Modulating the Fine Particle Fraction, Surface Area and Surface Energy of a High Dose Fluticasone Propionate Formulation Using Isothermal Dry Particle Coating (iDPC) Technology

Rhys J Jones[1], Jasdip S Koner[1], Shital P Lungare[1], Amandip Gill[1], Isobel Clark[1], David A Wyatt[1,2] & Afzal R Mohammed[1,2]

[1] Aston Particle Technologies Ltd., Aston University, Aston Triangle, Birmingham, B4 7ET, UK
[2] Aston University, Aston Triangle, Birmingham, B4 7ET, UK

Aston Particle Technologies

Key Message

High dose DPI formulation manufactured by iDPC enables the systematic manipulation of FPF performance, surface area and surface energy of the formulation.

Introduction and Background

The objectives of this study were to establish whether FPF performance, surface area (SA) and surface energy (SE) of high dose formulations could be systematically modified by adjusting / controlling the parameters in the novel iDPC process, a technology developed by APT, and to investigate how these parameters influence the level of deagglomeration and dispersion of the API and carrier particles. Change in measured SA and SE could indicate increased or reduced deagglomeration and dispersion, properties which fundamentally influence FPF performance. Insight into the processes involved in DPI formulation manufacture could lead to deliberate design choices rather than trial-and-error practices. With carrier-based DPI formulations in general, aerosolisation performance can be attributed to the adhesion and cohesion of the components within the formulation[1][2] so it is reasonable to assume that changes in the SE of a DPI formulation could alter its dispersion and ultimately its aerosolisation performance[3]. Total SE consists of dispersive (non-polar) and acid-base (polar) specific SE[4]. Building in quality by design through better formulation understanding of total SE may in turn improve the efficiency of DPI development. To this end, the total SE of selected high dose fluticasone propionate (FP, 50%$^{w}/_{w}$) formulations was analysed in this study.

Methods and Materials

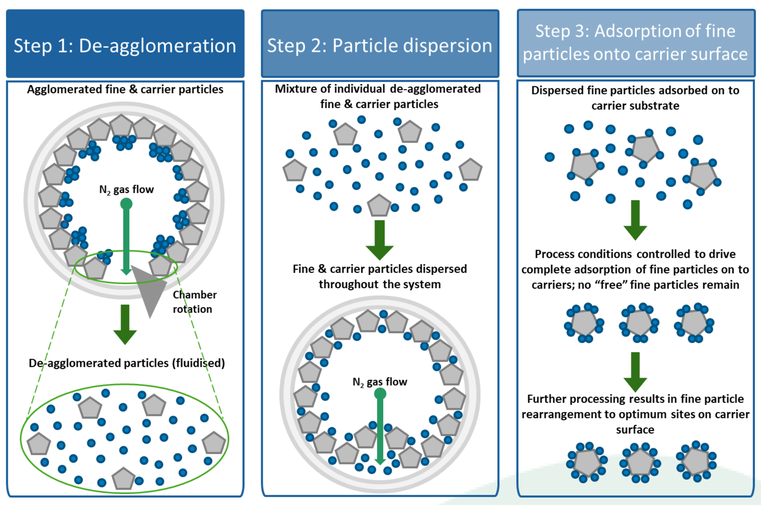

Figure 1. Schematic diagram of the three critical steps in the dry particle coating process. Finer particles are coated onto coarser particles in a thin layer at the surface of a rotating chamber during fluidisation by a nitrogen air-blade.

Method:

- A benchtop iDPC [5,6] (schematically presented in Figure 1 and equipment in Figure 2) was used to manufacture 5g powder blends of FP (50%$^{w}/_{w}$) in Inhalation Grade Lactose. 23 formulations were manufactured in total in which a range of operating conditions - different process speeds, nitrogen airflows and process times were investigated. Each of the formulations manufactured had the same composition, but each was processed in a different way – the process speed was varied from 1000 to 3000rpm, the nitrogen flow rate was varied from 10 to 75L/min, and the process time was varied from 5 to 10minutes. In addition, for some of the blends conditioning was adjusted during processing when process speed and/or nitrogen flow rate was modified mid-process
- Each powder blend was assessed for homogeneity (content uniformity) and aerosolisation performance in a capsule-based delivery system (Monodose™ 60L/min - Miat S.p.A., Milano, Italy) analysed using a Next Generation Impactor (NGI) (Copley Scientific, Nottingham, UK). 12.5mg was loaded into size 3 HPMC capsules for NGI testing.
- Five formulations were selected for SA and SE analysis using a Surface Measurement Systems (SMS) inverse gas chromatography (IGC) SE analyser instrument (SMS, London, UK). To calculate SA, the adsorption method of Brunauer, Emmett and Teller (BET) [7] was followed, to measure the octane adsorption isotherms within the partial pressure range of 0.05 – 0.35 P/Po. The analysis of total SE was performed by measuring the net retention volume for a series of alkane eluents and two monopolar probes. The Dorris and Gray method [8] was applied during the analysis.

