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Faculty of Pharmacy
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Summary of the Ph.D. thesis

STUDY OF FLUID BED GRANULATION PROCESSES WITH NEW TECHNOLOGY APPROACHES

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Study of fluid bed granulation processes with new technology approaches

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1. INTRODUCTION

Pharmaceutical granulation is a critical unit operation that is frequently utilized to modulate attributes of powder mixtures to aid in further processing. The granulation processes must be designed to impart a high degree of control on many important physical attributes, such as granule size distribution, shape, content uniformity, moisture content and distribution, porosity, density, tensile strength, and surface morphology. These physical attributes are often critical to process-ability of granulations and for final product quality and performance. An optimally designed granulation unit operation can be an excellent tool for minimizing variability and thereby reducing the risk of poor quality.

Implementing the PAT framework and having a greater understanding of the manufacturing process has obvious advantages to the pharmaceutical industry, the regulators, and the public health. The PAT Initiative provides a regulatory environment that encourages and facilitates pharmaceutical companies to innovate and employ the tools necessary to achieve an in-depth understanding of the manufacturing process. The true goal is to understand the fundamental governing phenomena at work during the process and incorporate this understanding during product development. Doing so will reduce the degree of empiricism that is necessary.

Granulation modelling is an area of growing importance. It is dominated by the population balance approach for developing mechanistic models. However, it requires an improved understanding of the key factors involved in particle growth and breakage. The growing importance of particulate flow patterns is being addressed through approaches such as DEM, which will hopefully provide a microscale view of particle motions in the granulation device. The challenge is in addressing the multiscale nature of granulation modelling that spans from particle interactions up to the plant level. The development of empirically based models has provided a simple means of addressing quickly a number of control-related applications. Application of models to design, advanced control, and diagnosis will require mechanistic models that continue to incorporate the latest understanding of the underlying mechanisms. Much work is currently underway in these areas and the incorporation into existing models of new knowledge will help extend the applicability of process models for granulation (Mašić et al., *Drug Dev. Ind. Pharm.* 2014, Zhai et al., *Chem. Eng. J.* 2010).

2. AIMS

Real time data acquisition and probe versatility makes monitoring and control of processes possible, but the numerous apparatus, process and product variables has led to fluidized bed granulation not fulfilling its full potential in pharmaceutical production.

For this purpose, a study was conducted where both wet and melt fluid bed granulation processes were controlled by the use of thermal sensors and computational tools to enable the acquisition of temperature maps for the quantification of the volume of the thermal zones inside the bed chamber under different material attributes and process parameters. The goal is the determination of the safe interval of granulation volume fraction for optimum granule size and size distribution by adjusting operating conditions during both FBMG processes.

The main steps in the experiments were as follows:

I. Use of conventional wet and innovative, solvent free melt granulation processes to ascertain their limitations and recognize the common individual variables to propose a novel way for process control.

II. Development of an in-line temperature acquisition tool for in-sight into the conditions governing during granules growth mechanisms by mapping the operating space and depicting the established thermal zones.

III. Investigation of the predictive capacity of ANN models for designing the optimal conditions for the desired quality attributes of products and estimation of the relative importance of variables controlling the granulation process.

IV. Demonstration of the correlation between granule size distribution and heat transfer zones and wetting volume inside the fluid bed for optimal control space.

V. Demonstration of the qualitative and quantitative use of thermal analysis in characterizing the structure, growth and properties of the final granules as a validation tool.

VI. Proposal of a real time data assessment for a developed and optimized process control system for industrial use.

3. MATERIALS

3.1. Wet granulation

In this study, α-lactose monohydrate (Biopharm Industry, Algeria) was used as a model filler. An aqueous solution of 5% w/w of Povidone K30 (Prochima Sigma, Algeria) was used as a binder to granulate the dry lactose powder.

3.2. Melt granulation

Alpha-lactose monohydrate (Ph. Eur. Biopharm, Algeria) was used as a model filler. Polyethylene glycol 2000 and 6000 (Fluka, Switzerland) were used as meltable binders. Paracetamol was used as a model drug (Biopharm, Algeria).

4. METHODS

4.1. Fluidized bed equipment

Experiments were performed in two different pieces of equipment. A conical fluidized bed built for this study (U.S.T.H.B., Algeria) labelled FBA and a Strea-1 conical fluidized bed (Niro Aeromatic, Bubendorf, Switzerland) labelled FBH. The procedures for both wet and melt granulations are summarized in Table 1.

Table 1: Equipment used and samples prepared for wet and melt granulation processes.

Process	**Wet granulation**	**Melt granulation**		
		Spray-on	**In-situ**	
Sample	Placebo	With API	Placebo	With API
Equipment	FBA	FBA	FBH	FBH

4.1.1. Wet granulation – Description of operating procedures

The granulation process of wet technique is demonstrated in Figure 1.

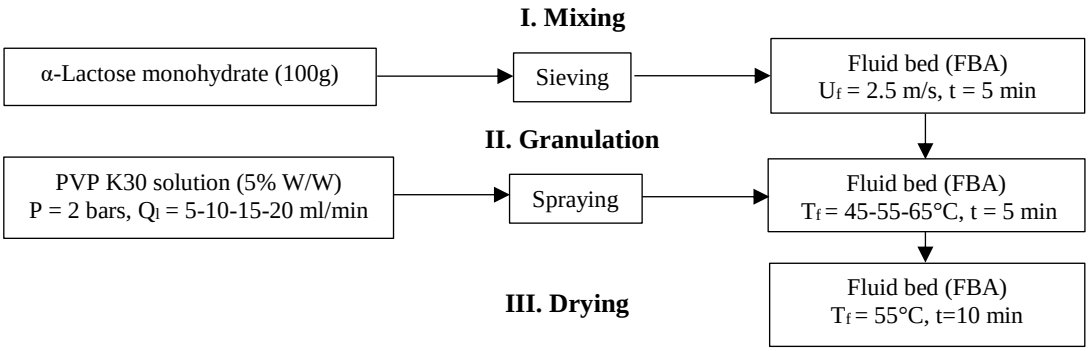

Figure 1: Flow chart of wet granulation - placebo granules.

4.1.2. Melt granulation – Description of operating procedures

4.1.2.1. Spray-on FBMG

The granulation process of spray-on and in-situ techniques is demonstrated in Figure 2, 3, 4.

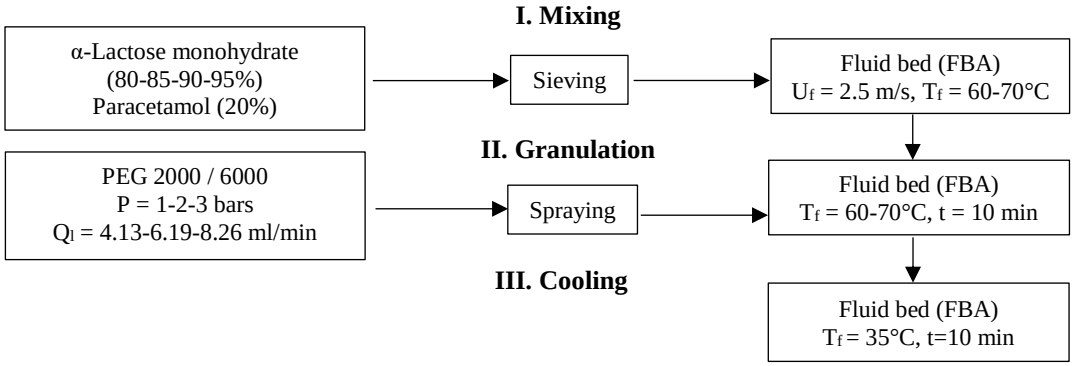

Figure 2: Flow chart of in-situ melt granulation – Granules with API.

