Focused Beam Reflectance Measurement as Innovative Process Analytical Technology Tool in Fluid Bed Granulation Process Control

Zur

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Dekan

To my loved ones

My parents Dina and Zoher

My wife Nesreen and my daughter Lana

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List of Abbreviations:

API	Active pharmaceutical ingredient
CLD	Chord length distribution
DOE	Design of experiment
FBG	Fluid bed granulation
FBRM	Focused beam reflectance measurement
FDA	Food and drug administration
MCC	Microcrystalline cellulose
NIR	Near infrared
PAT	Process analytical technology
PSD	Particle size distribution
PVP	Polyvinylpyrrolidone
RPM	Revolution per minute
WG	Wet granulation

Summary

In the pharmaceutical industry, wet granulation (WG) process is a commonly applied process in order to mainly improve the properties of the raw materials. Several main advantages are observed when applying WG, such as enlarging mean particle size, improving flowability, drug content uniformity, and dissolution rate, etc. Moreover, WG process is enhancing the physical properties of the granules that are required for the following tabletting step.

WG process is mostly carried out in a fluid bed granulator. Despite the various advantages of this technique such as producing a narrow mean particle size distribution and mixing-granulation-drying can be handled in one single piece, it is easy to monitor the process by moisture and temperature measurements. However, a great number of process variables that are affecting the quality of the final product have to be taken into account while designing the experiments and this is still challenging for the industry. The use of analyzer tools in order to monitor in-line the growth kinetics of the particles as well as defluidization and agglomeration that might occur in the process is fulfilling the FDA's recommendation for using Process Analytical Technology. Thus providing

continuous information about the process in real time with avoiding sample preparation, process interruption and operator efforts. Focused Beam Reflectance Measurement FBRM D600 (Mettler-Toledo Inc, Switzerland) was mounted inside the fluid bed granulator (Glatt GPCG2; Glatt Air techniques Inc GmbH, Binzen; Germany) in order to monitor in-line the particle growth during the granulation process. The starting formulation consisted of Paracetamol and microcrystalline cellulose MCC101, subsequently spraying binding solution of Polyvinylpyrrolidone K-30 onto the fluidized particles. The probe position was optimized and found to have the best position when it was mounted against the air flow with inclination of 45°. Further it was placed as close as possible to the distributer plate in order to avoid sticking of the particles during the spraying phase and having the probe in a zone where it can measure high and representative number of fluidized particles. A strong correlation was observed between the mean chord length that was computed by FBRM iC-FBRM software (version 4.0 Mettler-Toledo AutoChem, Inc Columbia) and mean particle size measured by sieve analysis. A design of experiment (DOE) of 16 runs was generated in order to study the effect of three process variables on the particle growth that was measured by FBRM

method. The results showed that the effect and the behavior of the factors (process variables) was very similar to sieve analysis results as well as to the literature papers that have been illustrated the effect of fluid bed process variables by other tools.

In order to study the relationship of granule physical properties and final tablet physical properties, granules were compressed using a compaction simulator (Presster™, Metropolitan Computing Corp., NJ, USA). Tablets were compressed under three different compression pressures and breaking force was determined. The results showed that FBRM method showed a better prediction accuracy and robustness than sieve analysis method. This was due to the ability of FBRM that it detects up to few thousands of particles per second, thus providing more representative and reliable results. After performing the disintegration test, the FBRM method gave a better linearity of the correlation between the particle size and disintegration time thanks to the features of FBRM that detect the changes in particle count which showed an effect on the disintegration time. This was the case for FBRM method that was able to detect the chord length as well as the counts of the particle. Compactibility and compressibility of

the powders are of crucial signs for the succeeded tabletting phase. However, they are markedly influenced by the mean particle size. Leuenberger equation was applied, which takes into account the compactibility and compressibility of the material. It was evident that an increase of mean particle size led to better compactibility and compressibility of the product. However, when plotting the compactibililty and compressibility values against the particle size measurements (FBRM and sieve analysis), the correlation linearity was clearly better with FBRM measurements than the ones of sieve analysis. The reason for this result was due to two reasons: (I) FBRM feature that highlights any changes of fine particles, since their presence in the formulation affect the physical properties of the compact. (II) the ability of FBRM technique that it considers the shape as well as dimension of the particles. . The use of FBRM is still not widespread for the monitoring of the wet granulation process in fluid bed, however it is a very promising method and provides the operator the information needed to understand the process as well as its variables in depth. It is a very efficient method to predict principle quality attributes of the tablet while the manufacturing process is still in the granulation phase.

