

Optimisation of Drying Processes in the Pharmaceutical Industry

Mass-spectrometric online gas analysis ensures better process understanding, simplifies monitoring and reduces drying times

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The partial or complete removal of solvents is an important process step in manufacturing pharmaceutical intermediate and final products. These drying processes extract water and other solvents from the substrate up to a precisely defined residual value. The extraction of solvents from a given batch is often accomplished considering substance and plant specific regimes of heating and evacuation cycles. Additionally many of these drying cycles use make-up or inert gas to support the drying process and protect product quality.

Batch production processes are dominant in the pharmaceutical industry and various drying apparatus types are used. The drying endpoint is reached at different times depending on the substance and solvent in the batch. The drying endpoint is the point where the residual content of solvent decreases to the required level. The current method to determine the solvent content of the batch is usually accomplished via manual sampling from the drying apparatus and offline analysis in the company laboratory. The repeated iterations on drying determinations are labour and time intensive using discrete sampling especially in the case of the vacuum drying processes which often results in interruptions of the process vacuum and thus the drying processes.

Online measuring methods offer a better alternative. The primary purpose is to draw conclusions about the progress of the drying process, to document the drying process as completely as possible and to reduce the number of manual samplings considerably or completely. The online measurements may be used advantageously for developing and optimising a specific temperature and pressure behaviour inside the drying apparatus with regard to reduced drying times.

The increased introduction of continuous process analytical technologies in the production schemes resulting from the PAT initiative of the FDA may thus be supported effectively.

Online Process Mass Spectrometer Gas Analysis

During the complete drying process, the gas atmosphere inside the drying apparatus may be monitored and documented continuously with a process gas mass spectrometer. For example the mass spectrometers of the types GAM 200, GAM 300 and GAM 400 from InProcess Instruments are suitable for this task.

The continuous sampling of gas samples can be taken at the drying apparatus outlet, in the outlet air or in the vacuum suction line. When the drying is to be monitored both in the vacuum area and when working with carrier gas, the mass spectrometer will be equipped with a two-stage, pressure controlled gas inlet to adjust constant pressure conditions for the mass spectrometer.

The pressure control at the gas inlet is done independently of the gas type and for an inlet pressure range of 1 - 1200 mbar (absolute). The sampling lines and the gas inlet can be heated to measure solvents with low vapour pressures.

Up to 32 drying apparatuses may be connected via a multi-port valve unit and measured consecutively with one mass spectrometer.

InProcess Instruments quadrupole mass spectrometers offer the following advantages in this type of application:

- 1) Mass spectrometers allow of continuous measuring of the solvent concentration in the gas phase without interruption of the drying process. Measurement may be done inside the drying apparatus at various pressure ranges.
- 2) Mass spectrometers have a high sensitivity (detection limit < 0.1 ppm) and a wide dynamic measuring range (0.1 ppm - 100%) allowing for continuous monitoring of the drying process up to very low Loss-On-Drying (LOD) values.
- 3) The measuring principle of mass spectrometry has a high selectivity for the individual solvents. Partial pressure curves for all solvents may be determined and evaluated individually.
- 4) In addition to the solvent concentrations in the gas phase, it is possible to measure further components like for example nitrogen, oxygen or argon and thus to detect possible malfunctions or leakages of the drying apparatus at an early point of time.
- 5) Solvent analysis can be accomplished fully automatically with measuring parameters (mass numbers MN), selected for given solvents(see table 1).

Table 1:
A selection of various solvents with mass numbers (MN 1 ... 4) of the most important mass spectrometric fragment ions

Solvent	MN 1	MN 2	MN 3	MN 4
commonly used solvents				
Water	18			
Methyl alcohol	31	32	29	
Ethyl alcohol	31	45	29	46
Acetone	43	58		
Isopropyl alcohol	45			
Cyclohexane	56	84	41	
N,N-Dimethylacetamide (DMA)	44	87	72	
Methyl-tert.-butylether (MTBE)	73	57	41	
Toluene	91	92		
Butylacetate	43	56	61	
some other solvents				
Acetonitrile	41	40	39	
Butanone (MEK)	43	72	57	
Tetrahydrofuran (THF)	42	71	72	
N,N-Dimethylformamide (DMF, DMFA)	73	44	42	
Isobutyl alcohol	43	41	42	74
Dimethyl sulfoxide (DMSO)	63	78	45	
1,4 Dioxan	28	88	58	
N-Methylpyrrolidinon (NMP)	99	98	44	
Methyl isobutyl ketone (MIBK)	43	58	85	100
Isopropyl acetate	43	61	87	
2,2,4-Trimethyl pentane (Isooctan)	57	56	41	

- 6) IPI QUADSTAR software ensures simple control, automatic and safe operation and communication with the process control system.

