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Process control and end-point determination of a fluid bed granulation by application of near infra-red spectroscopy

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Abstract

In the pharmaceutical industry, fluid bed granulation processes require tight control to ensure reliability. This is particularly the case when the product characteristics add to make the process intrinsically non-robust. Tight process control is generally achieved by careful and accurate control and monitoring of the process parameters affecting the granule wetting/drying equilibrium. However, these parameters are prone to natural unavoidable variation, causing variable and difficult to determine granulation end-points. Obtaining an immediate measure of a critical product characteristic during processing could help by leading to further improvements in process reliability. The application of in-line near infra-red spectroscopy (NIRS) to obtain granule moisture content and particle size change data is described. The technique is capable of monitoring the fluid bed process in 'real time', allowing modification of process conditions if required and end-point identification. This should lead to more optimum product characteristics and greater process reliability. © 1997 Elsevier Science B.V.

Keywords: Near infra-red spectroscopy; Fluid bed granulation; Process control

1. Introduction

In the pharmaceutical industry, wet granulation processes are generally conducted in a high speed mixer granulator or a fluid bed granulator. Occasionally there is a need to include a high level of 'binding' excipients in a formulation that has been optimised for processing stages beyond the granulation step. In this instance the top-spray fluid bed granulation technique is preferred to ensure the granules have an acceptable particle size distribution. Such high levels of 'binding' excipients also necessitate tight process control to avoid the possible danger of overwetting leading to non-retrievable bed collapse. The drug substance

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characteristics, e.g. high dose, hydrophobicity and low median particle size may also be a factor. These are properties not considered conducive to effective granule growth (Schaefer and Wortz, 1977a) adding to make the process less robust.

During the fluid bed granulation process, granule growth rate and size are influenced by the establishment of a critical dynamic equilibrium between granule wetting and evaporation from the granule surface. The process parameters affecting granule wetting are granulation fluid volume and addition rate, atomising air spray pressure and position and design of the spray nozzle. Evaporation from the granule surface is governed by the drying capacity of the inlet air, a factor in turn governed by inlet air temperature, flow rate, humidity and distribution. It is commonly understood that careful and accurate control and monitoring of this complex set of inter-related parameters is crucial to achieve tight process control (Schaefer and Wortz, 1977a,b, 1978a,b; Davies and Gloor, 1971, 1972, 1973). Despite this the wetting/drying equilibrium may be de-stabilised at any time by natural unavoidable variation in critical process parameters, leading to a less than reliable process.

However, enhanced process control and reliability may be obtained if an in-line measure of a property indicative of granulation process progress and end-point could be undertaken. The most important factor affecting granule growth rate and size, and therefore the best property to measure, is moisture content. Granule particle size change may also be a useful alternative or additional indicative measure. Previously Shibata (1987) described the application of a type of infra-red analyser to moisture content metering and control during fluid bed drying (and granulation). Watano et al. have applied this infra-red moisture analyser to feedback control and process automation in agitation fluid bed granulation (Watano et al., 1990, 1991, 1992).

Near infra-red spectroscopy (NIRS) is a technique ideally suited to this type of in-line analysis as it is known to display measurable spectroscopic features that can be assigned to both particle size (Ciurczak et al., 1986; Blanco et al., 1992), and moisture content (Sinsheimer and Poswalk, 1968; Last and Prebble, 1993). In addition NIRS is relatively immune to changes in bulk density caused by granule growth, it operates efficiently as a non-contact system, is non-destructive, and does not compromise product integrity. Via the use of fibre optic probes the technique can be placed at the very 'heart' of a given process (Galante et al., 1990; DeThomas and Hall, 1993; White, 1994; Benson, 1995; Kirsch and Drennen, 1995; Hailey et al., 1996; Sekulic et al., 1996).