1. Theoretical section

1.1. Introduction

Wet granulation (WG) has been first established 50 years ago and is still a process widely used in the pharmaceutical industry. It is often an unit operation before the tableting step and has not been replaced by direct compression technology. WG process, also known as agglomeration, pelletization or balling, finds application in a wide range of industries including mineral processing, agriculture products, detergents, pharmaceuticals, foodstuffs and specialty chemicals. The granulation process is defined as a process of size enlargement whereby small particles are gathered into larger ones, in which the original particles can still be identified. In the pharmacy world, the term granulation usually refers to processes whereby granules with sizes ranging from 0.1 to 2.0 mm are produced by agitation or fluidization of moistened powders or liquid sprayed onto dried powders (1). The liquid binds the particles together by a combination of capillary and viscous forces until more permanent bonds are formed by subsequent drying or sintering (2). WG is an example of *particle design.* The desired attributes of the

product granules are controlled by a combination of formulation design (choosing the feed powder and liquid properties) and process design (choosing the type of granulator and the operating parameters). Wet granulation delivers various advantages as well as improvement of the properties of the starting powders: flowability and handling of the product, increased bulk density, reduced dustiness which minimizes losses, decreased inhalation and explosion risk, appearance, controlling dissolution rates, avoiding segregation, improving the compactibility and compressibility behavior of powders, providing a better control of drug content uniformity during tableting even for low drug loads and masking the bitter or undesirable taste. However, there are two important aspects of agglomerated pharmaceutical products:

1- They are intermediate or final dosage forms, which must carry reliably and reproducible the required amount of active substance.

2- Final dosage forms are consumer products; therefore, consumer appeal is of great concern, which means for agglomerated specialties that they have uniform, aesthetically pleasing, and reproducible shape and weight.

1.2. Granulation mechanisms

Wet granulation proceeds by different mechanisms for agglomerate growth and degradation, which are dependent on the granulation equipment as well as the properties of the feed material. Hence, the granulation process is divided into three phases (see figure 1,(17)):

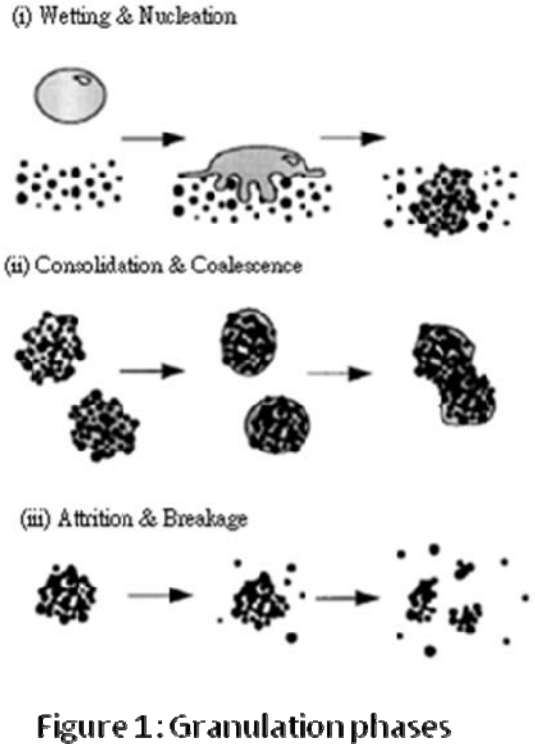

Figure 1: Granulation phases

1- **Wetting and nucleation:** where the liquid binder is brought into contact with a dry powder bed, and is distributed through the bed to give a distribution of nuclei granules. Nucleation is the first step in granulation where the binder begins to wet the powder and form initial agglomerates. The wetting thermodynamics are described in two aspects: the contact angle between the solid and the binder, and the spreading coefficients of the liquid phase over the solid phase and vice versa.

Wetting and nucleation can be defined using surface free energies. The spreading coefficient γ is a measure of the tendency of a liquid and solid combination to spread over each other and is related to the works of adhesion and cohesion (2,84,85):

Work of cohesion for a solid: $W_{CS} = 2\ \gamma_{SV}$ Equation (1)

Work of cohesion for a liquid: $W_{CL} = 2\ \gamma_{LV}$ Equation (2)

Work of cohesion for an interface: $W_A = \gamma_{SV} + \gamma_{LV} - \gamma_{SL}$ Equation (3)

$W_A = \gamma_{LV} (\cos\theta + 1)$ Equation (4)

Where γ is the surface free energy, θ is the solid-liquid contact angle and the subscripts ''L'', ''S'', and ''V'' denote liquid, solid and vapour phase respectively.

2- **Consolidation and growth:** where collisions between two granules, granules and feed powder, or a granule and the equipment lead to granule compaction and growth. Once the granules collide with other granules and equipment surfaces they gradually consolidate. This reduces their size and porosity, squeezes out entrapped air and may even squeeze liquid binder to their surface. Porosity controls granule strength. Granules with high porosity are weak and friable, see also next granulation phase, and this properties certainly influence the subsequent tableting step (86). For many products, it

is desirable that the granules are porous in order to facilitate fast dispersion and dissolution. Hence, granule porosity is an important product property to control and optimize. On the other hand, the granule growth is defined as a rate process, which may reach a maximum size and/or a dynamic equilibrium with breakage processes. However, determining the granule growth behavior might evaluate the granule size distribution during granulation process by plotting average granule size versus time (58,59,83,87).

