Title

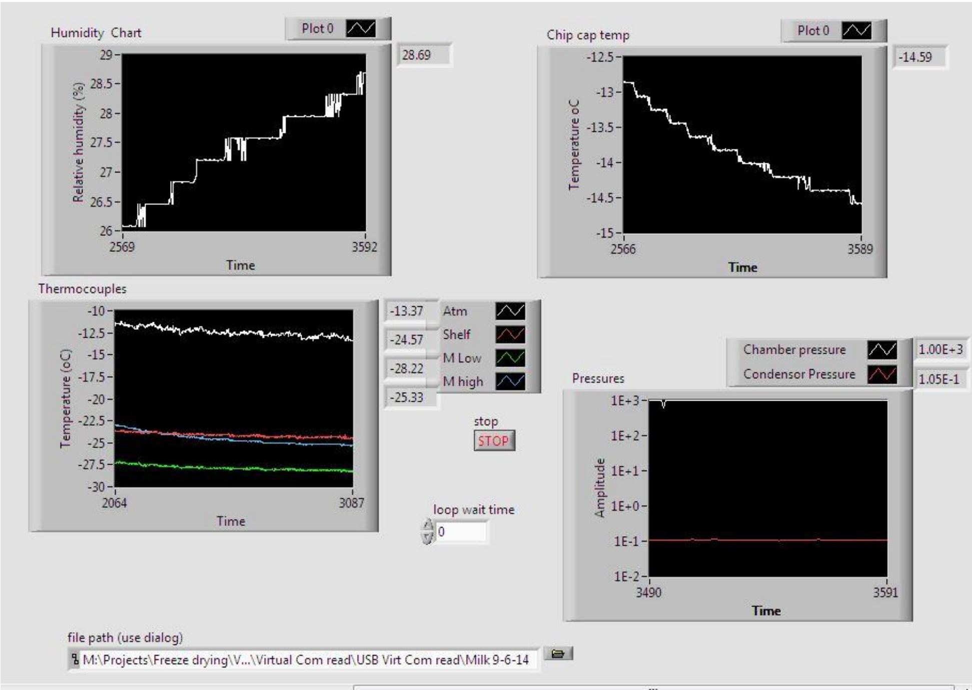
Freeze-Drying cycle monitoring

Problem Statement

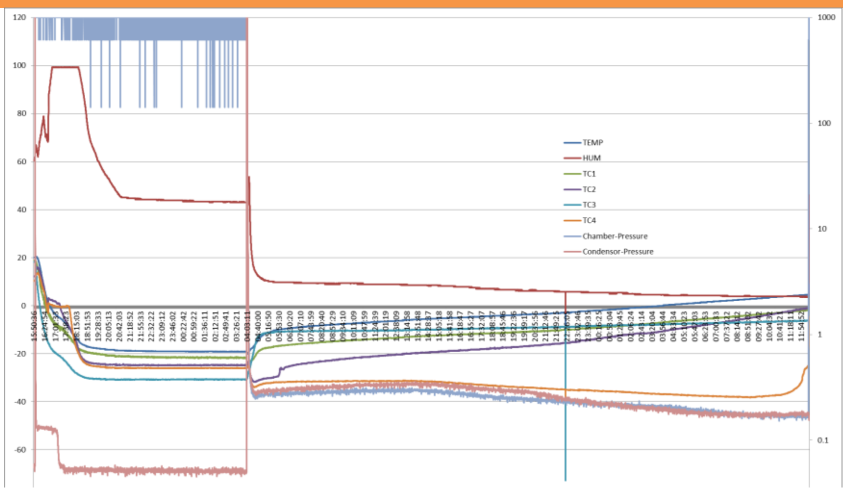
To develop hardware and software to allow the freeze drying Process variables to be monitored in real-time

Approach

An electronics module was developed which uses fine filament thermocouples and humidity sensors to monitor the temperature of product in vials at any desired position while also monitoring the humidity levels in the chamber. The dryer pressure measurements were also accessed and all this data is read by the computer in real-time, displayed on screed and saved to a file.



Result



Real-time monitoring, display and data storage of all the important process parameters during the primary and secondary stages of a Lyophilization process.

Impact

The instrumented system is available to interested parties who wish to monitor the drying of their product for process optimisation or new product development.

Title

Investigate the impact of vacuum drying process parameters on the phase transitions and visual appearance of a commercial formulation.