Table 1
Placebo formulation

	%w/w	
Heavy magnesium carbonate	57.0	(Merck Ltd)
Polyvinylpyrrolidone (grade 30)	34.5	(GAF Chemicals)
Hydroxypropyl methylcellulose	2.0	(Shin Etsu)
Liquid surfactant	3.5	(Surfachem Ltd)
Liquid plasticiser	3.0	(Honeywell and Stein Ltd)

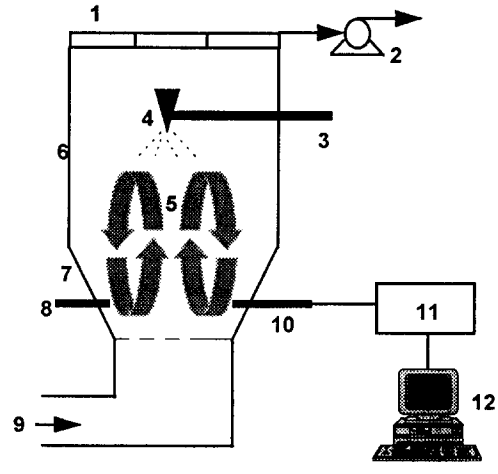

Fig. 1. Schematic diagram of the experimental equipment employed. 1, Filters; 2, Air fan; 3, Spray arm; 4, Spray gun/nozzle; 5, Direction of movement of product bed; 6, Expansion chamber; 7, Product bowl; 8, Sample probe; 9, heated/dehumidified inlet air flow; 10, NIR probe; 11, NIR monochromator; 12, PC.

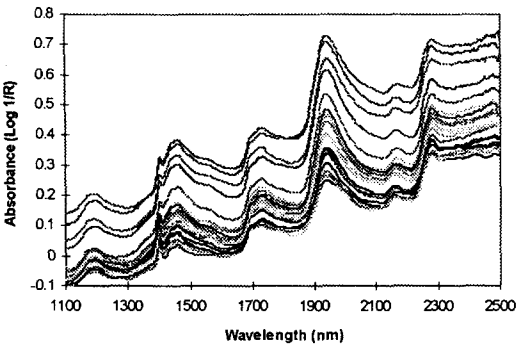

Fig. 2. Zero order spectra (Log 1/R) collected during granulation.

In this paper we report the application of in-line NIR to investigate granule water uptake and particle size change during aqueous top-spray fluid bed granulation.

2. Materials, methods and equipment

2.1. Materials

The formulation employed for this work is shown in Table 1.

2.2. Equipment

Granulation was performed on a 40-kg scale Glatt GPCG 30/50, representing closely the production scale equipment parameter control and process. This employs a single top/centre air atomised spray gun connected to a manually controlled peristaltic pump. A liquid orifice of 1.2 mm diameter was used.

In-line analysis was performed using a NIRSystems 6500 spectrophotometer equipped with a 1″ outside diameter fibre-optic probe (NIRSystems, Silver Springs MD), a 1 m fibre-optic bundle containing 210 fibres from source to sample and 210 fibres from sample to detector. NSAS software (NIRSystems, Silver Springs MD) version 3.30 was used. The probe was positioned a defined distance into the product bed in the downward flow (to ensure the probe is kept clean), at a point of high product density. During the process, spectra were obtained approximately every 2.5 min over the region 1100–2500 nm. A schematic of the experimental set up is given in Fig. 1.

2.3. Granulation process

Granulation of this product is divided into two stages. First, an aqueous solution of the liquid surfactant and plasticiser is sprayed onto the fluidised bed, followed by spraying of the required quantity of water. Only limited granule growth is attainable during spraying of the aqueous solution, probably due to the presence of surfactant reducing intragranular liquid bridge and hence solid bond strength. It is during spraying of water alone that significant granule growth occurs. Granulation is followed by a drying stage, although accurate control of dry granule moisture content is not an issue in this instance. The process parameters and method employed were identical to those defined during development of the active product.

2.4. Reference analysis

Granule samples were removed from the product bed during processing and the following end-of-process tests performed:

2.4.1. Water content

(a) Sartorius infra-red moisture balance. Sample (6–8 g) heated at 70°C for 10 min, weight loss on drying calculated. Sample for testing removed every 10 min during processing.

(b) Karl Fischer coulometric titrator (model CA-06, Mitsubishi, Japan) with vapouriser (model VA-06, Mitsubishi, Japan) attached. A sample of

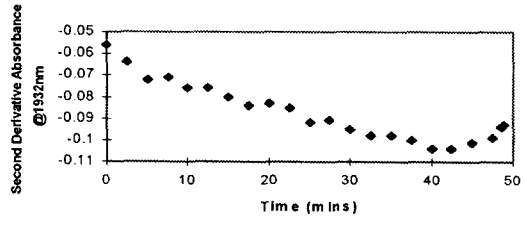

Fig. 3. Second derivative absorbance data (at 1932 nm) collected during granulation.

