INTEGRATED DESIGN SPACE TO DEVELOP BETTER DPI FORMULATIONS

Here, Filipa Maia, PhD, and Maria Palha, MSc, both Scientists at Hovione, report a study whose objective was to establish relationships between blend rheology, product performance and capsule filling process efficiency that would allow for the definition of an integrated design space, capable of recognising, and exploring, the trade-offs between the development (product angle) and manufacturing (process angle) stages.

INTRODUCTION

Successful formulation development for a dry powder inhaler (DPI) is strongly influenced by the choice of excipient grades and ratios between them, since the rheological behaviour of the powder mixture will have a significant impact on several aspects of the final product, such as content uniformity and stability of the formulation, overall aerodynamic performance and also on the robustness and effectiveness of the capsule filling process. Theory indicates that higher percentages of fine excipient particles in mixtures benefit the aerodynamic performance (e.g. Fine Particle Fraction, $FPF_{(5\mu m/ED)}$). However, the same approach may not benefit several downstream process steps, like the blending itself, from the perspective of yield, or the capsule filling step, from a rejection rate (RR) perspective.

> "An integrated design space analysis was derived where we demonstrated that a compromise between different parameters of aerodynamic performance and downstream process performance needs to be carefully considered."

In the same way, device performance, from an emitted dose (ED) or emitted mass (EM) perspective, can also be hindered, which could not necessarily be a problem if the $FPF_{(5\mu m/ED)}$ is indeed improved, but would be unnerving for a patient who observes a significant portion of the product remaining in the capsule. For example, a high percentage of fine lactose in a formulation may have a beneficial impact on the $FPF_{(5\mu m/ED)}$, but a negative impact on the rheology of the formulation and consequently on the downstream processes, causing a high RR during the automatic capsule filling steps, and making the rejected product (with fill weight of the capsules out of the acceptable range) so significant that the process is not economically viable.

METHODS

Eighteen placebo blends with different coarse and fine lactose grades and with different percentages of fines (0, 4, 10 and 16%) were prepared. Coarse lactose grades used were Respitose SV003 and SV010 from DFE Pharma (Goch, Germany); fine lactose grades were Lactohale 300 and Respitose ML006 from DFE Pharma, and Sorbolac 400 from Meggle Pharma (Wasserburg, Germany).

For each blend, both lactose grades (one coarse and one fine, total of 500 g) were screened through a 450 µm sieve and placed in a 2 L container. The mixture was then blended in a Turbula® T2F for 30 minutes at 46 rpm. The blends were left to rest for

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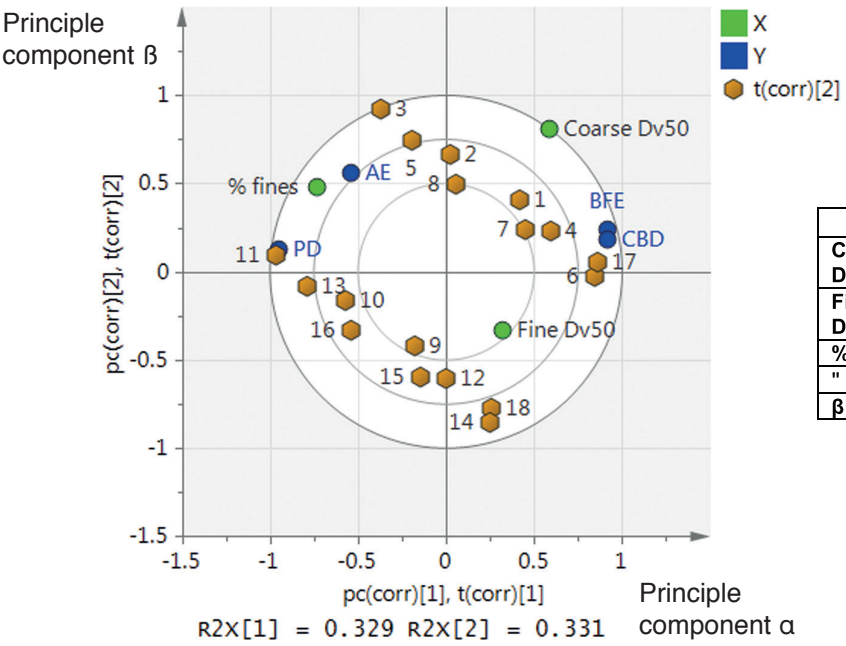

