Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 345 (2007) 101–107
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Novel description of a design space for fluidised bed granulation

Tanja Lipsanen[a,b,*], Osmo Antikainen[b], Heikki Räikkönen[b], Sari Airaksinen[b], Jouko Yliruusi[b]

[a] *Orion Corporation Orion Pharma, Orionintie 1, P.O. Box 65, FIN-02101 Espoo, Finland*
[b] *Division of Pharmaceutical Technology, Faculty of Pharmacy, P.O. Box 56, FIN-00014 University of Helsinki, Finland*

Received 25 March 2007; accepted 23 May 2007
Available online 29 May 2007

Abstract

The physical measurements of a fluid bed granulator can be exploited in construction of an operating window, a design space, for process performance. The purpose of this study was to determine the influence of inlet air humidity changes on temperature in different parts of a granulator system, on fluidisation behaviour and on the particle size of the final granules. A humidifying setup was constructed on a bench-scale fluid bed granulator that enabled elevated humidity levels and sharp humidity changes of the inlet air. Ibuprofen granules were produced at the various inlet air humidity levels classified as low, intermediate and high. A novel fluidisation parameter was developed. The more improperly the particles were fluidising the smaller was the relationship of airflow rate and fan speed. Four different failure modes were identified and classified, based on the fluidisation parameter: over-fluidisation, risk of improper fluidisation, improper fluidisation and collapsed bed. It was possible to construct process trajectories for smooth fluidisation, which the optimal granulation process should follow.

Keywords: Fluid bed granulation; Fluidisation; Humidity; Design space; Process trajectory; Process analytical technologies (PAT)

1. Introduction

Fluid bed granulation is a typical process step in manufacturing pharmaceutical solid dosage forms. The mixing, spraying and drying phases are the consequent process stages needed to convert powders to free-flowing granules. Numerous variables are known to affect the fluid bed process and thus the quality of the final granules. Airflow rate, temperature and humidity of the inlet air and the addition rate and droplet size of the granulating liquid are some of the most critical input variables. Temperature and humidity measurements of the process air are the most important parameters for monitoring heat and mass transfer. However, the inlet air humidity cannot usually be specified accurately because the seasonal variations in the process air humidity are difficult to control entirely. Changes in the humidity level of the process air are known to affect the total performance of a process and the final product, e.g. the particle size (Wurster, 1960). Another not as easily definable parameter is the fluidisation level of a granulation mass, which is dependent on numerous characteristics, e.g. the flow rate of the process air, inlet air humidity, moisture level of the granules, physical properties of the material and the process phase (Kunii and Levenspiel, 1991). Lately, the fluidisation behaviour of solids was monitored by pressure differences over the bed as a function of inlet air velocity (Räsänen et al., 2004).

Although water in vapour and liquid form is present at virtually all the processing steps, few studies have addressed the effect of inlet air humidity (seasonal effects) on the fluid bed granulation process (Jones, 1985; Kristensen and Schaefer, 1987; Dewettinck et al., 1999; Rambali et al., 2001). Elevated granulation mass temperature is a result of higher versus lower inlet air humidity (Schæfer and Wørts, 1978a). This phenomenon is also evident from psychrometry and thermodynamic principles (Carrier, 1921; Moyers and Baldwin, 1999) since the heat capacity of humid air is greater than that of dry air. The actual effect of different humidity levels of the inlet air on the various fluid bed process parameters has, however, not been clarified thoroughly. In the present study new aspects of this phenomenon are shown with a humidifying system connected to a fluid bed granulator equipped with accurate process measurements. This

* Corresponding author at: Orion Corporation Orion Pharma, Orionintie 1, P.O. Box 65, FIN-02101 Espoo, Finland. Tel.: +358 10 426 4778.
E-mail address: tanja.lipsanen@orionpharma.com (T. Lipsanen).

0378-5173/$ – see front matter
doi:10.1016/j.ijpharm.2007.05.051

humidity system enables controlled rapid changes to the inlet air humidity levels.