4.1.2.2. In-situ FBMG – Placebo granules

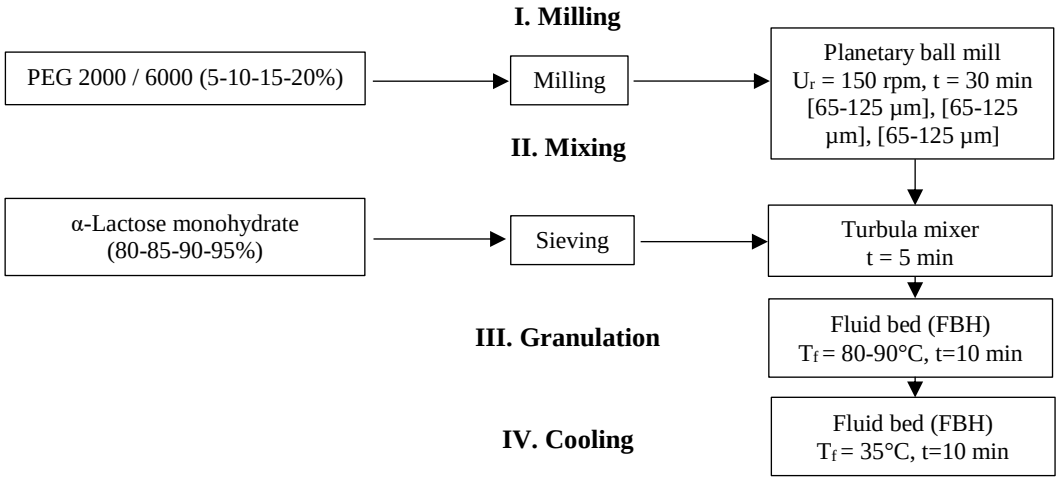

Figure 3: Flow chart of in-situ melt granulation – Placebo granules.

4.1.2.3. In-situ FBMG – Granules with API

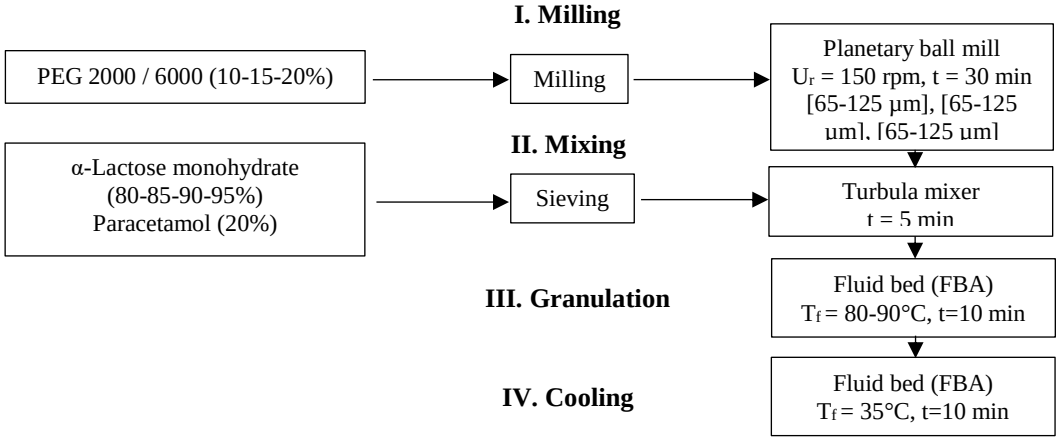

Figure 4: Flow chart of in-situ melt granulation – Granules with API.

4.2. Data acquisition and processing

The temperatures inside the fluid bed chamber were measured using thermocouples connected to data acquisition hardware (Pico technology, Germany). Temperatures were analysed in-line every 1s. Measurements were performed for both wet and melt granulation techniques in order to evaluate their differences and characteristics and the potential of each technique.

4.3. Modelling Using artificial neural networks

The ANNs toolbox on MATLAB® (R2015b, MathWorks®) was used in this study to design the architecture of the models for the wet and melt granulation. The ANN model also provides values of input strengths (weights), which indicate the significance of the effect of each input on the output and predicts the evolution of temperature profiles (Table 2).

Table 2: Selected inputs and outputs for wet and melt granulation.

Process	Inputs	Outputs
Wet granulation	Fluidizing temeprature Binder spraying rate X position Y position	Temperature inside the fluid bed chamber
Melt granulation (In-situ FBH)	Binder content Binder particle size Binder viscosity grade	Granule yield Granule mean diameter Coefficient of variation Hardness Aspect ratio

4.4. Wetting volume size measurement

Temperature mapping determines the isotherms inside the fluid bed chamber. The smallest distance between two adjacent isotherms limits two distinct thermal zones. The wetting volume is determined from two wetting surfaces. The total volume of the wetting zone is measured as the ratio of the volume of the wetting zone divided by the volume of the conical bed chamber.

4.5. Scanning electron microscopy

The morphology of the agglomerate was investigated by Scanning Electron Microscopy (SEM) (Hitachi 4700, Hitachi Ltd., Tokyo, Japan).

4.6. Granule strength measurement and yield

The breaking hardness was tested for all granules with a special hardness testing apparatus (University of Szeged). Ten parallel measurements were performed. The yield of the process (Y %) is defined as the ratio of the mass of granules above 125 μm and the batch mass.

4.7. Flowability properties and moisture content

The Carr and Hausner index were determined using a volumenometer (Erweka). Moisture content was measured by loss-on-drying at 105°C using a Precisa XM60 moisture analyzer.

4.8. Particle size analysis

The particle size distributions of the granules were determined by laser scattering (Malvern Mastersizer Scirocco 2000, Worcestershire, UK). The particle size distribution was characterized by the D (0.5) values and the specific surface area.

4.9. Thermal investigation

Samples were measured with a DSC 821^e (Mettler-Toledo GmbH, Switzerland) from 25 to 500°C, with a heating rate of $10°C.min^{-1}$ in a non-hermetically sealed 40 μl aluminum pan in Argon atmosphere. TGA was carried out with a Mettler-Toledo TGA/DSC1 instrument (Mettler-Toledo GmbH, Switzerland) coupled to a mass spectrometer (maximum 300 amu) in nitrogen atmosphere (70 cm^3 min^{-1}) and aluminium pans (100 μl) with a heating rate of $10°C \cdot min^{-1}$, from 25 to 500°C.

4.10. Dissolution and compression studies

Granules were compressed using an eccentric tablet machine (Deltalab). The tablet weight was 500 mg. The hardness of granules was measured using a durometer (Erweka). The dissolution trials were performed in a paddle apparatus (Erweka, Germany) at 50 rpm using 900 ml of phosphate buffer pH 6.8 as a dissolution medium. Samples were analyzed by an UV spectrometer (Shimadzu, Japan) at 243 nm.

5. RESULTS AND DISCUSSION

5.1. Wet granulation

5.1.1. Characterisation and architecture of the ANN

The ANN model in this research was generated from 70% of the temperature data. The input data points were combined with random weights as in a linear regression model (Σ) and were then transformed through the non-linear function, which enables the non-linear modelling of an ANN model.