3- **Attrition and breakage:** the attrition, which concerns the fracture of dried granules, leads to the generation of dust fines. As the aim of most granulation processes is to remove fines, this is generally an undesired effect to be avoided. On the other hand, breakage of wet granules will influence and may control the final granule size distribution. However, in some cases, breakage can be used to limit the maximum granule size or to help to distribute a viscous binder.

1.3. Instruments used for wet granulation

Mechanical aids to wet granulation have developed from the hand process of preparing a wet mass and forcing it through a screen onto trays that were placed into a convection oven where the granules were dried to more sophisticated devices, where the granulation process can be monitored and controlled by several parameters. In the early decades, fluid bed granulator and high shear mixer were predominant techniques for performing wet granulation in the pharmaceutical industries. The two techniques differ technically on the mode of solid agitation, and fundamentally on the mode of granule growth.

Figure 2: Top spray granulation in fluid bed

1.3.1. **High shear mixer:** An impeller maintains the powder in agitation in a closed vessel, and binder solution is sprayed from the top (sometimes, the binder is introduced in dried form mixed with the formulation). In spite that this method produces hard and dense granules two disadvantages are limiting the use of high shear mixer method: (I) wide range of particle size distribution and thus leads to either waste of the product of big agglomerates or further milling step is required (II) the high shear mixer does not have the ability for drying the granulated material; therefore the drying step takes place after transferring the damp mass into another piece of equipment, usually fluid bed dryer is used for this purpose.

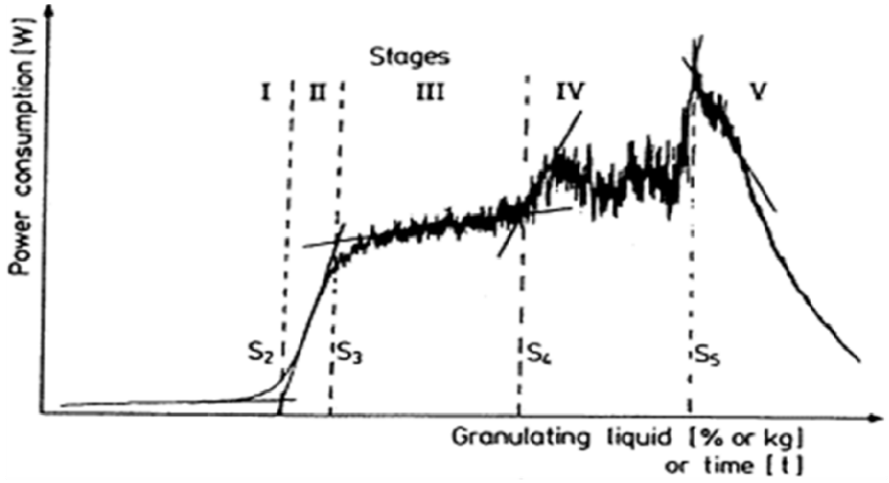

Figure 3: Power consumption profile

Power consumption profile can be obtained in a high shear mixer to monitor the granulation process where 5 different phases can be distinguished, see figure 3, (103, 104):

In the first phase, the powder material adsorbds the bindier liquid until the saturation of misture content with no liquid bridges formation. However, in the second phase, it is clearly observed that the power consumption significantly increases because of the liquid bridges that are being formed between the particles each other. The power consumption in the third phase keeps constant, in this phase inter-particulate void space is occupied by the binder solution. The fourth phase, represents the funicular saturation state with the presence of some particles that are already in the capillry state. The fifth phase which is the last one characterizes the transition from from the capillary stae to the suspension state due to an excess of sprayed binder solution (3).

1.3.2. **Fluid bed granulator** (see figure 2): the powder mixing is maintained as a fluidized bed by a flow of air injected upwards through the bottom screen of the granulator. The binder liquid is sprayed onto the powder bed, in opposite direction to the air flow. The granules result from the adhesion of solid particles to the liquid droplets that hit the bed. Partial drying by the fluidizing air occurs continuously during granulation. The process progresses until all the powder has been granulated. Complete drying is quickly

achieved in the hot air stream once the binder spraying is stopped. The principle benefit of fluid bed granulator is that it can carry out the entire granulation sequence in a single piece of equipment (the mixer – granulator – dryer) which may reduce granulation time by factors between 5 and 10 times when comparing with other traditional methods. Moreover, additional advantages are achieved such as reduced handling of product, reduced exposure of the ingredients to heat, yielding a narrower granule size distribution, which generally corresponds to more homogeneous granules, better drug content uniformity and better opportunity to precisely control the moisture level in the granulation (4). On the other hand, the main difficulty of using fluid bed granulator is to obtain a stable regime by carefully balancing the different input variables, hence to determine the process end point as well as the final product quality. Several studies have already shown the important effect of process variables on granule growth such as spray rate (5-12), air nozzle pressure (4-6,8,13-15), and temperature (6,12-14,16-19). Therefore, these variables have to be controlled and optimized in order to avoid any over or under-wetting and thus process collapse.

