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RISK ASSESSMENT IN FREEZE-DRYING PROCESSES

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Abstract
The risks identification is a key step for the safe design of a manufacturing process and, in this framework, once the threats to the process have been pointed out, it is important to evaluate their consequences, as well as their causes. In this paper, the risk assessment has been used to build the basis for the risk-based decision making in plant and process design of a pilot scale freeze-dryer, to be then exploited in the design of a full scale safer plant, taking into account also the experimental evaluation of possible human errors.

***Keywords**:* Freeze-drying, risk-based decision making, recursive operability analysis, human error probability.

1 Introduction

In the freeze-drying process the water is removed at low temperature and low pressure; this type of process is used to protect the product by the possible thermal degradation. The freeze-drying process is widely used in the food and pharmaceutical industry. Product obtained have long-term stability at the ambient temperature and the porous structure of the final product allows a fast reconstitution (Mellor 1978, Franks 2007). One of the more important factors that influences the product quality is the process temperature (Pikal 1990a, 1990b).
The development and management of a lyophilization process requires several steps and each of them can influence the probability that lyophilization could be successful. Early laboratory results, or the tests on pilot plants, can have influence on the final product, since these results are used to define the process parameters at the production phase.
A risk-based decision-making approach can be adopted for the process optimisation even in the early stages of process development.
The reliability of the lyophilization process can be evaluated through the identification of the hazards and the subsequent evaluation of the probability of occurrence, according to a traditional risk assessment approach, as in (Demichela and Baldissone 2019). One of the most used methodologies is Hazard and Operability analysis (HazOp). The HazOp methodology allows the analysis of process deviations, identifying the causes and consequences (Center for Chemical Process Safety 1992; Crawley 2003). An advancement of the HazOp technique is the Recursive Operability Analysis (ROA), developed by Piccinini and Ciarambino (1997), that allows an easier development of logical trees. This is made possible by the use of a recursive approach in identifying the causes, up to the primary causes and to the consequences, up to the identification of the Top Events (TE).
Following the identification of the hazards, the probability of occurrence is evaluated through the Fault Tree analysis (FT). The FT is a graphic representation that shows the link between the different causes and the TE. The FT methodology is also used for assessing the probability of TE occurrence (Witter 1992).

The assessment of the probability of occurrence of the TE is calculated starting from the probability of occurrence of the single primary causes.
Within the primary causes the human factor is often neglected, but in a complex system with still most of the sensitive operations carried on by operators, as freeze-drying processes are, this can bring to decisional errors.
It is the case of one of the parameters that are measured during the process development phase: the measure of the trends of the temperatures inside the vial. These data can influence the probability of successful lyophilization, as these data are used to design the control parameters of the lyophilization process and to identify the point at which the product freezes ends.
Several technologies have been proposed for measuring temperature trends within the vials. One of the most used methods requires the insertion of a thermocouple in the centre of the vial. This method is widely used as it is robust and the instrumentation can be easily sterilized (Willemer 1991, Oetjen 2004). In addition, the use of a sufficiently thin and sensitive thermocouple allows obtaining an approximately punctual measurement (Fissore et al. 2017). But at the same time the quality of the measurement depends on the position of the thermocouples inside the vial. The correct positioning of the thermocouples in the vial depends on the skill of the operator and the probability of the operator error. Consequently, one of the possible risks for the success of the lyophilization, connected to the process development phase, is the probability of an incorrect positioning of the thermocouple inside the vial.
According to what above, in paragraph 2.1 an analysis of the reliability of the lyophilization equipment is presented, evaluating the probability that there are problems in the production phase. *I*n paragraph 2.2 an example of the estimation of the possible risks that can be occur in the phase of development of the process is reported. In particular, an experimental measurement of the error in positioning the thermocouples in the vials is shown, highlighting the uncertainties in the measurement of the temperature profiles and consequently in the determination of the process control parameters.

2 Material and Methods

For productivity and safety sake, the reliability of the freeze-drying equipment can be assessed and the risks minimised (Bosca, et al., 2017). To exemplify the study of the reliability of the lyophilization process, an experimental freeze-drying plant was used as a case study, as described in Fig. 1.
The freeze-drying cycle is composed of three stages.

1. the freezing step, during which the aqueous solution is frozen and then undercooled to about −40 °C through a technological fluid flowing into the shelves of the chamber.
2. Primary drying. When the product is frozen, the pressure in the drying chamber is decreased to a value lower than the ice vapor pressure, thus causing ice sublimation. Simultaneously, the temperature of the technological fluid is increased, to a value that generally is below 0°C, thus heating the frozen product and favouring the sublimation of the ice crystals. The water vapor moves from the chamber to the condenser. For pressure control in the chamber, a nitrogen-controlled stream is introduced. As the drying goes on, a "cake" of dried material is obtained.
3. Secondary drying. At the end of the primary drying stage, the operating conditions are changed to start the secondary drying stage, when the desorption of the water bound to the product molecules is obtained. The pressure in the chamber is further lowered, and the temperature of the technological fluid rises to 20°C or more.