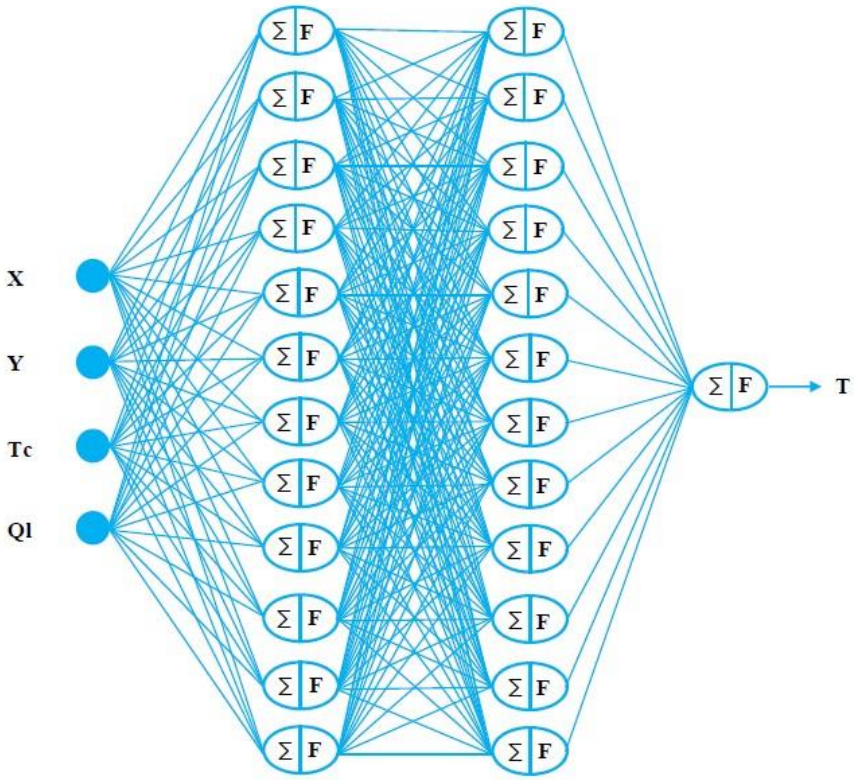

Figure 5: Schematic representation of the used ANN architecture.

The network with two hidden layers and twelve neurons in each hidden layer (Figure 5) presented the smallest validation mean square error (VMSE) of 1.4·10−3. The R^2 is 0.995. The result of the testing phase shows that the ANN model is capable of generalizing between input and output variables with good predictions.

5.1.2. Shapes of predicted temperature profiles and particles patterns

Temperature gradients correspond to the transition where the heat and mass transfer occurs due to the collision between the warm entering air and the cold spraying liquid. The developed ANN model allowed the identification and determination of thermal zones. The first is near the spraying nozzle where dry solid particles get sprayed and wet by the binder liquid

corresponding to the wetting zone, the second zone extends toward the bed's walls where the sprayed particles are dried and solidify to form liquid bridges and corresponds to the isothermal zone. The third zone is located near the air distribution plate where an important contact zone between the two hot and cold fluids is set corresponding to the heat transfer zone.

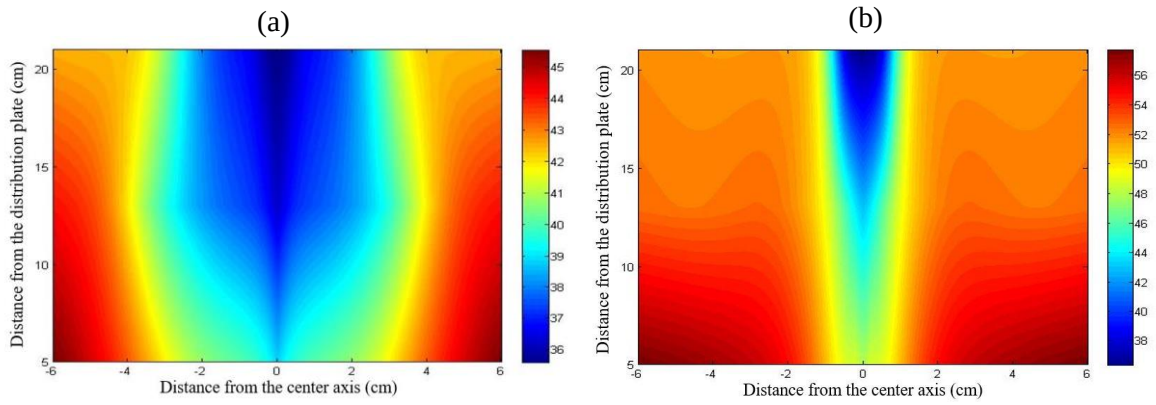

Figure 6: Temperature mapping a) Bell shaped, b) Funnel shaped.

The profiles obtained revealed that the outline of the low temperature zones is represented with a clear yellow band. They follow two main shapes. The outline of the low temperature zone formed a “bell” shape (Figure 6a). It was observed for high liquid spraying rates and low inlet air temperature. The second shape is called “funnel” shape (Figure 6b). It was observed for the lower liquid flow rate (5 ml/min) and both high and low inlet air temperatures. In this case, the risk of insufficiently dried particles is very high and may cause them to stick to the walls, making it hard to control the agglomeration.

5.1.3. Particle growth and temperature profiles

Particles can agglomerate when penetrating the wetting zone. The size of this zone and the transfer rate of particles to this portion of the fluidized bed are therefore very important factors for particle growth as they influence their final properties. For low inlet temperatures, the predicted volume of the wetting zone was large compared to the high inlet temperature conditions (65 °C). These predictions are in accordance with the properties of granules as they show for low inlet air temperature higher mean particle size and moisture content. A high liquid feed rate increased the median particle size and the size of the wetting zone.

The Carr index and Hausner ratio values are under 0.21 and 1.25, respectively, corresponding to the powder’s good ability for compaction and flowability. This results in defining particle size and moisture content as the critical quality attributes of the final granules, demonstrating the link between the characteristics of temperature profiles and critical quality attributes.

5.2. Melt Granulation

5.2.1. In-situ FBMG – Placebo granules

5.2.1.1. Model architecture and simulation

The database used for the training of the ANN model is the result of the quality attributes of the granule samples obtained from the size and size distribution, hardness and shape measurements. The selected optimal, one hidden layer with 5-neuron architecture (Figure 7) showed the lowest MSE of 0.01562.

(a)

(b)