Blend	3	11	6	14
Coarse lactose Dv50 (! m)	105	60	105	60
Fine lactose Dv50 (! m)	5	5	17	17
% Fine lactose	16	16	4	4
"	-0.369	-0.968	0.846	0.247
β	0.925	0.0963	-0.0241	-0.853

Figure 1: Left: PLS regression biplot showing X variables, Y variables and observations for Model 1. Right: linking formulation composition with rheological properties (principal components α and β).

at least 24 hours to allow for relaxation of the powder. After that, all blends were analysed in an FT4 powder rheometer. Stability and variable flow rate, aeration and permeability standard tests were performed in triplicate. The obtained data were analysed using Umetrics SIMCA software (MKS Instruments, Malmö, Sweden).

Capsules were automatically filled using FlexaLab (MG2, Bologna, Italy) using two different dosators and targeting fill weights of 5 and 15 mg of powder, with acceptance limits of ±5% of the target fill weight. 1,000 capsules were filled for each set of conditions at a constant filling speed of 2,000 capsules per hour.

EM was determined using a DUSA with the equipment set to a pressure drop across the device equal to 4 kPa and an inspiratory volume of 4 L. The capsules filled with 5 mg and 15 mg were aerosolised using Hovione's proprietary inhaler PowdAir, with a flowrate of 39 L/min at 4 kPa. The gravimetric EM was calculated by considering the average of ten actuations, and the corresponding Relative Standard Deviation (RSD) was calculated. Multivariate statistical analysis of the data obtained was performed using SIMCA software.

Sixteen blends, with different coarse and fine lactose grades and with fine lactose amounts of 4%, 10% and 16%,

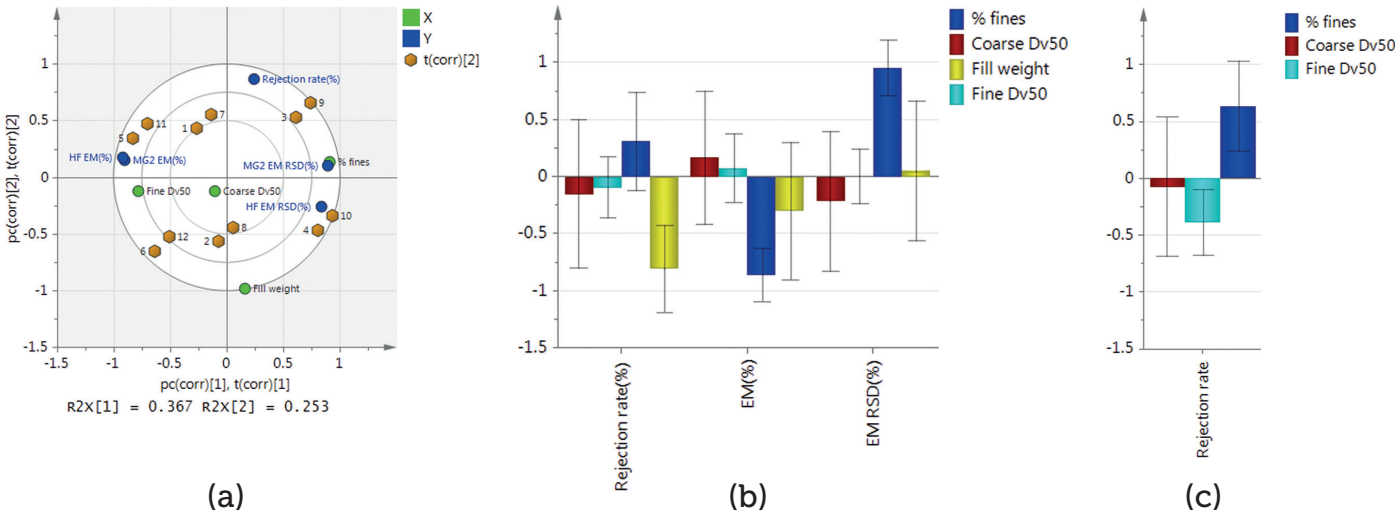

Figure 2: a) PLS results for the overall Model 2: biplot showing X variables, Y variables and observations, b) PLS results for the overall Model 2: co-efficients overview, showing the model coefficients and respective error for all the Y variables, and c) PLS model results: co-efficients overview for the rejection rate when the fill weight is not taken into account (Model 3).