Proper fluidisation with controlled airflow enables effective heat exchange and material movement in a fluid bed chamber and the temperature is for all purposes evenly distributed. Convective heat reaches single particles as the fluidisation is smooth. In the spraying phase, the atomized liquid protects the particles from experiencing the heat of the inlet air, because water absorbs heat efficiently and thereby cools process air (Carrier, 1921). The term evaporative cooling describes this phenomenon. In the drying phase, evaporation of the water and reduction of the water layer on the particle surfaces is the reason for the increasing conductive heat transfer within the solid mass. Three distinct temperature regions are identified during the drying phase (Newman, 1931). In the first stage, called the constant rate period, the particle surfaces are wet and therefore the rate of drying and temperature of the granules are constant. In the second stage, the surfaces become partially wet, the drying rate slows down and the temperature of the granules begins to increase. In the third step, the rate of drying is controlled by diffusion from the interior of the particles and the temperature of the granules approaches that of the inlet air. This temperature rise is used to indicate the end-point of drying.

A consistent and uniform granulation process and granules of optimal quality can be achieved when the effects of the critical parameters on the process and on the critical quality attributes are understood and controlled. Physical process measurements of a fluid bed granulator analysed in an integrated manner are included in the process analytical technologies (FDA, 2004). The regulatory guidelines (ICH Q8, 2005; ICH Q9, 2005) strongly encourage the pharmaceutical industry to apply scientific and risk management approaches to the development of a product and its manufacturing process. The ICH Q8 guideline Pharmaceutical Development defines the design space as "multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality". Operating within a design space will result in a product meeting the quality attributes designed. The material behaviour in a fluidised bed has traditionally relied on the observation and experience of an operator. There has been a lack of good quantitative criteria for fluidisation, although the entire performance of a process is dependent on it. In the present study a new parameter describing the quality of fluidisation was developed by calculating the ratio of the flow rate of the inlet air to the turbine fan speed.

The influence of inlet air humidity on the temperature measurements at different locations in the fluid bed granulator system was determined here. During the spraying phase it is critical that water addition and evaporation are in balance to prevent uncontrollable agglomeration. High inlet air humidity can throw a non-robust process out of the operation window by 'wet quenching'. Due to over-wetting and de-fluidisation there is a risk of deterioration of an entire batch (Westrup, 1996). In the present study the relationship of the flow rate of the process air and turbine fan speed was compared with the fluidisation behaviour and the particle size results. The process trajectories for smooth fluidisation were determined, based on this new fluidisation parameter, to avoid both excessive and improper fluidisation and bed collapse.

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 15% aqueous solution of polyvinylpyrrolidone (Kollidon K-30; BASF Corporation, Ludwigshafen, Germany).

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 and fluctuating humidity of the process air for granulation batches 10–15 (Fig. 1). Otherwise ambient air with humidity levels classified as low and intermediate was used.

2.3. Granulation process and measurements

The granulations are described in Table 1. The classification into the three categories was based on the humidity levels of the inlet air: 4–6 g/m^3 (low humidity), 7–12 g/m^3 (intermediate humidity) and above 13 g/m^3 (high humidity). The granulations were made in randomised order. The granules were produced in an automated bench-scale fluid bed granulator (Glatt WSG 5; Glatt GmbH, Binzen, Germany). The instrumentation is described in Fig. 2 and in further detail in Rantanen et al. (2000). The inlet air temperature, atomization pressure of the granulating liquid and nozzle height were constant. During the mixing,

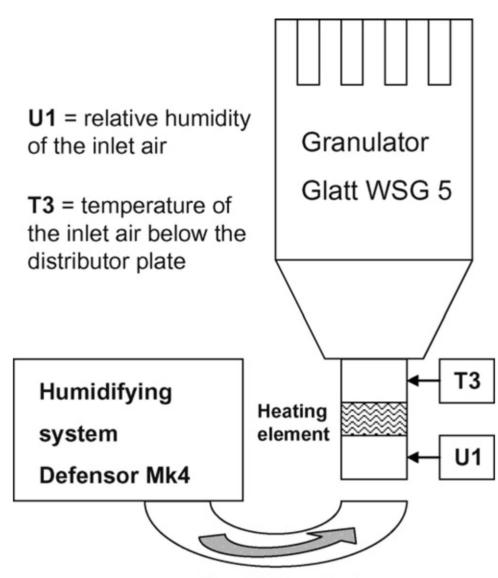

Fig. 1. The humidifying system and connection to the granulator. T3 and U1 were important measurements of the inlet process air.