1.3.2.1. Fluidization theory

A fluidized bed is a bed of solid particles with a stream of air or gas passing upward through the particles at a rate fast enough to set them fluidized. This velocity is higher than the incpient fluidizing velocity, but lower than the

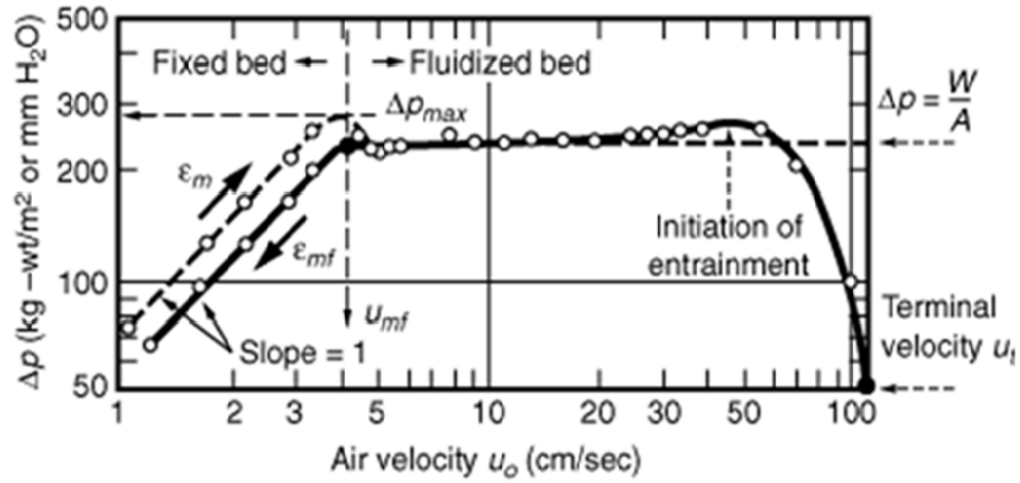

Figure 4: Relation between the air velocity and the pressure drop

entrainment velocity (88). Moreover, when the rate of flow increases, the pressure drop across the bed also increases until the fractional drag on the particles equals the effective weight of the bed. These conditions are called incipient fluidization and incipient velocity, respectively. The relation between the air velocity and the pressure drop is shown in the figure 4 (89).#At low gas velocity, the bed of particles is practically a packed bed, and the pressure drop is propertional to the superficial velocity. As the gas velocity is increased, a point is reached at which the bed behaviour changes from fixed particles to suspended ones. This superficial velocity is know as minimum fluidization

(U_{mf}). For granulation process in fluid bed granulator, the air velocity required is normally five to six times the minimum fluidization velocity. At the incipient point of fluidization, the pressure drop of the bed will be very close to the weight of the particles divided by the cross-sectional area of the bed (W/A). for the normal gas fluidized bed, the density of the gas is much less than the density of the solids and the balance of forces can be shown as :

$\Delta P_{mf} = W/A$ Equation (5)

$W = (1 - \varepsilon_{mf}) \rho p (g/gc)$ Equation (6)

Where ΔP = pressure drop, ε_{mf} = minimum fluidization avoid fraction, A = cross-sectional area, W = weight of the particles, ρp = density of the particles, g/gc = ratio of gravitational acceleration and gravitational conversion factor. As the velocity of the gas is increased further, the bed continues to expand and its height increases, whereas the concentration of particles per unit volume of the bed decreases. At a certain velocity of the fluidizing medium, termed as entrainment velocity, particles are carried over by the gas. This phenomenon is called entrainment.

A slugging bed is a fluid bed in which the gas bubbles ocuppy entire cross sections of the product container and divide the bed into layers.

