Master's Thesis Engineering Technology

2021-2022

Evaluating drying kinetics during humidified drying of an active pharmaceutical ingredient using in-line Near Infrared Spectroscopy

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Context

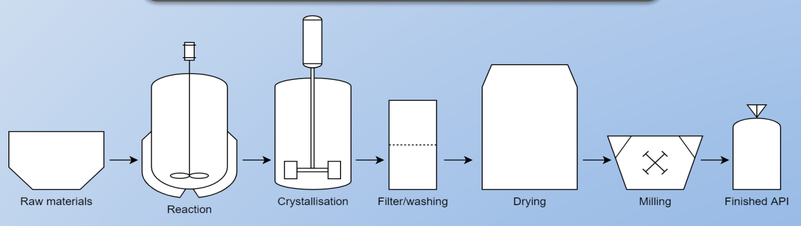


Figure 1. Production process API

The focus of this study is on the drying process and more specifically on **drying using a humidifier**. A schematic of the production of an API is shown in figure 1.

Many active pharmaceutical ingredients (API) are **hygroscopic** and readily exchange water molecules with the environment. If these water molecules are included in the crystal structure of an API, it is considered a pseudopolymorph, more precisely a **hydrate** (solvate in the case of solvent molecules). If the stable form of an API is a hydrate, it is important that this form is preserved during synthesis, isolation, drying and further processing. A certain water content is therefore desirable, as shown in figure 2.

Several parameters influence the formation and/or retention of the hydrate. The most important parameter is the **relative humidity** (RH), which is obtained by the ratio of the partial pressure of water present in the environment (p_{water}) to the saturation vapour pressure of water at a specific temperature (p_{sat}).

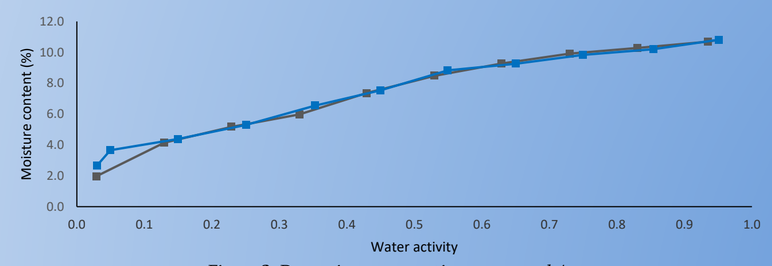


Figure 2. Dynamic vapor sorption compound A

Problem & Objectives

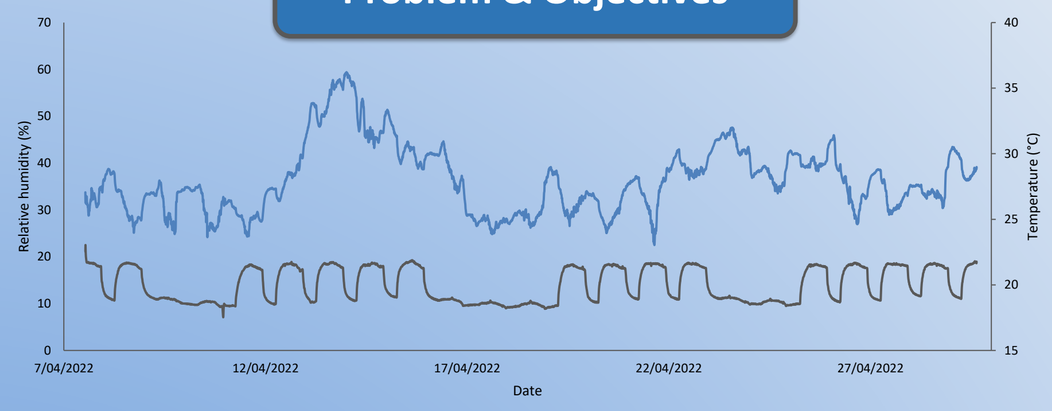


Figure 3. Relative humidity (blue) and temperature (black) monitored in the lab

- Understanding the **drying behaviour** of a drug substance (compound A) and the interaction/impact of water on the product. This water originates from the humidified N_2 in the dryer, the ambient air in the lab and the headspace of a sample. Different headspace ratios are shown in Figure 4.
- Reduction of the undesirable **residual solvents**, either 'free' or bound to the crystals, coming from the washing and crystallization steps to below the maximum allowed levels (ICH – guidelines, shown in table 1).

