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Effect of fluidisation activity on end-point detection of a fluid bed drying process

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Abstract

The influence of inlet air humidity variations on fluid bed drying end-point detection was the primary focus here. Various drying end-point criteria based on temperature and humidity measurements were compared. Seasonally changing inlet air humidity affects the moisture content of the finished granules, as long as the drying process remains unchanged. However, a specific moisture content of the finished granules is commonly desired after fluid bed drying. When experimental batches of varying inlet air humidity were compared at the beginning of the drying phase, the temperature of the granules increased linearly as the humidity of the inlet air increased. This effect causes variation in moisture contents of the final granules of different batches when the fixed temperature of the mass is used as an end-point criterion. With varying inlet air humidity, the often used ΔT temperature difference method resulted in more precise estimation of the drying end-point than the constant temperature criterion. In this study new insights were found into the correlation between moisture content and temperature of the fluidising mass. Fluidisation activity greatly affected detection of drying end-point. Use of the ΔT criterion requires proper fluidisation throughout the process.

Keywords: Fluid bed granulation; Drying; Temperature; Humidity; End-point; Temperature difference method ΔT

1. Introduction

Fluid bed granulation is a key pharmaceutical process that makes material more suitable for subsequent process steps, e.g. for tablet compression. During the wet granulation phase, a specific amount of granulation liquid is sprayed on the fluidising mass and evaporation of excess liquid occurs during the drying phase. The temperature measurements of the inlet and outlet air and the granulation mass are important means for describing heat transfer during the fluid bed process and for detecting the drying end-point. Very different granulation conditions may have to be used if the material is hydrophobic or hydrophilic and subsequent drying phase is affected by various circumstances. The humidity level of the process air is often ignored although it contributes significantly to total water balance and granule formation. It is evident that seasonal changes in the humidity level are remarkable, considering the performance of the process as a whole (Lipsanen et al., 2007). The 'weather effect' is a confounding factor that often occurs in the widely used method of detecting drying end-point by specific temperature of the outlet air or the granules (Jones, 1985). A specified residual moisture content for tablet compression is expected of the finished granules. Capping may occur at moisture contents that are too low and picking of tablets at moisture contents that are too high (Sucker, 1982). Basically, under optimal conditions the moisture content of granules is in equilibrium with the surrounding air so that sorption changes are small during the storage (Schæfer and Wørts, 1978). However, water activities in the region of 0.35–0.5 may be needed to gain the required hardness and crushing strength of the tablets (Hyland and Naunapper, 1986). Stability problems may result if the moisture content of the granules is too high.

Various end-point criteria for drying have been used. A fixed time criterion is not adequate for controlling the end-point of drying because all other process variables are ignored (Alden

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et al., 1988). The specific temperature value of the outlet air or mass is a widely used method of detecting the end-point (Davies and Gloor, 1971). This criterion may be repeatable only if the humidity level of the inlet air does not vary, because the temperature of the drying mass and that of the outlet air are influenced by the humidity content of the inlet air (Schæfer and Wørts, 1978; Lipsanen et al., 2007). The humidity level of the outlet air was used in some granulation studies as an indication to finalise drying (Niskanen et al., 1990; Merkku et al., 1992). Continuous measurement of the humidity of the air surrounding the substance was also examined (Hyland and Naunapper, 1986).

The temperature difference (ΔT) end-point indication technique was used in many investigations (Harbert, 1972, 1973, 1974; Ehrhardt, 1977; Schæfer and Wørts, 1978; Gore et al., 1985; Leuenberger and Imadidis, 1986; Alden et al., 1988). The ΔT technique exploits the relationship of temperature rise of a material from the wet-bulb temperature and simultaneous depletion of the moisture content of a material. When air passes through a moist material, its temperature drops toward the evaporative (wet-bulb) temperature as the vapour pressure and dew point of the air rise. Temperature phases of the drying material are best described with a three-phase system (Newman, 1931). The critical moisture content is the point at which the material is no longer saturated with liquid. Reduction of the water layer on the particle surfaces and slower diffusion of water from the internal capillaries results in increasing heat transfer within the solid mass. In theory, the ΔT technique is capable of determining any moisture content less than that required to saturate the material (Harbert, 1974). The final moisture content in dried powders could be kept in the range of $\pm 0.1\%$ if the inlet air temperature was maintained between 45 and 55 °C and the relative humidity (RH) varied between 30 and 60% (Ehrhardt, 1977).