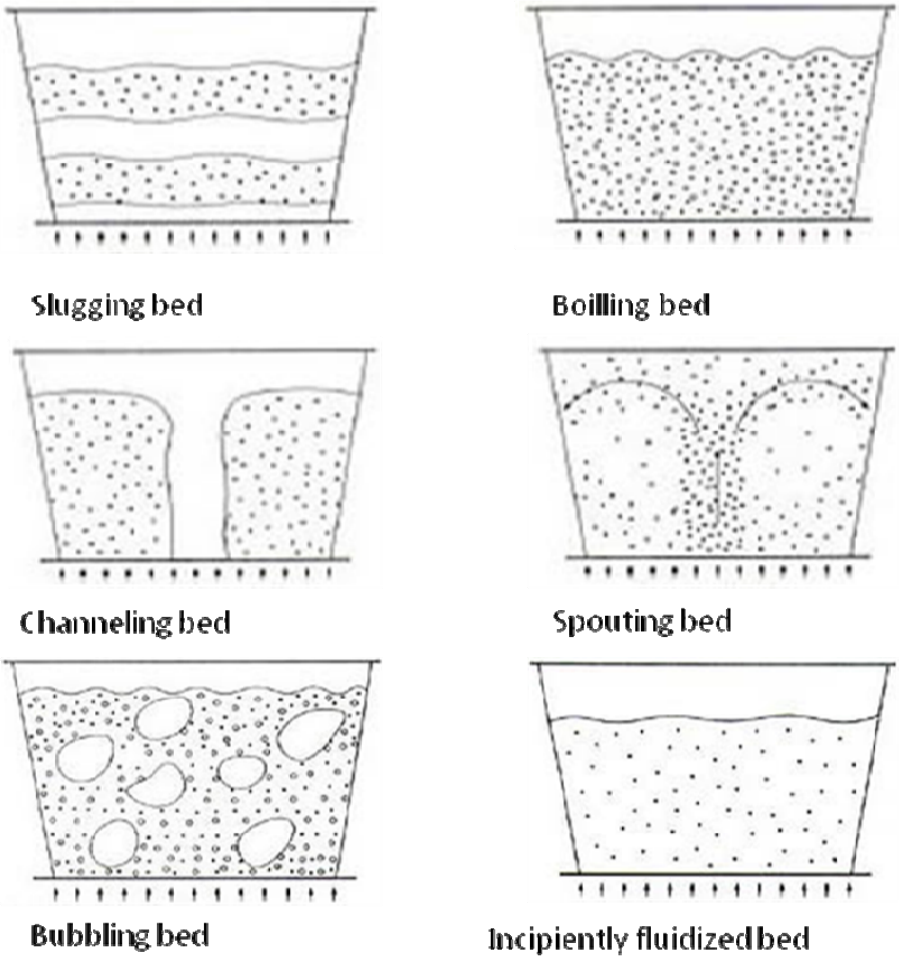

Figure 5: Various types of fluidized beds (90)

A boiling bed is a fluid bed in which the gas bubbles are approximately the same size as the solid particles.#

A channeling bed is a fluid bed in which the gas forms channels in the bed through which most of the air passes.

A spouting bed is a fluid bed in which the gas forms a single opening through which some particles flow and fall on the outside.#Figure 5 shows various types of fluidized beds.

1.3.2.2. Spray nozzle

A spray is a zone of liquid drops in a gas, and spraying is the act of breaking up liquid into a multitude of these droplets. The general purpose of spraying is to increase the surface area of iven mass of liquid to disperese it over the product area. The tow-fluid nozzle in which the binder solution (one fluid) is atomised by compressed air (second fluid) is the most commonly used nozzle for the fluid bed granulation figure (6).#

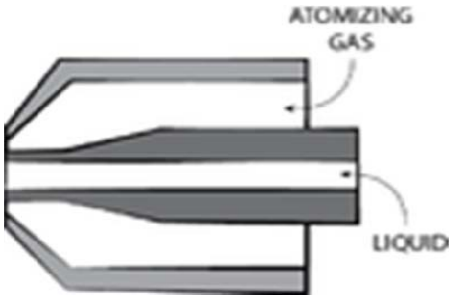

Figure 6: Schematic of spray nozzle

The air pressure required to atomize the binder liquid is set by means of pressure regulator. The spray pattern and spray angle is adjusted by controlling the air cap.#

The binder solution is delivered to the nozzle port through a spray lance and tubing. The peristaltic pump is commonly used to pump the binder solution. The pneumatically controlled nozzle needle prevents the binder liquid from dripping when the fluid flow is stopped. Nozzle port openings of between 0.8 and 2.8 mm in diameter are most common and are interchangeable.

1.4. Process analytical technology (PAT) initiative

The United States' Food and Drug Administration (FDA) has been pushing pharmaceutical industries to employ process analytical technology (PAT) in developing and manufacturing processes (20). The concept of ''Process Analytical Technology'' has been used to describe a system for designing and controlling manufacturing through timely measurements (during processing) of critical quality and performance attributes for raw and in-process materials and also processes with the goal of ensuring final product quality. The essential message of this initiative is that quality cannot be tested into products; it should be built-in or should be by design (20). The (PAT) initiative focuses on building quality into the product and manufacturing processes as well as continuous process improvement. Further, reducing production cycling time and minimizing rejected batches.

1.4.1. Process monitoring tools in fluid bed granulation

There is strong demand for tools implementation in order to monitor and control the granulation process in the fluid bed granulator. Those tools will help the operator to determine the process end point in order to get the desired mean particle size and

moreover to avoid the occurrence of defluidization such as channeling and blocking that can not be visually observed. The mean particle size of the granules is a key characterization of the product quality, since the granule and tablet properties are strongly dependent on it.