The plant considered in this study is a standard one, as described by Bosca et al. (2015), composed by a drying chamber, with the shelves for the product, a condenser (C-01), a vacuum pump (VP-01), a heater (EH-01), a pump (P-01), and a refrigeration unit, equipped with condensers (C-02 and C-03), evaporators (EV-01 and EV-02), and lamination valves (V-04 and V-05).

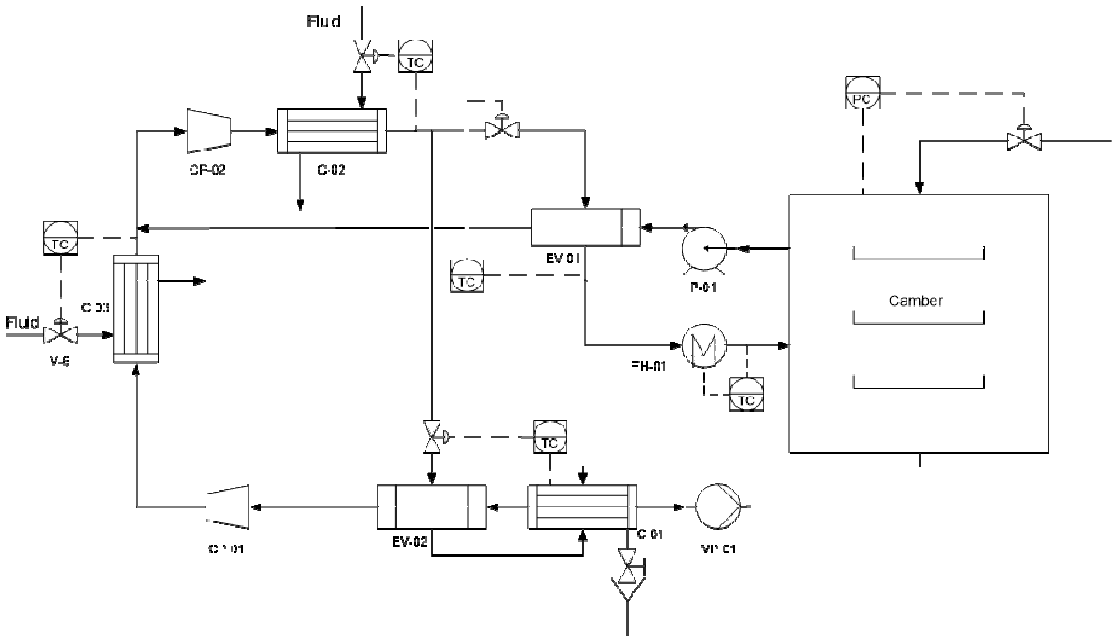


Fig. 1. Freeze-drying plant scheme

2.1 System reliability evaluation

This equipment is analysed using the ROA methodology. The ROA uses a recursive mechanism in the identification of causes and in the study of the consequences of the different deviations of the process. In this way the results of the analysis using the ROA facilitates the subsequent development of the logical trees (Fault Tree, Event Tree).
Being the equipment of the batch type, the ROA methodology is applied separately to the different processing phases: freezing, primary drying and secondary drying. The results of the ROA are used for the development of the FTs.
The FTs are a graphical representation that shows the logical relation among the causes and the TEs. The FT can be used to calculate the probability of occurrence of the TE starting from the probability of occurrence of the primary causes. The probabilities of occurrence of the primary causes concern both errors by the operators and component failures. The data concerning the probabilities of occurrence of the primary causes are derived from literature source (Mannan 2005, CCPS: Center for Chemical Process Safety 1989, Smith 1985, IAEA: International Atomic Energy Agency 1997, Williams et al., 1992).

2.2 Human error evaluation

The probabilities of occurrence of the error of the operator in positioning the thermocouple inside the vials, has been instead evaluated experimentally.
An experimental test was designed to estimate the probability that the thermocouple is correctly inserted (Demichela et al., 2018), with the aim of simulating the real operations: set up of the set of vials, thermocouple insertion and shifting of the tray with the vials inside the equipment.
The experimental set up is shown in Figure 2.
The test consisted in executing the insertion of the thermocouple in a series of vials (10 vials); different operators performed the test. After it was observed if the thermocouples were correctly positioned, the participants were asked to move the tray containing the vials. Then, the correct positioning of the thermocouples is checked again, thus evaluating the probability that at the beginning of the lyophilization tests the thermocouple is correctly positioned. The thermocouple positioning test

and tray movement test was carried out on two different vial sizes, 4R and 10R. In the experimental tests 12 participants were involved for the 4R and 11 vials for the 10R vials.