In the present study the effects of various air humidity conditions on temperature in different parts of a fluid bed granulator system were evaluated, considering end-point detection. Various end-point indication techniques were compared and the influence of fluidisation activity (behaviour) on end-point detection was determined. This effect has not been considered previously.

2. Materials and methods

2.1. Materials

Each batch consisting of 3.0 kg ibuprofen (USP/EP, BASF Corporation, Bishop, TX, USA) and 1.0 kg α-lactose monohydrate (200 M, DMV International GmbH, Veghel, The Netherlands) was granulated with 2 kg of a 15% aqueous solution of polyvinylpyrrolidone (Kollidon K-30; BASF Corporation, Ludwigshafen, Germany). Scanning electron microscope (SEM) images of the materials are shown in Fig. 1.

2.2. Humidifying system

The inlet air humidity of the process air was modified with a humidifying system (Defensor Mk4; Brautek Oy, Espoo, Finland). The system connected to the fluid bed granulator enabled high, fluctuating humidity of the process air for granulation batches 10–14 (Table 1). The humidifying system is described in Lipsanen et al. (2007). Otherwise the humidity levels varied from low to intermediate.

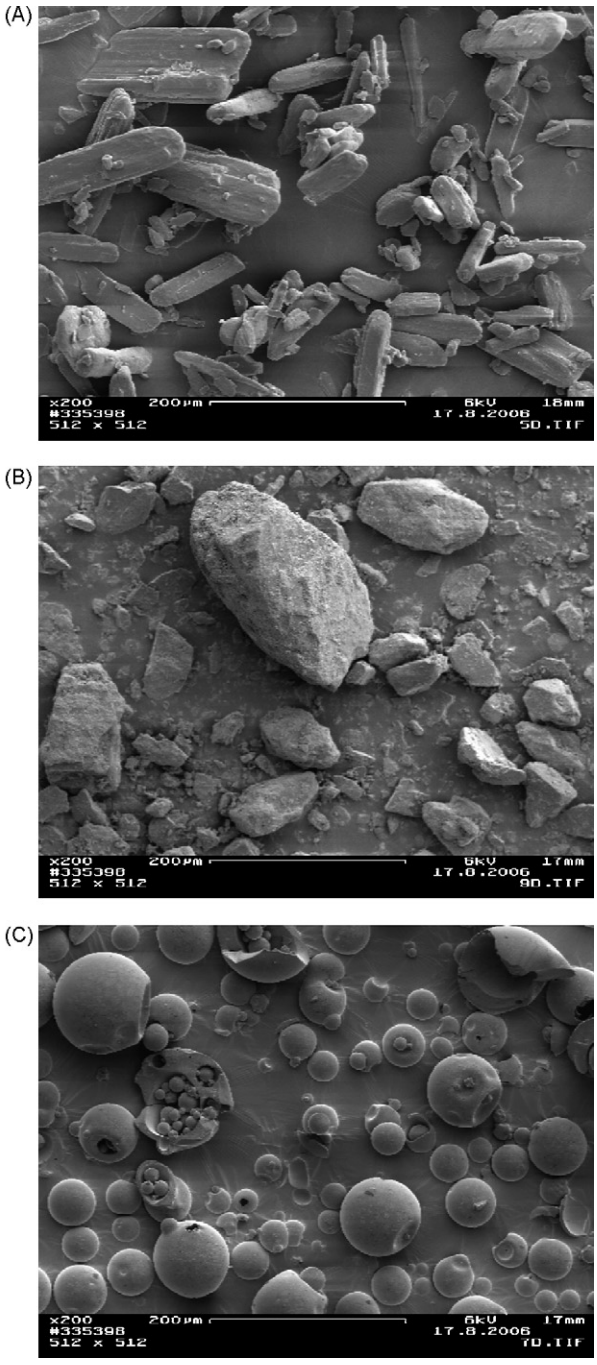

Fig. 1. The granulated starting materials: (A) Ibuprofen. (B) α-Lactose monohydrate. (C) Polyvinylpyrrolidone Kollidon K-30.

