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paper 137 (USB electronic support), 4 pp.

ON THE CUTTING EDGE OF FEEZE-DRYING PROCESSES

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INTRODUCTION

Freeze-drying is a process that allows water (or solvent) removal from a product with minimal (or no) damages: this is due to the fact that the process is carried out at low temperature and low pressure in such a way that drying occurs through sublimation of the frozen solvent.

In pharmaceuticals manufacturing freeze-drying aims recovering the active ingredient from a liquid solution, thus increasing its stability over time, beside obtaining a porous solid material that can be easily (and quickly) rehydrated. In food industry freeze-drying aims extending the foodstuffs shelf life, without impairing nutritional properties as well as quality characteristics (e.g. colour and shape). In this case the freeze-drying process can also be carried out at atmospheric pressure, using a stream of cold and dry air, as the driving force for the solvent flux is the difference between the solvent partial pressure in the product (at the interface of sublimation) and in the external air. The freeze-drying process has been applied also in other fields, e.g. the recovery of flooded documents, because of the high quality of the final product. In all cases, the operating conditions of the freeze-drying process have to be carefully selected, so that potential product damages are avoided: this generally requires that product temperature remains below a limit value that is a characteristic of the product being processed, aiming to avoid product degradation or the collapse of the dried cake in case a solute is recovered from a liquid solution.

Although freeze-drying is a well-established process, there are various issues still unresolved:

i. The (vacuum) freeze-drying is traditionally a batch process: processing time could be significantly shortened, and control over quality could be improved, if the process is carried out in a continuous manner.
ii. Monitoring of product critical quality attributes and dynamics is mandatory to get the targets of the process: model-based Process Analytical Technologies, combining a mathematical model and some available experimental measurements, could provide and effective and efficient solution.
iii. The rate of the atmospheric freeze-drying process can be very slow as the driving force is limited by the value of the solvent concentration that is obtained in the flow of air, and by the solvent diffusivity in the partially dried product.
iv. The freeze-drying of rather unusual materials, e.g. flooded paper, is based mainly on a trial-and-error approach, thus resulting in unreasonably high drying times.

The research activity of the LYOLab research team of the Politecnico di Torino is currently pursuing the development of new methodologies for the freeze-drying of food and pharmaceuticals, aiming to move beyond the state-of-the-art, and focusing on the development of continuous (vacuum) freeze-drying processes, on the design of innovative PAT tools for product monitoring, on the investigation of the effect of the use of power ultrasound in the rate of an atmospheric freeze-drying process (and on product quality), and on the development of efficient approaches to flooded paper freeze-drying. A selection of the main results is briefly presented in the following.

1 CONTINUOUS FREEZE-DRYING

In recent years, pharmaceutical companies are looking at new manufacturing strategies, moving from batch to continuous technologies. It has been estimated that this change might increase their revenues by 25% and only 5% of the pharmaceutical manufacturing currently operates in continuous. As the freeze-drying process, if present, represents the bottleneck of the chain of production, its conversion from batch to continuous is highly desirable. Therefore, the LYOLab research team is currently working on the development of new technologies to operate the lyophilization process as a continuous process. Various solutions are under investigation, among which the radiative freeze-drying of frozen micro-particles. Such a process comprises three steps: droplet generation, freezing and vacuum, radiative drying [1]. As first step, we have developed multi-scale, mechanistic models that provide valuable information about dynamic and steady-state process behaviour. These models were used, for example, to study the effects of different particle size distributions on the drying behaviour of a packed-bed made of frozen particles. The structural properties of the packing have been studied by coupling bullet physics and CFD [2] and used in a mathematical model for the process in order to simulate the product dynamics during the primary drying stage [1].