Figure 2 Experimental setup for the test of thermocouple positioning

An estimation of the probability that the thermocouple is correctly inserted and that it is still in the correct position after the movement of the vials was then obtained.

3 Results

3.1 System reliability

As introduced in section 2, the equipment was analysed separately for each one of the three stages of operation. For the step of freezing the undesired freezing velocity is identified as TE. This TE affect the ice crystals size (Bosca et al., 2015) and, as this influences the characteristics of the porous structure obtained in the successive drying stage, this undesired condition can affect the final quality of the dried product and can jeopardize the fast reconstitution of the product after rehydration.
Instead, for the primary drying an undesired heating profile and undesired pressure profile were identified as TE. Both TEs can lead to an increase in the temperature of the product, which can exceed the limit value or the temperature can be too low, lengthening the duration and costs of freeze-drying.
The same TE was identified also for secondary drying. In this phase when the pressure value is not the desired one, the vacuum level in the chamber can be not enough to favour the desorption of the residual water. If the temperature profile is not the desired one then the heat transferred to the product is not sufficient to desorb the "bound" water, and the target residual moisture is not achieved at the end of the process.
Through the application of the ROA the primary causes that lead to these TE have been identified, including the results of the experiments for the evaluation of human error probabilities. From the results of the ROA the FTs were elaborated. The FTs have been quantified using literature data for the failure rate of the components and the software ASTRA 3 for their numerical solution, obtaining the results contained in Table 1.
The TE with the higher probability is the undesired freezing velocity in the freezing phase, with a probability of occurrence of 14.9%.
For process optimisation sake, the analysis of the cut sets highlighted how the higher contribution to the TE is brought by the failure of the CP-02 compressor, followed at a distance from the failure of the P-01 pump. Consequently, CP-02 compressor is the most critical component in the freeze-drying equipment. In addition, this compressor is also the most critical component for the undesired heating profile during primary drying. Even if the latter TE has a probability of occurrence much lower than the previous one.

Table 1. The FT results

Phase	TE	Probability
Freezing	undesired freezing velocity	0.149
Primary drying	undesired heating profile	0.0018
	undesired pressure profile	0.0088
Secondary drying	undesired heating profile	0.0012
	undesired pressure profile	0.0003

The other TEs have a probability of occurrence of several orders of magnitude lower than the undesired freezing velocity case during the freezing phase. Even if the probability of occurrence of these TEs is not negligible. The analysis of the importance of the single events and of the minimal cut sets of the fault tree allows to support the choice of possible corrective actions.

3.2 Human error, experimental phase

From the experimental tests to evaluate the probability that the thermocouple is correctly inserted, it was obtained that for the 4R vials only 68.3% of the thermocouples were correctly inserted, value that increased to 70% for the 10R vials. But the correctly positioned thermocouples decreased to 61.8% for the 4R vials and 54.3% for the 10R vials after moving the vial tray. Probably, more experienced operators can reduce the error rate in thermocouple positioning.
With these tests it was also evaluated how many thermocouples are correctly inserted by each operator. Each operator on average correctly inserted 7 thermocouples over 10 into the vials 4R, about the same value for the 10R vials (7.0). The number of thermocouples correctly positioned after the movement decreased to about 6 out of 10.
As shown in the Fig. , the results of the vials 4R the different operators present a wide dispersion of the results obtained both before and after the movement of the vial sets.