2.3. Granulation process and measurements

The granulation conditions are described in Table 1. Classification into the three categories was based on the humidity levels of the inlet air: below 6 g/m^3 (low humidity), 7–12 g/m^3 (intermediate humidity) and above 13 g/m^3 (high humidity). The granules were produced in an automated bench-scale fluid

Table 1
The critical variables in this study were means of the inlet air humidity measurements during granulation of every batch

Batch	Absolute humidity of inlet air (g/m^3 dry air)	Relative humidity of inlet air (RH%)	Moisture of finished granules (w/w-%)
Low humidity:			
1	4.5	24.2	0.59±0.01
2	4.5	25.7	0.48±0.01
3	4.6	23.8	0.46±0.07
4	4.6	24.9	0.50±0.08
5	5.9	31.9	0.55±0.11
Intermediate humidity:			
6	7.4	35.8	0.97±0.18
7	9.3	43.8	0.67±0.07
8	10.0	47.5	0.84±0.02
9	11.1	58.1	0.79±0.11
High humidity:			
10	15.5	68.7	1.01±0.04
11	18.0	78.4	0.79±0.01
12	18.4	84.6	1.22±0.03
13	19.8	80.7	0.79±0.04
14	23.4	89.7	0.85±0.06

The batches were classified accordingly as low (dry), intermediate and high (humid).

bed granulator (Glatt WSG 5; Glatt GmbH, Binzen, Germany) and the granulations were performed in randomised order. The parameters measured are found in Fig. 2 and the instrumentation is described in further detail in Rantanen et al. (2000). The inlet air temperature (T3 in Fig. 2), atomization pressure of the granulating liquid and nozzle height were constant. A low T3 of 40 °C was used throughout the process because the melting point of the model compound ibuprofen is low (75 °C). The mixing phase lasted about 6 min until T3 had risen to 40 °C. The atomization pressure was 0.1 MPa. The nozzle height was 45 cm from the distributor plate. The granulating liquid flow rate was 29 g/min during the first 10 min, followed by 105 g/min. The inlet air volume was adjusted for smooth fluidisation and the flow rate of the inlet air varied between 0.040 and 0.100 m^3/s, depending on the granulation phase. The drying end-point was determined by T5 of 36 °C (38 °C for deviating and poorly fluidising batch 9). For further evaluation the ΔT increase was calculated for all batches as a temperature increase from T5 at the beginning