Materials:

Micronised FP (Sterling S.p.A., Corciano, Italy), Inhalation Grade Lactose (IGL), α-lactose monohydrate (Lactohale® 200) (DFE Pharma, Goch, Germany)

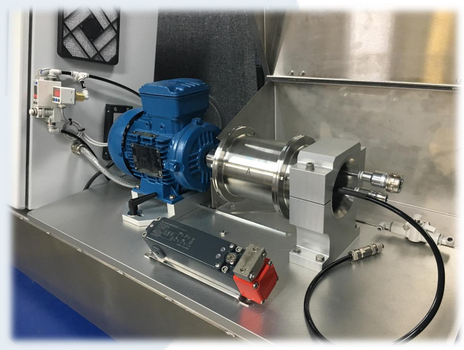

Figure 2. A benchtop iDPC system, which processes 1-20g, that was utilised in this study

Results

- Five formulations were selected for IGC analysis, with the formulations selected across the FPF, fine particle dose (FPD) and emitted dose range.
- The content uniformity and APSD performance data of the selected five FP formulations are detailed in Table 1, along with the iDPC process parameters used in preparation.

Table 1. Process parameters, content uniformity and APSD performance of the FP formulations.

Formulation	Process Speed (rpm)	Nitrogen Flow Rate (L/min)	Time (mins)	Emitted Dose (%)	% FPF (Emitted Dose)	FPD (mg)	Content Uniformity % RSD
HD112	1000	15	10	62.58	58.03	2.27	2.28
HD114	Step 1: 3000 Step 2: 3000	Step 1: 75 Step 2: 0	Step 1: 5 Step 2: 5	71.14	57.90	2.57	1.05
HD119	3000	20	5	69.19	62.06	2.68	2.28
HD122	Step 1: 3000 Step 2: 300	Step 1: 75 Step 2: 0	Step 1: 5 Step 2: 5	66.67	55.27	2.30	2.09
HD123	3000	10	5	70.61	64.51	2.85	0.91

- The FPF performance of the high dose FP formulations was found to be consistently in excess of 50% - varying from 55.27 to 64.51%., with fine particle doses in excess of 2mg varying from 2.27 to 2.85mg.
- Furthermore the data show that adjustment of the iDPC critical process parameters changed the aerosolisation performance of the FP formulations. Further systematic research is in hand to determine the role of each of the three critical process parameters in determining FPF performance.
- Surface Area analysis of the formulations (Table 2) revealed that the SA was significantly affected by the processing conditions. The highest value at 7.33m^2/g being 60% higher than the lowest at 4.58m^2/g. These values show that the iDPC modifies the deagglomeration and dispersion of the API and carrier.
- Surface Energy analysis (Table 2 and Figure 3) revealed that the formulations processed under different conditions differed in terms of SE homogeneity/heterogeneity.
- Formulation HD119 , which was processed under the highest speed and nitrogen flow rate was found to have the most homogeneous total surface energy with a range of 17.01 mJ/m^2.
- Formulation HD112 which was processed under the lowest speed and lower nitrogen flow rates showed the most heterogeneous total surface energy with a range of 22.14 mJ/m^2.
- These results demonstrate that adjusting the iDPC process parameters can modulate the SE.
- Further studies are in hand to identify the relationship between iDPC process parameters, SE and aerosolisation performance of the formulations.

Table 2. Surface area and surface energy of the FP formulations.

Formulation	Surface Area (m^2/g)	Dispersive Surface Energy Range (mJ/m^2)	Specific Surface Energy Range (mJ/m^2)	Total Surface Energy Range (mJ/m^2)
HD112	7.3328	16.91	6.15	22.14
HD114	6.6543	12.84	5.46	18.27
HD119	6.0357	12.02	4.99	17.01
HD122	4.7865	11.24	6.22	17.41
HD123	4.5776	12.58	6.29	18.87

