Dynamic Suspension Drying for Ostwald Ripening Phenomena Control

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SUMMARY

For the engineering of Mometasone Furoate Monohydrate (MFM) to a final Particle Size Distribution (PSD) within the inhalation range, microfluidization of the API suspension was performed, followed by isolation by spray drying. The microfluidization stage ended with a D50 ~ 2.1 µm; however, during spray drying, increasing values of particle size were observed over time on the final dried material fractions.

To study whether the observed PSD instability on the dried powder was caused by Ostwald Ripening (OR) phenomenon of the API in suspension, two suspensions of MFM were microfluidized to a different final PS and stored at different temperatures. The observed PSD growth followed a profile that can be ascribed to OR, being dependent on both temperature and initial PSD.

In order to overcome PSD growth in suspension, an innovative engineering approach was put in place: Dynamic Suspension Drying (DSD). According to DSD, the suspension, after being processed by microfluidization at elevated pressure (and the PSD has plateau at the target values), is isolated in the form of a dried powder while continuously recycling the suspension to the microfluidization unit at an optimized mild pressure. These mild conditions prevent any increase or any reduction in the PSD, since only particle growth by OR is being prevented.

DSD was successful in preventing OR without the need of stabilizing agents, offering a substantial advantage over other approaches, because it is a much simpler and effective process that will not impact the final product properties (e.g., stability, bioavailability, performance, composition) or manufacturability.

INTRODUCTION

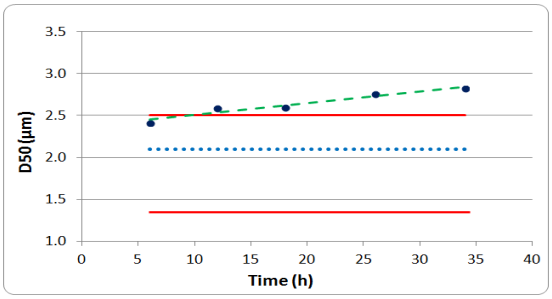
When using classical methods such as Jet Milling (JM), particle size (PS) reduction of active pharmaceutical ingredients (API) like mometasone furoate monohydrate (MFM) may partially change the crystalline form of the API to anhydrous or to amorphous forms, thus influencing the stability and performance of the finished products [**1**].
The control of such critical quality attributes becomes then crucial, a field where new technologies - most noteworthy microfluidization - have been gaining a growing importance, due to its i) superior PS control, ii) ability to avoid formation of amorphous domains and iii) keeping polymorphic form and levels of hydration unchanged [**2**].

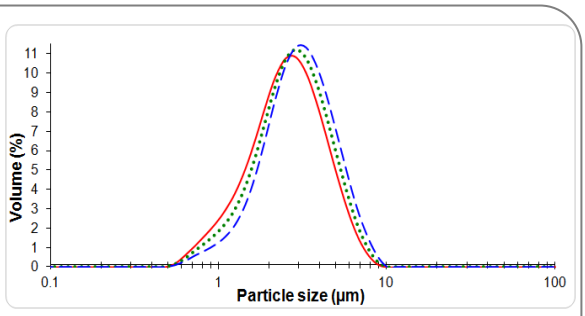
Although showing a wide range of advantages, microfluidization (as other wet media based technologies) requires the API to be suspended in an anti-solvent where a residual solubility will, in practice, be hard to avoid. Therefore the suspension can be vulnerable to PS instability phenomena, namely Ostwald Ripening (OR), representing a new set of challenges for API's like MFM. OR is an effect caused by the higher saturation solubility of very small particles as compared to larger ones. Molecules diffuse from the higher concentrated area around small particles to areas around larger particles, leading to the formation of a supersaturated solution around the larger particles and consequently to drug crystallization and PS growth [**3**].

This effect can be so significant that, in practice, may hinder the manufacturing process itself (microfluidization or similar), reason why understanding and overcoming it is of key importance as already underlined in previous works [**4**] [**5**].