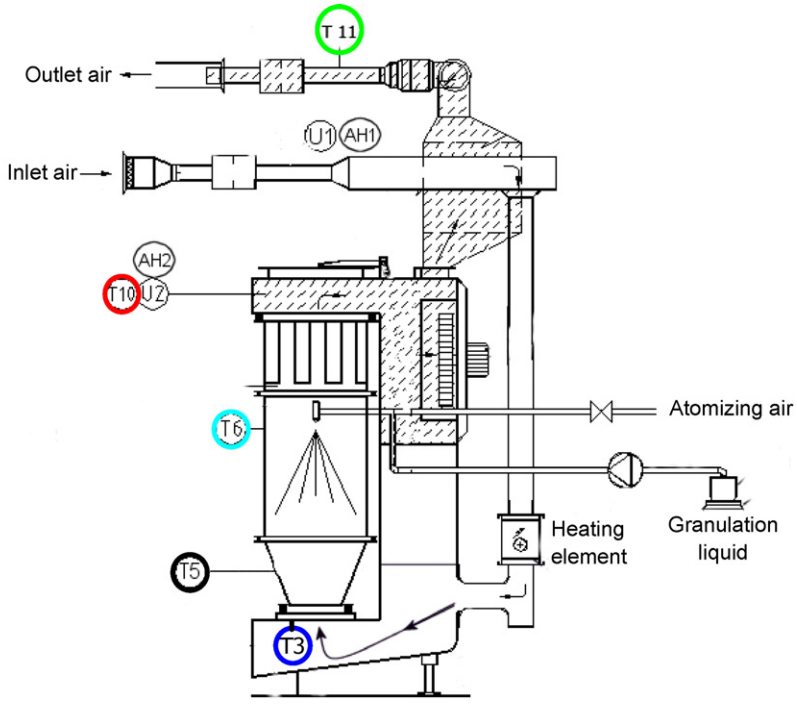

Fig. 2. Important measurements of this study are highlighted in the instrumented Glatt WSG 5 fluid bed granulator. T3 = temperature of the inlet air below the distributor plate; T5 = temperature of the mass measured at the bottom of the granulator bowl; T6 = temperature of the process air in the middle of the granulator bowl; T10 = temperature on the top side of the filters; T11 = temperature in the outlet air duct; U1 = relative humidity of the inlet air; U2 = relative humidity of the outlet air; AH1 = absolute humidity of the inlet air; AH2 = absolute humidity of the outlet air.

of the drying phase (wet-bulb temperature). The temperature of the process air was measured and analysed from five different locations (Fig. 2). The relative humidity of the inlet air (U1) was measured from the inlet air duct before the heating element and the relative humidity of the outlet air (U2) from the top side of the filters. The absolute humidity of the inlet (AH1) and outlet air (AH2) was calculated, using the RH and temperature information.

2.4. Moisture determinations

During the drying phase six samples were taken at different time points using a sample probe. Immediately after the granulation process they were analysed for loss-on-drying (LOD) in an infrared (IR) dryer (Sartorius Thermocontrol MA 100; Göttingen, Germany). The samples (about 3 g) were heated at 70 °C until the rate of weight loss dropped to 0.1% in 50 s. At least two measurements were made of each sample. To obtain more precise estimation on the moisture content of the granules between the sample points, a functional fitting was made. The following function was fitted to the data values of LOD:

$$\mathrm{WG\,(Time)} = \mathrm{WG_0} + \frac{a}{1 + \mathrm{e}^{-((\mathrm{Time}-\mathrm{Time_0})/b)}} \quad (1)$$

where WG is the water content of the granules; $\mathrm{WG_0}$ is the smallest water content of the granules; Time is the time from the onset of drying ($\mathrm{Time_0}$); a and b are the constants.

To confirm the validity of the IR dryer results, Karl Fischer titration was performed on a Mettler Karl Fischer titrator (model DL35; Mettler Toledo AG, Switzerland), using samples of 100 mg. The result was a mean of three tests. Hydranal solvent, formamide and hydranal titrant 5, purchased from Riedel-deHaën Laborchemikalien GmbH, Germany, were used as reagents.

3. Results

3.1. Temperature measurements

The temperature of the process air was measured at five different locations (Fig. 2). The measurement became less effective and therefore less usable for end-point detection the further it was performed from the distributor plate. The most effective locations for detecting granulation temperature were the bottom of the bowl (T5), where particles typically moved more slowly and there was efficient heat exchange with the inlet air, and the upper part of the bowl (T6) where granules moved more freely (Fig. 3). The top side of the filters (T10) represented a less dynamic point of temperature control and the outlet air duct (T11) appeared to be unsuitable due to effective damping. Even so, the outlet air duct (T11) is the usual location for detecting the end-point of drying, although the temperature of the surroundings affects the measurement significantly. A clear difference in temperature measurements between T5 and T6 was seen. The difference remained evident, independent of conditions in the process phase. The measurement at the bottom of

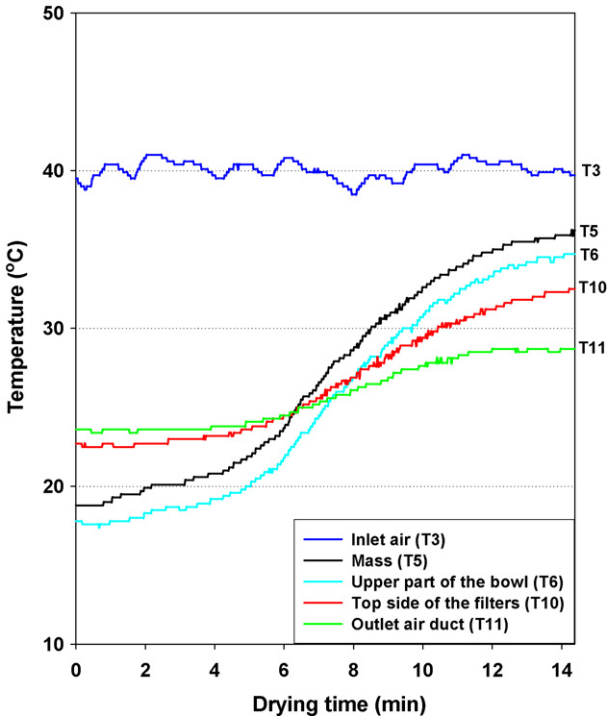

Fig. 3. Temperature measurements at different locations of batch 1 during the drying phase.