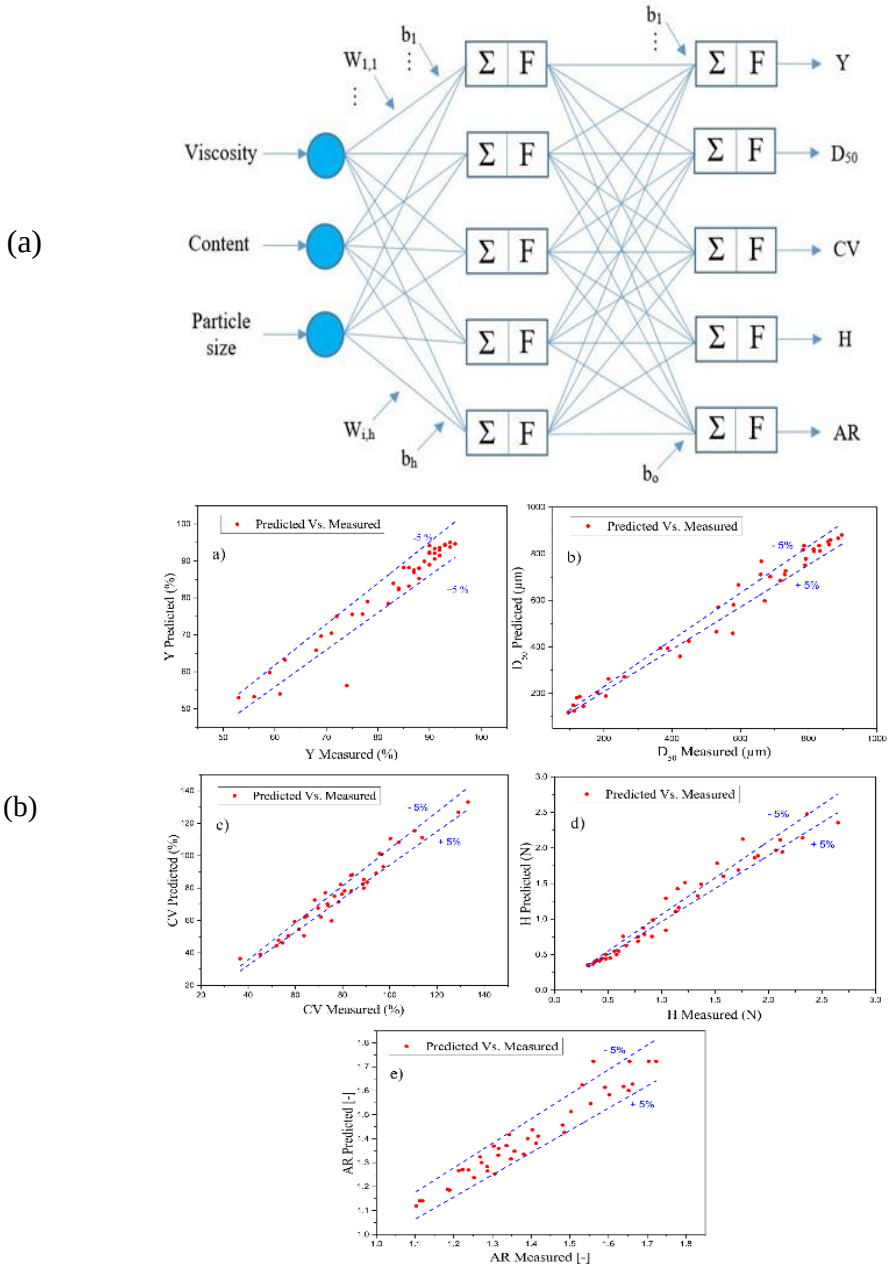

Figure 7: a) Schematic diagram of the ANN model architecture, b) Parity plot with the 95% CI of the five predicted outputs versus the measured experimental data.

Almost all data points are within the interval of confidence, which indicates the model's efficiency in predicting granule properties. The binder particle size was the most significant factor affecting the granulation growth mechanism, followed by the binder viscosity grade and content.

5.2.1.2. Agglomerate growth mechanism and morphology

For low particle size binder, granules are low in diameter (Figure 8a) with irregular morphology indicating agglomerates of smaller sub-granules. The recrystallization of melted PEG after cooling can be seen on the surface of lactose and on the solid bridges that coalesce nuclei together (Fig. 8b). The trapped binder particle will be squeezed to the surface due to densification and spreads around the lactose particles (Figure 8c). Low binder viscosity grade results in high sphericity for low binding strength of agglomerates and collision during fluidization. However, using high binder viscosity grade (Figure 8d) will result in irregularly shaped granules with a hollow core (Figure 8e).

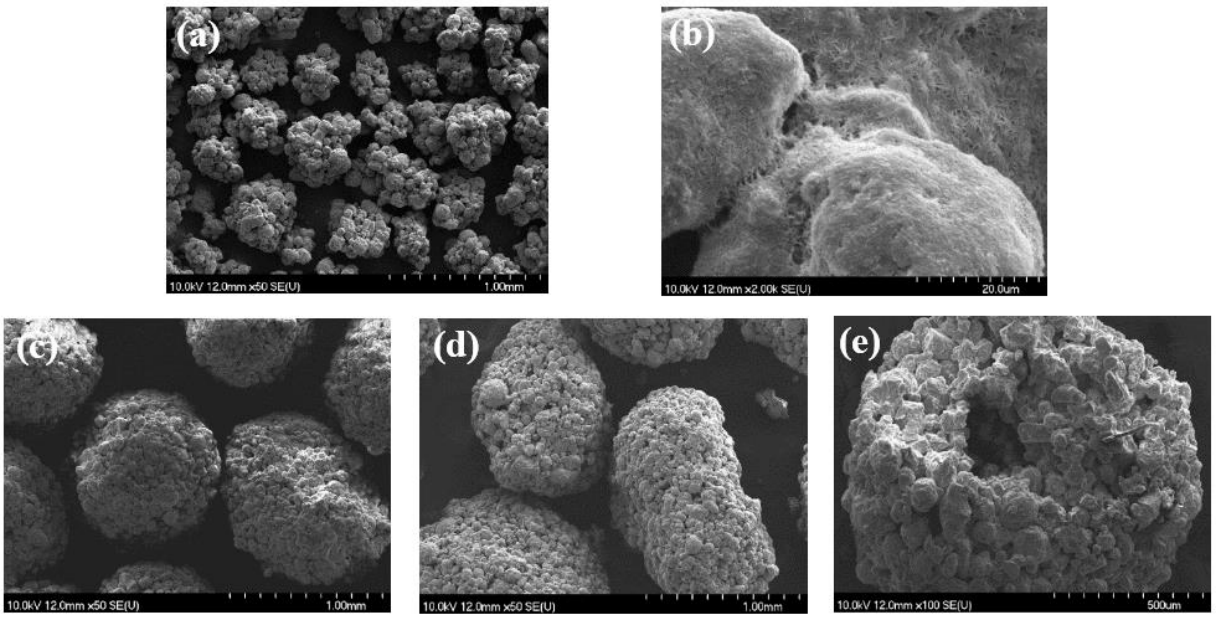

Figure 8: SEM pictures of granules with different binder particle size, viscosity grade and content.

5.2.1.3. Thermoanalytical investigations

The most predominant observation using DSC was the presence of an endothermic peak between the melting of α-lactose monohydrate and its decomposition (Figure 9). After the dehydration of lactose monohydrate and the melting of anhydrous α-lactose, recrystallization into β-lactose occurred, followed by the melting of anhydrous β-lactose. β-lactose is a low

hygroscopic material with high storage stability and appropriate for water sensitive drugs formulations, which is one of the key points of FBMG.

With low viscosity polymer, the increase in content proportionally increased the intensity of the peak. The binder particle size had an inversely proportional effect on this endotherm peak. With high viscosity polymer 6000 and a high particle size of binder, the peak height for the melting of lactose is relatively close to the pure filler. Also, the enthalpy of melting β-lactose is less pronounced.

