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STUDY OF MEASUREMENT UNCERTAINTY ISSUES IN FREEZE-DRYING

Mogal Anuja[1], Ahire Varsha[2], AherRahul[3],

[1,2,3]*B.E. Scholar BVCOE&RI Nashik Pune University (India)*

ABSTRACT

Lyophilization is a process commonly used in industrial field to prevent the deterioration of foods and drugs that are sensitive with respect to the heat. This paper deals with problems that have to be faced when performing mass and temperature measurements of substances subjected to freeze-drying processes. A brief description of a lyophilization process is initially presented and a deep investigation is performed in order to identify the main uncertainty contributions that affect mass temperature measurements. A measurement system is then described that has been specifically conceived to work inside a freeze-dryer. Experimental results are reported that refer to the metrological characterization of the proposed measurement system and to its use for the monitoring of real freeze-drying processes. Experimental tests are also described that have been conceived to estimate the uncertainty contributions strictly related to this specific condition.

I. INTRODUCTION

Freeze-drying, or lyophilisation, is like "suspended animation" for food. You can store a freeze-dried meal for years and years, and then, when you're finally ready to eat it, you can completely revitalize it with a little hot water. Even after all those years, the taste and texture will be pretty much the same. That's some trick! The basic idea of freeze-drying is to completely remove water from some material, such as food, while leaving the basic structure and composition of the material intact. There are two reasons someone might want to do this with food: Removing water keeps food from spoiling for a long period of time. Food spoils when microorganisms, such as bacteria, feed on the matter and decompose it. Bacteria may release chemicals that cause disease, or they may just release chemicals that make food taste bad. Additionally, naturally occurring enzymes in food can react with oxygen to cause spoiling and ripening. Like people, microorganisms need water to survive, so if you remove water from food, it won't spoil. Enzymes also need water to react with food, so dehydrating food will also stop ripening. Freeze-drying significantly reduces the total weight of the food. Most food is largely made up of water (many fruits are more than 80 to 90 percent water, in fact). Removing this water makes the food a lot lighter, which means it's easier to transport. The military and camping supply companies freeze-dry foods to make them easier for one person to carry. NASA has also freeze-dried foods for the cramped quarters onboard spacecraft. It's pretty simple to dry food, drugs and just about any other biological material. Set it out in a hot, arid area, and the liquid water inside will evaporate: The heat gives the watermolecules enough energy to "break free" of the liquid and become gas particles. Then you seal it in a container, and it stays dry. This is how manufacturers make dehydrated meals like powdered soup and baking mixes. There are two big problems with this approach. First, it's difficult to remove water completely using evaporation because most of the water isn't

directly exposed to air. Generally, dehydrating food in this way only removes 90 to 95 percent of the water, which will certainly slow down bacteria and enzyme activity, but won't stop it completely. Secondly, the heat involved in the evaporation process significantly changes the shape, texture and composition of the material, in the same way that heat in an oven changes food. Heat energy facilitates chemical reactions in the food that change its overall form, taste, smell or appearance. This is the fundamental purpose of cooking. These changes can be good, if they make the food taste better (or taste good in a different way), but if you're drying something so you can revitalize it later, the process compromises quality somewhat.

The basic idea of freeze-drying is to "lock in" the composition and structure of the material by drying it without applying the heat necessary for the evaporation process. Instead, the freeze-drying process converts solid water -- ice -- directly into water vapor, skipping the liquid phase entirely. In the next section, we'll find out how freeze-drying machines pull this off.

II. LITERTURE SURVEY

- **Measuring System Architecture**

The system the authors have arranged, whose block scheme is shown in Fig. 6, has been conceived to weigh a group of vials on the shelf of a freeze-dryer and to measure the temperature of the substance contained in some of these vials. The system has been designed in order to make the monitored vials as representative as possible of the whole batch. Apart from the definitional uncertainty, possible reasons that could make the monitored vials not representative of the whole batch are mainly related to the heattransfer processes. As far as the conduction is concerned, it is necessary to maintain the monitored vials in contact with the cooling shelf, but this does not allow a mass measurement to be obtained. In order to meet these conflictingdemands, a solution has been implemented by means of a step-motor based lifting system (see Fig. 1), which is driven in order to rise and release the monitored vials when a mass measurement has to be performed. During the measuring phase, the monitored vials are locked by their necks through a specifically designed comb-shaped moving plate . Such a plate does not lock firmly the vials but leaves them a certain grade of freedom, so that they can return in close contact with the cooling shelf after each measurement session.

