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Correspondence and manuscripts should be addressed to
The Editor, Scientific Section, 'The Indian Pharmacist',
F-8, Hauz Khas Enclave, New Delhi-110 016, India.

Case Study

THE EFFICIENCY OF POWDER BLEND HOMOGENEITY IN LOW-DOSE DPI PREPARATIONS USING THE ALPHIE 3D TUMBLER MIXER

Metin Karabulut, Cigdem Acar and Jigar Talati

A. Introduction:

Inhalation formulations are a way of treating the symptoms of respiratory diseases[1]. Dry Powder Inhalers (DPIs) for oral administration are prepared by mixing the micronised drug in a granulated or sieved powder diluent or carrier suitable for application to the lungs.

In this study, sieved and milled grades of lactose monohydrate were used to create formulations containing Formoterol Fumarate Dihydrate (FFD), using the geometric zero-shear mixing technique. The objective of the study was to evaluate the mixing efficiency of the equipment, Alphie 3D mixer, and the dependency of the low-dose DPI formulation blend homogeneity to applied process parameters, mixing speed (rpm), mixing time (min) and the mixing volume (L).

Photo 1: Alphie 3D Mixer

METIN KARABULUT and CIGDEM ACAR, Research & Development Center, World Medicine İlaç San. ve TİC. A.Ş., İstanbul, Turkey. JIGAR TALATI, Founder Director & Principal Designer, M/s Hexagon Product Development Pvt. Ltd., Por-391 243, India.

Address correspondence to JIGAR TALATI, Founder Director & Principal Designer, M/s Hexagon Product Development Pvt. Ltd., Por-391 243, India (Email: info@alphiemixer.com, URL: www.alphiemixer.com).

Table 1: Process Parameters Factorial Design for Formoterol Fumarate Dihydrate Blend

Factors:	3		
Runs:	60		
Blocks:	None	Centre pts (total):	0
Display Order:	Run Order		
Display Units:	Uncoded		
Factors and their Uncoded Levels			
Factor	**Name**	**Low**	**High**
A	Mixing speed, rpm	10	30
B	Mixing time, min	5	25
C	Mixing volume, L	20	120

The study furtherly able to be evaluated on particle interactions between the active sites on carriers in terms of adhesive and cohesive forces and their relation with zero-shear mixing design.

B. Methods:

The blend homogeneity of low-dose DPI formulation, active concentration of 0.048% (w/w), were evaluated using the HPLC system (Agilent, Empower). The amount of FFD were determined on 12 different sites of the total powder blend. Each set had 12 sampling points for each factorial design of total 60 runs (Minitab LLC. Inc.) *(Table 1)*. These were made by blending FFD with milled grade lactose Respitose ML001 (DFE Pharma) carrier particles.

The particle morphology of the powder blend was also evaluated using Scanning Electron Microscope (SEM, magnification 20,000X).

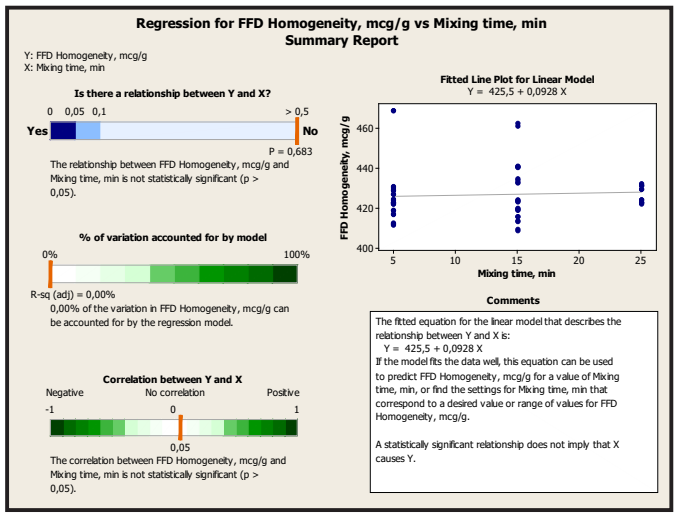

Figure 2: Minitab Regression for FFD Homogeneity, mcg/g *versus* Mixing time, min

C. Results and Discussion:

Table 1 shows the independent variables and their associated responses for the low-dose formulation. The optimization graphs *(Figures 1, 2 & 3)*, indicated the relationship between homogeneity amounts and related variables were not statistically significant, in terms of mixing speed (rpm), mixing time (min) and the mixing volume (L) with p-values of 0.319, 0.683 and 0.323, respectively ($p > 0.05$).