CASE STUDY

The current experimental work refers to the manufacturing of Mometasone Furoate Monohydrate (MFM) batches, where (i) microfluidization (using water as anti-solvent) was employed as the particle engineering technology to reduce the PSD to the set target range (1.5 < D50 < 2.5 µm), followed by (ii) isolation of the final size-reduced API by spray drying to the final form of a powder. When this conventional approach was used for engineering MFM, the final particle size of the suspension after microfluidization was D50 ~ 2.1 µm, being within target; however, during API isolation by spray drying, increasing values on particle size of the collected dried material were observed over time. In **Figure 1** the D50 for the different dried powder fractions throughout the spray drying of the final suspension is shown, which was determined by the average of three consecutive replicates of the same sample using a validated wet dispersion laser diffraction method (that ensures a RSD < 1% in the D50).





… D50 after at the end of size reduction;
● D50 IPC data during spray drying;
- - D50 IPC data (linear regression);
— D50 target range limits.

— PSD curve after 6h of spray drying
… PSD curve after 18h of spray drying;
- - PSD curve after 34h of drying;

Fig1. In-Process Control data during spray drying of a MFM batch after the conventional microfluidization followed by spray drying approach.

In order to study whether the observed PSD growth on the dried powder fractions was being caused by Ostwald ripening of the particles while in suspension, a laboratorial study was designed. In this study, two suspensions of MFM were size-reduced via microfluidization to a different PS (D50 = 2.0 µm and 3.0 µm) and, afterwards, stored at different temperatures, namely 5 and 45ºC. In all cases, PSD was monitored in five sampling time points (24, 72, 144 and 168 hours) using a wet dispersion laser diffraction method. The data presented in **Figure 2** was determined using the same laser diffraction method as in manufacturing.

Before fitting the obtained data, a literature review was conducted; several models can be found for OR modeling, with most of them being modifications of the Lifshitz, Slyozov and Wagner (LSW) theory (**Eq. 1**), which is a kinetic model that translates an isothermal variation of the more general problem [**6**]:

$$\bar{r}^N = \bar{r}_0^N + Kt \qquad with \qquad K = \frac{8\gamma V_m^2 D_m C_{(\infty)}}{9RT} \qquad \textbf{(Eq.1)}$$

where $\bar{r}$ is the average radius of the particle (µm), $\bar{r}_0^N$ is the radius of the particle at t=0, K is a constant that varies with T (absolute temperature), t is time, γ is the interfacial tension, V_m is the molar volume of the dispersed phase, $C_{(\infty)}$ is the bulk solubility of the dispersed phase, D_m is the molecular diffusion coefficient, R is the universal gas constant; additionally, N is an exponent that assumes the value of 3 or 2, depending on diffusion or agglomeration being the limiting step [**7**].

Based on the above equation, two important observations ([**6**];[**8**]) are expected when in the presence of OR: *i)* a cubic or quadratic growth (depending on the limiting step) and *ii)* a more pronounced increase of K for higher temperatures. As shown in **Figure 2** (left plot), both previous observations are valid for the current case-study, thus supporting the presence of OR of MFM in suspension. The obtained D50 data in suspension was transformed by calculating $r^3 - r_0^3$ and plotted as a function of time. The K value was determined by performing a linear regression on the transformed data where **Eq. 1** was assumed as the theoretical OR model; as shown in **Figure 2** (right plot) a good correlation coefficient between the observed data and the OR model predictions was obtained (R^2 = 0.94).