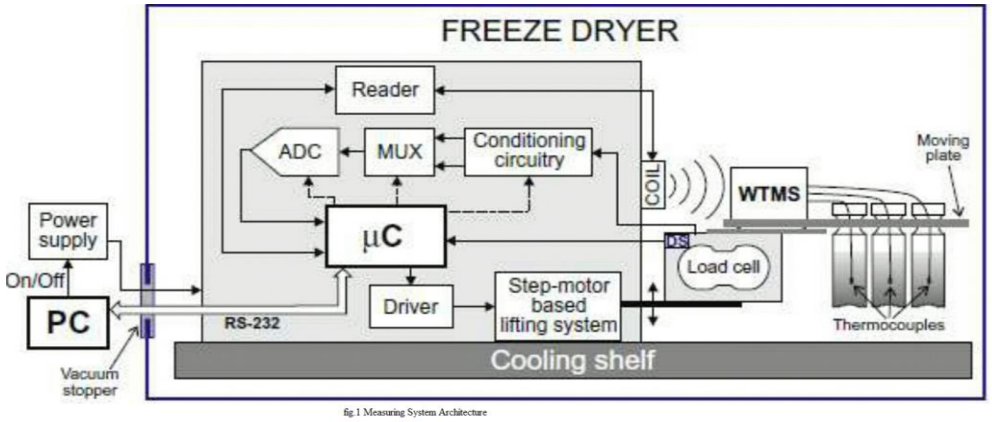

fig.1 Measuring System Architecture

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However, also for this measurement it is necessary to minimize the effect of the temperature sensor, which could affect the substance nucleation during the freezing phase. Non invasive techniques have been proposed that are based on the estimation of the substance temperature by meansof complex models that takes also the vial temperature into account. In this work, the authors have employed small thermocouples, which are placed inside the vials inorder to directly measure the substance temperature. The effects the thermocouple wires could exercise on the mass measurement have been eliminated thanks to a Wireless Temperature Measurement System (WTMS in Fig. 1) that is installed on the moving plate.