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%)	Total water content of inlet air (g)
Low humidity:			
1	4.5	24.2	2030
2	4.5	25.7	2000
3	4.6	23.8	2380
4	4.6	24.9	2100
5	5.9	31.9	2720
Intermediate humidity:			
6	7.4	35.8	3630
7	9.3	43.8	6020
8	10.0	47.5	6100
9	11.1	58.1	8560
High humidity:			
10	15.5	68.7	10 700
11	18.0	78.4	12 300
12	18.4	84.6	12 900
13	19.8	80.7	15 000
14	23.4	89.7	18 600
High humidity, collapsed bed:			
15	20.9	87.5	-

The batches were classified accordingly as low (dry), intermediate and high (humid). The total water content of the inlet air was calculated by using absolute humidity and airflow rate information.

spraying and drying phase, a low inlet air temperature of 40 °C was used, because the melting point of the model compound ibuprofen is low (75 °C). The mixing phase lasted about 6 min until inlet air temperature (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 and then 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 final moisture content of the granules varied between 0.5% and 1.2% (w/w) measured by loss on drying (Sartorius Thermocontrol MA 100; Sartorius, Göttingen, Germany). 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 topside of the filters. The absolute humidity of the inlet (AH1) and outlet air (AH2) was calculated, using the RH and temperature information. The inlet airflow rate was measured from the inlet air duct before the heating element and the fan speed (value of the frequency converter) from the turbine located upstream from the product processing area.

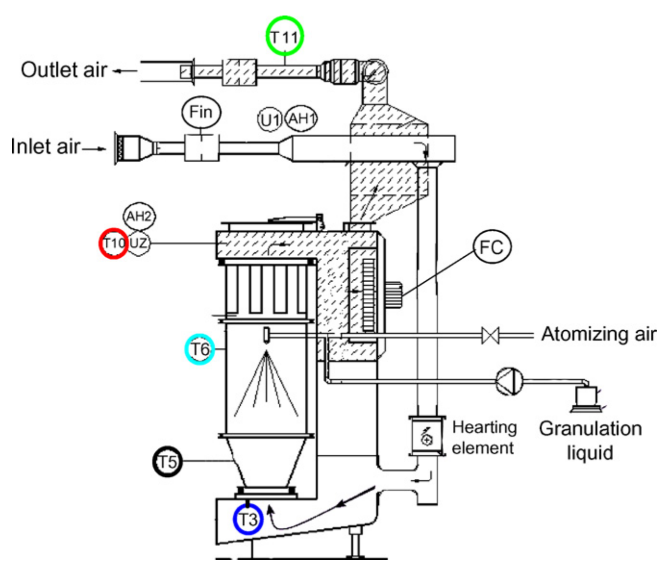

Fig. 2. Important measurements of this study are highlighted in the instrumented Glatt WSG 5 fluid bed granulator. The colours refer to Fig. 4. T3: temperature of the inlet air below the distributor plate. T5: temperature of the mass measured at the bottom of the granulator bowl. T6: temperature of the 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. Fin: flow rate of the inlet air. FC: fan speed (value of the frequency converter).

2.4. Particle size distribution

The volume particle size distribution was determined with laser diffractometry (Laser Diffraction Particle Size Analyzer LS13 320; Beckman Coulter Inc., Miami, FL, USA). The samples were measured using air as the medium and were prepared by dispersing powder (20 ml) in the unique Tornado Dry Powder System. The dispersion pressure was 4.7 kPa. The result was a mean of three measurements.

3. Results and discussion

Controlled changes in the level of inlet air humidity were the essential variables of this study. The inlet air humidity changes were studied within and between batches. The responses were temperature changes of the process air at different locations in the granulator and the fluidisation level and its effect on the size of the finished granules.

Fig. 3A and B demonstrates differences in the process measurements of typical granulations of the dry and humid batches described in Table 1. Controlled variations of high inlet air humidity resulted in fluctuations in temperature of the gran-

