonide/formoterol fumarate; Symbicort®</td>
<td>ICS/LABA</td>
<td>Marketed</td>
</tr>
<tr>
<td>GSK</td>
<td>Fluticasone furoate/ vilanterol trifenatate; Horizon®</td>
<td>ICS/LABA</td>
<td>Phase III</td>
</tr>
<tr>
<td>Skye Pharma</td>
<td>Fluticasone propionate/ formoterol fumarate; Flutiform®</td>
<td>ICS/LABA</td>
<td>Phase III (asthma)</td>
</tr>
<tr>
<td>Merck &amp; Co. Inc.</td>
<td>Mometasone furoate/ formoterol fumarate; Dulera®</td>
<td>ICS/LABA</td>
<td>Marketed (COPD, asthma)</td>
</tr>
<tr>
<td>Schering Plough-Merck/ Novartis</td>
<td>Mometasone furoate/ indacaterol maleate</td>
<td>ICS/LABA</td>
<td>Phase II (asthma)</td>
</tr>
<tr>
<td>Chiesi Pharmaceuticals</td>
<td>Beclometasone dipropionate/formoterol fumarate; Fostair®</td>
<td>ICS/LABA</td>
<td>Marketed</td>
</tr>
<tr>
<td>Nycromed</td>
<td>Ciclesonide/formoterol fumarate</td>
<td>ICS/LABA</td>
<td>Phase II (asthma)</td>
</tr>
<tr>
<td>Novartis</td>
<td>Glycopyronium bromide/ indacaterol maleate</td>
<td>LAMA/LABA</td>
<td>Phase II (COPD)</td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>Ipratropium bromide/albuterol; Combivent®</td>
<td>LAMA/LABA</td>
<td>Marketed</td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>Tiotropium bromide/ formoterol fumarate</td>
<td>LAMA/LABA</td>
<td>Phase II (COPD, asthma)</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β-agonist; SAMA = short-acting muscarinic antagonist.

Thus, given the benefit of a mutual synergistic approach, these products can demonstrate enhanced efficacy, which in turn can clinically differentiate the combination product in comparison with monotherapy. This can eventually lead to the development of a single
inhaler that can deliver combination respiratory medicine. The single-inhaler approach to treatment has also been reported to be very effective in reducing asthma exacerbations and it is likely that this will become widely used for asthma and COPD management in the future for both children and adults. Rather than using salmeterol, which has a slower onset of action and prolonged systemic side effects, formoterol, with a faster onset of action and reduced dose, can be used to facilitate flexible dosing. In addition to using formoterol with BDS, other combinations of an ICS with formoterol are now in clinical development, including those with beclomethasone dipropionate, fluticasone and ciclesonide. An MDI formulation of beclomethasone dipropionate and formoterol has been developed and, thus far, its efficacy as a maintenance therapy is similar to other combination inhalers.

Furthermore, it has been reported that corticosteroids activate the β2-receptor gene, increasing receptor density in the airway and decreasing sensitisation. Combination therapy for reducing airway inflammation in patients with COPD is also very topical. It is known that ICSs reduce COPD exacerbations, but their beneficial effects on airway inflammation appear to be limited. The addition of an LABA, however, not only reduces exacerbations but improves lung function and controls symptoms to a greater extent than either component alone.

It is worthy of mention that there are safety concerns with the use of high-dose inhaled LABAs with respect to causing severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma, although the mechanisms by which these drugs cause such severe asthma exacerbations and asthma-related deaths are not known.

**Engineering Next-generation Combination Respiratory Medicines**

One important aspect of respiratory combination therapy is the clear advantages it provides, such as delivering a synergistic effect at the same target cell in the lung epithelia when the drugs are given simultaneously. This, in turn, highlights the rationale for combining both substances into one particle rather than having a combination product containing both drugs but in a physical and mechanical mixture. Whilst the intimate mixing of powdered drugs seems an ideal way to formulate two or more active ingredients for dry powder delivery to the lung, it can be difficult to achieve due to complexities of material chemistry and possible interactions between the active components. This can be very complicated when dual and triple therapy options are considered.

With powder blends, the co-deposition of actives (ICS and LABA) occurs randomly when derived from the same aerosolised powder cloud. The most significant challenge is to maintain the ratio of components during the formulation stage and, importantly, upon re-dispersion and deposition, although clearly if the particles separate (or are separated) in the airstream there is little chance of co-deposition. The companies responsible for multi-component products make every effort to formulate their drug product with high precision in terms of maintaining the ratio of individual actives; however, they cannot guarantee this ratio when the dose is delivered to the actual lung. Despite the number of publications that cite synergy and the usefulness of co-deposition when referencing respiratory combination drugs, the data suggesting consistency of dose and the ratio of actives from formulation to re-dispersion to co-deposition are scarce or unavailable. This is mainly because it is difficult to retain the ratios of actives, especially in the case of inhalation products, when the selected drug substances are present as micronised particles, in turn derived from mechanical milling.

