

Divide and Conquer – A New Approach to Delivery of Inhaled Combination Therapies

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Introduction

Inhaled combination therapy is not a new idea. Early, adventurous attempts included the **Burroughs Wellcome** Vaporole ammonium chloride inhaler: a curious 'home chemistry set' style of device requiring the interaction of ammonia with hydrochloric acid (see *Figure 1*). Patented combinations of inhaled medications for the treatment of respiratory diseases such as asthma have been in use since 1909, when Sir Hiram Maxim (inventor of the Maxim machine gun) patented his Pipe of Peace for the pulmonary delivery of Menthol and 'Dirigo' pine essence (see *Figure 2*). Following the advent of modern, evidence-based



Figure 1 – Vaporole Ammonium Chloride Inhaler (Burroughs Wellcome).



Figure 2 – Maxim's Pipe of Peace – an example of early combination therapy.

medicine, and the introduction of pressurised metered dose inhalers and dry powder inhalers in the 1950s-1960s, the larger pharmaceutical companies have made attempts to put their inhalers to use in delivering combinations of drugs designed to combat different aspects of asthmatic disease. These have generally included short-acting bronchodilators (beta-agonists and anticholinergics) with corticosteroids or non-steroidal anti-inflammatories such as sodium cromoglycate. New inhalers, including **Innovata Biomed's** Clickhaler®, have meanwhile been introduced for use with available generic drugs, and are also being developed for the delivery of new chemical entities. As yet, however, no new device has ventured into the combination therapy marketplace (Smith and Parry-Billings, 2003). Traditionally, there has been considerable resistance to the concept of fixed dose combination therapy (Lindsay, 1988). Asthma Guidelines have not been strongly supportive and

the market has been weak (worldwide, US\$160 M pa in 1998). The key to a change of perception that has recently turned combination therapy into a runaway success is the introduction into the 'inhaled steroid +' equation of the long-acting beta-agonists, salmeterol and formoterol.

Combination Therapy in Respiratory Medicine – a Commercial Success Story

Combination therapies have never before had the level of success witnessed with the first two inhaled dry powder fixed combinations of long-acting beta-agonists and corticosteroids, produced by **GlaxoSmithKline** (GSK) (salmeterol + fluticasone: Seretide®; Advair® in the US) and **AstraZeneca** (formoterol + budesonide: Symbicort®), respectively. The worldwide market increased to over US\$2000 M pa in 2002, and the introduction of Advair® turned Respiratory into the key therapy growth area for North America, with a growth of 17% in the 12 months to June 2002 (source: IMS HEALTH Drug Monitor).

What are the factors underlying this dramatic change of heart? The commercial success of Seretide/Advair and Symbicort is undoubtedly due in no small measure to the quality and quantity of the promotional efforts made by the parent companies. The power of 'compression marketing' can be seen to justify the expense of phenomenal salesforce activity by condensing the time taken to optimise sales (Loden, 2000) (see *Figure 3*). When combined with a compelling pricing strategy that ensures the fixed combination is actually cheaper than the two separate treatments, combination therapy is poised to win new, as well as 'switch' patients. The days of 'snake

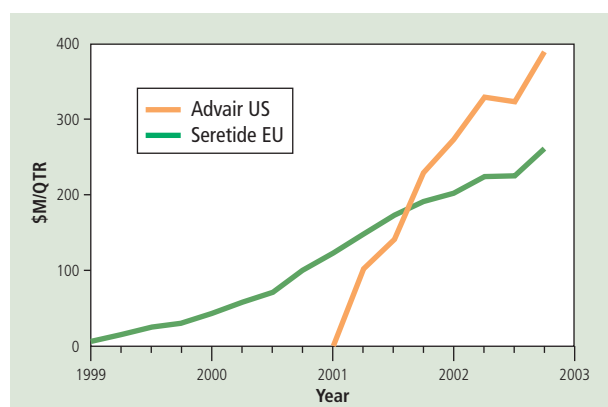


Figure 3 – Sales of GSK's Seretide (Advair) from launch in Europe (conventional marketing) and US (compression marketing). Units US\$ per quarter year.

