Keeping your powder dry -
PAT in the pharmaceutical industry

During the past number of years the pharmaceutical industry in Ireland has been adopting new techniques for monitoring and controlling processes such as reactions, crystallisations, drying and utilities. Diana Mesa and Cilian Ó Súilleabháin report on their study of the application of process analytical technology (PAT) to dryers in the Irish pharmaceutical industry

Most pharmaceuticals are powders and the final manufacturing step usually involves drying a powder. The product is usually heated to 40-65°C. Vacuum is used, with pressures of less than 200mbar absolute being the norm. The relatively low temperatures prevent products from deteriorating. The vacuum reduces the boiling temperature of the solvent, thus speeding up the drying process.

The initial moisture content of pharmaceutical products varies from 8 per cent to 35 per cent depending on the performance of earlier process steps such as crystallisation, filtration and centrifuging. Products are usually dried to a final moisture content of 1 per cent or less. Batch sizes range from 100kg to 2,000kg (wet basis). Drying times vary from 5 to 50 hours.

A typical equipment set-up is shown in Figure 1. The dryer is heated by hot water flowing through the jacket. The product is agitated so that all the material is heated equally. A dry running vacuum pump sucks the solvent out of the dryer.

The solvent leaves the vacuum pump at atmospheric pressure and condenses in the condenser. The liquid solvent is collected in the receiver tank. A variety of dryer designs are used: agitated dryers, conical dryers with augers, and dryers where the vessel rotates such as double cone dryers.

Process control

In the past, an operator would open the dryer, take a sample, and bring it to the laboratory. A chemist would analyse the sample and provide a result a couple of hours later. Effectively the operator would be told: "It was dry three hours ago at the time the sample was taken". Process analytical technology involves real-time measurement and results. This eliminates the time lag between the material meeting specification and the production staff getting approval to empty the dryer. The shorter cycle time saves energy and allows more batches to be produced. Labour costs are reduced. The elimination of sampling reduces operator exposure to hazardous pharmaceuticals while also reducing the risk of product contamination.

Instrumentation

Moisture content can be directly measured using Near Infra Red light spectra or by Mass Spectroscopy. These provide accurate data at low moisture levels. The capital cost of this type of equipment is high, up to €125,000.

Other parameters can be used to determine moisture content indirectly, these include: jacket temperature, product temperature and the pressure in the dryer. Occasionally, other parameters such as vapour temperature, condenser temperature and agitator torque are used. For processes where drying takes less than 10 hours, fixed drying times are often used.

The US Food and Drugs Administration have promoted the use of this type of technology since 2004 through the process analyticaly technology (PAT) initiative. They believe that if manufacturers achieve a deeper understanding of their processes, this will improve process quality and reliability. The vast increase in the data available makes troubleshooting easier should quality problems occur.

Drying process

Theoretically there are three stages in the drying process. First the dryer is heated up. Next drying occurs at a constant rate while unbound moisture is evaporated. During the third stage, the rate of drying becomes progressively slower. The product temperature

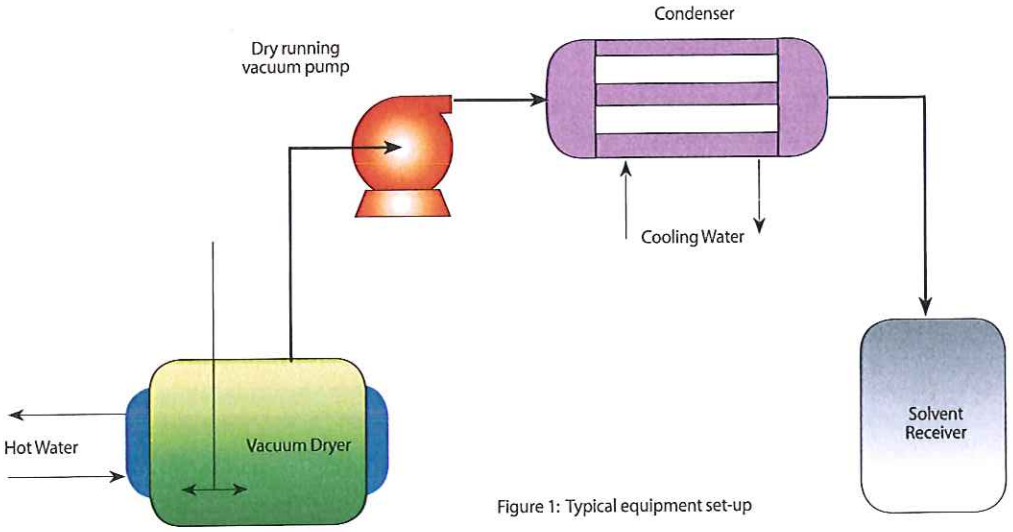

Figure 1: Typical equipment set-up

should stay constant during the constant drying rate period as the heat input from the jacket is balanced by the energy used in evaporating solvent.