- Regression for FFD homogeneity, mcg/g *versus* mixing speed, rpm; mixing time, min; mixing volume, L (20L, 50L & 120L).

Table 1 defines the factorial design which includes independent process parameters and their possible accepted range. Using three-factorial design method, experiments were performed to investigate the possible effect / or interaction of mixing speed (rpm), mixing

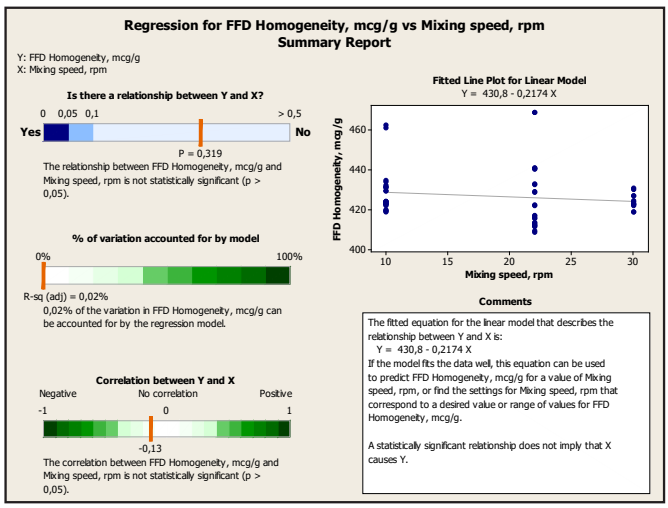

Figure 1: Minitab Regression for FFD Homogeneity, mcg/g *versus* Mixing speed, rpm

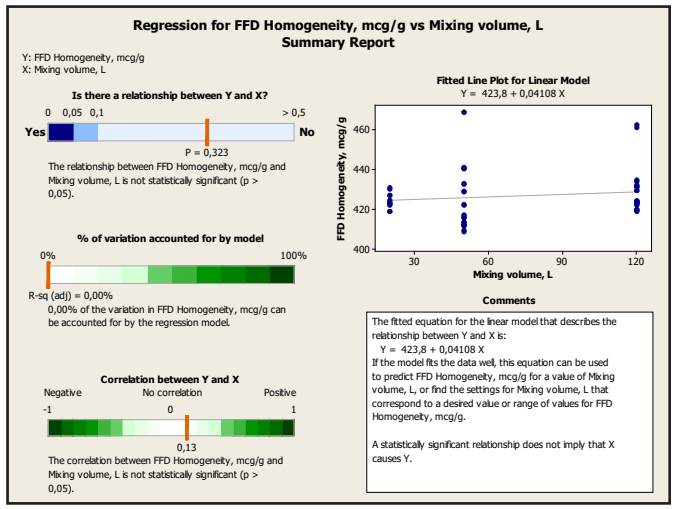

Figure 3: Minitab Regression for FFD Homogeneity, mcg/g *versus* Mixing volume, L