Sieve analysis, image analysis, and laser diffraction are the traditional off-line methods to determine the mean particle size of granulated material in fluid bed. Those traditional methods were inconvenient when using them off-line/at-line. They are often time-consuming procedures due to the additional sample preperation step. Moreover, the manual sampling and human errors do not provide representative results when comparing with continuous and automatic sampling. Direct in-line measurement facilitates the observation of the real state of the granulation process.

However, several researchers have been studied the use and performance of at-line, on-line, and in-line particle size measuring tools. Following a short definition of the terms:

At-line: Measurement where the sample is removed, isolted from, and analysed in close proximity to the process stream.

On-line: Meausrement where the sample is diverted from the manufacturing process, and may be returned to the process stream.

In-line: Meaurement where the sample is not removed from the process stream and can be invasive or noninvasive.

The use of on-line image analysis in fluid bed granulation was first performed by Watano et al (24, 25) and subsequently by Naervanen (81). Near infrared spectroscopy (NIR) was successfully introduced by Frake et al (27) and more recently by Rantanen et al (91) for the on-line moisture content measurement since NIR is strongly dependent on the chemical and physical composition and properties of a measured sample. Moreover, the NIR spectra are composed primarily of overtone and combination bands. Absorption in the NIR region is mainely due to the hydrogen stretching vibrations, involving C-H, O-H and N-H containing functional groups. On the other hand, Matero et al (82) have been developed an acoustic emissions (AE) method in order to monitor in-line the granulation process based on the concept that when granules grow larger and when the moisture content changes, thus their elastic properties also change. The changes in elasticity

property influences the acoustic emissions caused by the particle impact and friction, since acoustic emissions are generated between the fluidized particles and between the fluidized particles and granulator vessel walls.

1.5. Focused Beam Reflectance Measurement (FBRM) method

In recent years, FBRM D600 (Mettler-Toledo Inc) method has been extensively considered for in-situ characterization of different aspects of a particle. This technique has a wide range of applications in crystallization and polymorphism (33-36), flocculation (37-38), Petroleum and grinding (39), and biotechnology (40-41). Moreover, FBRM method has become a popular particle size analysis technique (42-45). First application to monitor the fluid bed granulation process at-line is performed by Hu et al (46). The main drawback of this study is that the particle size is measured off-line and therefore it includes sample preparation by the operator and contains sampling error and operator variability. In the present study, thanks to the cylindrical shape of FBRM probe, it could be implemented inside the granulator vessel in

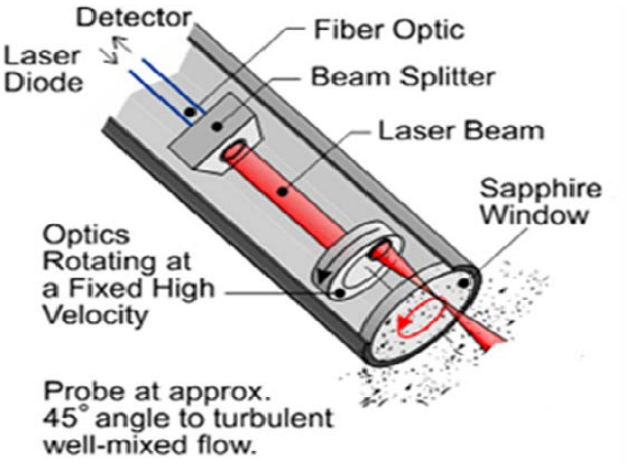

Figure 7: FBRM probe

order to perform in-line measurements. The great advantage of this method is that data are acquired in real time to give particle growth information and population trends of the fluidized particles. The FBRM method involves the use of a highly focused laser beam, rotating at fixed velocity (2m/s). The laser beam is projected through a sapphire window and scans across particles flowing past the probe window (figure 7). Back-scattering of the laser light occurs when the focused beam intersects the edge of a particle. The particle will continue to back-scatter until the focused beam has reached the opposite edge of the particle. This back-scattered light is collected by the FBRM optics. A unique discrimination circuit is used to isolate the time period of the back-scattered light from one edge of the particle to its opposite edge. This time period is multiplied by the scan speed and the result is a distance, which is called chord length. A chord length is a straight line between any two points on the edge of the particle. Typically, up to 100 000 chords are measured per second, which results in chord length number distribution. Hence, FBRM does not measure the particle size, but rather the chord length, which is related to the particle size and shape. Thus, the chord length distribution is not the same as the particle size distribution; however the particle size

distribution could be deduced from the measured chord length distribution specially when using spherical or round particles such as pellets or granules (47).

1.6. Sieve analysis method

A very common and traditional manner of measuring particle size in industry is sieve analysis (figure 8). The openings in the screens are described by a U.S. Mesh Number, which indicates the number of strands per inch. If sieve analysis is conducted on a sample W [g], then the masses (weights) of the fractions collected on the various sieves are denoted w_1, w_2,.. Each sieve is conventionally, assumed to collect particles of diameters of d_1,d_2…, of which the diameters are the average values of the diameters of the confining screens.