The temperature rises gradually as the rate of evaporation decreases during the falling rate period. Some of the industrial processes had temperature profiles similar to theory (those with high initial moisture contents) while others only had a falling rate period.

Typical profiles are shown in Figure 2. The pressure should drop during the falling rate period as less solvent evaporates to form vapour, thus enabling the vacuum pump to achieve a better vacuum. Analysis of the trends for individual parameters is unlikely to be of use. However, by analysing a combination of variables, one can often determine whether or not the product is dry. For example, in Figure 3 product temperature and vapour temperature have similar profiles until the material is nearly dry – then the profiles diverge towards the end of the drying process.

Absolute values of the various parameters often vary from batch to batch of the same material in the same dryer; however, the general trends remain consistent. A parameter that provides useful data for one powder may be of little value for another product. For example, the pressure in the dryer may vary during the drying of one product – whereas for another product the vacuum pump might be large enough such that the rate of evaporation has little effect on the level of vacuum that the vacuum pump can achieve.

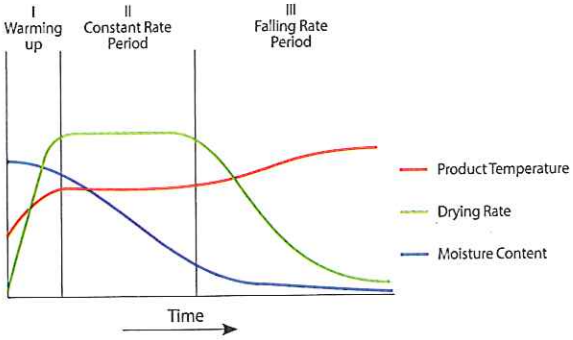

Figure 2: Drying profiles

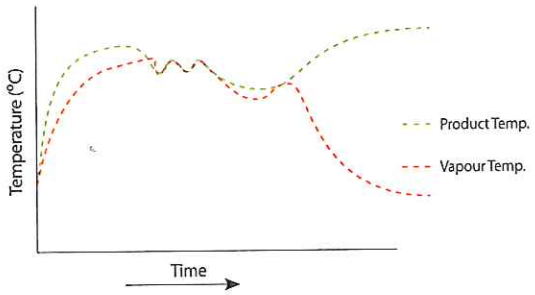

Figure 3: Temperature profiles

Alternatives

Torque measurements have been shown to have a high potential for monitoring drying processes where the product shows a transition from a viscous material to a granular state during drying. The

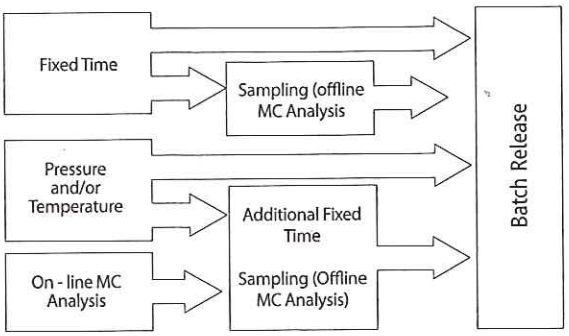

Figure 4.

current drawn by the agitator is easy and cheap to measure, and can be measured away from the production area without concern for personnel exposure or contamination. Industrial data indicates that the use of jacket inlet and outlet temperatures to monitor rotating dryers through heat balances may be of use – this would be convenient as installing probes in rotating equipment can be difficult.
Companies use a variety of different approaches in deciding when to empty dryers as shown in Figure 4.

Gradual adoption of PAT

Typically this type of technology is adopted one step at a time as confidence is built up in the new technology. Initially, the trend data is used to shadow the normal sampling procedure; the data from their instruments is reviewed to see if it is consistent with the laboratory results. Next, the instrumentation is used to decide when samples are to be taken. Lab results are still used to decide when the dryer is to be emptied. If this proves effective, the next step is to unload the dryer based on the data from the instruments. Lab tests are done after the material has been unloaded to confirm that the moisture content is within specification. A new batch can be started while the laboratory analysis is being done. One company has gone further and ships product based on the PAT data alone.

Recommendations

Start by reviewing existing data: look at whatever data is available, product temperature and dryer pressure data are available for most processes. Other data may also be available. This type of analysis may indicate that drying times can be shortened if samples are taken earlier. Next, consider fit additional inexpensive instrumentation such as temperature indicators, pressure probes and torque transducers. Usually a combination of parameters is required as they complement each other. If necessary, consider investing in the more expensive techniques such as NearIR and Mass Spectroscopy. At the start, use the technology to decide the timing of samples. Only when confidence has built up should you empty the dryer based on the PAT data.

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