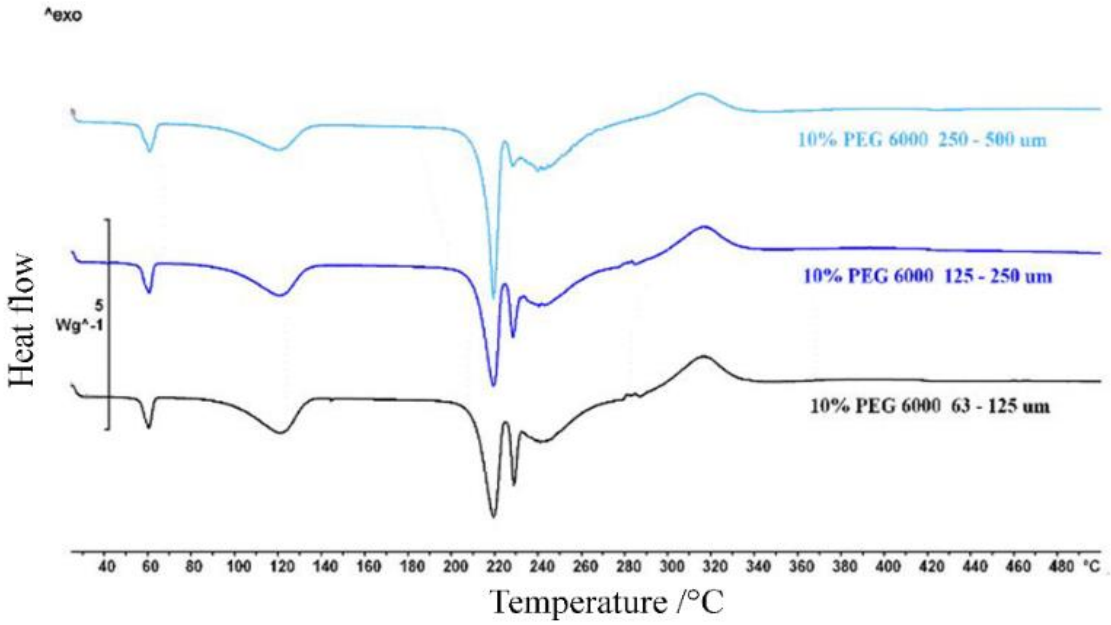

Figure 9: DSC curves of granules with PEG 6000 for different particle sizes.

When using a low binder particle size, the porosity and friability of the granules are increased, making the lactose particles subject to hot fluidizing air and hence to dehydration. Indeed, there was a small reduction in mass between 80 and 131°C indicating that the raw material α-lactose monohydrate contained more surface water than granules.

The mass loss slightly increased with the increase in binder content as it helped shield the lactose particle from the hot fluidizing air. Low-viscosity grade binder combined with a low binder content and particle size showed a poor mass loss as lactose particles were submitted to high temperature during granulation. From the MS curves water is given out at 125, 250 and 315°C, which is consistent with the mass loss observed from the TG curves (Figure 10).

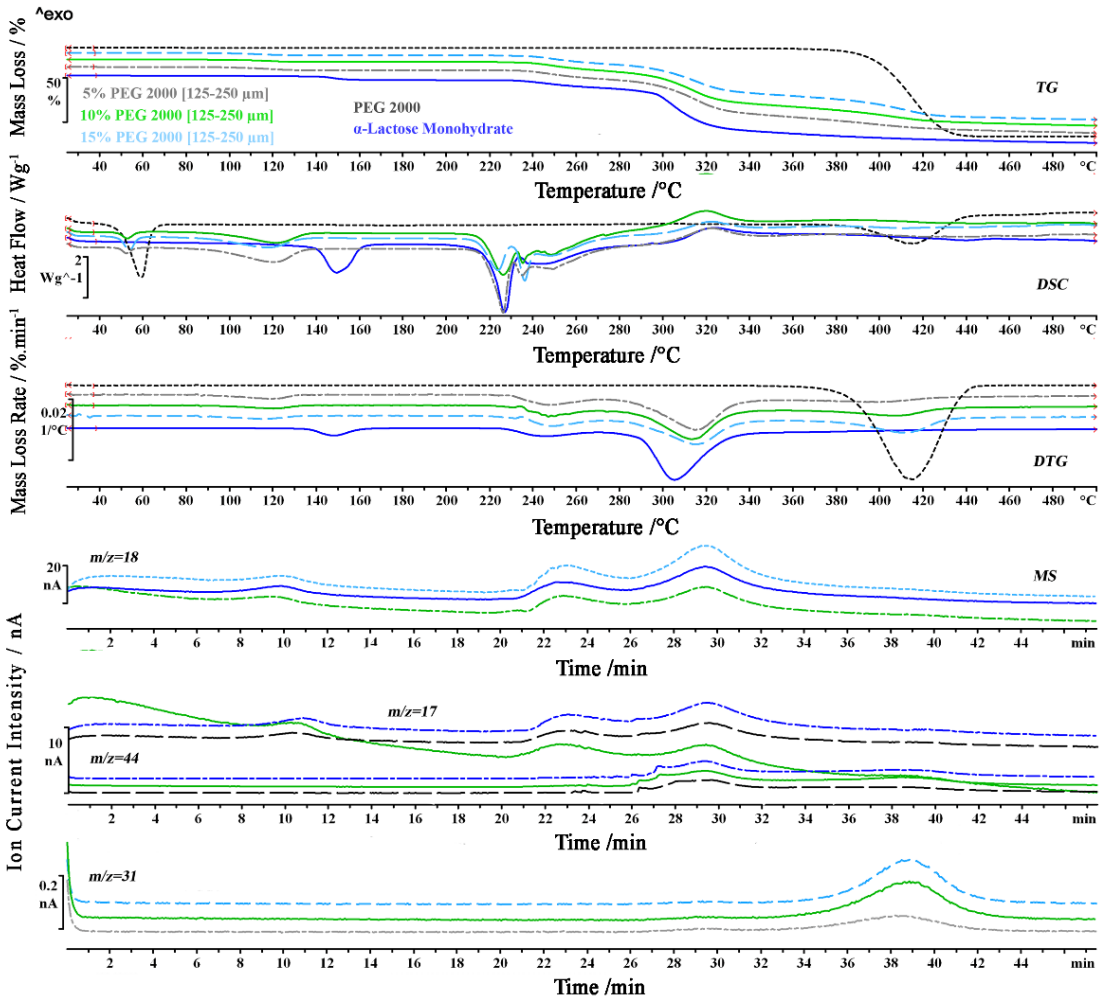

Figure 10: TG, DSC, DTG and MS curves of granules with PEG 2000.

Dehydration takes place in the minor step at around 125°C, which is attributed to the dehydration of lactose monohydrate. The comparison of the granules has shown that their thermal decomposition is determined by different factors, such as their structure and composition, and the increase in concentration in the MS curves corresponds precisely to the mass loss in the TG curves.

5.2.2. In-situ FBMG – Granules with API

5.2.2.1. Temperature mapping and volume of the wetting zone

During in-situ FBMG, two distinct thermal zones were detected (Figure 11). The wetting zone starting from the bottom of the bed to the upper part is represented by yellow colour in the maps.