were prepared. Each blend comprised a total amount of 200 g of two lactose grades, screened through a 450 µm sieve and placed in a 1 L container. The lactose mixtures were blended in a Turbula® T2F, followed by a four-step addition of the API that represented 1% w/w of the blend. Two different APIs were evaluated: fluticasone propionate (FP) and mometasone furoate (MF). The blends were left resting for at least 24 hours and afterwards evaluated for blend uniformity.

Capsules were hand filled with a target label claim of 125 µg of API with acceptance limits of ±5% of the target fill weight. The aerodynamic performance was assessed by Next Generation Impactor (NGI) (n=3 replicates) using PowdAir inhaler. The multivariate analysis was conducted, once again, using SIMCA software.

The creation of individual design spaces for rheology parameters *versus* ED, $FPF_{(5\mu m/ED)}$ and RR and of the combination of the three design spaces was performed using Mathematica 7 from Wolfram (Hanborough, UK).

RESULTS AND DISCUSSION

The three formulation parameters of particle size of the coarse lactose, particle size of the fine lactose and percentage of the fine lactose grade were correlated, using a partial least squares (PLS) regression with two principle components, with the rheological behaviour of the blends [Aeration Energy (AE), Basic Flowability Energy (BFE), Pressure Drop (PD) across the powder bed and Condensed Bulk Density (CBD)]. This is considered Model 1.

In Figure 1, the biplot with all X variables (inputs = formulation parameters), Y variables (outputs = rheology parameters) and observations is presented. The axes of the biplot represent the principal components. The points of the biplot represent the scores of the observations and variables on the principal components. The results for the global model demonstrate that the experimental data is well fitted, with an R^2 of 0.83 and a χ^2 of 0.75. From the regression performed, it is possible to capture the relationships between

