strongly needed that the PAT tools should allow monitoring the variables of interest in the lyophilization process.

## DYNAMIC PARAMETERS ESTIMATOR: THE ALTERNATIVE

A noninvasive monitoring technique, useful for estimating the average state of the whole batch, is proposed as a valuable alternative to the lack of sensors previously mentioned. Barresi et al. have described this method in detail in chapter 20. In many engineering applications it is desirable to have estimates of hard-to-measure or even nonmeasurable quantities. A dynamic model sensor combines a priori knowledge about the physical system (mathematical model) with experimental data (in-line measurements) to provide an in-line estimation of the sought quantities.

There are two types of models: statistical (empirical) and mechanistic. A mechanistic model is derived from the knowledge about the underlying physics of the unit operation. If there is not any knowledge about the mechanism, there is only the option of traditional statistical design of experiments (DoE). In advance of an explanatory theory, these statistical models have the ability to identify the key variables and their relationships, providing focus for monitoring and, ultimately, providing the data that theory building and proving requires.

In this case, nevertheless, the dynamic model sensor is the mechanistic model describing the heat and mass transfer both in the frozen phase and the already dry phase of a product being lyophilized. The equations are transient state, so they are valid even if the process is not in steady state.

However, the actual parameters of these equations are not known because they depend on the product properties and the specific conditions at which the process is run.

The way to overcome it is introducing a small perturbation in the process and acquiring the system response to this perturbation. The set of equations are then solved to interpret the experimentally acquired pressure rise curve used as the perturbation, in order that the system response can be reproduced (Fig. 2).

The easiest perturbation sensitive to both heat and mass transfer is closing for a few seconds the valve between the chamber and condenser. The system to analyze is, then, a closed system (unless the unit has a significant leak) and the

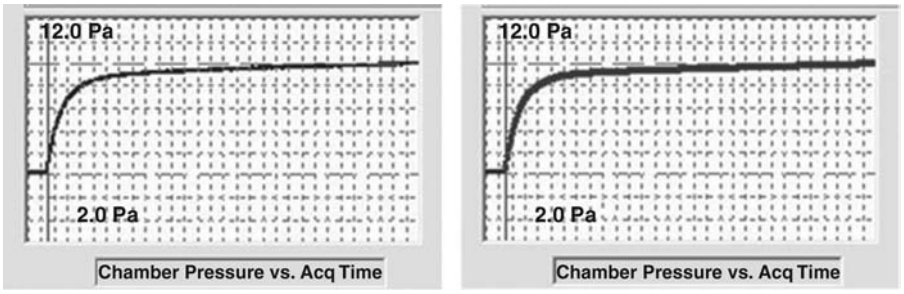


**FIGURE 2** Experimental pressure rise acquisition (*left*) and calculated one after solving the equations. Test parameters: vials filled with 1 mL 10% sucrose solution; product height: 7.21 mm; vial internal diameter: 14.25 mm; no. of vials: 609; shelf temperature: −32.6°C; elapsed drying time: 30 minutes; chamber volume: 201 L; and acq. time: 30 seconds.