Table 1. ICH-values IPA & MeOH

Solvent	ICH-value
MeOH	3000 ppm
IPA	5000 ppm

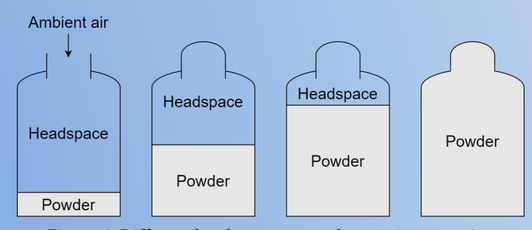
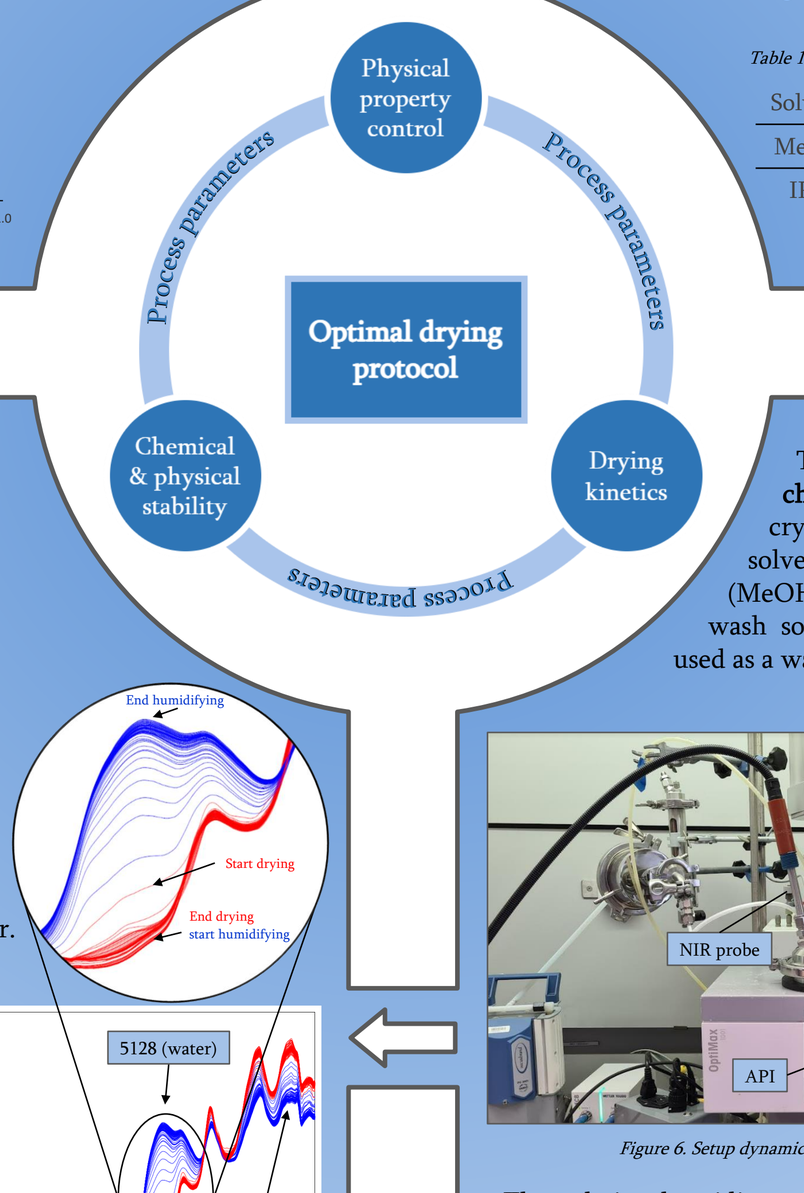


Figure 4. Different headspace to sample ratio in a container



The API used in this study is a **chlorohydrate salt**. The rod-shaped crystals are shown in Figure 5. The solvents used in this study are **methanol** (MeOH), used for crystallization and as a wash solvent, and **isopropyl alcohol** (IPA), used as a wash solvent.