the chamber (T5) reflected more the temperature of inlet air (T3) than did the upper locations (T6, T10, and T11). T5 was therefore more susceptible to temperature fluctuations in the inlet air than T6. However, temperature measurement in the middle of the chamber allowed a greater cooling effect of water evaporation. Despite the heat absorbed as the process air moved upwards, the T6 measurement was virtually as dynamic as T5. A temperature sensor in the middle of a chamber above the granulation mass is a preferable choice for drying end-point detection if sticking of the mass on the surface of a sensor is a problem.

3.2. Humidity and moisture measurements

The inlet and outlet air humidity measurements of the same batch are presented in Fig. 4. The difference between AH2 and AH1 absolute humidity measurements offered another way to estimate the drying end-point, especially when inlet air humidity was low. When the AH1 increased, interpretation was difficult because the difference between AH2 and AH1 was not constant. In this setup the humidity measurements did not give reliable estimates of the moisture contents of the granules , especially when AH1 was high. As seen in Fig. 4, the differences between U2 and U1 were not applicable because these values were temperature-dependent. In Fig. 5 the absolute water content of the mass of the same batch during the drying phase is described. The fitted curve (Eq. (1)) appeared to model the water decrease well. Later, these fitted moisture curves of different batches were correlated with the temperature measurements of the granules (Figs. 8 and 9).

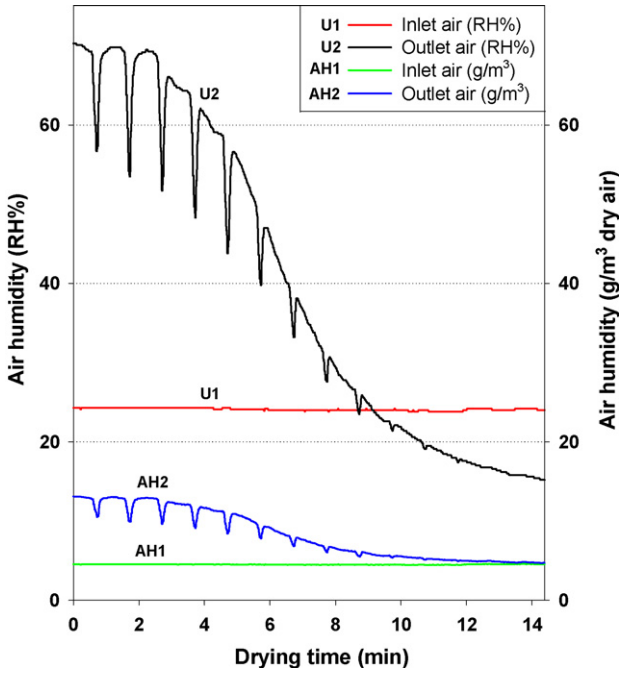

Fig. 4. Absolute and relative humidity of the inlet and outlet air of batch 1 during the drying phase. The filter shakings caused systematic periodic decrease in values.

3.3. Effect of inlet air humidity on temperature of the granulation mass and end-point moisture content

The effect of AH1 on T5 was clearly demonstrated when different batches were compared at the beginning of the drying phase (Fig. 6). When the inlet air was dry, T5 was significantly lower than when the inlet air had high humidity, because the heat capacity of humid air is greater than that of dry air. When the humidity of the inlet air increased, more heat was transferred to the wet mass during fluidisation. Fig. 6 also demonstrates