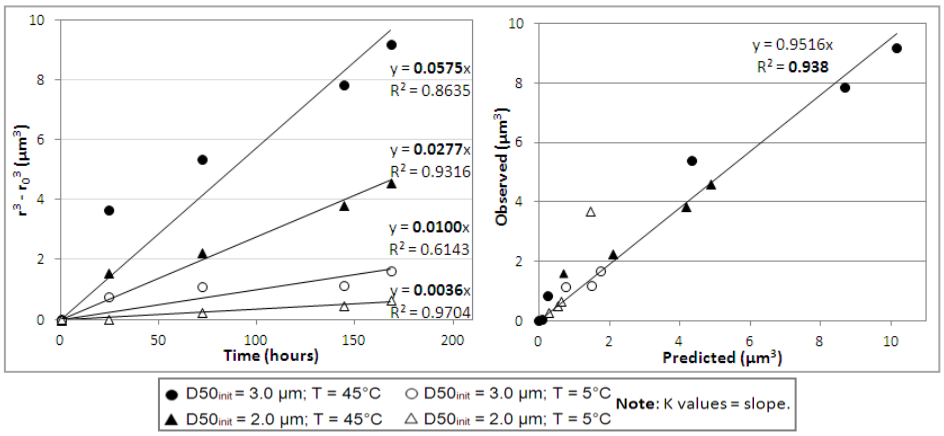


Fig2. Theoretical OR model versus experimental data (left plot) and observed versus predicted results (right plot)

Overall, the results show a significant decrease of the phenomenon when temperature is decreased (due to its effect on reducing solubility), as K values are more than five times lower for 5ºC, when compared to 45ºC.

However, for the specific target range of D50 (~2 μm), OR is still significant at 5ºC and lower temperatures would not be feasible in manufacturing since water is the process anti-solvent during microfluidization of MFM.

Typical ways of preventing Ostwald Ripening include the addition of stabilizing agents to the original suspension. However, stabilizing agents (e.g. surfactants, polymers) need to be carefully selected and their concentration optimized in order to ensure control over the phenomena. Additionally, using these stabilizing agents may not be desirable and/or feasible in all cases; for example, there is a reduced number of excipients approved for inhalation delivery and, even if approved, their addition can impact the aerodynamic performance of the particles (product). Based on the earlier, approaches that can control OR without further addition of stabilization agents would always be preferable – the key concept behind the process of **Figure 3**.

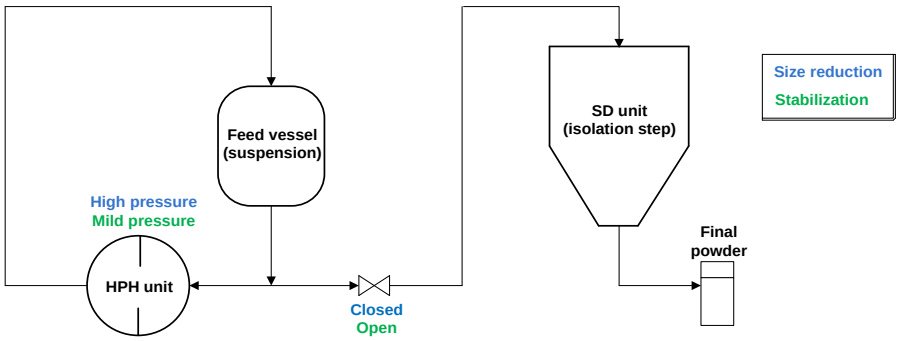


Fig3. Schematic representation of the Dynamic Suspension Drying (DSD) process.

For the size-reduction process of MFM, an innovative engineering approach was applied which has been designated as Dynamic Suspension Drying (DSD) [**9**]. The DSD process comprises the following steps:

i) Microfluidization of the API suspension at elevated process pressures until the PSD has reached a plateau at the target size values (much lower in comparison to the starting material);
ii) Recycle the suspension to the microfluidization unit previously applied to reduce the PSD under optimized mild pressure conditions while continuously feeding the suspension to the spray dryer to isolate the final dry size-reduced API.

These mild operating pressure conditions are carefully selected in a way that (i) any increase in particle size due to OR is prevented by continuous microfluidization while (ii) further reduction in particle size distribution does not occur (since the PSD has reached a plateau beforehand, no further decrease in PS is expected at a lower pressure).