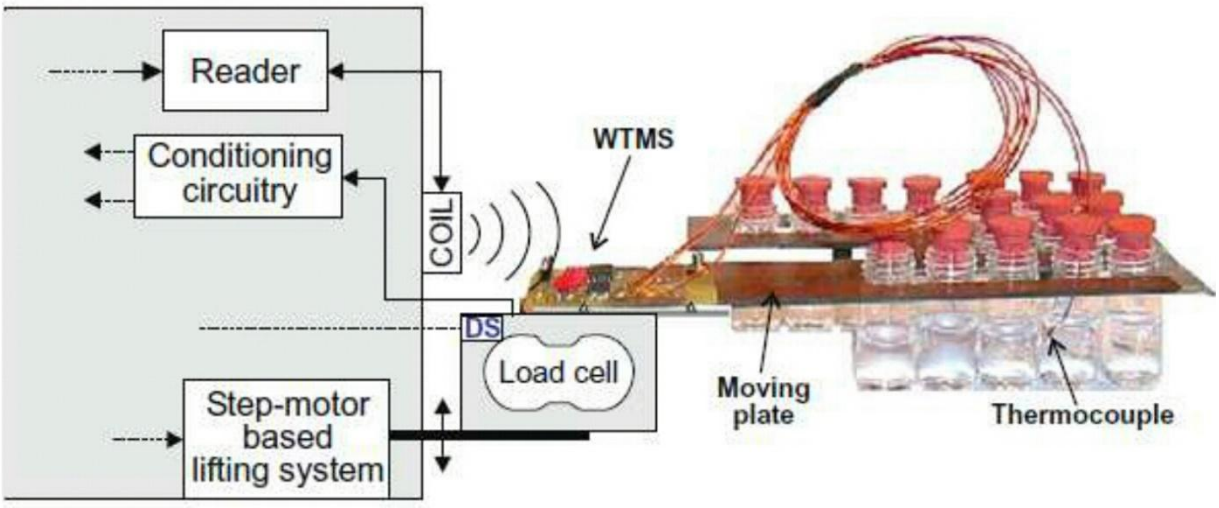

Fig 2. Picture of moving plate

- **Mass Measurement System**

The mass measurement is carried out by means of a commercial load cell, whose lower surface is mechanically coupled to the lifting system, while the upper surface holds the moving plate. The load cell, which has a full range of 2 kg, embeds four strain gauges connected in a full-bridge configuration. The voltage output of the bridge is amplified and filtered through a conditioning circuitry that is based on a low-noise amplifier. The amplifier output-signal Voutand the voltage supply Vs of the bridge are multiplexed and acquired by means of a 24-bit RD Analogue-to-Digital Converter (ADC), whose acquisition time has been set to 0.1 s. A digital sensor (DS in Fig. 2) is attached to the load cell by means of a thermo-conductive rubber in order to measure its temperature. A micro-controller (µC) manages the whole measurement system and also communicates with the PC through a serial RS-232 interface. After the PC turns the power supply on, a command is sent to the µC to start a measurement session, which can be subdivided into the following step:

1. the µC drives the step motor in order to rise the loadcell, which senses the mass of moving plate and vials.
2. the voltages Vout and Vs are obtained as the average values of the corresponding voltages measured reversing the cell voltage supply, then an estimation of the mass mT of moving plate and vials is obtained as:

$$mT = A.Vout(+) - Vout(-) / Vs(+) - Vs(-) \quad (1)$$

where the constant A is obtained during the calibration of the measuring system;

3. the vials are released on the shelf and the mass measurement procedure based on the Eq. (1) is repeated in order to obtain the zero mass mZ;
4. the mass mV of the monitored vials is obtained subtracting the zero mass from the first measurement:

$$mV = mT \_ mZ \quad (2)$$

5. the µC reads the output of the temperature sensor DS through an I2C interface and acquires the measurement of the substance temperature, as explained in the next section;
6. all the measurements are transferred to the PC, which eventually turns the power supply off.

Each measurement session lasts about 15 s, which are mainly required by the lifting system for rising and releasing the moving plate. The proposed procedure allows the effects of offset and thermoelectric voltages to be minimized. In addition, the thermal effects on load-cell and conditioning circuitry have also to be taken into account, since during a lyophilization process temperature changes of more than 60 0C are expected. For this reason, the PC implements a compensation technique based on a linear model that takes the load-cell temperature into account, whose effectiveness will be showed in the tater section.

- **Temperature Measurement System**

The architecture of the temperature measurement system is similar to Radio Frequency IDentifications (RFID) devices , since it is based on a circuit that is powered through a radio frequency signal sent by a coil, thus avoiding the use of supply wires or battery. Furthermore, the same radio frequency signal is used to send back the measurement results. The arranged Wireless Temperature Measurement System (WTMS) is located on the moving plate, as indicated in the Fig.7. It embeds a conditioning circuitry that amplifies the voltage output of three thermocouples, which are placed inside three of the monitored vials. A micro-controller acquires the voltage signals related to the thermocouples and the output of a digital sensor, which provides the cold-junction temperature. The micro-controller is also responsible for the WTMS management and sends the results to the reader, which is placed into thebody of the measurement system.

- **System Calibration**

The mass measurement system has been calibrated against a standard analytical balance (Mettler AT200), which ensures a standard uncertainty of 1 mg in a measurement range of 200 g. The calibration constant A of Eq. (1) has been obtained by weighing a mass with a value of about 200 g previously measured with the standard balance. Multiple readings have been performed during the calibration procedure in order to estimate the uncertainty contribution related to random effects, whose standard deviation was of about 10 mg. After the calibration constant has been obtained, the linearity of the measurement system has been characterized by weighing a set of vials with masses in the range from 100 g to 200 g, obtaining a maximum deviation froma straight line of 10 mg. The behavior of the mass measurement system with respect to the temperature has been tested by employing a constant mass of about 190 g. During this test, the system has been placed inside a climatic chamber, whose temperature has been changed in the range from -400C to 400C. Attention has been paid in order to avoid condensation on the vials, which could affect the measurement results. Fig. 8 shows the total mass mT of moving plate and vials, the zero mass mZ and the vial mass mV, which is obtained according to Eq. (2). The behaviors of mV and mZ highlight the thermal drift of the system under test, since mass hanges of more than 25 g have been observed. The same figure shows that the vial mass mV exhibits a residual masschange of about ±40 mg over the whole investigated temperature range after a linear model has been

implemented for compensating temperature effects. Such an algorithm takes into account the load-cell temperature measured by the digital sensor DS.