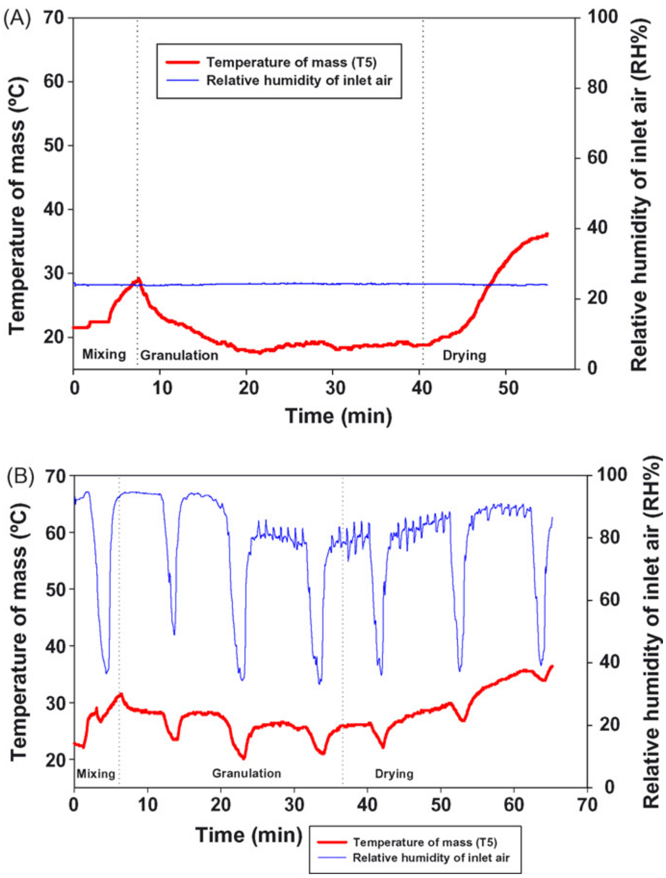

Fig. 3. (A) Temperature of the granulation mass (T5) and inlet air relative humidity (U1) of batch 1, which represents a granulation with dry air. (B) Temperature of the granulation mass (T5) and inlet air relative humidity (U1) of batch 11, which represents a granulation with humid air. The humidifying system enabled sharp fluctuations in inlet air humidity.

ulation mass (Fig. 3B). Rapid falling of the high inlet air humidity content caused the temperature of the fluidising mass to decrease, while it was assured that the other parameters affecting the temperature of the mass were kept constant, e.g. the temperatures of the inlet air and the granulating liquid. A granulation with low ambient and constant inlet air humidity, in comparison to the batch with fluctuating and high air humidity, is shown in Fig. 3A. Temperature fluctuations were absent in this granulation.

A more detailed description of how the variations in inlet air humidity affected the temperature at different locations is seen in Fig. 4. The temperature measurements of the granulation bowl (T5 and T6) were prone to change as the inlet air humidity decreased, which highlighted the dynamic nature of these measurements. In contrast, the temperature measurements upstream from the product processing area (T10 and T11) clearly changed less because they were not as sensitive to the changes of the inlet air in general. Therefore, the granulation bowl was a more optimal place to monitor and control the progression of wet granulation and drying, compared with the measurements in the outlet air duct. The effect of inlet air humidity on the granulation mass temperature was also clearly demonstrated when different granulation batches were compared (Fig. 5). A linear tempera-

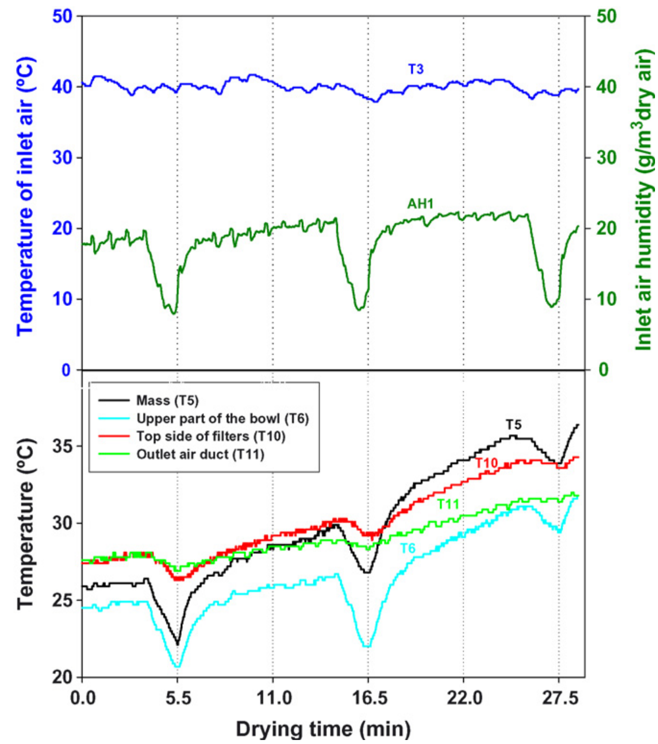

Fig. 4. Inlet air humidity fluctuations of batch 11 during the drying phase. The input variables of the inlet air are drawn above and the derived temperature measurements are found in the lower figure.