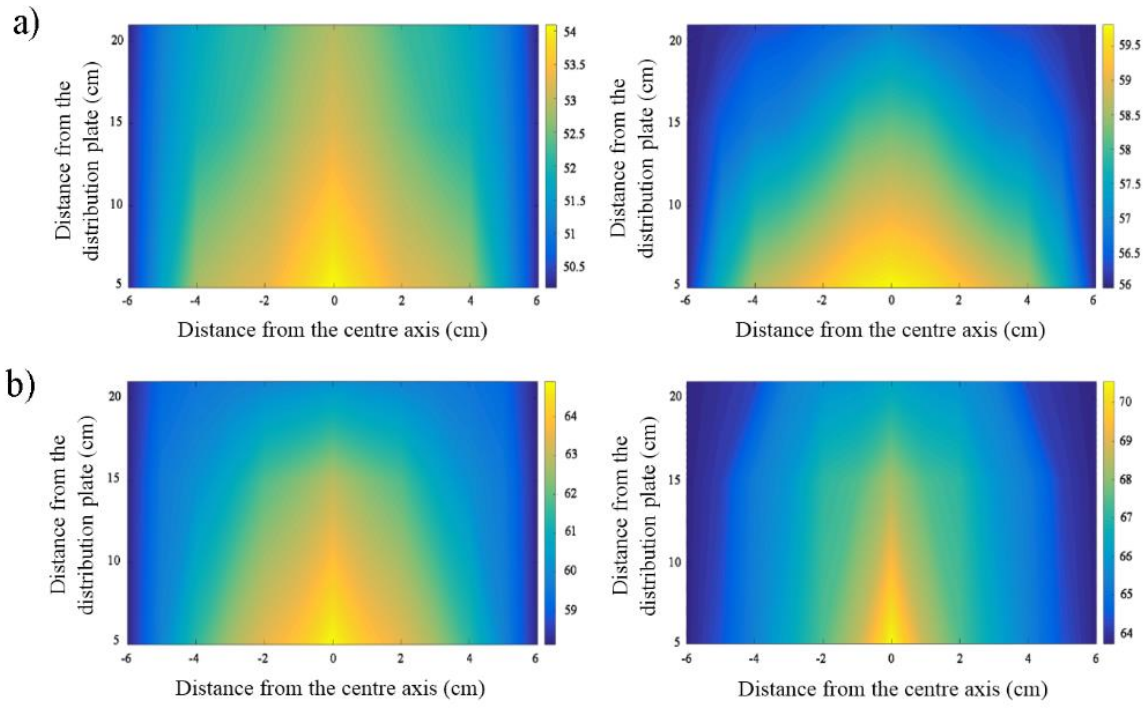

Figure 11: Temperature maps as a function of binder content for binder particle size between [125-350 µm], a) PEG 2000, b) PEG 6000.

The volume of the wetting zone increase is proportional to the binder content and inversely proportional to the binder particle size and viscosity grade. The air temperatures measured in the wetting zone were near the melting temperature of the binders due to the thermal energy transferred from the hot fluidizing air to the solid binder particles to change their physical state from solid to molten, resulting in constant temperatures in the wetting zones. Therefore, heat transfer zones and hence wetting zones are determined only by the difference between two adjacent isotherms.

5.2.2.2. Granule size distribution and the volume of the wetting zone

The increase in binder viscosity grade widened the size distribution of the granules, especially at high binder particle size, as the immersion mechanism will trap the binder particle inside layers of paracetamol and lactose, resulting in dense granules with particle sizes approximating the initial size of the binder particles. Lower volumes of wetting zone were recorded for PEG 2000 than 6000 (27 and 25%, respectively, for 20% content and a binder size of [300-610 µm]). The effect on the distribution of the granules was an increase in the mean diameter with a decrease in distribution uniformity (Figure 12).

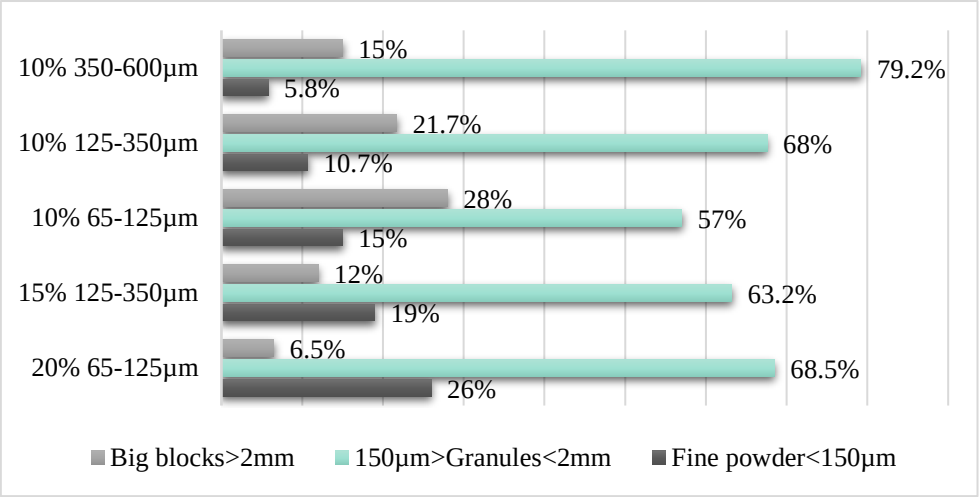

Figure 12: Variations of the size distribution of the granules as a function of binder particle/droplet size and content with PEG 6000 binder.

In the immersion mechanism, content uniformity is harder to achieve because adhesion will be favoured for the lower dry particle sizes (paracetamol). The final batch will then have a higher content of drug in the granules with a higher amount of ungranulated lactose. Hence, the use of temperature maps for in-situ granulation showed that the small volume of the wetting zones resulted in growth by immersion. Too small volumes resulted in over-wetting and collapsing of the fluid bed.

5.2.2.3. Tablet hardness and dissolution testing

Tablets resulted in high hardness when using high binder particle size and low binder particle resulted in lower hardness (Figure 15). The in-situ FBMG showed a slower drug release attributed to the denser granules formed and hence a tighter tablet. The greatest influencing factor was found to be the binder content in the drug, therefore the binder distribution during the FBMG was of high importance.

5.2.3. Spray-on FBMG – Granules with API

5.2.3.1. Temperature Mapping and volume of the wetting zone

The results showed that a wetting volume below 16% resulted in a large fraction of ungranulated material, with a mean diameter not higher than 130 µm. This condition implies that particle growth was made mainly by layering. However, for wetting volumes above 28%, massing of the powder bed and wet quenching occurred (Figure 13).

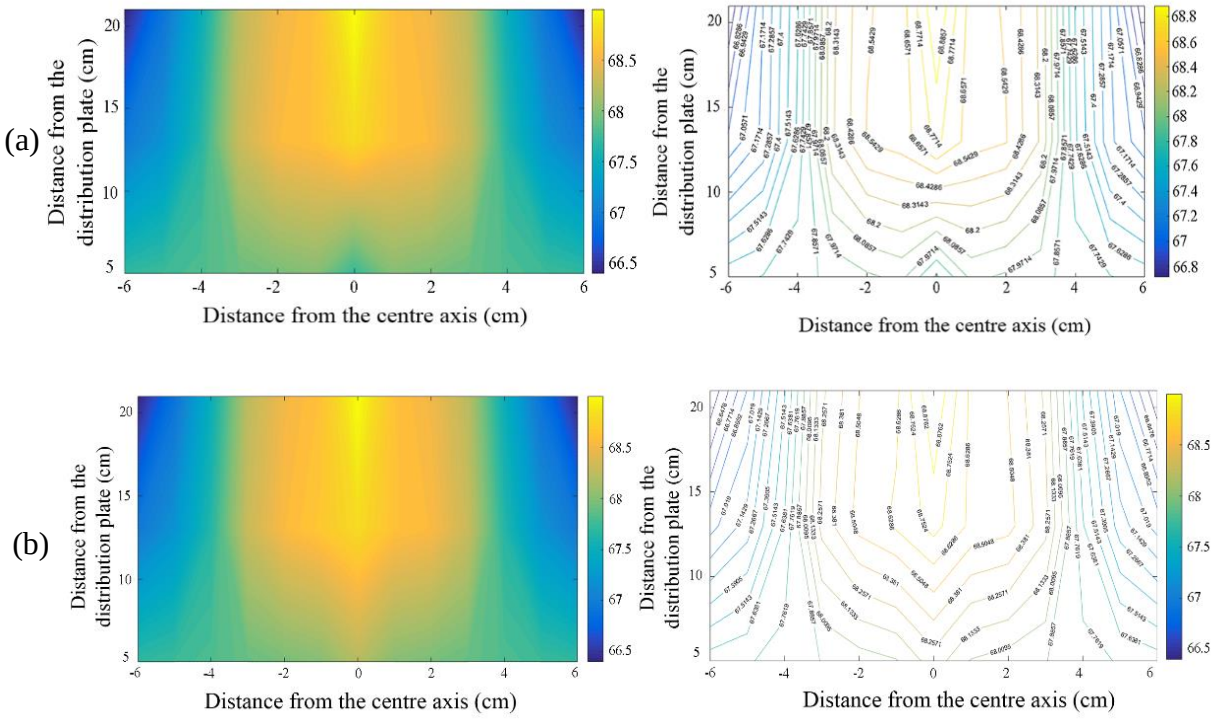

Figure 13: Temperature distribution and isotherm maps for spray-on with binder PEG 2000, a) 8.26 ml/min, 2 bars, b) 6.19 ml/min, 1 bar.