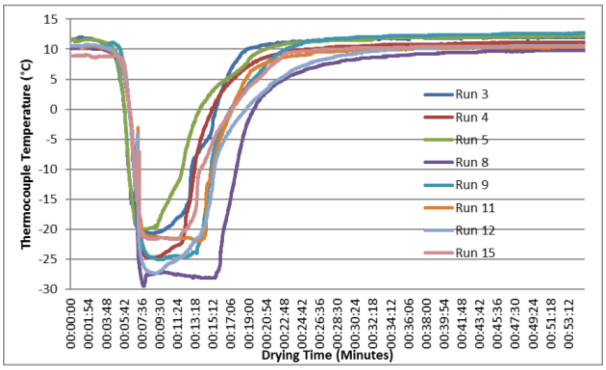
Problem Statement

Working with a partner we provided a better understanding of the relationship between its process' critical parameters and final dried product physical properties including appearance and residual water content.

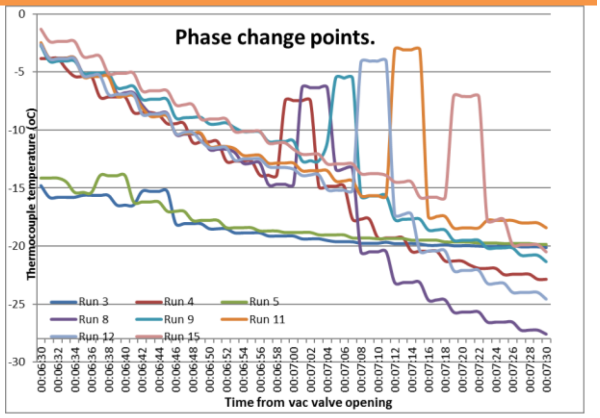
Approach

A two-level experimental design using a placebo formulation was undertaken on a laboratory scale investigating Pre-processing time, Chamber pressure, Shelf temperature, Cycle time and Vacuum rate.

Result



Plot of product temperature for a group of DoE experiments over the primary drying cycle.



Fine filament thermocouples allows observation of the increase in temperature on product freezing

Monitoring the product temperature identified the instant of freezing as shown in the charts below. The analysis successfully identified Chamber pressure and Shelf temperature as the process factors that affect cake quality. A higher quality cake, which remains intact and doesn't flake off, is achieved by having a higher shelf temperature and a higher chamber pressure.

Impact

The partner learned which parameters were important to product quality and which were not. This work showed that the drying process can be monitored and valuable information gained which can help improve product quality as shown in the images below.

Good quality product

Bad quality product

Title

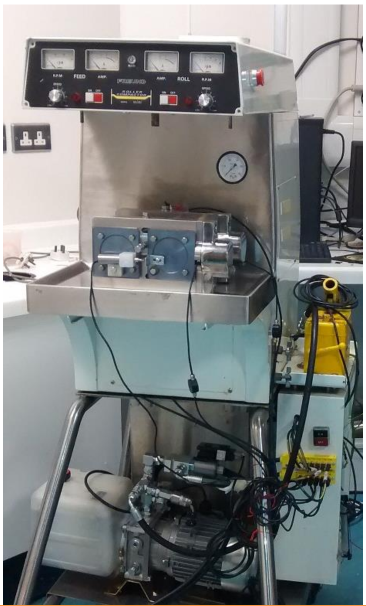
Roller Compactor instrumentation

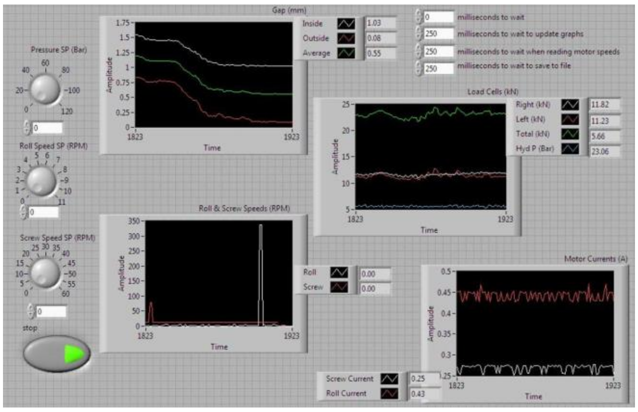
Problem Statement

To properly study the roller compaction technique a machine with real-time monitoring of the process parameters was required but such a product was not commercially available on a laboratory scale.