The industrial practice of mechanically milling large particulate material in order to produce particles suitable for inhalation can lead to substantial problems with both the micronised material and its use in inhaled drug product development. The high-energy process causes poor chemical and physical stability, electrostatic charge, the formation of amorphous domains, unwanted surface free energy and polymorph transition. Collectively, these deleterious effects bring about variation and limitations in performance. Micronised particles can be very cohesive (auto-adhesion), which leads to significant agglomeration due to higher surface free energy and surface area per unit mass. In addition to this, the moisture sorption...
profile of the material and cohesivity further influence the drug product rheological properties. Furthermore, the high heterogeneity in particle–particle interaction intensifies the problems of maintaining the ratio of actives at all stages of the drug delivery profile. This ultimately affects the therapeutic efficiency and contributes to a decreased level of drug product performance.

In order to overcome the considerable problems in the delivery of two or more micronised drug substances to the lung and ensure optimal co-deposition and co-location of the molecules, particle engineering technologies have been conceived to satisfy this unmet need. Now constructive sonocrystallisation particle engineering offers significant benefits for the manufacture of inhalable drug powders. The solution atomisation and crystallisation procedure was developed in order to design respiratory particles with the optimal attributes for their intended use and involves forming concentrated droplets of a drug substance solution and treating with ultrasound in order to crystallise as spheroidal particles. The processing of engineered combination particles of FP–SX by this sonocrystallisation methodology with high homogeneity and retention of ratio of actives, both in formulation and deposition, along with analyses to establish the distribution of actives within the given particles, is described elsewhere.

Sonocrystallisation involves the application of power ultrasound to a processing medium, which in turn leads to the formation of energetic cavitation bubbles, where crystal nucleation can take place. The technology requires the use of a Prosonitron™ ultrasonic flow cell operating at 20–100 kHz. The more robust industrial variant of SAX, ultrasound-mediated amorphous-to-crystalline transition (uMAX®), can be used for the manufacture of combination particles with optimal performance attributes for inhalation, including content uniformity of the drugs, size, shape, surface rugosity, surface free energy, crystallinity and stability; the particles being ultimately designed for asthma and COPD structured drug products. UMAX facilitates the preparation of both spheroidal and more regular shaped particles for DPI or MDI.

It is particularly important to consider ICS/LABA formulations when the LABA is low dose strength and is present in the powder blend in a low concentration, perhaps as low as 1 % weight/weight. In this instance it is extremely difficult to achieve suitable homogeneity in the powder blend and, crucially, ensure consistency of the target mass ratio in the final dosage form. For example, carmoterol hydrochloride is a very low dosage LABA which is administered by inhalation, at a very low daily therapeutic dose ranging from 1 to 4 μg, concurrently with BDS in a mass ratio of up to 100:1. This combination therapy is in clinical development. Trying to manufacture compositions by dry powder blending and achieving constant ratio with each delivered dose is fraught with problems. The UMAX technique starts by preparing a solution of both actives which can be established by precision weighing. Subsequent processing yields individual particles with the correct ratio of the two actives and with extremely good blend content uniformity.

Using the UMAX technology it is now possible to produce improved combination products that will help deliver all active respiratory molecules present in combination with increased airway co-location. This improved co-location to targeted parts of the lung may help achieve more pronounced synergy and additive efficacy on the key target cells and pathologies of inflammation and bronchoconstriction, in turn leading to lower doses and improved safety and adherence. Highly crystalline inhalable-size combination particles of FP–SX (10:1, PXL8043-112-D1-VD-3, formulation reference EF11162) and BDS–formoterol fumarate dehydrate (FFD) (100:6, PXL8045-134-E1, formulation reference EF11165) were manufactured by the UMAX technology, demonstrating that novel dual therapy for both new products and lifecycle management via appropriately engineered multi-component particles can be leveraged successfully (see Figure 2).

The aerosolisation efficiency of the combination particles was evaluated in MDI formulations using 1,1,1,2-tetrafluoroethane (HFA134a) propellant. The blend strengths of the FP–SX (EF11162) and BDS–FFD (EF11165) combination formulations equated to 250 μg.