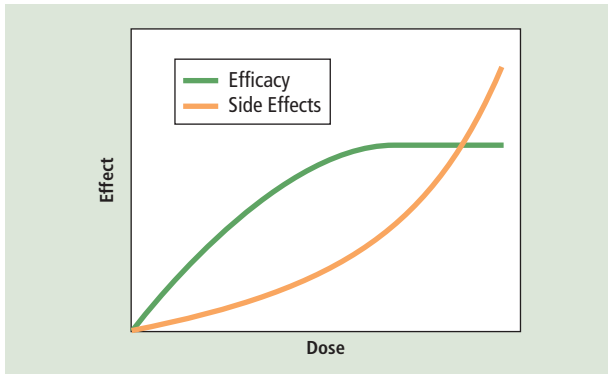


Figure 4 – Inhaled corticosteroid efficacy and side-effects with increasing dose.

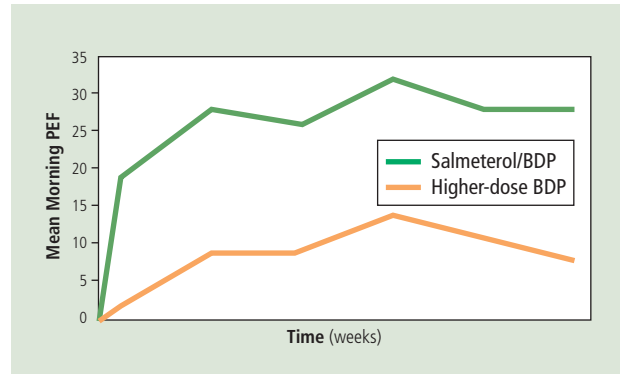


Figure 5 – Impact on peak expiratory flow (PEF) of adding a long-acting beta₂-agonist to (BDP) steroid treatment (from Greening et al., 1994).

oil' purveyors are past, however, and clever marketing is certainly not sufficient to change the collective clinical viewpoint. The answer to this success lies in demonstrable improvements in therapeutic efficacy, and in the convenience and acceptability of the combined treatment to the patient. These factors are interlinked because the patient is more likely to take a bronchodilator, which has a perceptible relieving effect, than to take a steroid regularly. The anti-inflammatory activity of the steroid may be crucial in controlling the asthmatic condition, but as there is no immediate feeling of relief, the patient may think it unhelpful and therefore stop taking it. The importance of inhaled steroids in asthma therapy was demonstrated recently in a large safety study of add-on salmeterol versus placebo. Interim analysis of 25,858 patients showed a trend in deaths from asthma to be higher among African Americans: but this sub-group was also found to have more severe asthma and to be taking less inhaled corticosteroid (*Smart Study GlaxoSmithKline, 2003*).

The scientific rationale for inhaled combination therapy with long-acting beta-agonists and steroids has been comprehensively reviewed (Barnes, 2002; Stoloff et al.,

2002). Studies have shown that inhaled steroids can exert most of their pulmonary efficacy at low doses, so that increasing the dose of steroid has little beneficial effect, showing a rather flat dose response curve (Sims et al., 2002) (see Figure 4). At the same time, adverse side-effects of steroids are more directly dose-related, increasing the risk at high doses. Adding a long-acting beta-agonist onto the steroid dose provides effective additional benefit because this acts via a different mechanism (Greening et al., 1994) (see Figure 5). Experimental evidence also suggests that concurrent activation of drug binding sites may produce complementary, synergistic interactions between long-acting beta₂-agonists and inhaled corticosteroids (Barnes, 2002) (see Figure 6).