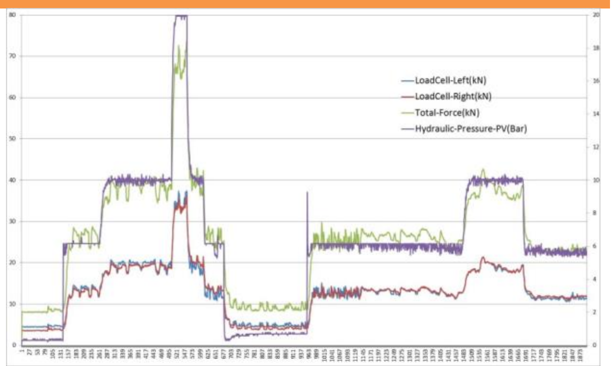
Approach

A used laboratory roller compactor was purchased and instrumented in-house (1st image below) such that the control parameters of Roll speed, Screw speed and Hydraulic pressure can be controlled by a computer; while at the same time reading real-time process parameters (Gap, motor speeds and Compaction force) displaying on the screen (second image below) and saving into a file.





Result



When studying the roller compaction of a powder mixture, the process parameters are available on screen and can be investigated in more detail subsequently. In the two images below, the roll gap and load cell forces are shown for an experimental run

Impact

Pharmaceutical companies who use roller compaction or want to investigate this process can compact their product under non-GMP laboratory conditions for process optimisation or product development.

Title

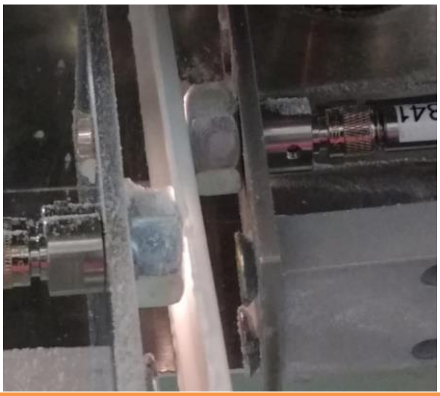
Installation and testing of an in-line Near InfraRed (NIR) Process Analytical Technology (PAT) on a roller compaction process.

Problem Statement

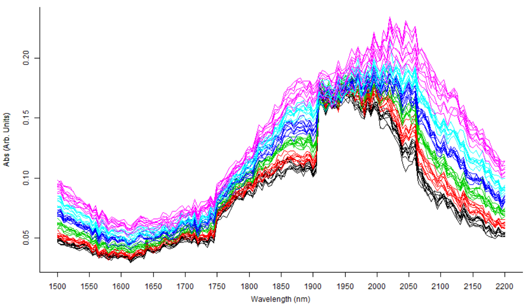
To monitor the compaction density of ribbon in-line using PAT, install a multi-probe NIR system on a roller compactor and use multi-variate data analysis to model the density from the spectra.

Approach

A four probe NIR system was mounted beneath the rolls in a manner that the exiting ribbon could be interrogated in both reflection and transmission mode as shown in the images below.



Result



Training spectra from four probes in reflection mode when compaction pressure is increased from 5 to 30 Bar in 5 Bar steps. Baseline shifts upwards with increasing pressure.

Powder was compacted at increasing pressures on the RC to produce ribbon for a density calibration model. The density and NIR training spectra (above) was measured on each and used to build the PLS calibration model.

This model was used to estimate the density of the ribbon in real-time while compacting at 3 different pressures. These spectra showed the same baseline shift with increasing pressure. Multiple spectral measurements were taken and the model estimated the ribbon density from the spectra. During online testing, the PLS model showed a reasonable correlation between the density predicted and subsequent off line ribbon density measurements.

Impact

This showed that using NIR and a calibrated PLS model, the bulk density of a ribbon can be estimated to on-line while the equipment is running. This will further allow feedback control of ribbon density to ensure product homogeneity.

Title

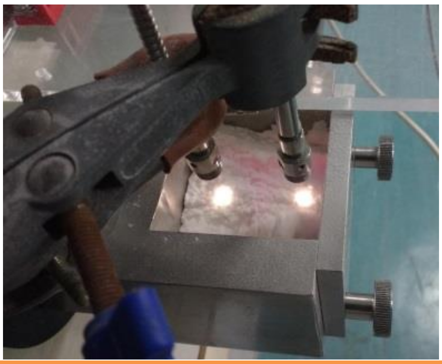
Investigating NIR as a PAT in powder blending for homogeneity endpoint determination

Problem Statement

To build a multi-probe NIR system on powder mixing equipment to monitor the blending of a mixture in-line; use multi-variate data analysis to model the composition from the spectra and determine when mixing is complete.