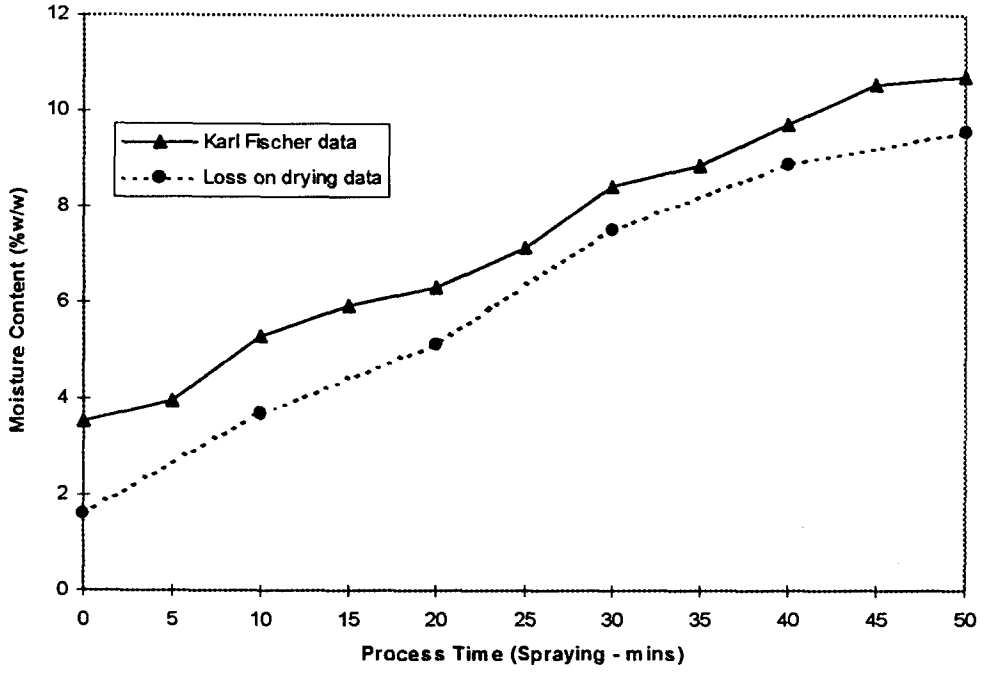

Fig. 4. Granule moisture content increase with process time.

about 35 mg was heated to 120°C in the vapouriser and the moisture emitted carried by a stream of nitrogen into the titration vessel containing the cathode solution. Aquimicron® AX and Aquimicron® CXU (Mitsubishi, Japan) were used as anode and cathode solutions respectively. Sample for testing removed every 5 min during processing.

2.4.2. Size analysis

Samples removed every 5 min during processing were oven-dried and particle size analysed using a Gilsonic Autosiever GA-1 and stack of seven sieves. Median particle size data were obtained from plots of cumulative percent undersize versus sieve aperture size

The data generated by the end-of-process tests were then used to correlate with NIR response.

3. Results and discussion

The typical NIR zero order spectra obtained during the fluid bed wet granulation are shown in

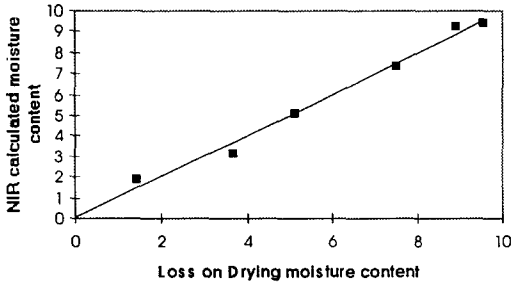

Fig. 5. Calibration of NIR second derivative absorbance data against Loss on Drying data.