Figure 3: Formulation Performance of Fluticasone Propionate–Salmeterol Xinafoate 10:1 (EF11162) and Budesonide–Formoterol Fumarate Dihydrate 100:6 (EF11165) Following Aerosolisation of Ultrasound-mediated Amorphous-to-crystalline Transition Combination Particles
In the design of respiratory combination particles one must consider not only the total mass of drug deposited on the fine particle stages, and stages III–V in particular, of the impactor, but also the uniformity of delivery of both drug substances. Figure 3 shows the comparison of the ACI profile in percentage/target for both the combination products. These data suggest that consistent deposition profiles were seen for both FP–SX (EF11162) and BDS–FFD (EF11165), indicating maintenance of co-deposition of both FP–SX and BDS–FFD on various stages of the ACI. It is to be expected that the use of such engineered particles will lead to near 100 % co-location and uniform delivery throughout the full volume of the lung alongside an expected enhanced synergistic action.

Process Scale-up
The manufacture of up to kilogram scale to current good manufacturing practice (cGMP) has been demonstrated using a GEA Niro Mobile Minor™ spray dryer (see Figure 4). This unit is one of the smallest industrial spray dryers using either rotary or nozzle atomisers. This type of system has a water evaporative capacity of up to 7 kg/h, and 50–100 % greater when volatile solvents are used.

The part-amorphous particles containing both active ingredients in the prescribed ratio are further ultrasonically treated in a selected non-solvent (e.g., perfluorodecalin) until the resultant particles are stable and appreciably crystalline. With respect to pilot scale operation, the stage II crystalline transition may be carried out using the Prosonitron equipment (see Figure 4), using a diverse range of non-solvents including hydrocarbons, water and fluorohydrocarbons.

Conclusions
The use of combination therapy, and in particular the concurrent delivery of an ICS and an LABA, is a mainstay treatment of asthma and COPD in order to treat inflammation and bronchodilatation in these debilitating diseases. The Advair/Seretide combination of FP and SX and the Symbicort combination of BDS and FFD have been used as very effective treatments over a number of years. There is now very compelling evidence for complementary and mutual synergistic actions of the drugs when taken together, including the activation of the GR by the LABA and the effects of the ICS on increasing the number of β2-receptors. However, there are safety concerns with the use of high-dose inhaled LABAs, with respect to causing severe asthma-related exacerbations.

This article has focused on the rationale that improved topical delivery for combination formulations can be expected if both substances are co-associated with high homogeneity, rather than using physical and mechanical mixtures that are not only difficult to prepare with such homogeneity but are only very poorly co-associated. Whilst physical mixture combination products offer a solution to achieve the desired and targeted material mix, the co-deposition of actives occurs randomly when derived from the same aerosolised cloud and, as a result, there is inconsistency in the ratio of deposition in various regions of the lung, despite the use of a precise formulation mass ratio of the actives. Particle engineering techniques involving the use of ultrasound can be used to manufacture microcrystalline dual-component particles for inhalation drug delivery with high homogeneity, and in particular particles consisting of an ICS and an LABA, as in this investigation. In turn these particles should facilitate optimal and concurrent delivery of both drugs to the lung. The UMAX sonocrystallisation process used for manufacture of such particles circumvents the use of mechanical milling and, in turn, avoidance of poor and variable performance, and the effects of comminution on sensitive organic crystals. These particles can have optimal performance attributes for inhalation products designed for asthma and COPD.

Particulates of BDS–FFD and FP–SX have been engineered and formulated as an MDI. Furthermore, aerosol performance has been assessed by ACI to identify co-deposition of individual drug particles within the impactor. The studies to date have shown that these combination particle formulations are very consistent with respect to the delivery of each active ingredient at each stage of the impactor, and presented excellent content uniformity. These improved medicines could help achieve acceptable efficacy at reduced dose, thus improving topical delivery due to enhanced safety and mutual synergistic approach.

Inhaled combination therapy is an exciting area of research in order to develop improved respiratory medicines, and potentially offers patients the best medication options for pulmonary disease. Co-associated drugs will not only improve any synergy of action but may yield opportunities for dose sparing when designing new ICS/LABA structure drug products for respiratory disease.

FP/25 μg SX and 125 μg BDS/7.5 μg FFD per actuation, respectively. Aerodynamic assessment was carried out using an Anderson cascade impactor (ACI) calibrated at 28.5 l/min flow rate. The mass of drug deposited on each part of the ACI was determined by high-performance liquid chromatography (hPLC) and the mass median aerodynamic diameter (MMAD) and fine particle fraction (FPF) were determined.
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