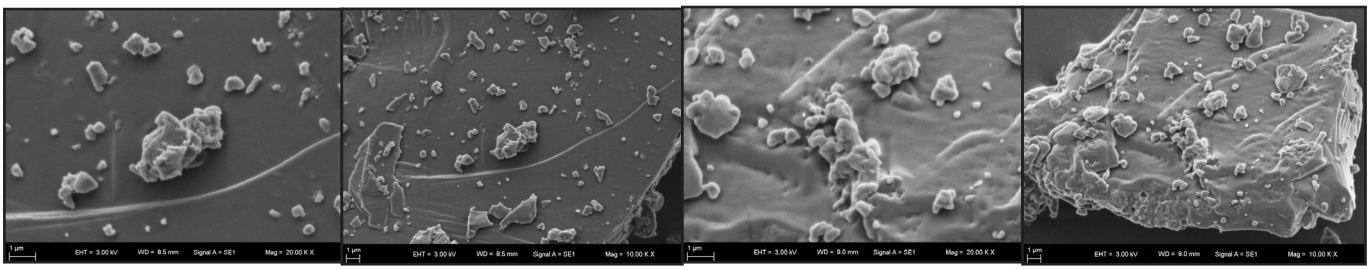

Figure 4: SEM micrographs at 20,000X and 10,000X magnification (scale bar indicates 1 µm). Zero-shear blend particles (2a), and shear applied blend particles (2b).

time (min) and mixing volume (L) on powder blend homogeneity (mcg/g).

According to *Figure 1*, it can be resulted that the relationship between FFD blend homogeneity and the mixing speed, rpm, is not statistically significant at 'p' value of 0.319 ($p > 0.05$). The trend of FFD homogeneity (mcg/g) results is nearly constant where an increase in mixing speed, 10 to 30 rpm, do not have a significant effect on obtained blend homogeneity between the values of 428.62 mcg/g to 424.27 mcg/g.

Figure 2 shows that the relationship between FFD blend homogeneity and the mixing time, min, is not statistically significant at 'p' value of 0.683 ($p > 0.05$). The graphical trend of FFD homogeneity (mcg/g) line is nearly constant where the increase in the mixing time, 5 to 25 minutes, does not have a significant effect on obtained blend homogeneity between the values of 425.96 mcg/g to 427.82 mcg/g.

The achievement of decreasing mixing time is a very cost-effective parameter during production as well.

Figure 3 shows that the relationship between FFD blend homogeneity and the Mixing volume, L, is not statistically significant at 'p' value of 0.323 ($p > 0.05$). The graphical trend of FFD homogeneity (mcg/g) line is nearly constant where the increase in the mixing volume, 20 to 120L, does not have a significant effect on obtained blend homogeneity between the values of 424.62 mcg/g to 428.73 mcg/g.

The Alphie 3-D Mixer showed that the container volume can be effectively used for different batch sizes where obtained homogeneity results stay nearly constant with precise and robust blend results. The minimum workable volume were selected as 13.785% for each container size, 20L, 50L and 120L. The peripheral speed settled as a constant value of 0.416 m/s for each container trial.

Figure 4 shows the morphology of zero-shear mixed blend, API-containing powder blend (2a) and sieving-shear applied API-containing lactose mixture (2b). The zero-shear blend morphology have a uniform appearance in contrast to the shear applied lactose mixture which appears as more cracks on agglomerates.

D. Conclusion:

If considered the low-dose DPI product, the mixing efficiency can be described as an independent parameter from variables in terms of mixing speed (rpm), mixing time (min) and the mixing volume (L) which indicates that the critical factor is an equipment design. This concluded from the zero-shear mixing on active agent particles allows them attached mechanically easily on carrier surface without cracks, and enables this structure aerodynamically suitable with the efficient and effective therapeutic DPI systems in particular.

Alphie 3D mixers are ideal for such blending as they operate on the kinematic inversion principle having minimal centrifugal force.

E. Acknowledgements:

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F. Abbreviations:

API = Active Pharmaceutical Ingredient. *DPI* = Dry Powder Inhaler. *FFD* = Formoterol Fumarate Dihydrate. *HPLC* = High Performance Liquid Chromatography. *RPM* = Revolutions Per Minute. *SEM* = Scanning Electron Microscope.

G. References:

1. Cordula Weiss, Peter McLoughlin, Helen Cathcart: Characterisation of dry powder inhaler formulations using atomic force microscopy, International Journal of Pharmaceutics, 2015, 494: 393-407. ◆