Development of dry powder formulations combining both a biologic therapeutic entity and a small molecule drug substance

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Summary

An inhalation product combining a biological therapeutic entity with a small molecule drug substance is still a very novel concept in inhalation. A combination product would potentially have significant compliance and patient benefits via simplifying and reducing the time of treatment.

This study assessed the combination of an immunomodulatory protein (Omalizumab) with a co-prescribed corticosteroid (Fluticasone Propionate). The objective was to produce a biologically, chemically and physically stable powder formulation as evidenced by the stability data presented.

Small molecules and biologics are typically formulated and delivered in different ways, with biologics commonly developed as liquid formulations for injection. For this study the formulation was designed for delivery via a dry powder inhaler (DPI). Biologics can be rendered more stable in the solid state via co-formulation with specific excipients therefore a dry powder format can offer improved stability and potentially remove the necessity for refrigerated storage and transport.

The development of a combination dry powder formulation presented a number of challenges that were addressed through the combined use of spray drying and low intensity blending techniques. Excipients were identified to provide protein stability and improve aerosol performance. The physical stability (via aerosol performance testing) and biological integrity of the formulation was assessed for 6 months at 30ºC/65% relative humidity. The study demonstrated that a small molecule and a biologic can be combined successfully to produce a novel model dry powder formulation with good homogeneity and stability.

Introduction

Currently, the most investigated approach to combining a biologic and small molecule is antibody drug conjugates (ADCs). ADCs are produced using complex manufacturing methods and can restrict dose ratios[1], therefore manufacturing techniques were identified to simplify and improve the flexibility of a combination formulation whilst maintaining protein stability.

A number of small molecule drug products are co-prescribed with a biologic therapy , for example the combination of mucolytics and bronchodilators for the treatment of cystic fibrosis[2]. Current treatment may require time-consuming nebuliser regimens or parenteral administration, therefore reducing the need for these will simplify treatment and potentially improve patients' quality of life. Providing more than one method of treatment in a single device also has the potential to increase patient compliance[3].

Biologics are generally more stable in the solid state[4] therefore biomolecules in a dry powder format can offer improved stability. As well as increasing the shelf life, the dry powder format may also remove the requirement for refrigerated storage and transport. There is also the potential for therapeutic benefit in applying the molecule directly to the site of action as opposed to delivering systemically.

Manufacturing a combination formulation

The aim of this work was to produce a proof-of-concept formulation combining a biologic with a co-prescribed small molecule. The study assessed the combination of a monoclonal antibody (Omalizumab) with a corticosteroid (Fluticasone Propionate), both prescribed for the treatment of severe asthma. These molecules were selected as models to demonstrate capability as they pose the additional challenge of cold chain storage of Omalizumab and low dosage of FP.

The small molecule and biologic were initially formulated separately with suitable excipients to produce optimum pre-blend formulations independently. Common blending excipients include sugars such as lactose or force control agents (FCAs) such as magnesium stearate. Reducing sugars may not be compatible with proteins due to the Maillard reaction therefore a taurine carrier system was selected over lactose for this study. The mono formulations were developed to improve aerosol performance, particle size, homogeneity and protein stability. Producing separate pre-blends and coating the particles with excipients reduces the interactions between the two drugs which may lead to variability in aerosol performance and differences between the mono and combination blends[5]. API concentrations of the final blend were based on delivering standard doses of each drug using a dry powder inhaler.

The objective was to produce stable combination formulations as evidenced by 6 months stability data. Physical-chemical analysis, protein stability and aerosol testing were performed over 6 month's stability and results were compared to the mono biologic formulation.

