MASS MEASUREMENT INTO A FREEZE-DRYER

A. Carullo, M. Parvis and A. Vallan
Dipartimento di Elettronica - Politecnico di Torino
Corso Duca degli Abruzzi, 24 – 10129, Torino, Italy

Abstract: This paper deals with two scales that are conceived to operate inside a freeze-dryer, where the environmental conditions (temperature down to – 80 ºC and pressure down to 0.5 Pa) prevent traditional mass transducers to be employed. One scale is based on a parallel-electrode capacitor, whose capacity depends on the position of a moving electrode that, in turn, depends on the unknown mass. The capacity change is converted into a frequency change by means of an oscillator circuit. The second scale, which is still under development, is based on electrostatic levitation. A fixed metallic plate is divided into four sectors connected to a high voltage generator. The resulting electric field is used to levitate a moving metallic plate which carries the unknown mass. A prototype of the capacitor-based scale has shown an uncertainty of a few tenths of grams in the range of 0 g to 250 g.

Keywords: Mass measurement, Capacitance transducers, Lyophilisation systems.

1   INTRODUCTION

The experimental analysis of lyophilisation processes is becoming an important task for many researchers that work in pharmaceutical and food fields [1,2,3]. Such an analysis require the availability of electrical-output transducers that are able to carry out temperature, pressure and mass measurements inside a freeze-dryer. Main problems are related to the wide temperature and pressure changes such transducers are subjected to (from $-80\,°C$ to room temperature and from $0.5\,Pa$ to atmospheric pressure) and to the reduced space that is available inside a freeze-dryer.

Temperature and pressure measurements can be easily carried out by means of thermocouples and solid state devices, while an electrical-output mass transducer is not available that is able to guarantee a low uncertainty in the described conditions.

For this reason the authors have designed two different measurement systems that are conceived to work in wide temperature and pressure ranges.

Advantages and drawbacks of the two systems are discussed in the paper, then preliminary results are shown that refer to experimental tests performed with the capacitor-based system.

2   OPERATING PRINCIPLES

2.1   Design constraints

A scale designed to be employed inside a freeze-dryer has to satisfy a series of requirement that are not present in other situations. Five of the most important are:

1. The wide operating temperature range: during a typical lyophilisation process the temperature changes from room temperature to $-80\,°C$ (drying phase). Such a change of almost a hundred celsius degrees represents a challenge for scale designers due to the remarkable change in the material properties at low temperature.
2. The very low pressure: the vacuum thermal conductivity is dramatically low, so that even a very low power dissipation leads to a remarkable overheating. This is one of the reasons commercial analytical balances based on strain-gauge-type transducers can hardly be used inside freeze-dryers.
3. The sealed ambient nature that prevents the use of out-of-dryer measuring systems.
4. The limited space available inside freeze-dryers that limits the overall scale dimensions (the freeze-dryer for which the authors have designed the measurement system allows scale with 20 cm of diameter and 10 cm of height to be arranged).
5. The necessity to measure the temperature inside the lyophilised product during the lyophilisation process. This requirement leads to the necessity of inserting temperature

sensors, usually thermocouples, inside the product. The connection of these sensors has to be obtained by means of wires since other solutions, e.g. of optical type, cannot be used due to the extreme environmental conditions and limited space. Unfortunately, the wires add a variable, temperature-dependent force to the measured mass.

The constraint related to the power dissipation greatly limits the available scale choices: as an example, strain gauges and servo-scales based on electromagnetic system can hardly be used. The authors have therefore investigated two solutions where the power dissipation can be kept at a minimum value. Both solutions make use of a capacitor to maintain the current at a negligible value. In one case the capacity is made mass-dependent and measured; in the other case the electrostatic force is used to arrange a servo-scale.

2.2   The capacitor-based transducer

The first mass measurement system the authors have developed is basically a mass-to-frequency converter. Such a system can be subdivided into two physically separated systems: a mass-to-capacity converter and a capacity-to-frequency converter (see figure 1).