5.2.3.2. Granule size distribution and the volume of the wetting zone

A high binder spraying rate (8.26 ml/min) promoted higher mean diameters and high spraying air pressures (3 bars) resulted in lower granule diameters since lower binder droplets were formed (Figure 14). The hydrophilic property of both paracetamol and α-lactose monohydrate made their different size the only factor influencing successful adhesion to the binder.

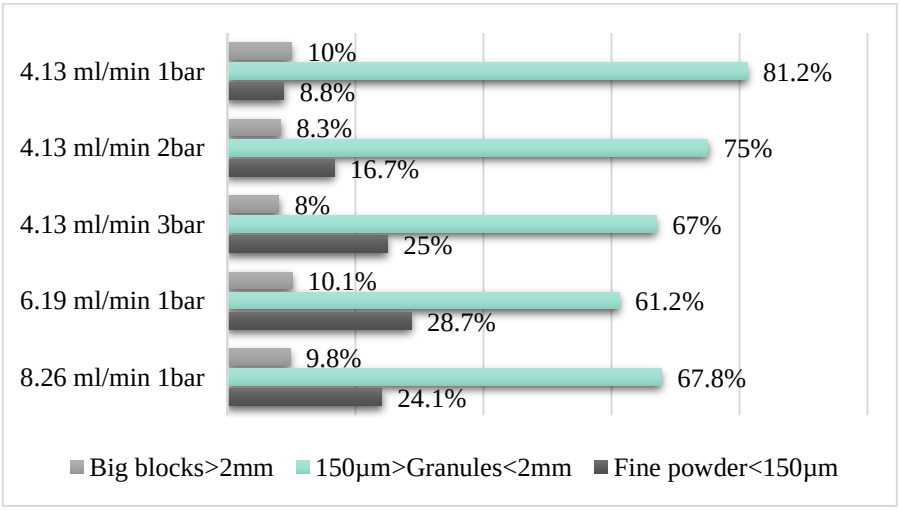

Figure 14: Variation of the granule size distribution with PEG 6000 binder.

Low binder spraying rates (4.13 ml/min) lowered the wetting volume to 19% and gave rise to small granule mean diameter with a uniform size distribution. However, too small binder droplets resulted in inefficient wetting as the volume of the wetting zone was 14%, giving rise to a Gaussian leaning towards the right side of the distribution with a low mean diameter of the granules. The latter result was observed with PEG 2000 but not with PEG 6000, where a broad droplet size distribution resulted in a slight bimodal with a higher amount of low granule sizes. Low droplet sizes will trap paracetamol particles and spread on the surface of lactose particles if enough binding liquid is available, favouring formation of paracetamol nuclei. As a result, the optimal wetting volume interval for a controlled granulation for both spray-on and in-situ techniques in the design space of our study is given in Table 3. It will be helpful for the optimization of the size of the bed during scale-up, for example.

Table 3: Optimized volume of the melting zone interval for spay-on and in-situ FMBG.

FBMG Technique	Minimum wetting volume %	Maximum wetting volume %
Spray-on	16	26
In-situ	16	27

5.2.3.3. Tablet hardness and dissolution testing

Spray air pressure had the most significant influence on drug release time, but the binder feed rate was also found to be a significant factor (Figure 15). Drug release was slower from tablets compressed from granules obtained at higher spray air pressure and higher binder feed rate. When granules were compressed into tablets, a binder matrix was formed and kept the drug particles more tightly. After the gradual eroding and dissolving of the tablet matrix, a more uniform binder distribution led to a slower drug release.

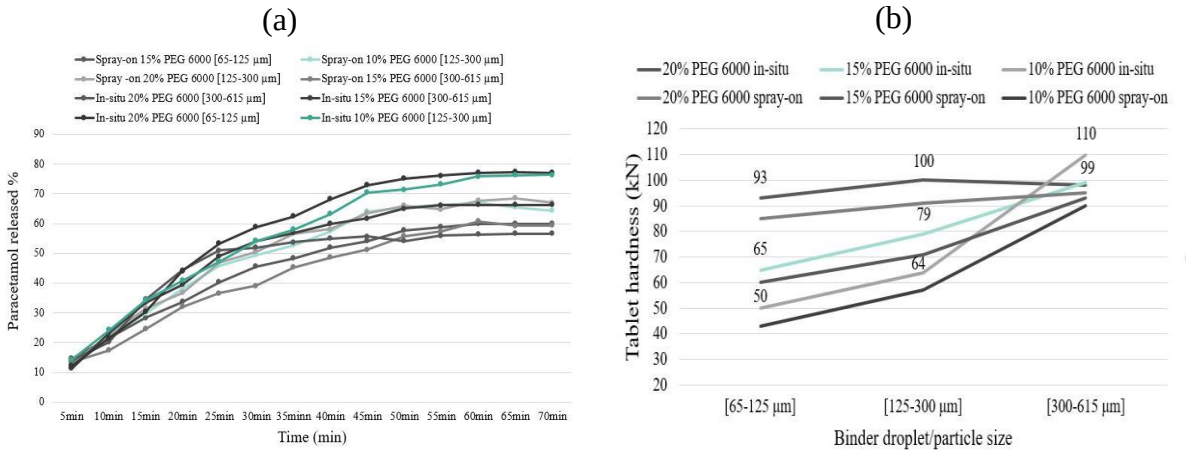

Figure 15: a) Variation of the hardness of tablets with different granule compositions, b) In vitro dissolution profiles of tablets prepared by spray-on and in-situ FBMG.

6. CONCLUSIONS AND PRACTICAL USEFULNESS

The in-line control of pharmaceutical granulation processes was investigated as a possible tool for the evaluation and follow-up of granule formation. In this study, a novel approach to the evaluation of conditions established in a conical fluid bed granulator during the wet and melt fluid bed granulation processes was developed. The two techniques were explored in order to distinguish their linking factors enabling optimal modelling processes.

I. First, the possibility to control the granulation process with predicted temperature distribution profiles was demonstrated. An experimental set-up for the acquisition of temperatures under the PAT in a conical fluidized bed was used for the wet granulation trials and served as a database for a developed artificial neural network model.
II. The hidden layers with a twelve-neuron architecture of the ANN model showed a very good predicting ability of R^2 = 0.994 and allowed the prediction of temperature mappings and the establishment of temperature profiles.
III. These profiles provide information about the hydrodynamic and thermodynamic conditions inside the bed which directly influence particle behavior during granulation as two shapes were identified: bell and funnel shape.
IV. The properties of the final granules are in concordance with the predicted profiles, indicating a distinct connection between the established temperature profiles and the quality attributes of the final particles.

Melt granulation was used as a non-conventional, solvent free and energy friendly technique and the applied process control tool and model brought a new insight into the thermal conditions established during spray-on and in-situ techniques.

V. The Garson equation enabled the determination of the relative importance of each independent input variable and it predicted the particle size of the binder as having the highest impact on the properties of the final granules, followed by binder viscosity grade and binder content. These predictions were in perfect agreement with the experimental results and enabled a very good correlation with R=0.99 for the simulation and prediction of the formation behavior of the granules.
VI. SEM was used as a complementary tool with particle size analysis to evaluate the effect of the material properties on the quality attributes of the final granules to and provide further insight into the growth mechanisms.