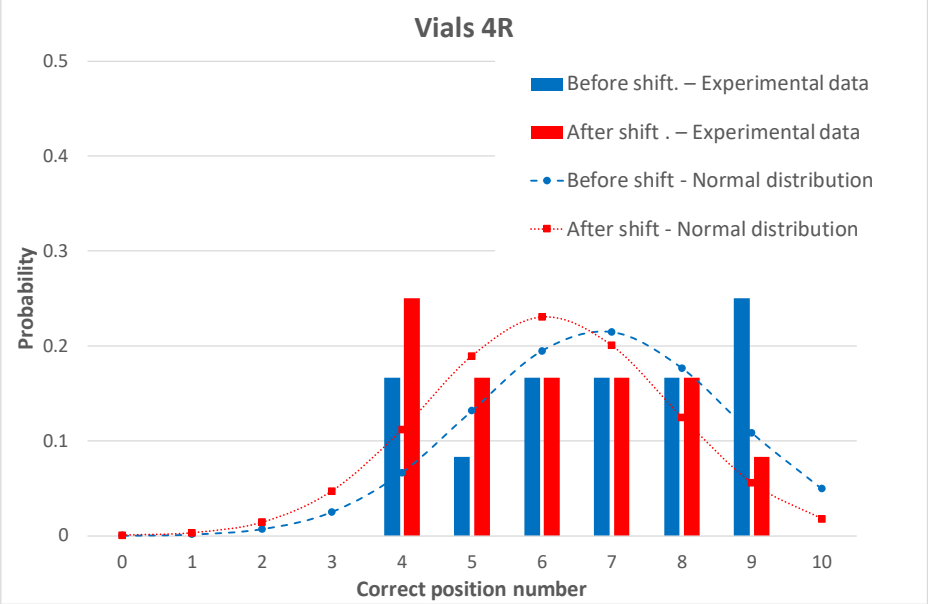


Fig. 3. Thermocouples correctly positioned in the 4R vials by each operator

Instead for the 10R vials the results of the different operators (Fig.) are more constant around the value of 7 thermocouples correctly positioned.

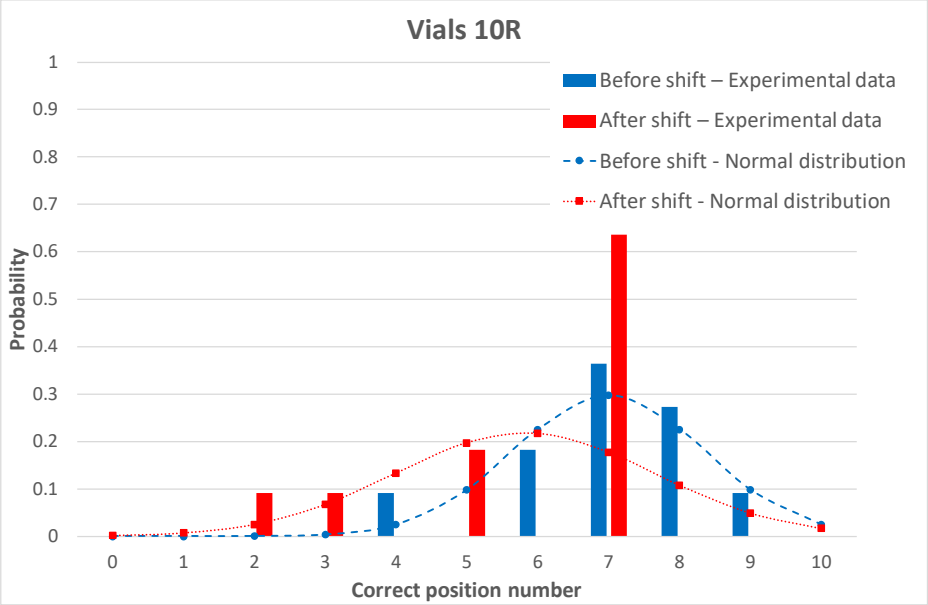


Fig. 4. Thermocouples correctly positioned in the 4R vials by each operator

The experimental data can be approximated through Normal distribution, also shown in Fig. 3 and Fig. 4. In Table 2 the mean value and the standard deviation that characterize the Normal distribution used for approximating the experimental data are shown.

Table 2. Normal distributions parameters for the experimental data approximation

Vials	Data	Mean value	Standard deviation
4R	Before shift	6.83	1.85
	After shift	6.08	1.73
10R	Before shift	7.00	1.34
	After shift	5.82	1.83

4 Conclusion

A risk assessment for the lyophilization process was shown in this work. The case study was a pilot plant for the freeze-drying process. The recursive operability analysis (ROA) was used to determine the top events and to identify their primary causes in all stages of the process. From the tables of the ROA, the fault trees of the top events were extracted, and were quantified, providing results such as the probability of occurrence of each top event, the minimal cut-sets, and the percent contribution of each primary cause to the unavailability of the system. Among the analysed top events, those with the highest probability were the undesired cooling velocity during the freezing step and the undesired pressure profile during the primary drying stage.
The primary causes that mainly contribute to the occurrence of the top event undesired cooling velocity are the fault of CP-02 of the mechanical refrigeration cycle, the fault of P-01, and the failure of the temperature sensors that measure the technological fluid temperature. This allows guiding the optimisation phase of the process and of the equipment control and inspection.
The model took into account also the probability of occurrence of the operator failure in positioning the thermocouples used to control the process, as evaluated according to an ad-hoc experimental setup. Human and organisational factors are often neglected in technical risk assessment, but their

contribution, in complex systems were the manual operations are still relevant, can be more critical than the failure of technical equipment, as in the present case.

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