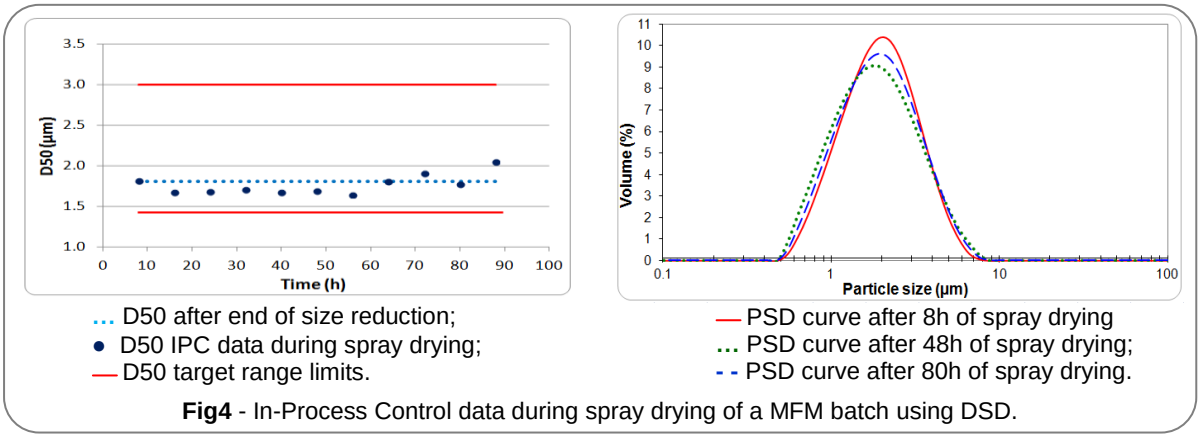


Fig4 - In-Process Control data during spray drying of a MFM batch using DSD.

Figure 4 shows the evolution of the particle size during spray drying of a size-reduced MFM suspension following the DSD process. The obtained results show a stable particle size throughout the drying process, as no size reduction or increase is taking place, being a significant improvement on ensuring process robustness and reproducibility for MFM engineering over the traditional approach previously discussed in **Figure 1**. In addition no impact on the polymorphic form was noticeable by XPRD analysis.

CONCLUSIONS

OR is a phenomenon that can hinder size reduction technologies based on wet media. The current work showed how the LSW model can be used to capture PS growth during the particle engineering step by microfluidization of MFM suspensions and the success of DSD as an innovative process capable of overcoming OR without the need of stabilizing agents.

REFERENCES

[1] Cacela, C. et al: Advances in Size Reduction Process for Mometasone Furoate Monohydrate. In *Respiratory Drug delivery,* 2012.

[2] Gil, M. et al: A process for particle processing of active pharmaceutical ingredients. Patent WO/2011/131947, 2011.

[3] Patravale, V. et al.: Nanosuspensions: a promising drug delivery strategy, *J Pharm Pharmacol* 2004, 56: 827-840.

[4] Verma, S. et al.: (2011), Physical stability of nanosuspensions: Investigation of the role of stabilizers on Ostwald ripening, International Journal of Pharmaceutics 406 145–152.

[5] Lindfors, L. e tal.: (2006), Inhibition of Ostwald ripening, Langmuir, 2006, 22 (3), 906–910.

[6] Mrotzek, M and Nembach, E: Ostwald ripening of precipitates during two successive heat treatments performed at different temperatures, *Acta Mater* 2008, 56(1): 150-154.

[7] Lee, E.J.H. et al: Growth kinetics of tin oxide nanocrystals in colloidal suspensions under hydrothermal conditions, *Chem Phys* 2006, 328(1-3): 229-235.

[8] Sadtler, V M et al.: Ostwald Ripening of Oil-in-Water Emulsions Stabilized by Phenoxy-Substituted Dextrans, *J Colloid Interf Sci* 2002, 254(2): 355-361.

[9] Botas, P. et al.: (2012), Portuguese provisional patent pending “Dynamic Suspension Drying (DSD) to control Ostwald Ripening phenomenon”.