UNDERSTANDING THE EFFECT OF MIXING ON THE PERFORMANCE OF DRY POWDERS FOR INHALATION

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INTRODUCTION

Despite many years of research on adhesive mixtures there is limited understanding of what is governing the dispersion of the active pharmaceutical ingredient, API [1]. Obviously, several parameters affect the performance, and these interact with each other in complex ways [2]. Our hypothesis is that the mixing force, MF, and the mixing energy, ME, applied in the mixing process can be used to better understand and control the dispersibility of adhesive mixtures [3]. In a high shear mixer, these are defined as:

$$\text{Mixing Force, } MF = m * \frac{v^2}{r} \qquad \text{Equation 1}$$

$$\text{Mixing Energy, } ME = MF * vt = m * \frac{v^3}{r} t = 8\pi^3 m \left(\frac{rpm}{60}\right)^3 r^2 t \qquad \text{Equation 2}$$

v = peripheral speed, r = radius of bowl, m = carrier particle mass, rpm = revolutions per minute, t = time in seconds.

EXPERIMENTAL

Adhesive mixtures containing micronized budesonide (AstraZeneca), lactose carriers (Respitose SV003 and Lactohale LH100, DFE Pharma), and L-leucine (AK Scientific) as the coating agent, were blended in a Diosna P1-6 high shear mixer, using speeds from 400 to 800 rpm and mixing times from 1 to 20 min. The coating agent was mixed with lactose carrier in a first step at similar conditions to the API mixing step.

The Next Generation Impactor, NGI, was used to assess the dispersibility of the formulations from the Genuair (AstraZeneca), with UPLC detection of budesonide. The fine particle fraction, FPF, calculated as the amount of API in aerodynamic size < 5.0 µm divided by the total amount of API delivered to the NGI, was the key parameter for subsequent modeling.

RESULTS AND DISCUSSION

Coating agent and carrier

Two different lactose carriers (Respitose SV003 (D50 ≅ 60 µm and Lactohale LH100 (D50 ≅ 130 µm) were coated with 1% and with 3% leucine [3]. TOF-SIMS images for the latter carrier are shown in Figure 1. As seen in Figure 2, the degree of coating overlaps for the two carriers when plotted versus the mixing energy, ME. This demonstrates that ME is the key parameter governing the coating process.

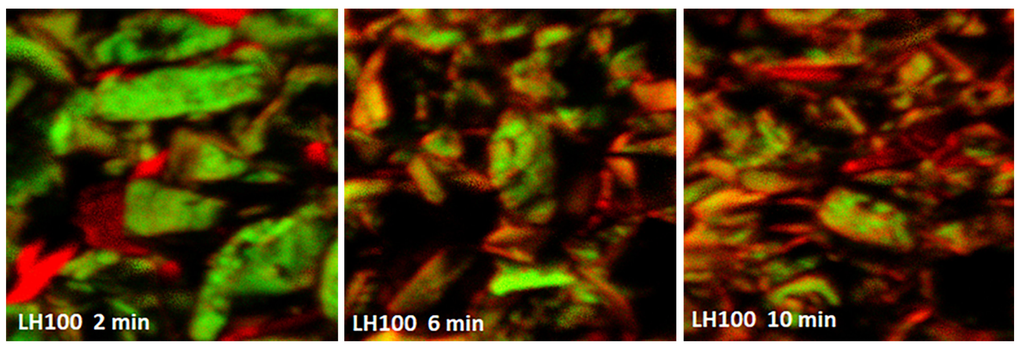

Figure 1 *- TOF-SIMS pictures of LH100 coated with 1.0% leucine. Green represents lactose and red is leucine. Each picture covers an area of 500 x 500 µm.*