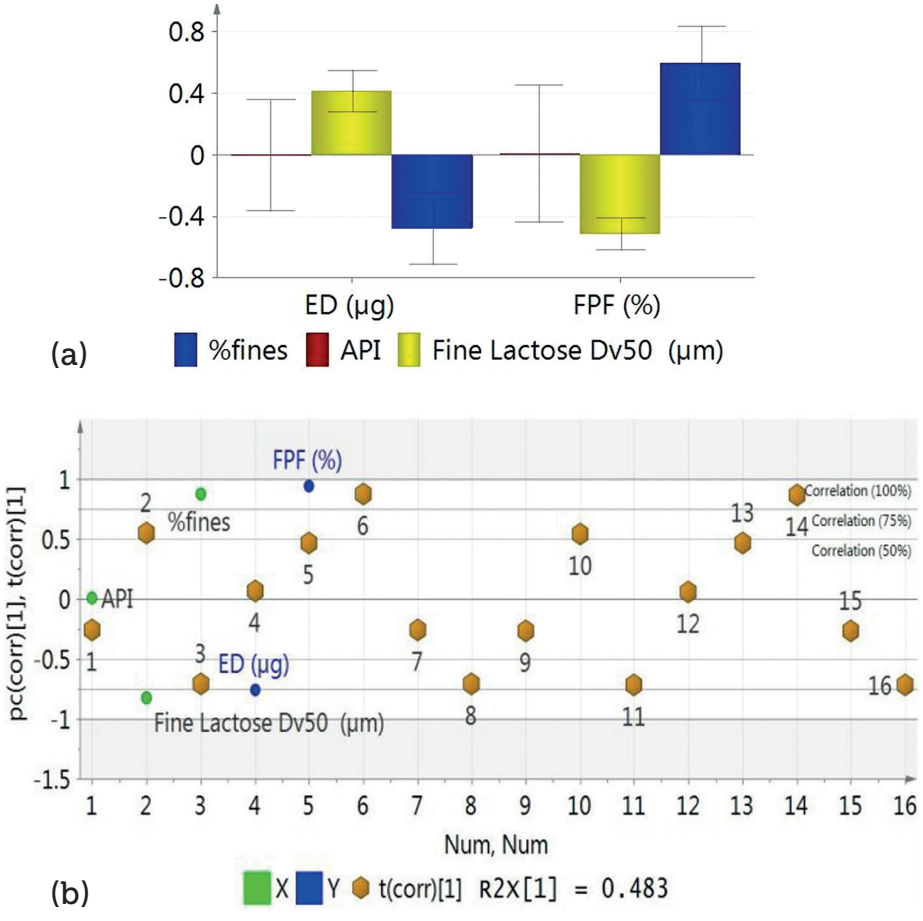

Figure 3: PLS results for Model 4: a) model co-efficients with corresponding error bars), and b) biplot showing X variables, Y variables and observations.

formulation parameters (blend composition) and rheology parameters (AE, BFE, PD, CBD) via two principal components (α and β), thus reduce the number of fundamental variables and facilitating subsequent mathematical treatment. The table presented in Figure 1 illustrates how these transformations work in practice for some representative blends, selected due to their distinctive nature.

A second model (Model 2) was developed considering the blends composition as input variables and both capsule filling rejection rate and gravimetric EM results as output variables. The results for the global model demonstrate that the entire set of experimental data is well fitted, with an R^2 of 0.82 and a χ^2 of 0.65. In terms of the individual output variables, all local models also showed good fits with R^2 values above 0.8 and χ^2 values above 0.5, thus validating the hypothesis that downstream processes (e.g. capsule filling) and inhaler performance correlate strongly to the nature of the carrier blends employed.

The biplot of the overall model is shown in Figure 2a, while Figure 2b shows the co-efficients, and corresponding error bars, for each of the individual output variables. In the biplot of the model, output variables perpendicular to input variables when considering the origin as a reference point show no correlation. On the other hand, output and input variables close to each other or in opposite locations of the plot are highly correlated. From the observation of these plots it is possible to conclude that the major contributor to capsule filling performance is the selected fill weight of the capsule: a high fill weight of 15 mg will reduce the rejection rate to practically zero, given its impact on the admissible (absolute) filling tolerance. Since with a 15 mg fill weight no relationship could be