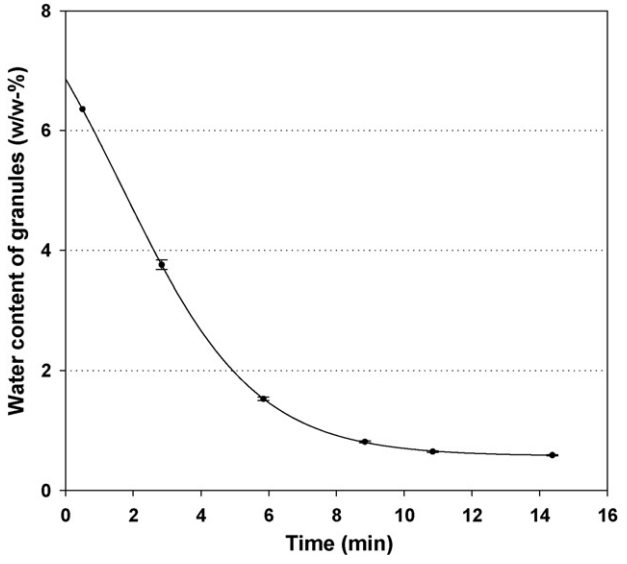

Fig. 5. Absolute moisture content (%, w/w) of the granules of batch 1 during the drying phase. A functional fitting is made using Eq. (1).

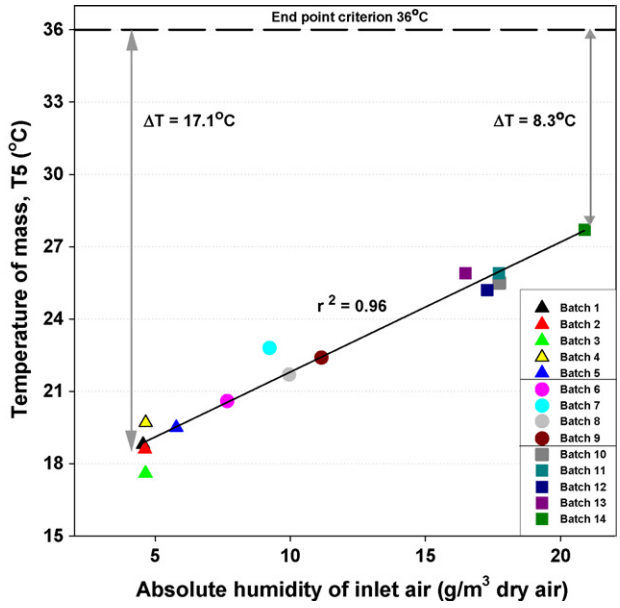

Fig. 6. Correlation of inlet air humidity (AH1) and granulation mass temperature (T5) at the point of beginning of the drying phase. A constant end-point criterion of 36 °C is illustrated and as is the level of temperature rise (ΔT).

the case in which the drying phase is finished when T5 reaches 36 °C, which was the criterion applied to finish the process. T5 of 36 °C was a favourable criterion when the inlet air was dry, however, when the inlet air was humid, the final granules were clearly too moist at 36 °C. Fig. 6 shows that T5 increased by 17.1 °C during the drying phase when the humidity was low. However, when the inlet air was humid T5 increased by only 8.3 °C. It is clear from these results that a constant temperature criterion for the end-point of drying is not applicable when inlet air humidity changes on a large scale. However, a constant temperature increase ΔT from the wet-bulb temperature level should be used (Harbert, 1972). ΔT is the difference between the end-point temperature of the granules and the temperature of the granules at the onset of the drying phase. Fig. 7 shows that there

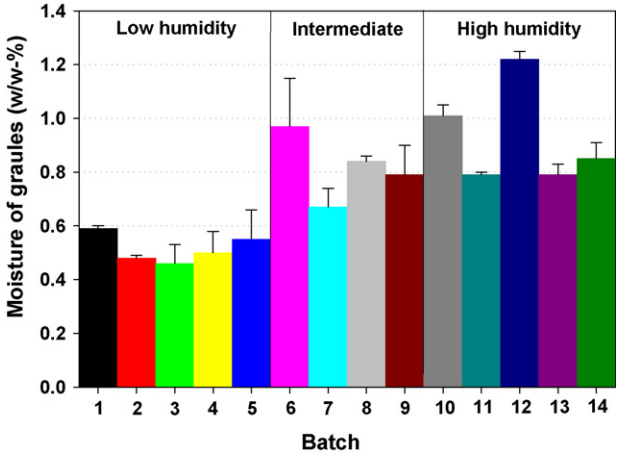

Fig. 7. End-point moisture contents of the final granules and classification as low, intermediate and high humidified batches are illustrated. Batch 9 was deviated with respect to fluidisation activity and end-point criterion (38 °C vs. 36 °C).