2 ATMOSPHERIC FREEZE-DRYING

The atmospheric freeze-drying process consists of the convective drying of a completely frozen product using a stream of dried and cold air. The process is feasible as long as a difference in solvent (water) vapour partial pressure is established between the product and the air stream. Power ultrasound, i.e. acoustic waves with frequencies between 20 and 100 kHz and a power higher than 1 W cm^{-2}, proved to be an effective, non-toxic and environmentally friendly way to accelerate the process [3]. In a solid porous product, the ultrasound application induces a series of rapid compressions and expansions, like what happens to a sponge squeezed and quickly released and this mechanical stress helps water to flow out of the dried cake through the natural channels and other micro-pathways created by the ultrasonic wave propagation [4].

The experimental investigation was focused on the drying of *Solanum Melongena* samples: this product was selected because of the high amount of water, up to ninety-three percent of the whole weight, and the huge amount of seeds, increasing the heterogeneity of the sample. The drying experiments were carried out in the laboratory of the ASPA group of Universitat Politecnica de Valencia, varying the air temperature and flow rate, and the ultrasound power according to a factorial design of experiments. As it is possible to see from Figure 1a a drying time reduction of 72% is achieved when 25 W were applied, and almost 82% when the acoustic power is doubled.

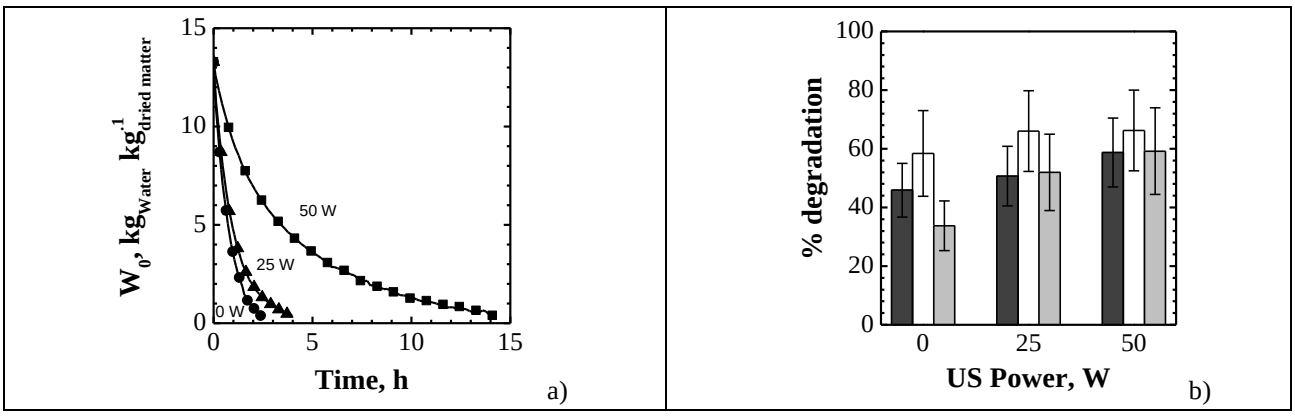

Fig. 1. a) Weight loss in the sample at different levels of applied acoustic power.; b) Effect of the US power on the degradation of various nutritional properties (■, Vitamin C; □, Phenolic compounds; ▭, FRAP)

With respect to nutritional properties, mainly antioxidant content, the amount of vitamin C (using Jagota and Dani method), phenolic compounds (using Folin-Ciocalteau method), and the whole antioxidant capacity (using FRAP method) of the product were measured before and after the

treatment. From the results shown in Figure 1b it appears that, acoustic power appeared to have no significant effects on nutritional properties.

The uniformly retreating interface model was then modified to account for the cubic shape of the samples and used to establish the kinetic parameters of the process, looking for the best fit between measured and calculated moisture content. The model was used to optimize *in silico* the process considering an industrial unit as test case. In this case it appeared that power ultrasound can increase the productivity of a tunnel drier up to four or five times, thus significantly reducing both the operational and the fixed costs of the plant.