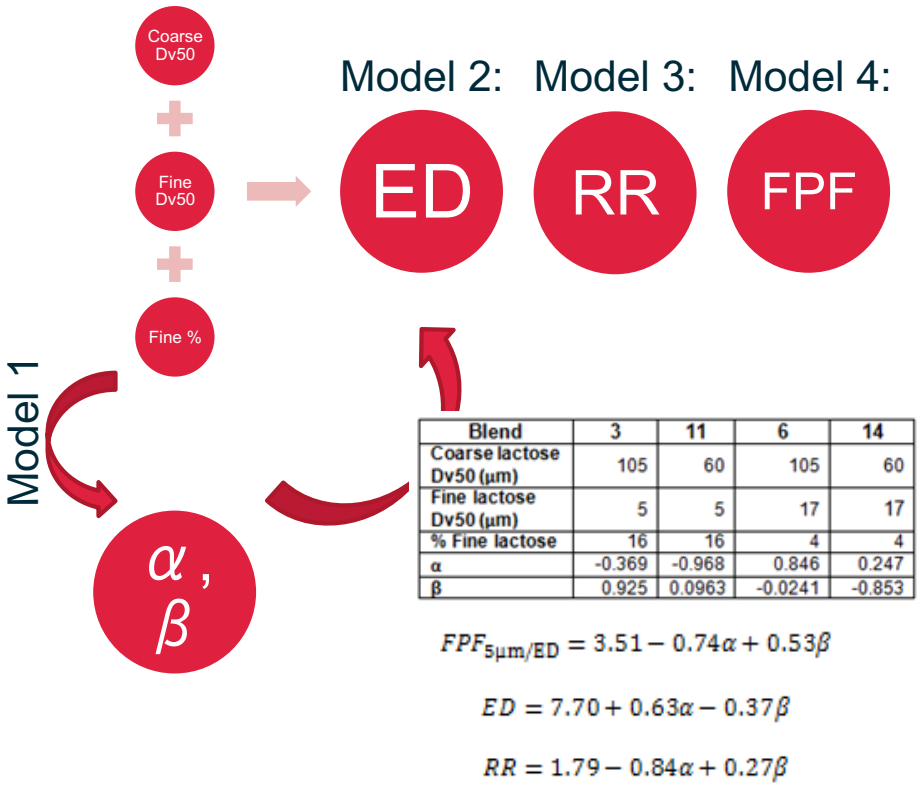

Figure 4: Schematic of the different statistical models applied to generate the design space and derived models for ED, $FPF_{(5\mu m/ED)}$ and RR as a function of α and β, via treatment of the experimental data.

observed between the rejection rate and the blends composition/rheology, a similar regression using only the 5 mg fill weight results was performed (Model 3); the results are depicted in Figure 2c where it can be observed that the percentage of fines and the particle size of the fine lactose grade are the major contributors to the rejection rate, while in opposing directions.

Finally, a statistical model was applied to the blends with both APIs (Model 4). This model presents a R^2 of 0.57 and χ^2 of 0.49 for the ED, and R^2 of 0.89 and χ^2 of 0.83 for the $FPF_{(5\mu m/ED)}$. These results indicate that this model has a high predictive power for the $FPF_{(5\mu m/ED)}$ but not as significantly for the ED. The model co-efficients and the biplot for both variables are presented in Figures 3a and 3b. It was observed that the API has no effect on either the ED or the $FPF_{(5\mu m/ED)}$. On the other hand, the Dv50 of the fine lactose has a positive contribution to the ED and a negative one to the $FPF_{(5\mu m/ED)}$. The percentage of fine lactose has the opposite effect on both variables. These results were expected since higher percentages and lower PSDs of fine lactose are associated with improved $FPF_{(5\mu m/ED)}$ but have a negative impact on the ED.

From the previous Models, as depicted in Figure 4, it was possible to derive a set of equations (presented in their scaled and centred version), which allow