The described tests have been performed over a time interval of about a week, thenthe obtained results also include reproducibility and short-term drift of the system under test. Accounting for the different uncertainty contributions and assuming a bimodal probability density function (pdf) for the non-linearity contribution and a uniform pdf for the contribution related to temperature effects, the estimated instrumental standard uncertainty of the mass measurement system is of about 27 mg, which is of the same order of magnitude of the expected definitional uncertainty. The verification of the WTMS has been carried out in the temperature range from -40 0C to 20 0C against a standard thermometer that ensures a standard uncertainty of 0.3 0C, obtaining a maximum error of 1.5 0C and a reproducibility among the three thermocouples of about 0.020C.

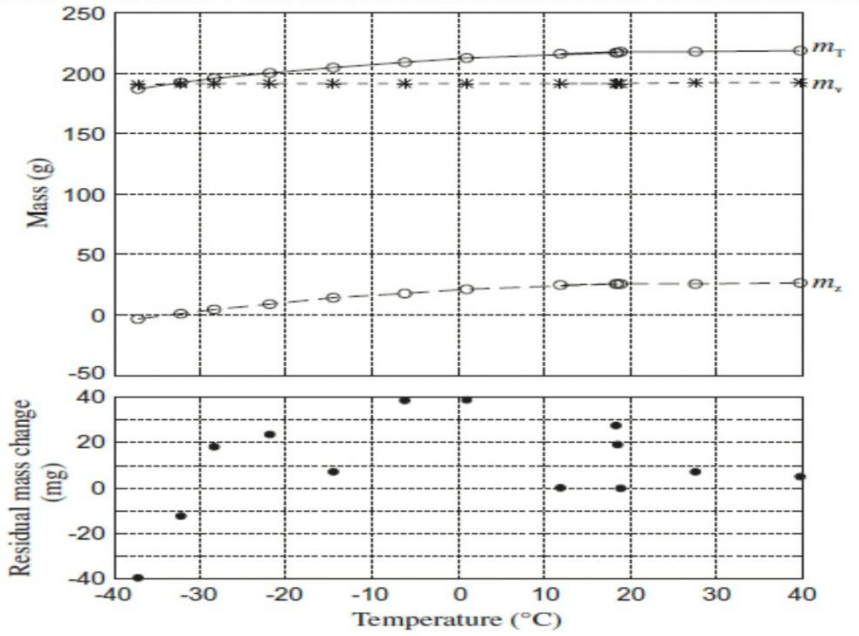

Fig 3.Results of the temp.test; behavior of the quantities mT,mZand mV(top graph);residual change of the mass mv after the temp. compensation has been implemented(bottom graph)[1].

III. EXPERIMENTAL RESULTS

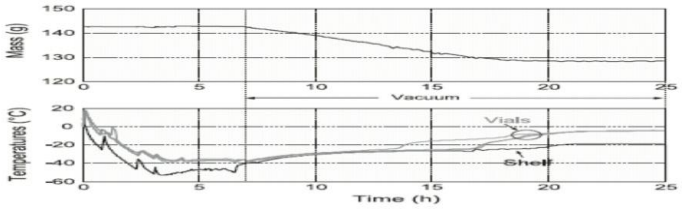

Fig 4. . Results obtained during the primary drying of a lyophilization process[1].

Several experimental tests have been performed in order to characterize the described measurement system in operating conditions. Initially, the proposed system has been placed inside a freeze-dryer for monitoring a lyophilization process, then the load-effect of the system on the monitored vials has been estimated, in order to evaluate the representativeness of these vials with respect to the full batch.