ture increase of 10 °C was clearly seen in the granulation mass during the spraying phase, when the absolute inlet air humidity (AH1) increased from 4.5 to 23.4 g/m^3, which confounds readings when the specific temperature of the granulation mass is used to indicate the end-point of drying. This criterion may be applicable when the inlet air humidity does not vary. There are

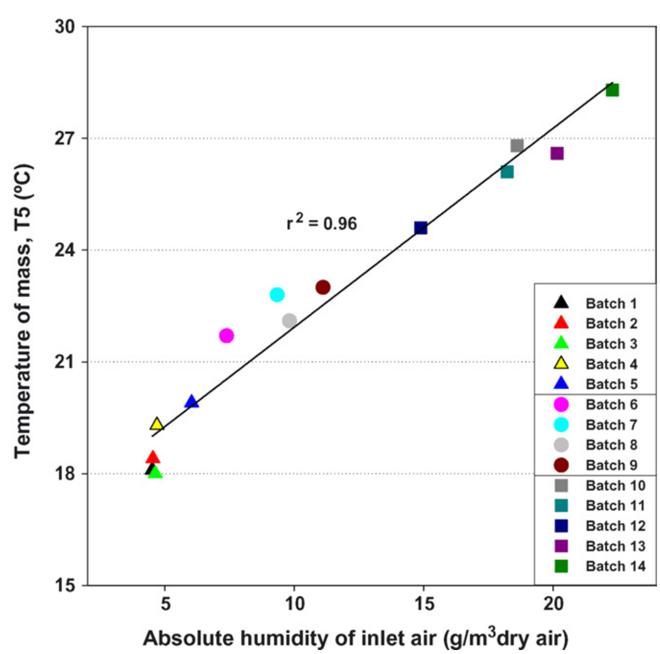

Fig. 5. Correlation of absolute inlet air humidity (AH1) with temperature of the granulation mass (T5) at a point 10 min before the drying phase.

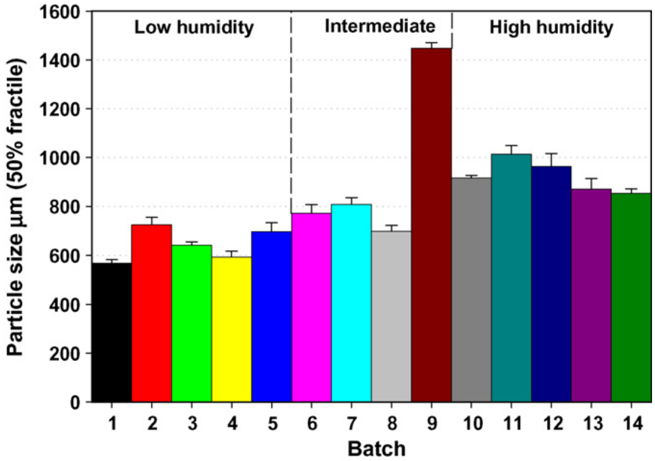

Fig. 6. Particle size by 50% fractile. Batch 9 differed in fluidisation behaviour, which resulted in out of the line particle-size.

accordingly two contrasting ways in which water in liquid and vapour form affects the temperature of the granulation mass. The granulation liquid sprayed absorbs heat energy from the process air and the temperature of the mass falls. The effect of spray rate of the binder solution on the temperature of the outlet air was studied previously (Abberger et al., 1996). On the other hand, the water vapour in air has latent heat and this thermodynamic heating property of the humid process air was clearly seen in this study as a temperature increase in the wet mass.

The granule size results are given in Fig. 6. The particle size of the granulations of dry and humid air differed clearly. In humid air the mean particle size of the granules increased by 280 µm when batches with low humidity (1–5) were compared with batches with high air humidity (10–14), which is in accordance with previous studies (Wurster, 1960; Schæfer and Wørts, 1978a,b). Batches of dry air included more small particles than granulations with high humidity, because in dry inlet air fewer liquid bridges, thereby fewer solid bridges, are formed between particles. The higher particle size distribution of batch 9 is explained by improper fluidisation with U1 of 58%. This ambient, comparatively high but steady inlet air humidity unexpectedly caused more problems in fluidisation behaviour than the overall higher but fluctuating humidity levels. Pulses of dry air (Fig. 3B) improved the fluidisation of batches with high overall humidity. There is a strong possibility that without these pulses there would have been more deviating batches. Rambali et al. (2001) evaluated three inlet air humidity levels (6, 10 and 14 g/kg), but the real effect of inlet air humidity on the particle size was not clarified, because the inlet air temperature, inlet airflow and spray rate also varied. Schaafsma et al. (1999) detected granule growth, when the relative humidity attained a critical value above 50% with lactose formulation. Above 75% RH severe channelling was detected, which is a result of improper fluidisation. Hemati et al. (2003) noted a significant effect on the particle growth when RH was above 40%. There seem to be a critical, formulation- and process-dependent humidity level above which the granulation is more vulnerable to particle enlargement and de-fluidisation, even irreversible bed collapse. In this study an RH value of 50% was considered a risk level for excessive particle size enlargement and de-fluidisation.