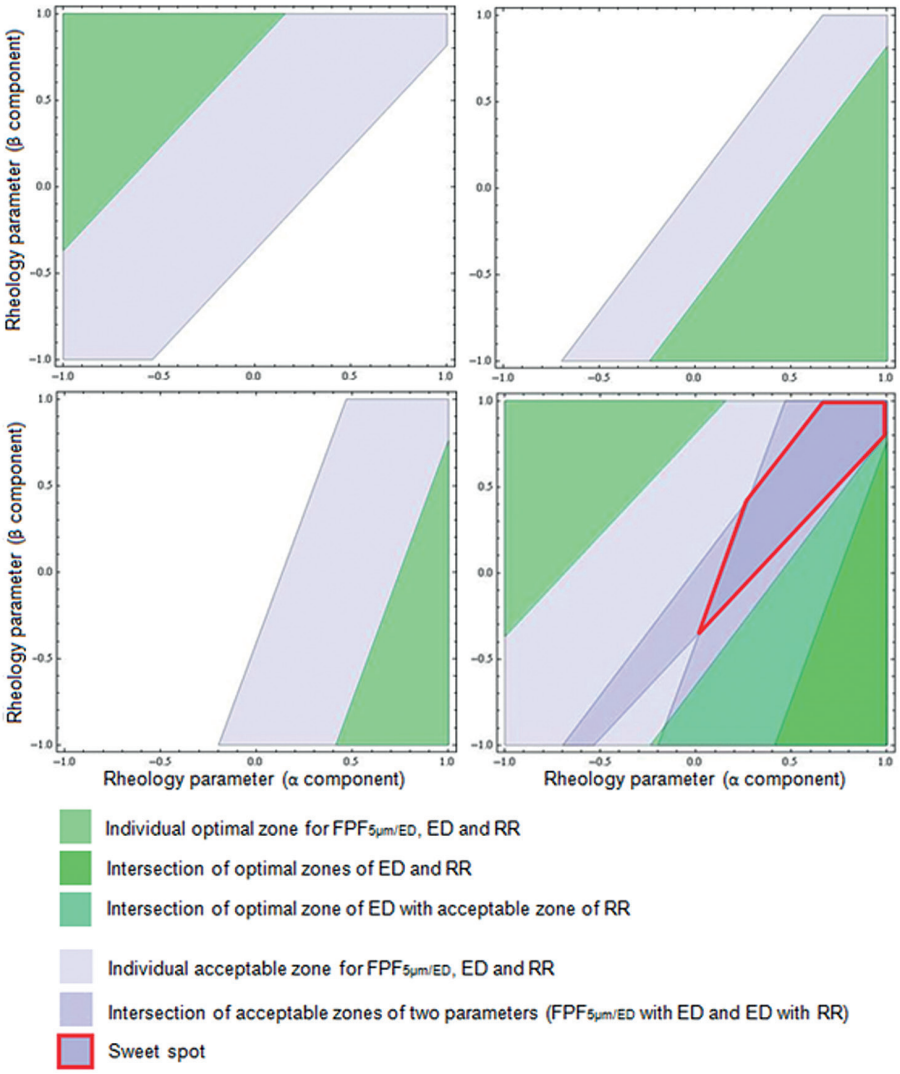

Figure 5: Design spaces regarding (a) $FPF_{(5\mu m/ED)}$, (b) ED, and (c) RR versus rheology parameters; and d) integrated design space.

the projection of the design spaces for $FPF_{(5\mu m/ED)}$, ED and RR, in function of α and β. The design spaces for each individual output variable are depicted in Figures 5a, b and c.

For the development of the design space regarding $FPF_{(5\mu m/ED)}$ *versus* rheology parameters, the optimal limit for $FPF_{(5\mu m/ED)}$ was ≥35% and the acceptable limit of $FPF_{(5\mu m/ED)}$ was ≥25%. For the development of the design space regarding ED versus rheology parameters, the optimal limit for ED was ≥80% (that corresponds to 100 µg of API) and the acceptable limit of ED was ≥75% (that corresponds to 94 µg of API), in order to comply with the US Pharmacopeia (USP) criteria for delivered dose uniformity, as defined in chapter <601>. For the development of the design space regarding RR *versus* rheology parameters, the optimal limit for RR was ≤10% and the acceptable limit of RR was ≤20%.

The integrated design space combining the three factors is presented in Figure 5d. Ideally, the sweet spot would be the area where the three optimal zones would intersect. However, from the figure presented above it can be observed that the optimal region for the $FPF_{(5\mu m/ED)}$ never intercepts the other two optimal/acceptable regions, and therefore the sweet spot obtained considers only the acceptable zones for all three parameters.

This result once again suggests that maximising the formulation's aerodynamic performance (i.e. by increasing the % of fine excipients) has a deleterious effect on both the capsule filling performance and also on the device performance (in an ED perspective). These two parameters are however correlated, as formulations that favour capsule filling performance also favour the ED.

CONCLUSION

Several conclusions can be drawn from the work performed including that, firstly, the rheology properties of lactose blends played an important role during the prediction of capsule filling and device performance, with high percentages of fine lactose and finer lactose grades yielding higher RR and lower EM. Secondly, the grade of fine lactose and the percentage of fine lactose also contribute to the aerodynamic performance of the formulations, since higher percentages and lower PSDs of fine lactose are typically associated with improved $FPF_{(5\mu m/ED)}$ and deleterious ED.

From these conclusions, an integrated design space analysis was derived where we demonstrated that a compromise between different parameters of aerodynamic performance and downstream process performance needs to be carefully considered, since formulations with maximum $FPF_{(5\mu m/ED)}$ may present poor ED results and higher rejection rates during capsule filling. Evaluating trade-offs is, therefore, of critical importance.

ABOUT THE AUTHORS

Filipa Maia holds a PhD in Chemical and Biological Engineering from the University of Porto. She joined the R&D Drug Product Development group at Hovione in 2013, where she has been working on particle design and formulation development projects, with particular focus on the area of Inhalation drug products. At Hovione, she is also scientific advisor for a PhD program focused on the development of *in vitro* dissolution techniques for evaluation of inhalation products.