was a clear trend for the final moisture contents to increase when the humidity content of the air increased. The residual moisture contents of the finished granules varied between 0.46% (w/w) and 1.22% (w/w). The variation would have been smaller if the ΔT technique was used as the end-point criterion.

3.4. Correlation between temperature measurements and moisture contents

The level of moisture in the mass cannot be directly predicted from the temperature measurements, as described in the previous chapter. There is a clear interaction between the temperature and the moisture content of the granules during the drying phase. The variables influencing these parameters must be understood before clear correlations can be made. Fig. 8 shows the absolute moisture level of the granules (%, w/w) as a function of T5. If the temperature and moisture of the mass were directly correlated, the curves should be superimposed, instead, the different humidity levels were separated clearly. Batch 9 deviated from the humidity pattern because the maximum inlet airflow was not high enough to maintain proper fluidisation of the wet mass. The mass experienced relatively higher temperature because it was partially collapsed and evaporative cooling was insufficient. When ΔT calculated with T5 was correlated with the absolute moisture level of the granules, the humidity level differences mostly disappeared (Fig. 9). No further significant differences between the curves was observed, suggesting that ΔT is capable

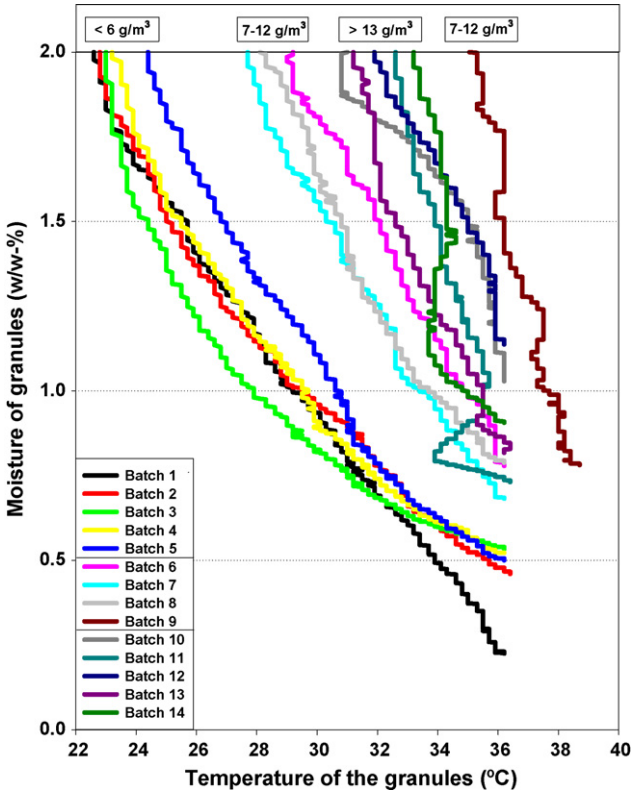

Fig. 8. Temperature of the granules (T5) correlated with the absolute moisture content of the granules modelled with Eq. (1). The inlet air humidity levels of the granulation batches are above the figure.