Accurate adjustment of the inlet airflow rate was vital for successful granulation processes, especially when granulated with high process air humidity. The airflow was created by turbine fan suction located upstream from the product processing area, a common configuration (Olsen, 1989). Flow rate (g/s) was measured from the inlet air duct and fan speed (Hz, 1/s) from the turbine. The flow rate of the process air and proper fluidisation of the mass were for the most part a consequence of fan speed adjustment. However, improper fluidisation of the mass caused the relationship of flow rate and fan speed to fall because the de-fluidising mass partially blocked the upward-moving gas. Therefore, the following parameter was developed (Eq. (1)).

$$\text{Fluidisation parameter} = \frac{\text{Airflow rate}}{\text{Fan speed}} \tag{1}$$

The fluidisation parameters of the various batches were drawn as a function of time. The dry batches (1–5) and most intermediate batches (6–8) had no fluidisation problems. Therefore, comparison was made with the most humid batches (9–15) and these parameters are shown in Fig. 7. The batch with the highest inlet air humidity (14) showed some deviating profile and risk of improper fluidisation was identified, although the particle size results were not deviating. As seen in Fig. 7 the fluidisation parameter progression of batch 9 was very low during wet granulation and drying. A state of over-wetting already evolved at the beginning of spraying phase II and this state could no longer be prevented by adjusting the fan speed to its maximum value. The deviating high particle size of batch 9 was caused by this over-wetting of the mass and subsequent improper fluidisation. Batch 15 collapsed unexpectedly after spraying 75% (1500 g) of

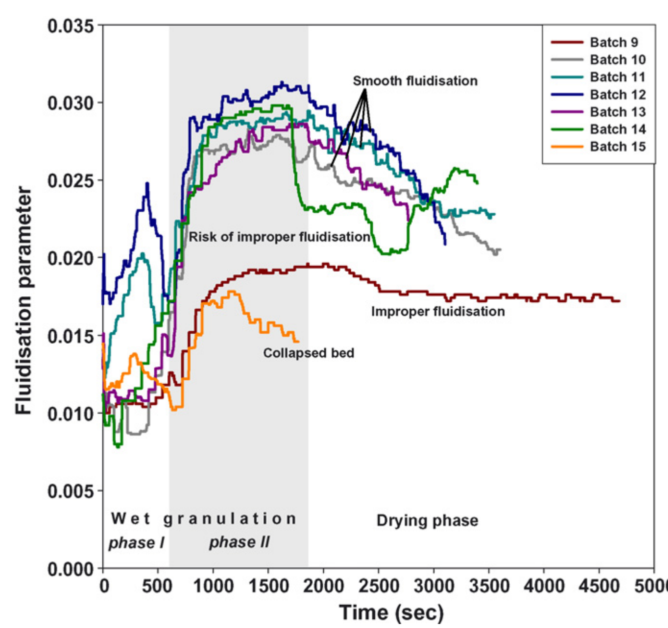

Fig. 7. Relationship of flow rate (g/s) and fan speed (Hz) as a function of time for the most humid batches. Various failure modes can be identified. The spraying and drying phases are included. The granulating liquid flow rate was slower in phase I (29 g/min) than in phase II (105 g/min) of wet granulation.