Figure 8: Sieve analysis apparatus

The average diameter of the entire batch sample may be expressed as (92):

$$d_{avg} = d_{vm} = \sum w_j d_j / \sum W = \sum n_j d_j^4 / \sum n_j d_j^3 \quad \text{Equation (7)}$$

Where, W =$\sum W$. This is a fourth-moment diameter and is denoted as the weight mean diameter.

Therefore, it is clearly noticed that sieve analysis method is strongly dependent on the weight mass of the sample measured. On the other hand, this measurement is not considering the particle shape changes in the sample. Therefore, sieve analysis method might give the same mean particle size for particles that have the same width but different shape. It is important to know that sieving measurement will ''size'' based on the second largest particle dimension (figure 9) (102). Therefore, measuring particles

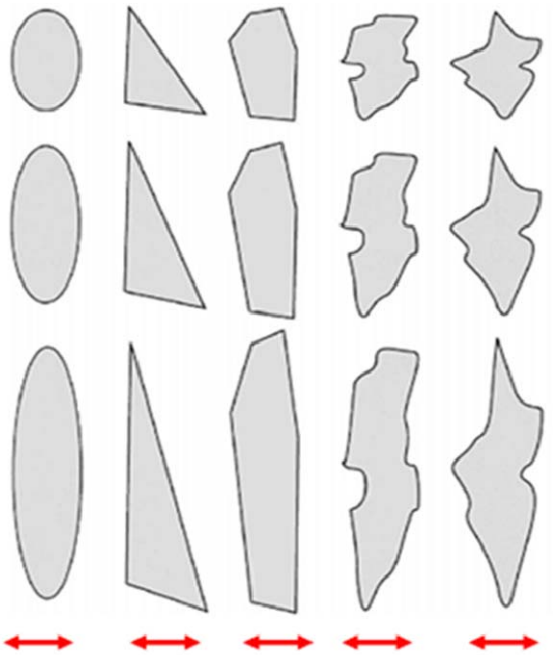

Figure 9: Effect of particle shape on sieve analysis

that have needle-like shape or particles that are not completely spherical could not be representative since this measurement will be influenced by the orientation of the particle when it passes through the screen.

1.7. Tablet compaction

The most common method of drug delivery is the oral solid dosage form, of which tablets are predominant. Tablets are more widely accepted and used for a number of reasons, such as low cost, tamper resistance, they provide an accurately measured dosage in a convenient portable package, ease of handling and packaging and they can be designed to protect unstable medications or mask unpalatable ingredients. Although, tablets are convenient to transport in bulk, since they contain relatively small proportions of ingredients unlike, for example, oral liquid that occupy much more space. Tablets are defined in the European Pharmacopoeia 2010 as following: ‘’solid preparation each containing a single dose of one or more active substances, they are obtained by compressing uniform volumes of particles or by another suitable manufacturing technique, such as extrusion, modeling or freeze-drying (Lyophilization)

(48). In order to get tablets of satisfactory quality, it is important that all ingredients are fairly dried, powdered or granular, uniform in particle size and freely flowing. The formulations that have wide particle size distribution or non-homogeneous particle size could segregate during manufacturing operations due to different densities, which can result in tablets with poor drug or active pharmaceutical ingredient (API) content uniformity, however wet granulation should prevent this phenomena.

1.7.1. Tablet manufacturing

Tabletting is the conversion from powder form into a coherent compact of defined shape and strength. The compact property could be defined by two terms; compression and compaction. The compression term represents the reduction of powder volume while the compaction one (solid consolidation) shows the increase in the mechanical strength (49-51). Tablets are produced from granules and direct compressed powders. A comparison between those two methods is discussed in the table (1) below.

Table (1): Advantages and disadvantages of granulated and non-granulated material:

Method	Advantages	Disadvantages
Direct	• Short time of manufacturing cycle,	• Inappropriate for high drug

compression	no wetting and drying steps • Minimum loss of material	load • High costs for the excipients • Decreased content uniformity of the drug due to segregation that might occur • Dusty material • Not possible for bulky and fine powders
Dry granulation	• • Suitable for heat and moist sensitive ingredients, no wetting and drying step	• Loss of material • Wide particle size distribution • Not suitable for bulky powders • High compaction pressures needed (reworkability of the API)
Wet granulation	• Narrow particle size distribution (even for low drug load) • Properties and ratio of the excipients are less important • Bulky and fine powders can be granulated • Producing a material with good plasticity • Suitable for all the types of the tablets	• Complex and multiphase process • Time consuming, high expenses • Non suitable for heat and moist sensitive APIs