Vacuum Drying in a Blade Dryer

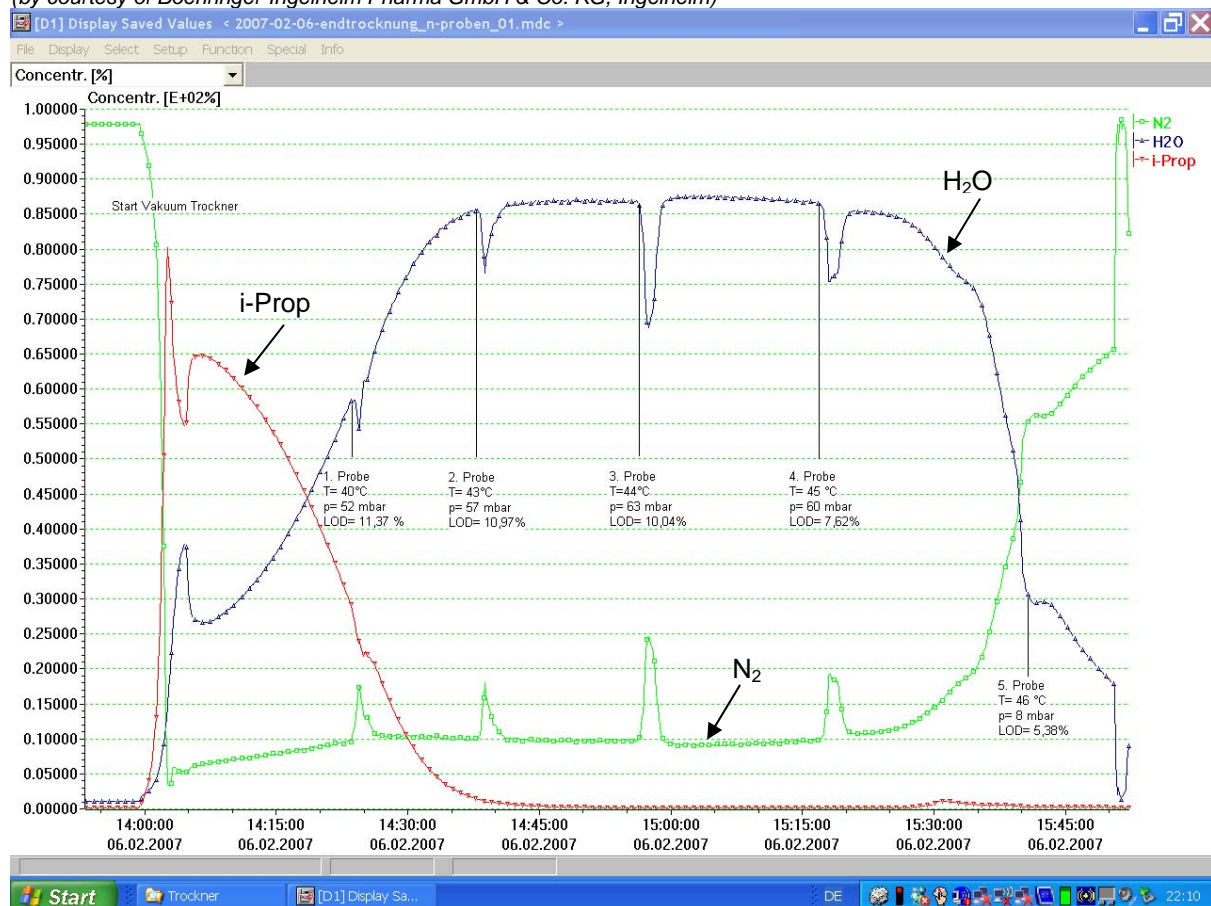
The following example is to illustrate a typical application of an InProcess Instruments mass spectrometer. The quadrupole mass spectrometer GAM 400 used for this study was connected via a pressure controlled gas inlet to the vacuum suction line of a blade dryer. During the drying process, the air constituents and the two solvents water and isopropanol were measured in the residual gas from the suction line of the drying apparatus.

Figure 1 shows the concentration curve for water, isopropanol and nitrogen during the final phase of the drying process. For comparison the results of five manual samplings with subsequent determination of the LOD are also stated in the figure. In the example the target nominal value for the LOD is 6%.

Figure 1:

Example of a concentration curve of water (H₂O), isopropanol (i-Prop) and nitrogen (N₂) in the suction line of a blade dryer

(by courtesy of Boehringer-Ingelheim Pharma GmbH & Co. KG, Ingelheim)



T temperature in the drying apparatus
 p total pressure in the drying apparatus
 LOD Loss-On-Drying

In this example the blade dryer was bathed with nitrogen. The sample lock chamber is flushed with nitrogen resulting in considerable N₂ concentration increases during sampling.

As shown in figure 1, at the start of the drying apparatus evacuation, isopropanol is volatilized first from the substance. After 50 min the drying rate for isopropanol drops to < 1% of the stationary value. In this example, the necessary drying time is mainly determined by slower water vaporization. In the drying phase from 2:35 p.m. – 3:25 p.m., the concentration value for water remains nearly constant. The transition of water from the surface of the substance particles into the gas phase is the limiting effect on drying in this example. From about 3:25 p.m. the measured water concentration in the suction line starts to drop and may be related to the degree of dryness. If this correlation is once determined, it is no longer necessary to take samples for repeated determination of the LOD and the drying process can be controlled via parameters that are measured online.

The concentrations or partial pressures of the solvents measured with the mass spectrometer may be used directly or after calculation with further process quantities like temperature or absolute pressure in the dryer. Calculation of the process variables may be done directly with the control software of the mass spectrometer.

Summary:

The mass spectrometric determination of solvent concentrations or solvent partial pressures in the gas atmosphere of a drying apparatus results in data sets that are very suitable for optimisation of drying processes.

The drying curve may be tracked and documented online with the mass spectrometer. As soon as the correlation to the Loss-On-Drying (LOD) values has been determined once, the end of the drying process can be inferred from the mass spectrometric data without delay. The time saving resulting from this allows for an improved plant utilisation and reduces energy costs. The avoidance of unnecessary offline analyses also contributes to cost reduction.

The mass spectrometric data gives important information for optimisation of the temperature, pressure and carrier gas parameters in process development, particularly with regard to influencing the sequence of individual drying steps if there are several solvents. It is also easy to detect critical dryer conditions (leakages, starting disintegration of the product, etc.).

Further information:

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