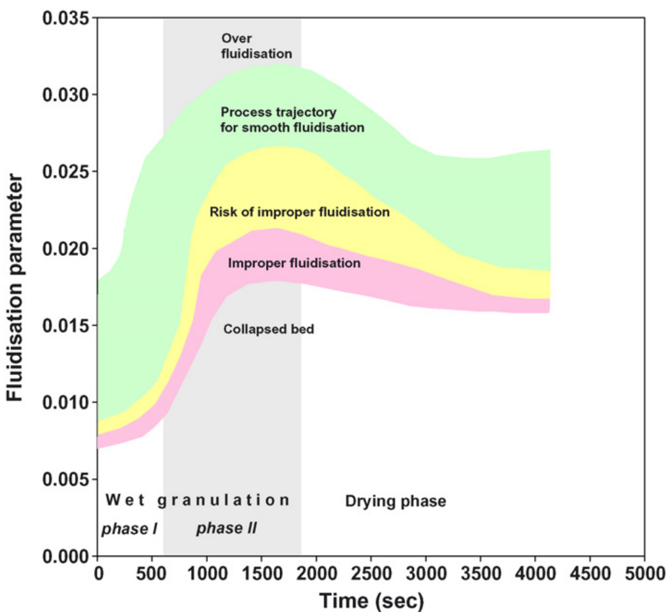

Fig. 8. Design space process trajectories for the fluidisation level. These trajectories are unique for this formulation and process.

granulation liquid. We observed that improper fluidisation was the reason for the quality deviation in both batch 9 and 15. Fig. 7 shows that batches 9 and 15 had the very same progression of the fluidisation parameter initially.

One prime idea was to develop the design space for the fluid bed granulation process. The ICH Q8 guideline states that the unexpected results of pharmaceutical development studies can be useful in constructing the design space. In the present study batches 9 and 15 fell into this category. Finally the process trajectories for the fluidisation parameter were developed (Fig. 8). The mode 'smooth fluidisation' was identified which caused expected particle size results. Failure mode classification included 'over fluidisation', 'improper fluidisation' and 'bed collapse'. The mode 'risk of improper fluidisation' was also identified. With this design space it is possible to avoid failure modes during granulation. The risk factors for this model formulation and process were identified: occasionally insufficient airflow rate, the hydrophobic nature of the ibuprofen formulation, low temperature of the inlet air and relatively high spraying rate of the granulating liquid. The flow rate of the inlet air at the beginning of spraying phase II was especially critical when the inlet air humidity was high, which was seen as over-wetting of the mass and as a low fluidisation parameter value. On the other hand, over-fluidisation with high airflow rate could result in excessive particle attrition (Niskanen and Yliruusi, 1994). Compensating techniques should be evaluated to further support the design space: higher temperature of the inlet air, higher flow rate of the inlet air (if possible) and slower or pulse spraying of the granulating liquid (Schæfer and Wørts, 1978a; Schaafsma et al., 1999; Morris et al., 2000). The best option would, however, be sophistication of the process air: a humidifier and a dehumidifier together control the dew point of the process air (Olsen, 1989; Greenhalgh and Westrup, 1997). If dehumidification is not possible, pulses of dry air may prevent over-wetting and bed collapse.

The regulatory climate is strongly encouraging in the science- and risk-based manufacturing which takes advantage of process analytical technologies. The fluidisation parameter can be used as a prognostic and control tool to prevent over-wetting and improper fluidisation. It is possible to control the inlet airflow rate automatically, based on this fluidisation parameter. The fluidisation parameter and the design space together achieve control over fluidisation process performance.

4. Conclusions

The humidifying system connected to the fluid bed granulator enabled us to study wide variations in process air humidity. The effect of inlet air humidity on the temperature measurements was clearly seen within single batches and between batches. Ibuprofen formulation was more vulnerable to particle enlargement and de-fluidisation when the RH level of the process air was above 50%. The new fluidisation parameter was developed, which was based on the relationship of inlet airflow rate and turbine fan speed. This fluidisation parameter of deviating batches was successfully used to construct trajectories to describe the boundaries of the design space. These trajectories were developed to identify risk factors and to avoid failure modes (over-fluidisation, improper fluidisation and bed collapse). The fluidisation parameter can be used as part of a control system to optimise the flow rate of the process air. It is possible to use this parameter as a quality assurance tool to indicate that manufacturing has proceeded in the design space.

Acknowledgements

This work was financially supported by the Finnish Funding Agency for Technology and Innovation TEKES. Tero Närvänen, Kirsi Salomäki, Anni Liimatainen, Heli Rita and Pekka Pohjanjoki from Orion Pharma are acknowledged for their contribution to this project.

References

Abberger, T., Raneburger, J.A., Egermann, H., 1996. Instrumentation of a laboratory-scale fluid-bed granulator for control of critical spray rate and of free moisture. Sci. Pharm. 64, 255–262.