The mass-to-capacity converter, which is located inside the freeze-dryer, is a parallel-electrode capacitor. One electrode of such capacitor is fixed, while the other (hereafter called the moving electrode) is suspended by means of three helical steel springs. The substance that has to be dried is placed on the moving electrode, so that its mass affects the distance between the two electrodes and hence the capacity value.

The capacity-to-frequency converter is an oscillator circuit, whose reactive element is the mass-to-capacity converter. The oscillation frequency of the circuit is hence related to the capacity of the parallel-electrode capacitor and eventually to the unknown mass. The oscillator circuit is located outside the freeze-dryer, thus allowing low-cost components that work in a reduced temperature range to be used.

A microprocessor acquires the frequency of the oscillator circuit and the temperatures of the springs and of the capacitor electrodes. Such temperatures have to be taken into account in order to obtain meaningful mass measurements.

Among the advantages of the capacitor-based transducer, it can be mentioned its simplicity and its low cost. The main disadvantages come from the sensitivity of the spring characteristics and of the capacitor dimensions with respect to the temperature, which requires a compensation for this quantity to be applied.

2.3   The electrostatic servo-transducer

The second measurement system, which has not been completed yet, is based on electrostatic levitation.

In this case the unknown mass is placed onto a moving metallic plate, which is subjected to the electric field produced by a fixed plate. The fixed plate is subdivided into four electrodes connected to four controlled high-voltage DC sources. The fixed plate attracts the moving one with a force that depends on the applied voltages and on the plate distance. The measurement of the voltages that permit to hold the moving plate at a fixed distance from the fixed plate allows an estimation of the
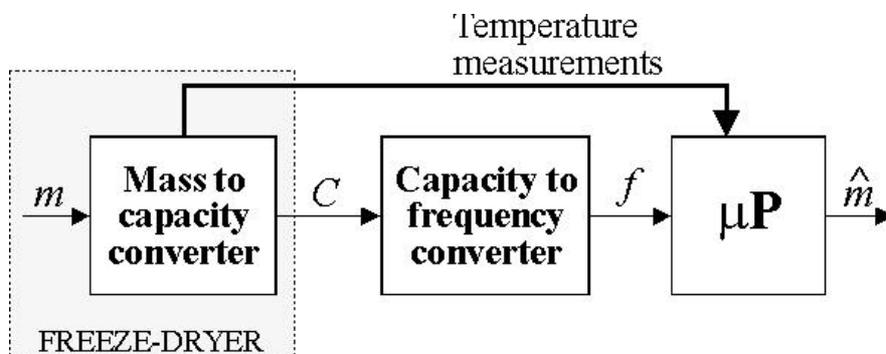

Figure 1. Principle scheme of the capacitor-based mass transducer.

unknown mass to be obtained. This kind of scale is much less temperature sensitive than the capacitor-based one, but it requires:

- the use of high voltages to obtain the required force;
- a distance measurement system to detect the moving plate position;
- a position control system in order to keep the moving plate at a fixed position.

The force F that attracts the moving plate can be approximately expressed as [4]:

$$F = \frac{e_0 \cdot S \cdot V_E^2}{2 \cdot d^2} \tag{1}$$

where

S	is the electrode surface;
V_E	is the voltage applied between the electrodes;
d	is the distance between fixed and moving plates;
e_0	is the vacuum permettivity ($8.86 \cdot 10^{-12}$ F/m).

As previously mentioned, the available space inside freeze-dryers is limited. The freeze-dryer for which the authors have designed the scale allows a fixed plate with an electrode surface of about $0.08 \, m^2$ to be arranged. If a mass range of about 0.2 kg has to be obtained, which corresponds to a force of about 2 N, a voltage of about 1.2 kV has to be applied between the electrodes when their distance is of 0.5 mm.

Besides the generation of such a high voltage, problems arise from the electric connection between the electrodes (inside the freeze-dryer) and the circuitry (outside the freeze-dryer). Furthermore, once the electrode surface has been fixed, the maximum voltage applied between the electrodes, and hence the maximum force the fixed plate can produce, is limited by sparking phenomena. The electric field in air has to be maintained below 3 kV/mm in order to avoid electric discharges. In the designed scale such limit value can be reached if the electrode distance becomes 0.4 mm, therefore attention has to be paid in order to avoid position errors greater than 0.1 mm.