It should not be forgotten that to the patient, the convenience of regular treatment may be far more important than the science. Patient compliance with fixed combination inhalers is likely to be improved as a result of the simplified regimen that a single inhaler affords, and the prospect of real benefit to the asthmatic patient has already led to the amendment of treatment guidelines, the inclusion of long-acting beta-agonists now being recommended *before* increasing the inhaled corticosteroid dose in stepwise asthma therapy (British Thoracic Society, 2003). Furthermore, there is evidence that long-acting beta-agonist/steroid combination therapy may also be effective in reducing exacerbations of chronic obstructive pulmonary disease (COPD) (Calverley et al., 2003). Given the huge commercial success of these fixed combinations in asthma, the likely invigoration of growth with approvals in COPD and the diminishing patent life of the individual entities, it is small wonder that an array of patent applications has already been made for the readily imaginable combinations. The development of Symbicort as an 'all-in-one'/'all-you-need' asthma inhaler strongly emphasises the requirement for a user-friendly, portable and convenient delivery format.

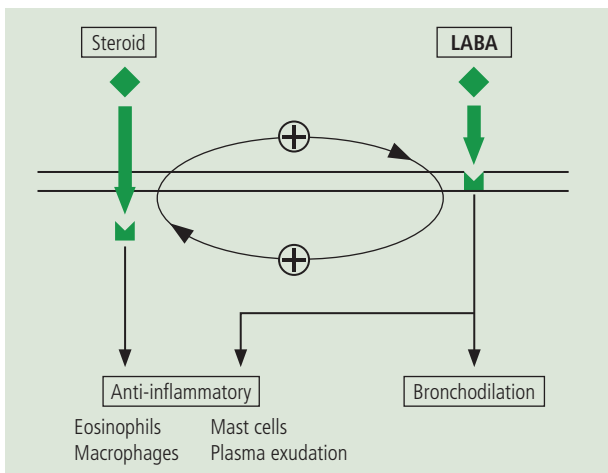


Figure 6 – Complementary effects of long acting beta₂-agonists (LABA) and steroids. Studies have shown a synergistic interaction between these two drug classes such that LABA binding enhances steroid receptor translocation into the nucleus and steroid may increase density of LABA receptors.

A New Approach to the Formulation Challenge of Combined Therapies

For dry powder technology, the combination therapy approach puts a serious burden on the formulator, who

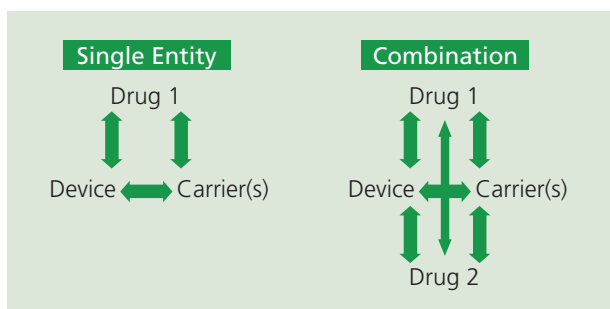


Figure 7 – Interactions within and between drug, device and carrier particles – illustrating the complexity of formulating combinations.

must try to create a formulation in which the needs of both actives are satisfied without the two interacting. Ordinarily, for a single entity inhaled medication, the formulator would need to consider three interactions: cohesive drug-drug, adhesive drug-carrier and segregative drug-device; but for combinations there is a further, drug1-drug2, set of adhesive forces to take into account, as well as each of the usual interactions twice-over (see Figure 7). This is a significant challenge to achieve in a single formulation, especially where the dose of long-acting beta-agonist is routinely very low (e.g. 6 µg formoterol) compared with the inhaled corticosteroid (100s µg budesonide). This problem may be solved by adopting a new approach to the delivery of combination asthma therapy.

Twinhaler™ – a problem shared is a problem halved

The Twinhaler™ (Innovata Biomed Ltd, St Albans, UK) represents a new approach to the delivery of inhaled combination therapies. In essence, it combines two distinct reservoir dry powder inhalers into a single device, while keeping the formulations completely separate. The dose metering mechanism uses the established Clickhaler® process in which powder from the storage hopper precisely fills a dimple on the rotating metering cone before delivery into the inhalation passage (Parry-Billings *et al.*, 1999) (see Figure 8). By virtue of its having two reservoirs, each active