Maria Palha has a degree in Pharmaceutical Sciences from the University of Porto. She has a strong expertise in development of particle design procedures and formulation development concerned with dry powder inhalers. Currently she works as a scientist at the Inhalation & Biopharmaceuticals group within R&D Drug Product Development at Hovione.

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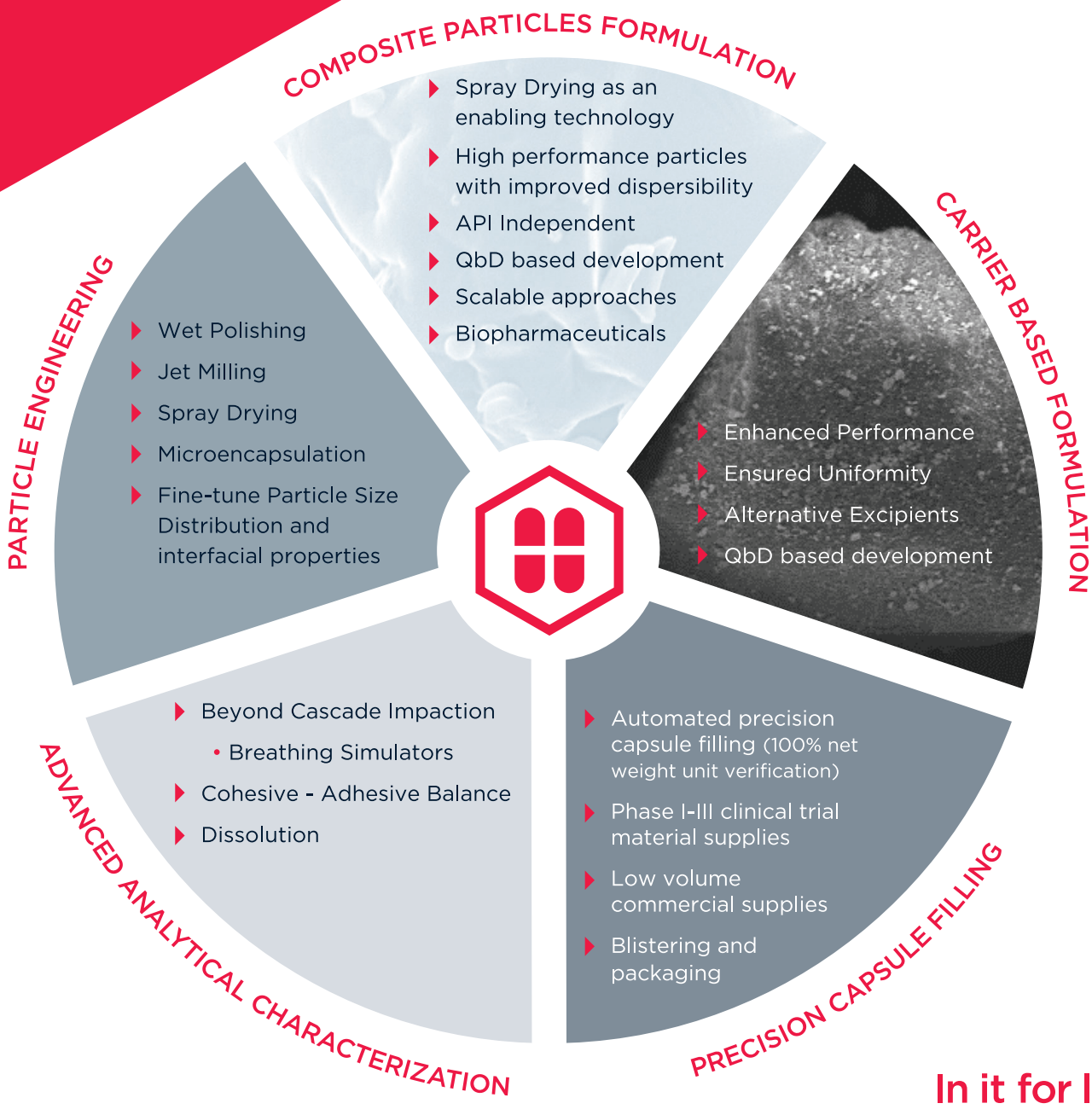

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