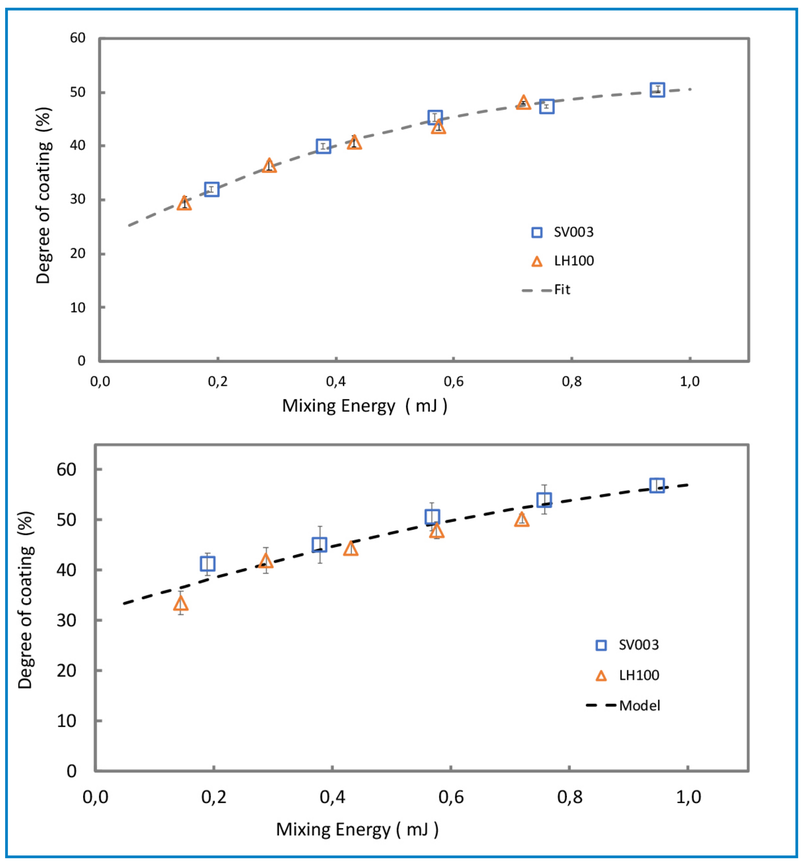

Figure 2 *- degree of coating of the two lactose carriers plotted against the applied mixing energy. Abowe; 1.0% leucine; Below 3.0% leucine. Surface coverage was quantified by use of multi-variate analysis of TOF-SIMS images [4].*

Drug, coating agent and carrier

Budesonide, 1% or 5%, was added to leucine - coated LH100 carrier and mixed for different times. Fine particle data obtained using Genuair® are plotted versus the applied mixing energy in Figure 3. As can be seen, FPF initially increases but decreases at extended mixing.

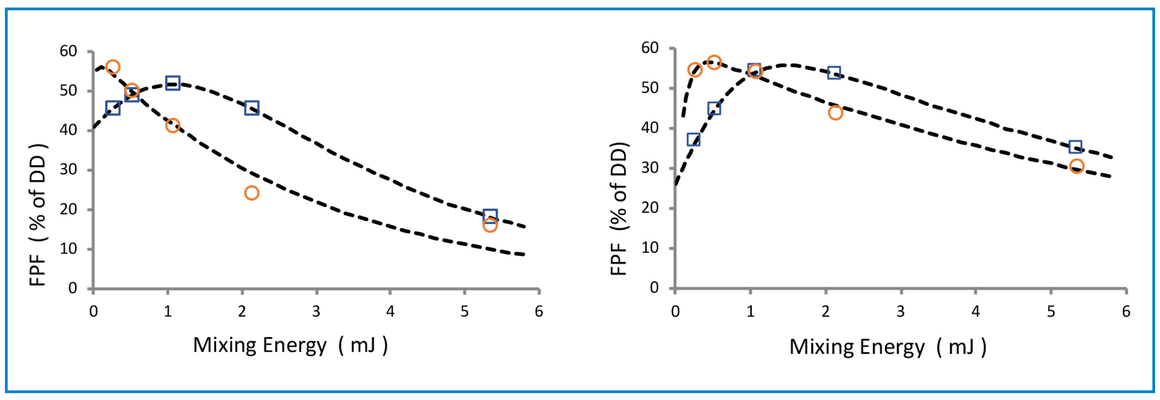

Figure 3 *- FPF data for formulations with, left: 1% leucine, right: 3% leucine. Circles refer to 1% Bud and squares to 5% Bud.*

$$FPF = \left[A + \frac{B}{1+e^{-k_1 x}}\right] * (e^{-k_2 x}) \qquad \text{Equation 3}$$

x = Mixing Energy,
$k1$, $k2$ = rate constants,
$A + B$ = maximum FPF accessible by the system

The behavior of the systems can be modeled using Equation 3, which consists of one part accounting for the initial FPF increase and one part for the subsequent decrease. Optimization of A and B allows for interpretation of the rate constants k1 and k2 in terms of the load of coating agent and the drug load. Predicted versus observed rate constants are plotted in Figure 4, which also shows the fitting equations. It can be observed that k_1 is affected mainly by the drug load, while k_2 is predominantly affected by the amount of coating agent.