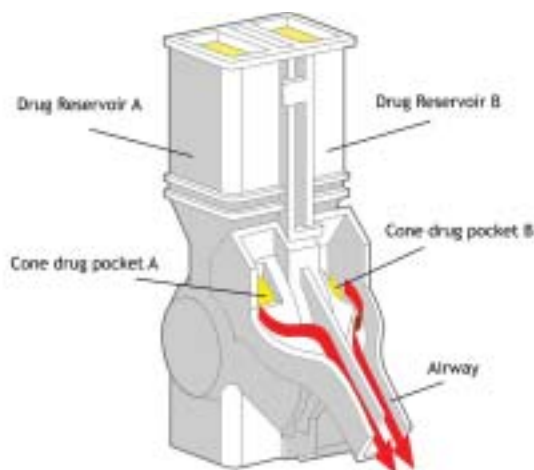


Figure 8 – Internal view of Twinhaler.

drug in the Twinhaler can be formulated independently and optimised fully without the other being compromised by the formulation strategy. Each dosing member can also be fine-tuned to suit a particular formulation, with differently sized metering dimples facilitating the delivery of different dose sizes.

The 'black art' of formulation development for a dry powder is an iterative process involving experimentation with a number of different carrier systems (usually lactose) and often combinations of different grades and sizes of lactose, that continues until performance targets are met. The active drug formulations, including salbutamol 100 µg and beclomethasone 50, 100, 250 µg, that have been developed for the original Clickhaler technology have each had quite different needs from the carrier system, aided by the ability to increase dose size simply by using larger dimples on the metering cone. For future combination medications, it is likely that the individual actives may each have quite different formulation requirements that dictate separate handling. Given the likelihood of a range of strengths required for steroid products, the benefits of separate handling become even more important at each step of the way – from storage, through metering, to delivery.

Design of a user-friendly dual delivery inhaler

The Twinhaler has been designed to be no bigger than the Clickhaler, yet to have twice the delivery capability (see Figure 9). Like its predecessor, Twinhaler is actuated by simply pushing down on the top button. This rotates the two loaded metering dimples into the inhalation airway. Twinhaler thus retains the features of ease of use and patient acceptability that have contributed to the success of the Clickhaler. The airway passages in the Twinhaler device are separate and can be optimised individually, as necessary, to provide additional de-aggregation.

The formulations already developed or in progress for the Clickhaler (salbutamol, beclomethasone, formoterol, budesonide and fluticasone) constitute a library of expertise and compatible know-how for the rapid development



Figure 9 – External view of Twinhaler.

of future combinations employing one or more of the established powders. For new drugs that may first appear as mono-entities but ultimately as combinations, the attractiveness of this forwardly mobile technology is compelling. Innovata Biomed has investigated and applied for a series of patents covering formulation and delivery strategies to give further support to the core Intellectual Property platform for Twinhaler. Additionally, by deploying both reservoirs to deliver the same drug, Twinhaler provides a device technology suitable for achieving delivery of higher doses of monotherapy to the lung.

Matching patient requirements

Both in asthma and COPD, improved patient compliance and hence cost-effectiveness of treatment depends on providing a delivery device suited to the real needs of the patients. Innovata Biomed's careful approach in researching patient acceptability and practical requirements with the Clickhaler, in terms of device interface and required inspiratory flow, has ensured that the Twinhaler platform is suitable for the needs of both asthmatic and COPD patients. In common with the Clickhaler, the Twinhaler device is similar in handling to the familiar pressurised metered dose inhaler and is intuitive to use. It can be colour-coded in line with the convention or to pharmaceutical partner requirements, and it has user-helpful features including a retained mouthpiece cover, a dose-counter, low-dose warning, and a lock-out feature when empty. Ease of use of inhalers is a key factor in ensuring their correct use and hence effective treatment.

Conclusion

The future of inhaled combination therapy for respiratory disease looks very bright, with the marketed products containing fixed combination formulations of long-acting beta-agonists and corticosteroids achieving outstanding commercial success. Innovative devices such as the dual-reservoir Twinhaler offer a more flexible option towards the successful inhaled combination products of the future.

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