If equation (1) is employed to estimate the force that corresponds to the unknown mass, the expected combined standard uncertainty can be computed as [5]:

$$u_C(F) = \sqrt{\sum_{i=1}^{3} c_i^2 \cdot u^2(x_i)} \tag{2}$$

where c_i are the sensitivity coefficients of F with respect to the quantities S, V_E and d, which can be computed from the equation (1), and $u(x_i)$ are their standard uncertainties. In the equation (2) the covariance terms are not present because the measurements of S, V_E and d can be reasonably considered uncorrelated.

A standard uncertainty of the measured force of 10 mN (mass standard uncertainty of about 1 g) can be obtained if, as an example, the distance standard uncertainty is fixed to 1 μm and the residual uncertainty contribution is equally distributed between the applied voltage and the electrode surface. In this case the required standard uncertainties are of about 1 V for the voltage and 1.6 cm^2 for the surface. The temperature of the fixed and moving plates has to be measured with a standard uncertainty of a few celsius degrees in order to take thermal dilatation effects into account.

The electrostatic scale is an unstable system, thus requiring an active control on two axes that measures the moving-plate position and modifies the voltage applied between the electrodes in order to hold the moving plate to a fixed position.

The necessity to arrange the position control system and to measure the moving-plate position with a very low uncertainty highlights the complexity and the high cost of a scale based on electrostatic levitation.

3   CAPACITOR-BASED TRANSDUCER PROTOTYPE

A prototype of capacitor-based transducer has been arranged by employing a circular aluminium plate as moving electrode. Such a plate, which has a diameter of about 16 cm, is suspended by means of three helical steel springs connected to an external aluminium tray with 18 cm of diameter. The two electrodes are composed of two circular single-sided printed-circuit boards, which are insulated with respect to the aluminium structure. One board is screwed to the moving aluminium plate, while the other is screwed to the tray. Both the tray and the moving plate are connected to the electric-circuit shield, so that the capacitor is completely shielded with respect to external electric fields.

Two thermocouples sense tray and moving plate temperatures, while a third is positioned near to one of the springs. Other two thermocouples are available to measure the temperature inside the lyophilised product. The three thermocouples on the moving electrode are composed of two wire types. A shielded, rugged wire is used from the product to a stop point near to the spring, then a couple of very thin wires are twisted to the springs up to the tray. Eventually, the rugged wire is used from the tray to the connector. By using this configuration a rugged system is obtained while minimising the force transmitted by the wires to the moving electrode.

The mechanical design of the system has been performed in order to allow mass measurements in the range of 0 g to 250 g to be obtained. The distance between the capacitor electrodes is in the range of about 15 mm (moving electrode not loaded) to about 3 mm (full mass range). Capacity values in the range of 12 pF to 60 pF are hence expected to be measured.

The capacity-to-frequency converter is a square/triangle wave generator, whose reactive element is the parallel-electrode capacitor. The generator has been designed so that its frequency oscillation is in the range of 5 kHz to 25 kHz.

4   EXPERIMENTAL RESULTS

An experimental set-up has been arranged to test the capacitor-based transducer by employing a multi-channel acquisition unit that communicates with a personal computer by means of a standard IEEE-488 interface. The instrument, which provides an internal reference-junction for thermocouples, measures the oscillation frequency of the wave generator, the voltage outputs of the thermocouples that sense spring and electrode temperatures, and the output of a transducer that senses the pressure inside the freeze-dryer. A gas-tight connector is employed to connect the parallel-electrode capacitor and the thermocouple (located inside the freeze-dryer) to the oscillator circuit and to the acquisition unit (located outside the freeze-dryer).