Carrier, W.H., 1921. The theory of atmospheric evaporation—with special reference to compartment dryers. J. Ind. Eng. Chem. 13, 432–438.

Dewettinck, K., De Visscher, A., Deroo, L., Huyghebaert, A., 1999. Modeling the steady-state thermodynamic operation point of top-spray fluidized bed processing. J. Food Eng. 39, 131–143.

Food and Drug Administration FDA, 2004. Guidance for Industry; PAT-A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance.

Greenhalgh, D., Westrup, J., 1997. Process control during fluid bed granulation-the importance of humidity control. J. Pharm. Pharmacol. 49, 22.

Hemati, M., Cherif, R., Saleh, K., Pont, V., 2003. Fluidized bed coating and granulation: influence of process-related variables and physicochemical properties on the growth kinetics. Powder Tech. 130, 18–34.

International Conference on Harmonisation, 2005. ICH Harmonised Tripartite Guideline; Pharmaceutical Development Q8.

International Conference on Harmonisation, 2005. ICH harmonised tripartite guideline; Quality Risk Management Q9.

Jones, D.M., 1985. Factors to consider in fluid-bed processing. Pharm. Tech. 9, 50–62.

Kristensen, H.G., Schaefer, T., 1987. Granulation. A review on pharmaceutical wet granulation. Drug Dev. Ind. Pharm. 13, 803–872.

Kunii, D., Levenspiel, O., 1991. Fluidization Engineering, second ed. Butterworth-Heinemann, Newton.

Morris, K.R., Stowell, J.G., Byrn, S.R., Placette, A.W., Davis, T.D., Peck, G.E., 2000. Accelerated fluid bed drying using NIR monitoring and phenomenological modeling. Drug Dev. Ind. Pharm. 26, 985–988.

Moyers, C.G., Baldwin, G.W., 1999. Psychrometry, evaporative cooling and solids drying. In: Perry, R.H., Green, D.W., Maloney, J.O. (Eds.), Perry's Chemical Engineers Handbook, seventh ed. McGraw Hill, Chapter 12.

Newman, A.B., 1931. The drying of porous solids: diffusion and surface emission equations. Trans. AIChE 27, 203–219.

Niskanen, T., Yliruusi, J., 1994. Attrition of theophylline granules during drying in a fluidized bed granulator. Pharm. Ind. 56, 282–285.

Olsen, K.W., 1989. Batch fluid bed processing equipment—a design overview: Part 1. Pharm. Tech. 13, p. 34, 36, 38, 40, 42, 44, 46.

Rambali, B., Baert, L., Massart, D.L., 2001. Using experimental design to optimize the process parameters in fluidized bed granulation on a semi-full scale. Int. J. Pharm. 220, 149–160.

Rantanen, J., Känsäkoski, M., Suhonen, J., Tenhunen, J., Lehtonen, S., Rajalahti, T., Mannermaa, J.-P., Yliruusi, J., 2000. Next generation fluidized bed granulator automation. AAPS PharmSciTech 1, article 10 (http://www.pharmscitech.com\).

Räsänen, E., Rantanen, J., Mannermaa, J.-P., Yliruusi, J., 2004. The characterization of fluidization behavior using a novel multichamber microscale fluid bed. J. Pharm. Sci. 93, 780–791.

Schaafsma, S.H., Kossen, N.W.F., Mos, M.T., Blauw, L., Hoffmann, A.C., 1999. Effects and control of humidity and particle mixing in fluid-bed granulation. AIChE J. 45, 1202–1210.

Schæfer, T., Wørts, O., 1978a. Control of fluidized-bed granulation III: effects of inlet air temperature and liquid flow rate on granule size and size distribution. Control of moisture content of granules in the drying phase. Arch. Pharm. Chem. Sci. Ed. 6, 1–13.

Schæfer, T., Wørts, O., 1978b. Control of fluidized bed granulation IV. Effects of binder solution and atomization on granule size and size distribution. Arch. Pharm. Chem. Sci. Ed. 6, 14–25.

Westrup, J., 1996. Process control during fluid bed granulation. The importance of humidity control. Pharm. Res. 13, 220.

Wurster, D.E., 1960. Preparation of compressed tablet granulations by the air-suspension technique II. J. Am. Pharm. Assoc. Sci. Ed. 49, 82–84.