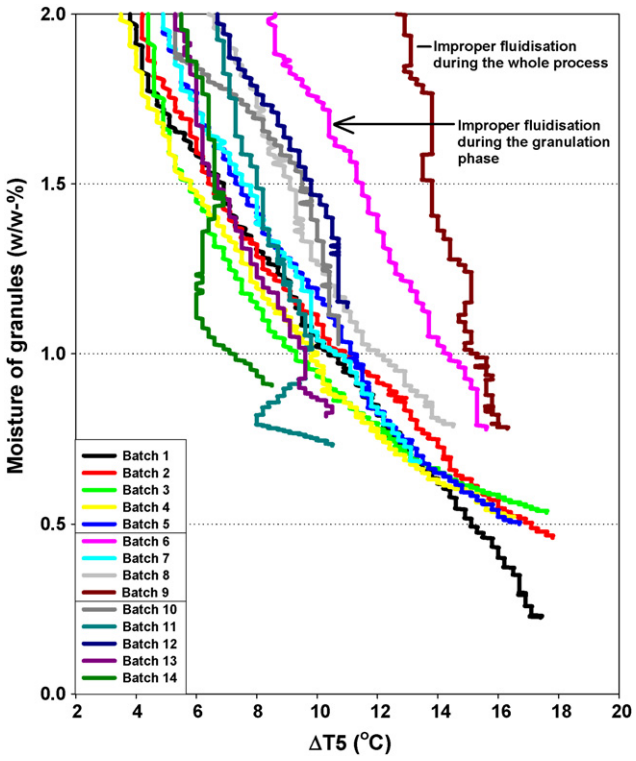

Fig. 9. ΔT (calculated with T5) correlated with the absolute moisture content of the granules (modelled with Eq. (1)).

of predicting the moisture level of the mass better than T5. Still, two batches (6 and 9) deviated from the general curve; these two batches were moister than other batches with the same ΔT value. Batch 9 deviated due to divergent fluidisation activity, while batch 6 also showed a divergent profile. Short-term improper fluidisation during the wet granulation phase was identified as a likely reason for this deviation. The effect of humidity fluctuations caused by the humidifying system is also seen in the end curve of batch 10. It is clear from these results that the ΔT criterion is valid only if there are no fluidisation differences between batches. A method for assessing fluidisation activity quantitatively with the new fluidisation parameter was described recently (Lipsanen et al., 2007).

4. Discussion

Dynamic temperature measurements near the granulation mass depict the drying end-point better than humidity measurements especially when inlet air humidity changes over a wide range. The effect of air humidity on temperature is crucial to take into account when temperature measurements are used to indicate the end-point of drying. The ΔT method for detecting the drying end-point eliminated the effects of the remarkably changing humidity levels of the process air. The effect of fluidisation on the ΔT technique has not been highlighted in previous studies (Harbert, 1972, 1973, 1974; Ehrhardt, 1977; Schæfer and Wørts, 1978; Gore et al., 1985; Leuenberger and Imadidis, 1986; Alden et al., 1988). De-fluidisation, even for short periods, can be considered a major source of deviation of the technique, because

the granulation mass has a relatively higher temperature when fluidisation is low than when it is at proper levels. Although the ΔT technique efficiently eliminates the effect of inlet air humidity variations, de-fluidisation caused by elevated humidity levels nevertheless affects the criterion and thus the end-point moisture contents. The inlet air temperature variations are also a potential source of error. It is also vital that temperature detection is made as dynamically as possible, in this case at locations T5 and T6 near the fluidising mass.

Physical measurements from the granulator, the processed samples and line fitting analyses identified significant correlations between the control parameters and the outcome. Multivariate analysis methods, such as principal components analysis (PCA), are widely used to identify correlations between variables and responses. However, these types of analyses typically do not show the dynamic role of process measurements in an unambiguous way. The approach adopted in this work is possible to implement in a straightforward manner. The direct observation of dynamic temperature changes is vital for using ΔT method in practice. Adopted correlation methods enabled us to establish the influence of fluidisation activity on end-point detection.

5. Conclusions

Various temperature measurement points for end-point detection were compared in this study. Temperature measurements near the granulation mass gave the most dynamic and therefore the most precise information on temperature changes occurring during the fluid bed granulation process. The end-point determination of drying using fixed temperature values of the granules was found to be inadequate if the humidity of the inlet air varies considerably between granulation batches. This was demonstrated when the humidity of the inlet air was correlated with temperature of the mass. The ΔT method for detecting the drying end-point was a preferable choice if the humidity of the inlet air could not be maintained at constant levels. New insights were obtained into the relationship of temperature and moisture of the drying mass. The effect of fluidisation activity on the end-point detection of drying was found here. The feasibility of the ΔT method and thus the similarities of end-point moisture contents were dependent on the fluidisation variation between manufacturing batches. Different modes of fluidisation thereby influence the ΔT criterion. The ΔT criterion requires proper fluidisation throughout the process.

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