3 MONITORING OF FREEZE-DRYING PROCESSES

An essential prerequisite to achieve high levels of quality in lyophilized products is the development and implementation of appropriate analytical techniques for the process monitoring. In the last decade, the LYOLab research team has given a substantial contribution to achieve this result. The list of developed tools includes methods based on the regression of step response data [5], software sensors [6], thin-film thermocouples [7], Near-infrared and Raman spectroscopy [8, 9]. These technologies have to satisfy a number of characteristics; they have to be non-invasive, give chemical and physical information without requiring sampling and sample manipulation, and have extremely fast response.

These Process Analytical Technologies, if combined together, can track the various transformations involved in a typical freeze-drying cycle and, thus, have great potential as in-line monitoring tools. They can track the drying behaviour (evolution of temperature and moisture), detect primary and secondary drying endpoints, solid-state transformations, as well as conformational stability of proteins thus enhancing the process understanding. It follows a selection of results for two of the above technologies, the thin-film thermocouples and the Raman spectroscopy. Figure 2 (left picture) shows an example of thin-film thermocouples array (TFTC) which metallic strip was coated by a SiO2-like insulating layer.

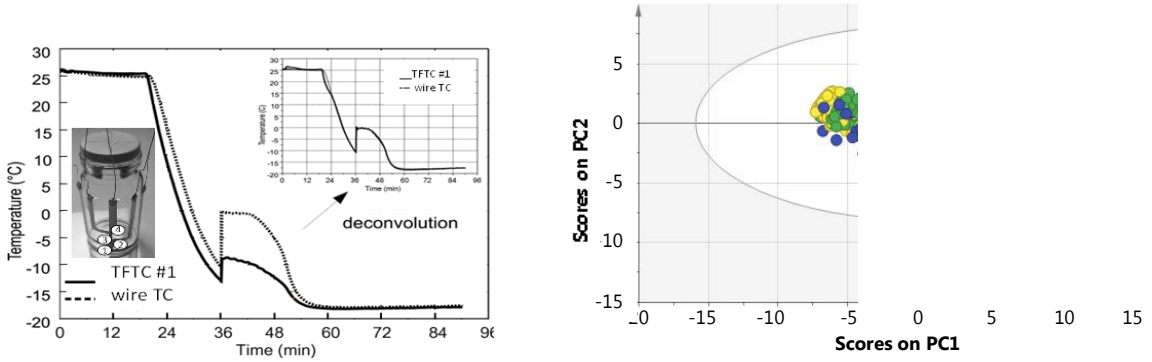

Fig. 2. (Left picture) The vial equipped by thin-film thermocouples developed by LYOLab team and (left graph) example of evolution of the product temperature as detected by wire and thin-film thermocouples. (Right graph) Score scatter plot of Raman spectra in the case of (●) shelf-ramped freezing and vacuum-induced freezing at various nucleation temperature: (●) +5 °C, (●) -5 °C and (●) -10 °C.

Raman spectroscopy can give essential information about the solid-state transformations that occurs during the lyophilization process. As an example, we used the Raman spectroscopy to better investigate the impact of the freezing protocol on the formation of mannitol polymorphs. An example of results is given in Figure 4 that shows the score scatter plot for the Raman spectra of lyophilised samples in the case of two freezing protocols (shelf-ramped freezing *vs.* vacuum-induced surface freezing), and various values of nucleation temperature. It can be observed that in the case of vacuum-induced surface freezing the Raman spectra were very close one another, while were more spread for the shelf-ramped freezing. This result indicates that the mannitol composition of samples produced by the vacuum-induced surface freezing was more uniform than that of obtained through the shelf-ramped freezing. This results was then confirmed by the loading plot of the Raman spectra and by the X-ray diffraction analyses of the various samples (data not shown).

This information is useful to guide the lyophilization professional during the selection of the freezing conditions.