- **Lyophilisation-Process Monitoring**

Once the system has been calibrated, it has been placed inside a freeze dryer and different lyophilization processes have been monitored. During these tests, the moving plate showed in Fig 5 has been used, which holds 15 glass vials containing a 10%mannitol water solution. Fig 5 summarizes the results of one of these tests: the upper trace shows the measured mass mV, while the lower trace reports the temperature of cooling shelf (black line) and of the solution inside three of the monitored vials (gray lines). Before placing the moving plate inside the freeze dryer, its mass has been measured with the same analytical balance used during the calibration, obtaining a value of 142.52 g. During the freezing phase, which lasted about 7 h, the system under test showed a mean value of 142.56 g and a standard deviation of about 20 mg, which is mainly due to freeze-dryer vibrations. During this phase, the temperature of the cooling shelf reached -55 0 C while the solution inside the vials reached a temperature of-40 0C. The pressure inside the freeze dryer was then decreased down to 8 Pa in order to enable the ice sublimation process, which caused the mass loss highlighted in the upper trace of Fig. 9. After about 15 h, the measured mass was almost constant (128.26 g with a standard deviation of 20 mg), thus indicating the end of the primary drying. Eventually, the mass of the moving plate was measured by means of the analytical balance, obtaining a value of 128.20 g. The obtained measurement error with respect to the reference analytical balance is in agreement with the expected uncertainty of the system under test, whose expanded value (coverage factor k = 2) is of about 0.065 g if the noise contribution due to the freeze-dryer vibration is taken into account.

- **Load-Effect Estimation**

In the lyophilization tests described in the previous section, the primary drying has been always completed, thus not allowing the effects of the measuring device on the drying rate to be estimated. For this reason, specific tests have been performed in order to estimate the effects of the heating transfer processes between the body of the proposed measurement system and the monitored vials, which have been already discussed . The measurement system has been placed on the cooling shelf of the freeze dryer and the monitored vials have been surrounded by other vials, as shown in Fig. 5. A gap of few centimeters was left between the moving plate and the surrounding vials.

Fig 5. The measurement system on the cooling shelf[1].

The same procedure already used for the estimation of the definitional uncertainty has been performed : measurement of the mass of each vial before the lyophilization process; interruption of the primary drying process; sealing of the vials and mass measurement. Fig. 5 shows the obtained results in terms of histogram of water loss of:

- 227 vials placed on the cooling shelf with the exception of the vials on the moving plate (upper trace);
- 15 vials placed on the moving plate (middle trace);
- 60 vials that lie on the edges of the shelf (lower trace).

It clearly appears that, in average, the monitored vials are subjected to a greater sublimation rate than the other vials of the batch. The mean water loss of the monitored vials is of about 490 mg (standard deviation 50 mg), while the other vials of the batch exhibit a mean water loss of 400 mg (standard deviation 55 mg). Further tests performed without turning on the measurement system have shown that this behavior is not related to the overheating such a system provides to the monitored vials, but it mainly depends on the gap around the monitored vials, which is necessary for allowing the lifting of the moving plate. This means that the vials on the moving plate almost behave like the vials that lie on the edges of the shelf. The lower trace in Fig. 6 confirm this assumption: here the water-loss distribution of the edge vials is shown, whose meanvalue is of about 470 mg.