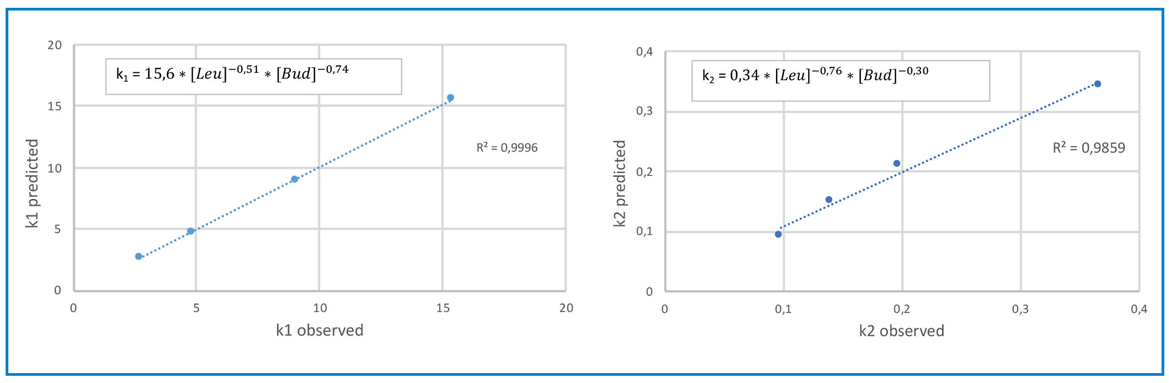

Figure 4 *- Fitting of k1 and k2 data to power law equations.*

Drug, lactose fines and carrier

Data from Littringer et al. [5] were analyzed using the mixing energy equation. In this work, the order of addition was varied, as well as mixing times and speeds. As can be seen in Figure 5, FPF decreases exponentially with increasing mixing energy.

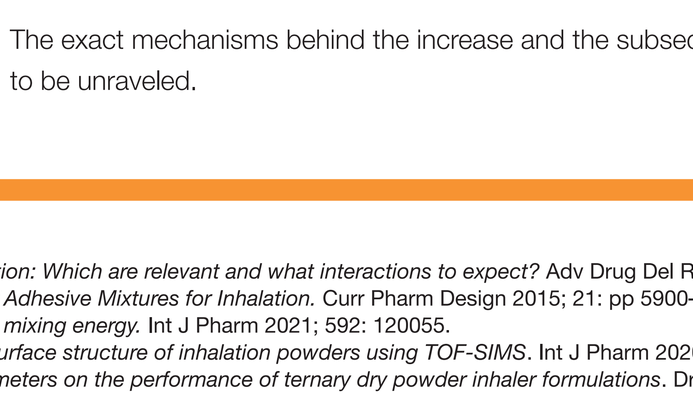

Figure 5 *- FPF plotted as function of the mixing energy applied to the API, for formulations of 1.5% Bud, 7.5% lactose fines and lactose carrier Inhalac 230 blended in the Picomix®. Diamonds and X's refer to variation in mixing time, squares and circles to variation in mixing speed.*

CONCLUSIONS

For adhesive mixtures blended in a high shear mixer, the mixing energy, ME, calculated from carrier particle mass, the radius of the mixer bowl, and mixing time and speed, has been identified as a key factor governing the dispersibility of the API.

Formulations comprising a coating agent give rise to an increase in FPF followed by a decrease at extended mixing. The dispersibility behavior can be modelled by the product of two exponential functions.

The exact mechanisms behind the increase and the subsequent decrease in FPF remains to be unraveled.

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