4 FLOODED PAPER FREEZE-DRYING

Freeze-drying is an effective process to recover flooded paper material The study has been carried out experimentally, considering different types of materials, simulating a flooding by soaking in distilled water, and then freeze-drying the samples. An example of the results obtained in shown in Table 1: it appears that the freeze-drying process is able to completely remove the water from the samples, without affecting paper size and quality characteristics (e.g. colour and texture).

Table 1. Weight and size variations of various paper samples after soaking and freeze-drying.

Sample ID	Type of material	Age	Original size, cm	Original weight, g	Weigth after soaking, g	Size after freeze-drying, cm	Weight after freeze-drying, g
1	Book	1931	11.8x17.9x0.3	19.8	36.6	11.8x17.9x0.5	18.8
2	Book	1934	13x19.2x2.7	350.64	755	13x19.2x3	352
3	Coated papers	1990	21.1x29.5x1	578.3	949.6	21.1x29.5x2	556
4	Small folder with papers	1990	24.5x33x1	396	876	24.5x33x3	382.4
5	New parchement	1990	9.2x8	0.89	4.8	9.2x8	1.8
6	Parchement with lace	1580/1581	4.4x7	1.65	3.6	4.4x7	1.6
7	Print test	XVIII century	12x8	0.58	1.9	12x8	0.65
8	Darken parchement	XIII/XVI century	3.5x4.2	0.26	0.8	3.5x4.2	0.3
10	Book	1943	13.4x19.5x2.2	393	788.8	13.4x19.5x3.8	410.7
12	Paper with foxing	XVI century	9.9x11.5	0.57	2.2	9.9x11.5	0.6
14	Score	XIII century	6.5x15.8	1.86	4.1	6.5x15.8	1.7

These results were used for the development of a risk management plan, aiming to provide some general guidelines to both private and public archives.

REFERENCES

[1] Capozzi, C.L., Boccardo, G., Barresi, A.A., Pisano, R., 2015. Coupled bullet physics and computational fluid dynamics as a tool for modeling the freeze-drying of microparticles. *In*: EuroDrying 2015, Budapest, Bulgaria, October 21-23, pp. 75-83.

[2] Boccardo, G., Augier, F., Haroun, Y., Ferré, D., Marchisio, D.L., 2015. Validation of a novel open-source work-flow for the simulation of packed-bed reactors. *Chemical Engineering Journal* 279(*1*): 809-820.

[3] Garcia-Pérez J.V., Cárcel J.A., Mulet A., Riera E., Gallego-Juarez J., 2015. Power ultrasonics: Application of high-intensity ultrasounds, *Ultrasonic drying for food preservation*, Gallego-Juarez J.A., Graff K.F. eds., Elsevier, Cambridge, pp. 875-910.

[4] Liang, H., 1993. *Modelling of ultrasound assisted and osmotically induced diffusion in plant tissue*. PhD Thesis, Purdue University.

[5] Pisano R., Fissore D., Barresi A.A., 2014. A New method based on the regression of step response data for monitoring a freeze-drying cycle. *Journal of Pharmaceutical Sciences* 103(*6*): 1756–1765.

[6] Bosca S., Fissore D., 2014. Monitoring of a pharmaceuticals freeze-drying process by model-based process analytical technology tools. *Chemical Engineering and Technology* 37(*2*): 240-248.

[7] Oddone, I., Fulginiti, D., Barresi, A.A., Grassini, S., Pisano, R., 2015. Non-invasive temperature monitoring in freeze drying: control of freezing as a case study. *Drying Technology* 33(*13*): 1621-1630.

[8] Pieters S., De Beer T., Vander Heyden Y., 2012. Near-infrared and Raman spectroscopy: potential tools for monitoring of protein conformational instability during freeze-drying processes. *American Pharmaceutical Review* 15(*1*): 1-3.

[9] Oddone I., Van Bockstal P.-J., De Beer T., Pisano R., 2016. Impact of vacuum-induced surface freezing on inter- and intra-vial heterogeneity. *European Journal of Pharmaceutics and Biopharmaceutics* 103(*1*): 167-178.