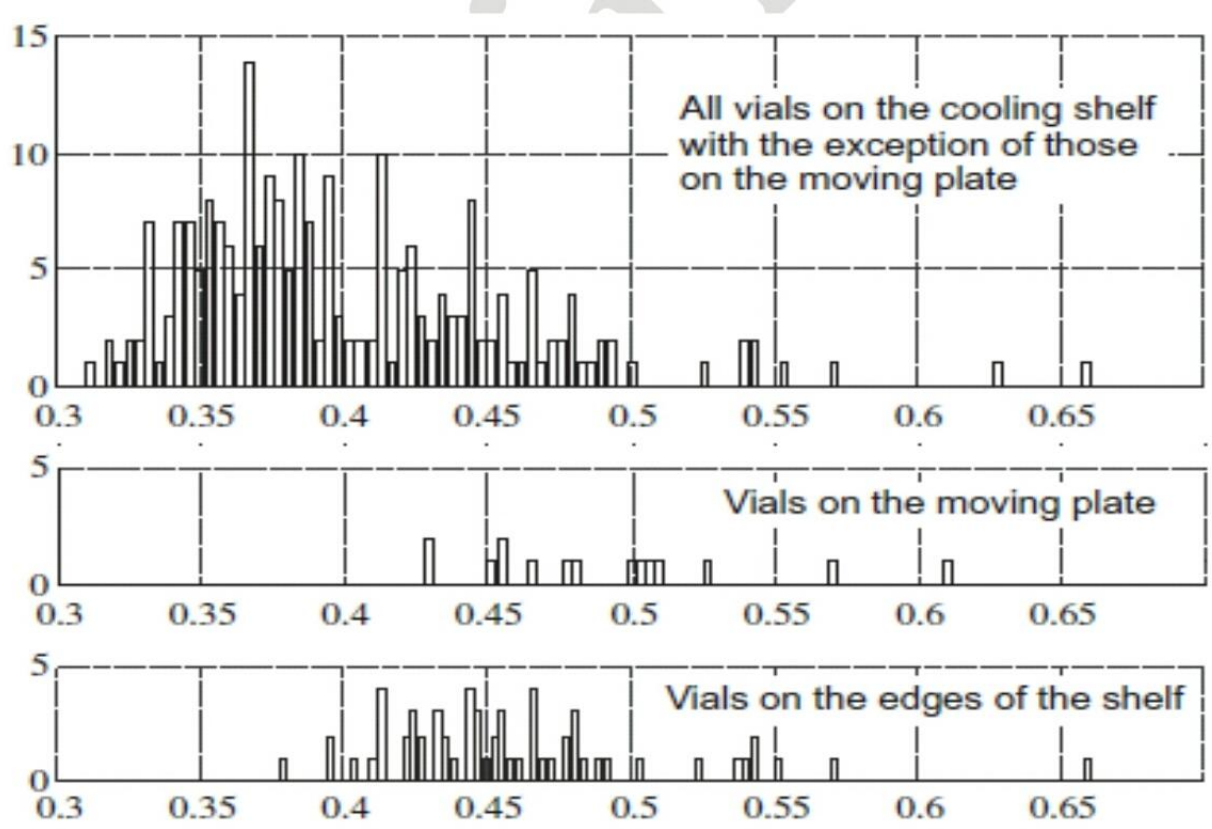

Fig 6.Water-loss distribution of:all the vials on the cooling shelf with the exception of the monitored ones(upper trace);vials on the moving plate (middle trace);vials on the edges of the shelf(lower trace)[1].

Eventually, it is possible to state that the presence of the measurement system on the cooling shelf contributes in making worst the representativeness of the monitored vials with respect to the whole batch. It therefore can be assimilated to an added contribution to the definitional uncertainty and can be estimated as the difference between the mean water losses of the monitored vials and of the other vials, whose value is of about 90 mg. However, this contribution can be reduced by using suitable models that relate the vial packing density to the quantity of interest, e.g. to the drying rate**.**

IV. CONCLUSION

A system that is able to weigh a group of vials and to measure the temperature of the substance contained in some of these vials has been described in this paper. Such a system has been designed to operate in the harsh environment that is present inside a freeze dryer and to make negligible the effects of the system itself on the heating exchange flows that occur during lyophilization processes. Particular attention has been paid in identifying and estimating the main uncertainty contributions, which can be essentially subdivided into three categories: definitional uncertainty, instrumental uncertainty, load effect. Definitional uncertainty and load effect, which take into account the representativeness of the monitored vials with respect to the whole batch, seem to be the major contributions, with an absolute value of 90 mg when a water loss of about 0.5 g is measured. This value can be decreased by means of an improved version of moving plate that is now under development, but it cannot be reduced below 50 mg, which is the definitional uncertainty related to the different thermal processes the vials are subjected to inside the investigated freeze-dryer. The solution that allows this uncertainty contribution to be drastically reduced consists in arranging a device that is able to pick up and weigh any individual vials on the shelf during a lyophilization process. Such a solution is very expensive and its implementation can only be justified for pilot freeze-dryers used in a laboratory.

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