VII. DSC showed that the binder particle size was responsible for the transition from the distribution to the immersion mechanism. This transition was identified by the conversion from α-lactose into β-lactose monohydrate caused by the dehydration of lactose during the FHMG process.

VIII. MS has detected and monitored thermally evolved H_2O^+ (m/z = 18), CO_2 (m/z = 44) and polyethylene glycol (m/z = 31, 33). The temperature of the dehydroxylation of the granules is influenced by the free volume depending on the content and the particle size of the polymer.

IX. Regarding granule growth, the distribution mechanism occurred when using a low binder particle size and viscosity. The lactose particles lose a fraction of the adsorbed water during the heating phase of granulation. When a high binder particle size is used, the lactose particles will be trapped and immersed in the PEG particles, causing the adsorbed water to be trapped inside the granules.

X. The optimal melting zone volume for the in-situ and spray-on granulation was between 16 and 27% and 16 and 26% respectively.

Practical relevance and new approaches of this research work are the following:

1. Wet and melt fluid bed granulation processes can be monitored and controlled using the novel in-line temperature acquisition enabling the thermal characterization of the fluidized bed volume.
2. The correlation between the shape and volume of the wetting zones and the particle size distribution of granules can be used as means for further quality control factor.
3. Thermal analysis proved to be a promising technique for granulation growth control by giving a qualitative and quantitative insight into FBMG.
4. ANN is a potential and useful PAT tool in modelling and developing robust agglomeration processes.

LIST OF ORIGINAL PUBLICATIONS RELATED TO THE THESIS

I. **Korteby, Y**., Mahdi, Y., Azizou, A., Daoud, K., Regdon, G. jr.: Implementation of an artificial neural network as a PAT tool for the prediction of temperature distribution within a pharmaceutical fluidized bed granulator, Eur. J. Pharm. Sci., 88 (2016) 219-232

IF: 3.756

II. Regdon, G. jr., **Korteby, Y**.: Quantitative and qualitative use of thermal analysis for the investigation of the properties of granules during fluid bed melt granulation, J. Therm. Anal. Cal. (2017). DOI: 10.1007/s10973-017-6848-5

IF: 1.953

III. **Korteby, Y**., Sovány, T., Kristó, K., Regdon, G. jr.: The use of machine learning tool and differential scanning calorimetry to elucidate and characterize the growth mechanism of an in situ fluid bed melt granulation. Powder Technol., 331 (2018) 286–295

IF: 2.942

IV. **Korteby, Y**., Mahdi, Y., Daoud, K., Regdon, G. jr.: A novel insight into Fluid Bed Melt Granulation: Temperature mapping for the determination of granule formation with the In-situ and spray-on techniques. Eur. J. Pharm. Sci. (EJPS-D-18-00247). Under revision

(IF: 3.756)

PRESENTATIONS RELATED TO THE THESIS

Verbal presentations:

1. **Yasmine Korteby**, Katalin Kristó, Tamás Sovány, Géza Regdon jr.: Preparation of granules via fluid hot melt granulation and characterization by thermal analysis. MKE Termoanalitikai Szakcsoport és az MTA Termoanalitikai Munkabizottság közös szervezésében rendezett ülés 2016.

2. **Yasmine Korteby:** Characterization of a fluid hot melt granulation by thermal analysis and investigation of the influence of different process parameters. XII. Clauder Ottó Emlékverseny 2016, Budapest, Hungary.

3. **Yasmine Korteby**, Yassine Mahdi, Amel Azizou, Kamel Daoud, Géza Regdon jr.: In-line temperature monitoring of a fluid bed granulation for the prediction of temperature distribution profiles via artificial neural networks. Kristályosítási és Gyógyszerformulálási Szakosztály 10. Kerekasztal Konferenciája. Balatonszemes, May 19 – 20, 2017.

4. **Yasmine Korteby**, Géza Regdon jr.: Quantitative and qualitative use of thermal analysis to depict fluid bed melt granulation growth and granules structure. JTACC+V4 1st Journal of Thermal Analysis and Calorimetry Conference and 6th V4 (Joint Czech-Hungarian-Polish-Slovakian) Thermoanalytical Conference June 6–9, 2017. Budapest, Hungary

5. **Yasmine Korteby**, Katalin Kristó, Tamás Sovány, Géza Regdon jr.: Evaluation of in-situ fluid bed melt granulation growth using ANN modelling and thermal analysis. MTA Szerves és Biomolekuláris Kémiai Bizottság Gyógyszerkémiai és Gyógyszertechnológiai Munkabizottsága. September 11-12, 2017. Szeged, Hungary

6. **Yasmine Korteby**, Yassine Mahdi, Kamel Daud, Géza Regdon jr.: A novel insight into fluid bed melt granulation: temperature mapping for the determination of granule formation with the in-situ and spray-on techniques. 7th BBBB International Conference of Pharmaceutical Sciences. October 5-7, 2017. Balatonfüred, Hungary.

7. **Yasmine Korteby**, Yassine Mahdi, Kamel Daud, Géza Regdon jr.: Heat transfer zones determination inside a fluid bed granulator for the optimization of melt granulation processes.Az MTA Termoanalitikai Munkabizottságának valamit az MKE Termoanalitikai Szakcsoportjának közös rendezvényére. December, 2017. Budapest, Hungary.

Poster presentations:

8. **Yasmine Korteby**, Yassine Mahdi, Amel Azizou, Kamel Daoud, Géza Regdon jr.: In-line monitoring of temperature distribution profiles for a quality by design approach to the prediction of fluid bed granulation via artificial neural networks. 11th Central European Symposium on Pharmaceutical Technology. September 22-24, 2016. Belgrade, Serbia

9. **Yasmine Korteby**, Katalin Kristó, Tamás Sovány, Géza Regdon jr.: Characterization of a fluid hot melt granulation by thermal analysis and investigation of the influence of different process parameters. 11th Central European Symposium on Pharmaceutical Technology. September 22-24, 2016. Belgrade, Serbia.

10. **Yasmine Korteby**, Yassine Mahdi, Kamel Daoud, Géza Regdon jr.: Investigation of in-situ and spray-on FBMG granule compression and dissolution behavior. 11th world meeting on pharmaceutical sciences and technology, March 19-22, 2018. Grenada, Spain.

PRESENTATIONS NOT RELATED TO THE THESIS

1. Farid Agouillal, Houria Moghrani, Daya Mancer, **Yasmine Korteby**: Nouradine Nasrallah: Development of alginate microspheres containing essential oils microemulsions: Laser diffractometry characterization and loading capacity optimization by response surface methodology. 7th BBBB International Conference of Pharmaceutical Sciences. October 5-7, 2017. Balatonfüred, Hungary.

2. Daya Mancer, Ahmed Zaid , Yasmine Zanoune, **Yasmine Korteby**, Kamel Daoud: Design of experiment of hydrophobic drug encapsulation using biopolymers : Particles size based study. 7th BBBB International Conference of Pharmaceutical Sciences. October 5-7, 2017. Balatonfüred, Hungary.

3. Wissem Boutraa, Samah Belkacemi, Amel Toubane, **Yasmine Korteby**, Kamel Daoud: Extraction, purification and crystallisation of rebaudioside A, a sweetener from Algerian cultivated Stevia rebaudiana. 7th BBBB International Conference of Pharmaceutical Sciences. October 5-7, 2017. Balatonfüred, Hungary.