A frequency-vs-mass model that takes temperature effects into account has been identified by performing a series of tests at constant mass in the temperature range of $-70\,°C$ to $20\,°C$. The employed masses have been measured with a standard uncertainty of 0.1 g by means of an analytical balance. A mean sensitivity coefficient of about 75 Hz/g has been estimated in the mass range of 0 g to about 250 g, therefore by measuring the oscillation frequency of the circuit with a standard uncertainty of $1\,Hz$, a mass uncertainty contribution of about 0.01 g is expected.

The obtained model shows a sensitivity with respect to the temperature of about $10\,Hz/°C$, thus indicating an uncertainty contribution of the measured mass of about 0.06 g for temperature standard uncertainty of $0.5\,°C$.

The capacitor-based transducer has been then employed during typical lyophilisation processes. Figure 2 shows an example of unprocessed data acquired during the lyophilisation of a Potassium-dymethil succinate buffer solution (Ph 5.5). The solution was composed of about 0.3 g of solute and of 11.5 g of soluble. In the figure, the top diagram shows the temperature of moving (dashed line) and fixed (thick line) electrodes and that one near a spring (thin line), the middle diagram refers to the pressure and the bottom shows the oscillation frequency of the wave generator.

During the freezing phase, the mass of the substance that has to be lyophilised is constant, because no sublimation occurs. The measurements acquired during the freezing-phase are employed in order to refine the model that takes the temperature effects into account. The identification is performed by minimising the standard deviation of the difference between the outputs of the capacitor-based transducer and of a reference value, which is obtained by measuring the mass solution with a precision analytical balance before putting the solution into the freeze-dryer. The experimental standard deviation of the difference between the estimated mass and the reference value is of about 0.1 g in the freezing-phase. This model error is of the same order of the uncertainty contributions related to the measurement of frequency, temperature and reference mass, therefore an overall uncertainty of a few tenths of gram is expected.

The model identified during the freezing-phase is employed to compensate for temperature effects in the next phases of the lyophilisation process (primary and secondary drying). Figure 3 shows the data of figure 2 after the processing based on the identified model has been applied. The top trace is the mass of the lyophilised substance, while in the bottom diagram are shown the temperature of the fixed electrode (thick line), of the substance subjected to lyophilisation (thin line), and that one near to a spring (dashed line).
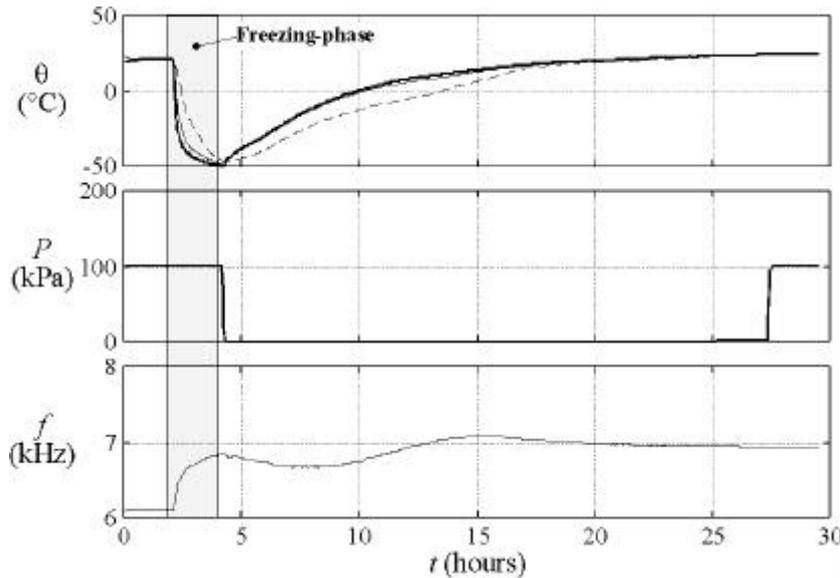
Figure 2. Unprocessed data acquired during a typical lyophilisation process.
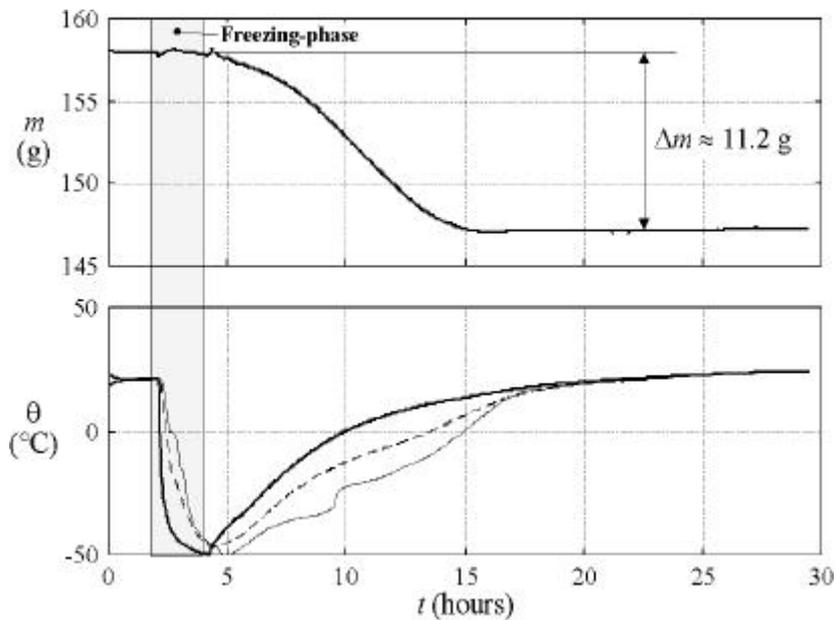