Materials and Methods

Spray drying and LabRAM acoustic blending

Spray drying, mechano chemical bonding (MCB) and LabRAM ResonantAcoustic® Mixer (RAM) techniques were selected for rapid manufacture of the combination product. Spray drying was used to produce the initial biologic 'pre-blend'; combining the biologic with a stabilising excipient and FCA. Spray drying provides control over the powder particle size, morphology and density via adjustment of process parameters. The FP particles were coated with FCA in 'pre-blend' 2 using a mechano chemical bonding method. The LabRAM acoustic blending technique was chosen for combining the spray dried pre-blend with the small molecule pre-blend as it is an efficient low shear mixing process which reduces the stress applied to the formulation and ensures homogeneity[6]. Spray dried particles are particularly friable and may fracture, therefore this low shear process can reduce particulate damage.

Three 'pre-blends' were manufactured using the components and manufacturing methods detailed in Table 1. The 'pre-blends' were not assessed for homogeneity as the processes used are considered intrinsically uniform. These pre-blends were subsequently combined using the LabRAM to produce a Omalizumab / FP combination formulation.

Table 1: Pre-blend components of the Omalizumab / Fluticasone propionate combination formulation

Pre-blend #	Material	Blending method	%w/w in combination formulation	PSD (D_{50})
1	Omalizumab / stabilising excipient / FCA	Spray drying – bespoke spray dryer	32	2.6
2	Fluticasone Propionate / FCA	Mechano chemical bonding (MCB)	2	1.8
3	Taurine / FCA	Spray drying – bespoke spray dryer	66	1.7

Analytical requirements

In general, analysis of a biologic entity requires additional complexity compared to small molecule analytical methods therefore a combination of both requires method assessment and development[7]. SDS-PAGE, size exclusion and activity assay methods were assessed and deemed acceptable to analyse the protein in the presence of the small molecule. Additionally particle size, water content and glass transition temperature (T_g) were also measured. Content uniformity was analysed by RP-HPLC, using a separate method for each API due to diluent solubility incompatibility. A fast screen impactor (FSI) was used to assess aerodynamic performance using a Vectura unit dose inhaler at a 60L/min flow rate and a 5µm insert.

Results and Discussion

Process Development

Initial process development investigated the effect of LabRAM blending intensity on the homogeneity of the combination formulation at a 1g scale. Content uniformity results (figure 1) show optimum assay results for both molecules were achieved at the highest intensity (80%). However the Omalizumab %RSD result remains high suggesting wall losses during the blending process. Adjustments were put in place to reduce this issue including increasing batch size, increasing the particle size of the carrier and assessing the effect of order of addition in the final blending step. The main improvement in homogeneity was identified when the final blend was increased from a 1.0g to a 5.0g scale. This resulted in an Omalizumab content of 99% of nominal and 1.5% RSD in the final formulation (see table 2, initial data).

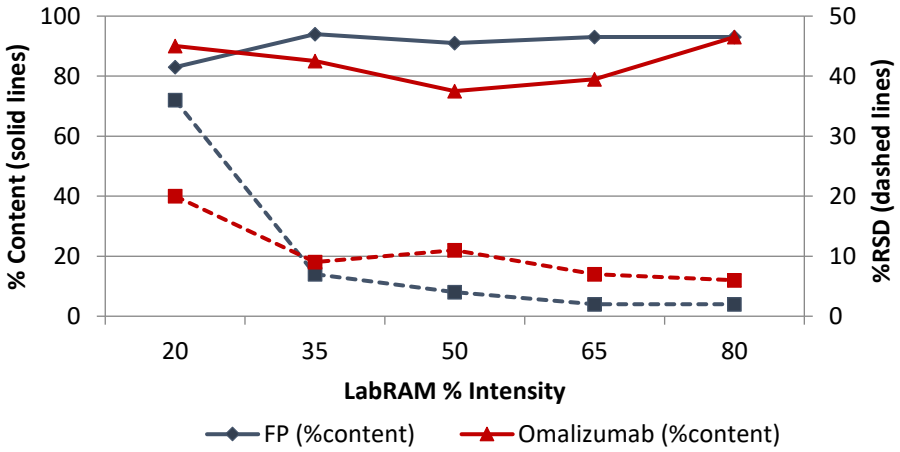

Figure 1: Process optimisation – content homogeneity assessment at a range of LabRAM blending intensities (mean of 5 content uniformity replicates)

Stability assessment

Following development a final 5g combination blend was manufactured and set down for a 6 month stability assessment at 30˚C/65%RH. Figure 2 shows an SEM image of the formulation placed on stability.