Approach

Two mixing setups were investigated; a twin paddle mixer and a domestic bowl mixer. Probes interrogated the MCC/Paracetamol surface of the paddle mixer (first image below) while windows were installed in the bowl mixer to interrogate the CMC / Enriched Milk powder inside, second image below



Result

For the paddle mixer, the spectra was constantly taken while adding Paracetamol at two time points. Spectral changes were seen between 1600 & 1800nm, 1st image below. A Principle Component Analysis (PCA) showed PC2 contained information about paracetamol concentration, 2nd image below. Compositional mixing was complete when the PC2 measurement variation reduced to a minimum.Each of the powders NIR spectra were first measured for the mixing bowl work. The second Principle Component (PC2) describes the differences between the spectra as shown in the first image below. A half bowl of CMC was first added, then the EMP on top to fill. Monitoring PC2 while mixing progressed, second image below, shows when mixing is complete as the variability in PC2 reduced.

Impact

This work showed that a Principle Component model of NIR measurements can be used to monitor powder mixing in-line to determine when the mixture becomes compositionally homogeneous. This could further be used to feedback into a system the completes the mixing process so as not to over mix or allow an overall process to move forward to the next step.

Title

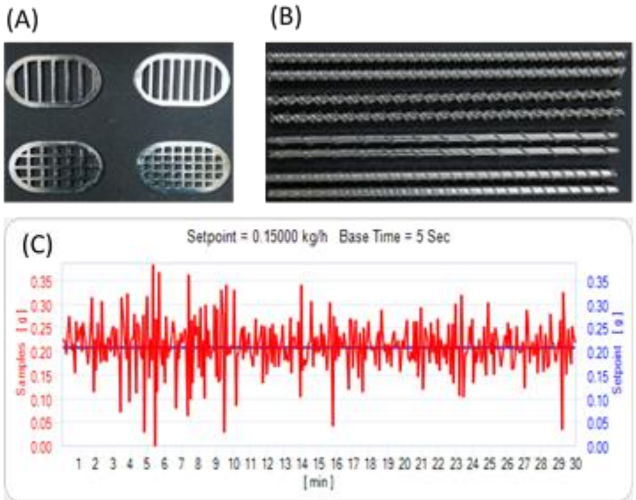
Continuous lubricant feeding: Equipment Set-up Considerations

Problem Statement

The ability to feed powder accurately and continuously is regarded as one of the critical requirements of any pharmaceutical continuous manufacturing process. Inaccuracies in powder feeding passes any inconsistencies to downstream unit operations such as blending or granulation leading to poor uniformity and weight variability in the resulting dosage form. Continuous feeding of lubricants, such as magnesium stearate, is particularly challenging due to low concentration in powder blends (<1% w/w) and cohesive nature.

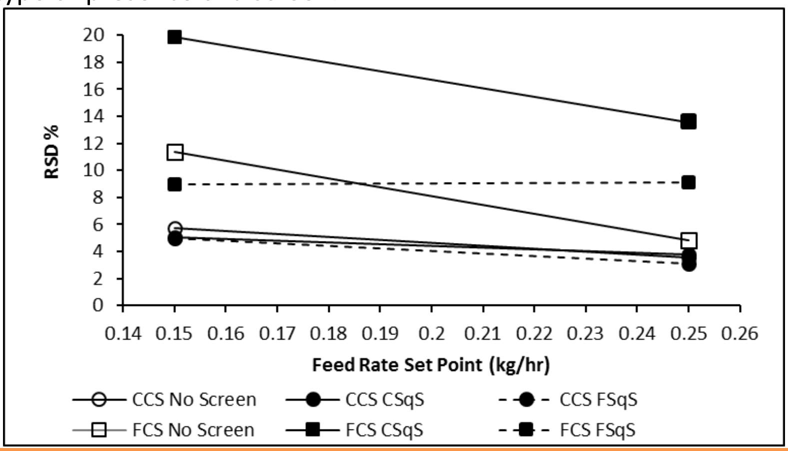
Approach

Study was designed to ascertain the impact of continuous feeding equipment set-up (feed rate set point, screen design, screw design) on magnesium stearate feeding variability (%RSD).



Result

Feed rate variability was found to be influenced by both feed rate and screw design. A coarse concave screw design resulted in a lower level of feed rate variability, lower % RSD (Figure 2). When feeding magnesium stearate using a coarse concave screw design, the type or presence of screen did not influence the % RSD. However, when feeding with a fine concave screw design, % RSD was impacted by the type or presence of a screen.



Impact

This work demonstrates the importance of equipment set-up when optimising the continuous feeding of cohesive pharmaceutical powders such as magnesium stearate.

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