Figure 3. The mass obtained by processing the acquired data by means of the model identified during the freezing-phase.

The obtained results confirm the estimated uncertainty, as the dried mass measured by means of the capacitor-based transducer, which is of about 11.2 g, differs of 0.3 g from the expected value.

Similar experimental results have been obtained during several lyophilisation processes, even though the estimated model-parameters have shown a poor repeatability. This problem, which is now under investigation, could be due to the important thermal cycles the parallel-electrode capacitor is subjected to and to mechanical hysteresis phenomena.

5   CONCLUSIONS

The main constraints that make difficult the design of analytical scales suitable for mass measurements inside freeze-dryers have been highlighted in this paper. These constraints prevent the use of traditional mass-transducer, so that the authors have designed two capacitor-based scales conceived to operate in extreme environmental conditions.

A prototype of the scale that is based on a mass-to-frequency converter and employs a parallel-electrode capacitor has been arranged and tested during typical lyophilisation processes. The prototype allows measurements of mass up to 250 g to be obtained with expected standard uncertainty of a few tenths of gram. The obtained experimental results have shown the effectiveness of the employed technique, even though some problems remain that are related to the mechanical repeatability of the measurement system.

The other proposed scale, which is based on the equilibrium between the gravity force due to the mass that has to be measured and the electrostatic force related to an electric field, should avoid the repeatability problems. The authors are currently working in order to develop a prototype of such a scale by minimising its cost and complexity.

REFERENCES

[1] E. Wolff, H. Gibert, F. Rodolphe, Vacuum freeze drying kinetics and modelling of a liquid in a vial, *Chem. Eng. J.* **25** (1989) 153-158.

[2] R. Bruttini, G. Rovero, G. Baldi, Experimentation and modelling of pharmaceutical lyophilisation using pilot plant, *Chem. Eng. J.* **45** (1991) 66-77.

[3] A.I. Liapsis, M.J. Pikal, R. Bruttini, Research and development needs and opportunities in freeze drying, *Drying Technol.* **14**(6) (1996) 1265-1300.

[4] J. Jin, T. Higuchi, M. Kanemoto, Electrostatic Levitator for Hard Disk Media, *IEEE on Industrial electronics* **42**(5) (1995) 467-473.

[5] International Organization for Standardization, Guide to the Expression of Uncertainty in Measurement.

AUTHORS: Alessio CARULLO, M. PARVIS and Alberto VALLAN, Dipartimento di Elettronica, Politecnico di Torino, corso Duca degli Abruzzi, 24 – 10129 Torino, Italy, Phone: +39-011-564-4114; Fax: +39-011-564-4099,   E-mail: carullo@polito.it