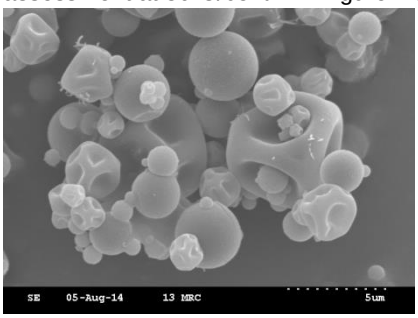

Figure 2: SEM image of the final Omalizumab / FP combination blend.

Aerosol performance results (figure 3) show consistent blister evacuation and %FPF across time points. FP content uniformity results (table 2) are also stable throughout the study. Omalizumab content uniformity results are however inconsistent which may be due to protein blister retention. Size exclusion aggregation data (table 2) shows no clear trends however an additional degradation peak is observed at the 2 week time point and shows an increase at 24 weeks.

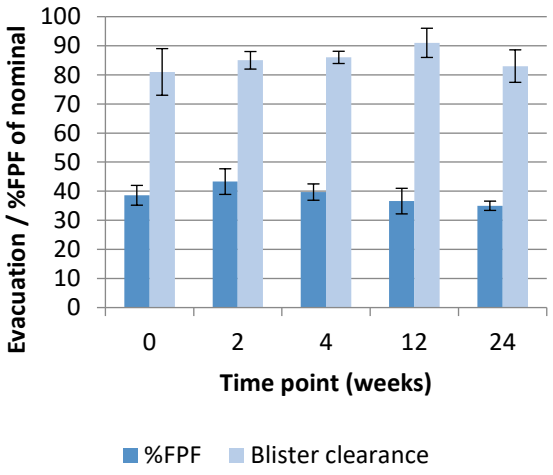

Figure 3: Gravimetric FSI stability results- evacuation and percentage fine particle fraction (%FPF)

Table 2: Physical properties, content uniformity and size exclusion stability results of the combination blend

	Time point (weeks)				
Test	**0**	**2**	**4**	**12**	**24**
Particle size (D_{90}, µm)	4.7	5.0	5.0	4.8	4.6
Moisture content (%w/w)	1.2	1.0	2.2	1.0	1.1
Glass transition temperature (T_g, ˚C)	81	80	79	79	77
Content Uniformity: Omalizumab					
%w/w of nominal	99	*	88	91	83
%RSD	1.5		5.8	2.3	4.7
Content Uniformity: FP					
%w/w of nominal	102	*	96	97	97
%RSD	5.4		4.4	1.2	2.4
Size exclusion					
Aggregation (% of total peak area)	0.2	0.0	0.3	0.2	0.1
Degradation (% of total peak area)	0.0	0.3	0.0	0.0	1.4

*No result generated due to methodology reasons

Overall, results demonstrate physical properties, aerodynamic performance and protein stability data (table 2) are within the project assigned acceptable limits for up to 6 months stability at 30˚C/65%RH. Stability results of the combination formulation are comparable to the mono Omalizumab formulation (data not presented), supporting the concept of a combination product.

Following the successful combination formulation, the manufacturing methods were applied to an alternative model combination; an enzyme and formoterol. These results are not presented in this summary however the study also showed positive results following a 3 month stability study at accelerated storage conditions (40˚C/75%RH).

Conclusion

The overall project objectives were met; a small molecule and biologic were successfully combined to produce a homogenous dry powder inhalable product. While a number of potential challenges around mixing uniformity and analytical assessment were encountered, positive stability trends were produced following storage for 6 months at 30˚C/65%RH. Although further development of the formulation may be possible, the study demonstrates feasibility for the use of spray drying and LabRAM blending technology to produce a DPI combination product of both small molecule and biologic drug substance.

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