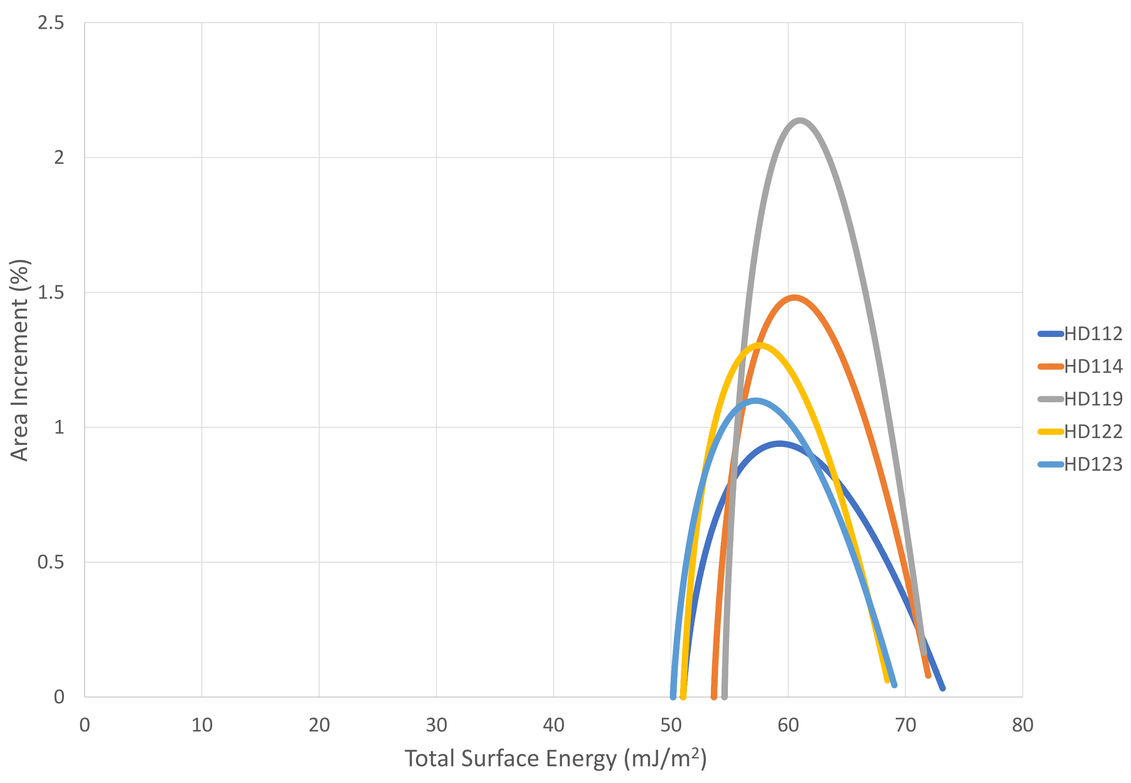

Figure 3. Total surface energy heterogeneity distributions of the FP formulations.

Conclusions

This study demonstrates that exceptional performance can be achieved from high dose DPI formulations processed by iDPC. Furthermore, clear evidence is presented that the APSD performance, SA and SE of a high dose FP formulation can be modulated by adjusting the iDPC process. Although further systematic research is required to elucidate the exact influence of each of the critical process parameters, Process Speed, Nitrogen Flow Rate and Process Time on formulation performance, it can be concluded that the higher the exposure of the API and IGL to the iDPC process the more homogenous the SE. This is significant as it highlights that the iDPC process may be utilised to develop DPI formulations with optimum aerosolisation performance, by careful selection of the iDPC input process parameters, providing the industry with a more controllable and predictable formulation strategy for the formulation of DPIs, especially at high API concentrations.

References

1 Saintlorant G, Leterme P, Gayot A, Flament M: *Influence of carrier on the performance of dry powder inhalers,* Int J Pharm 2007; 334 (1-2): pp85–91.
2 Staniforth J N, Rees J E, Lai F K, Hersey J A: *Interparticle forces in binary and ternary ordered powder mixes,* J Pharm Pharmacol 1982; 34: pp141–145.
3 Saleem I, Smyth H, Telko M*: Prediction of dry powder inhaler formulation performance from surface energetics and blending dynamics,* Drug Dev Ind Pharm 2008; 34 (9):pp1002–1010.
4 Fowkes F M: *Role of acid-base interfacial bonding in adhesion,* J Adhes Sci Technol 1987; 1 (1): pp7–27.
5 Mohammed A R, Dahmash E, Ahmed J, Drew T: *Patent WO2016066462A1 Coating apparatus and method.* 2016.
6 Mohammed A R. *Fluidised Powder Blending to control particle-particle interaction – The future of DPI Formulation* DDL2018.
7 Brunauer S, Emmet P H, Teller E; *Adsorption of Gases in Multimolecular Layers;* Journal of the American Chemical Society 1938; 60 (2) pp309-319.
8 Shi B, Wang y, Jia L; *Comparison of Dorris–Gray and Schultz methods for the calculation of surface dispersive free energy by inverse gas chromatography* 2011; 1218 (6) pp860-862.