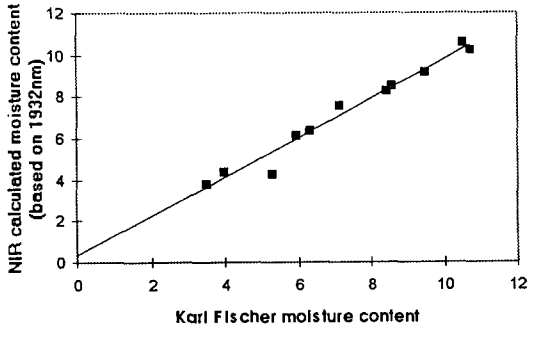

Fig. 6. Correlation of NIR second derivative absorbance data against Karl Fischer data.

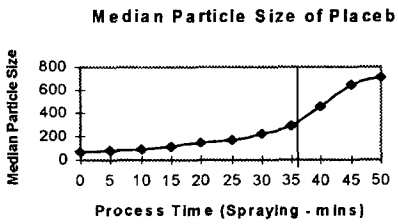

Fig. 7. Granule growth profile determined by sieve analysis.

Fig. 2, illustrating an increase in absorbance (y-axis) across the entire spectrum as granulation proceeds, indicative of growth in granule size.

NIR spectroscopic water determination manifests itself as the first O–H combination band with a peak at approximately 1940 nm. Fig. 3 shows second derivative absorbance change at this wavelength with process time. The gradual decrease in absorbance value may be correlated to actual end-of-process moisture content data.

The granulation end-point occurred after approximately 40 min. The upward absorbance trend observed after 45 min is considered to be a result of a significant change in the system dynamics at or around this time. Bed collapse caused by over wetting had occurred and the product was no longer fluid, but static.

Fig. 4 shows how granule moisture content increases with time during granulation. Loss on drying analysis quantifies the free water present whilst Karl Fischer analysis provides a more accurate quantification of both free and bound water.

Trend analysis has clearly shown that NIR spectral data can detect changes in the granulation state. However, the objective of this application was to determine whether a quantitative product characteristic could be used to determine the exact progress and end-point of the granulation. In order to achieve this, it is necessary to calibrate NIR spectral response against a reference technique. In this example the second derivative absorbance changes at 1932 nm are calibrated against loss on drying and Karl Fischer moisture content data. A satisfactory calibration would therefore demonstrate a linear relationship between the NIR spectral response and the reference technique. Figs. 5 and 6 show linear relationships between NIR data and loss on drying, and Karl Fischer. Correlation coefficients of 0.996 based on loss on drying data and 0.99 based on Karl Fischer data were calculated. A standard error of calibration (SEC) in the order of 0.5% was calculated for both models. At granulation end-point an acceptable granule will have a moisture content of between 9.0% w/w and 10.5% w/w (Karl Fischer). An SEC of 0.5% is therefore considered acceptable to achieve the level of control required for this in-process moisture specification.

Only limited granule growth is obtained during spraying of the aqueous solution. It is not until the addition of water alone (from 35 min onwards) that rapid granule growth occurs. This is illustrated in Fig. 7, a plot of median particle size determined by sieve analysis vs process time.

The change in zero order absorbance across the entire spectrum, as highlighted in Fig. 2, is indicative of granule size increase. By selecting a single wavelength (2282 nm) and plotting the absorbance vs. process time (Fig. 8) a comparable profile to that generated by sieve analysis is obtained, i.e. gradual increase during solution spraying, followed by a more rapid increase during water addition.

However, owing to the complexity of modelling particle size, it has not been possible so far to generate suitable calibration models for quantitative determinations. It is anticipated this will be achieved with further development of the technique. The use of the particle size data provides an additional qualitative parameter which can be used to support the primary moisture content information. At granulation end-point an acceptable granule will have a median particle size of $> 350\ \mu m$. This is in the order of a 5-fold increase from the particle size of the initial starting material and can easily be identified by NIRS.

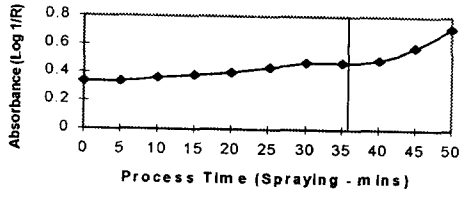

Fig. 8. NIR zero order absorbance profile (at 2282 nm).

4. Conclusion

Continual in-line NIR monitoring of water content and particle size data has been shown to provide a suitable means of process control and end-point determination for a fluid bed granulation process. This can lead to greater process reliability.

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