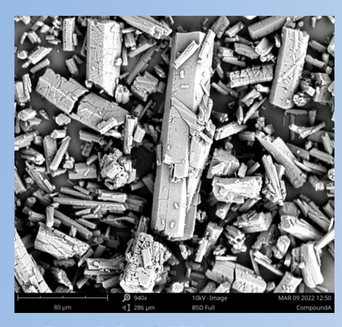


Figure 5. Result SEM compound A

Analytical techniques:

- In-line near-infrared spectroscopy (**NIR**)
- Dynamic vapor sorption (**DVS**)
- Thermogravimetric analysis (**TGA**)
- Karl fisher titration (**KF**)
- Gas chromatography (**GC**)

Figure 6. Setup dynamic dryer

The relative humidity within the dryer was regulated with the help of a humidified nitrogen flow. Both **static** and **dynamic** drying were used. As static dryers, a vacuum oven and a filter tube dryer, shown in figure 7, were used. As a dynamic dryer, an agitated vacuum dryer was used, shown in figure 6.

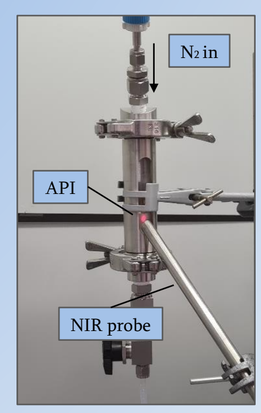


Figure 7. Setup static filter dryer

Materials & Methods

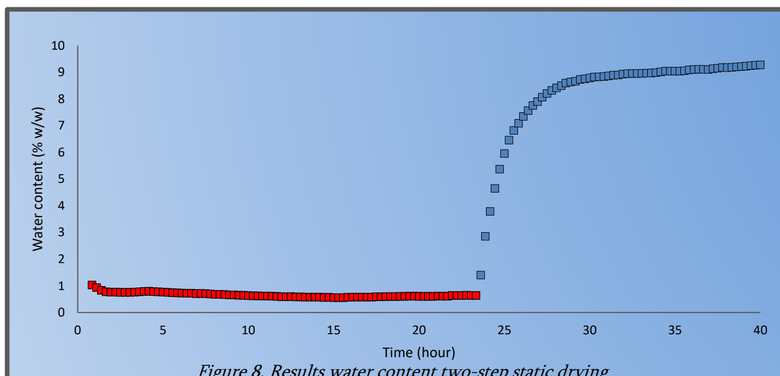


Figure 8. Results water content two-step static drying

- Constructed a **drying process** for compound A.
- Established a in-line NIR model, shown in Figures 8 and 9.
- A **higher relative humidity** resulted in a **faster uptake** of water.
- The presence of water promoted the removal of MeOH and IPA by replacing the bound solvent.
- The influence of the **ambient air**, directly and in the **headspace** of sample vials, proved to be a problem for the analysis of the water content. For an accurate result, the exposure to ambient air and the headspace should be **minimized**.

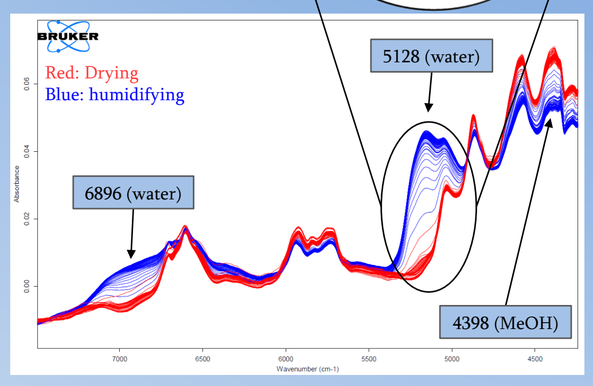


Figure 9. NIR spectra two-step static drying

Results & Conclusion

Supervisors / Co-supervisors / Advisors

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