The tablet manufacturing process of rotary tablet presses occurs in three main steps, die filling, precompression and compression, and ejection. Die filling stage depends on the flowability of the formulation that is mainly affected by the particle shape and size. The die is filled volumetrically by the influence of gravity and the volume is determined by

the depth of the cavity, which is usually set by the lower punch. Inappropriate dosage die filling might arise due to different reasons such as non-uniform particle size distribution resulting in segregation and high inter-particle friction. The compaction stage begins with the precompression step when the upper punch descends and enters the die, in which the bulk volume and the porosity of the material are extremely reduced hence the gaseous phase (air) is displaced (52). When the particles are close enough to each other; inter-particulate bondings are formed causing the individual particles to aggregate, forming a tablet, see also next section. The smaller the distance between punches, the higher the compaction pressure, causing the particles to cohere together. However, further volume reduction results in deformation behavior and subsequently fragmentation into smaller particles. Once the load of punches is removed, some particles are able to return to their original shape, which is called elastic deformation, while plastic deformation occurs when particles are permanently deformed. After removal of the compression force, the tablet is ejected from the die upon the removal of the upper punch and at the same time pushing the tablet by the lower punch out of the

die. It is necessary to diminish the frictional forces that occur between the powder particle and the die wall. Strong frictional forces may lead to failure in the ejection step.

1.7.2. Bonding mechanisms in tablets

Rumpf has been classified the general bonding mechanisms in five types (59):

- Solid bridges (sintering, melting, crystallization, chemical reactions, and hardened binders)
- Attractions between solid particles (molecular and electrostatic forces)
- Shape related bonding (mechanical interlocking)
- Bonding due to movable liquids (capillary and surface tension forces)
- Non freely movable binder bridges (viscous binders and adsorption layers)

This classification was widely accepted by researchers of the field; nevertheless Fürher (53) has been suggested that the principle bonds between particles in a tablet are classified in three types:

1- Mechanical interlocking: This mechanism can be described as hooking and twisting of packed material. Mechanical interlocking is dependent on the shape and surface of the particles and also on their deformation behaviour during the compaction process. The long needle-formed fibers and irregular particles have a higher tendency to hook and twist together more than smooth spherical ones. This mechanism is not based on atomic interaction forces and thus plays a minor role (Führer 1977) (53).

2- Intermolecular forces: These forces are considered as the most important ones for the mechanical strength of a tablet. This term represents several bonding forces such as van der Waals forces, electrostatic forces and hydrogen bonding (54), which act between surfaces separated by some distance.

3- Solid bridges: They contribute from re-crystallization or melting and solidification (55-59). The solid bridges appear when very high pressure is applied to the material during compaction. Moreover, the pressure performed to a particulate system is transmitted through contact points between particles. Thus creates high friction zones where temperature increases.

1.7.3. Particle deformation

When the compression pressure increases during the main compaction step, and no further particle rearrangement occurs, the original particles change their shape and the further increase of compression pressure conducts to particle deformation. Depending on their attitude to defromation, deformation behaviour can be divided into three groups: plastic, elastic and brittle. Plastic materials are permanently deformed, ones the compaction load is removed. While elastic materials can expand up to their original conformation or even different shape. The brittle ones break into pieces. The compression pressure requiered to initiate a plastic deformation is termed as yied stress (93).#

1.7.4. Compaction simulator

The transfer of a formulation from development scale to production scale is called scale-up and is very critical.

Tablets often show variability in their crucial characteristics such as breaking force and disintegration time. Indeed, scale-up of tablets is strongly dependent on the speed of the tabletting machine together with the applied compression pressure on the material. Therefore it would be ideal to keep the same compaction conditions during development and production. However, this is often not possible because different equipment is used. In this case, a robust and reproducible formulation should sustain its physical properties as well as avoiding capping and lamination (60-68), picking and sticking (69-72), and chipping (73-74), which can affect the appearance of the tablet and also the dissolution, and consequently the bioavailability.

In order to minimize the scale-up problems and number of trials that are required to optimize the production process, compaction simulators were designed. They simulate the production conditions and facilitate the development of formulations. Different researchers have been reported the use of compaction simulators as tools for robust

formulations (49, 52, 75-76). However, the only limitation that can restrict the use of a compaction simulator is the high price of it.#

Presster™ (Figure 10) is a single high speed station, linear compaction simulator, which can mimic any rotary tablet press on the basis of dwell time using small amount of materials. No hydraulic controls are required; therefore it can simulate the tablet presses without any artificial, theoretical or prerecorded punch displacement profiles. Punches and die are built in a carriage that moves linearly through the pre- and main compression step. The linear speed of the carriage is variable. The die volume and the powder weight is controlled by adjusting the lower punch position. The distance

Figure 10: Tablet press simulator Presster™

between the rolls is adjustable and can fit to any special tooling. The linear movement of the carriage allows the calculation of RPM and Dwell time for any press regardless of the number of stations. However, the Presster™ is incapable to simulate the centrifugal forces of a rotary tablet press, the die fill and feeding when investigating the compression speed nor studying the temperature that arises from friction and vibration fluctuations during tableting.

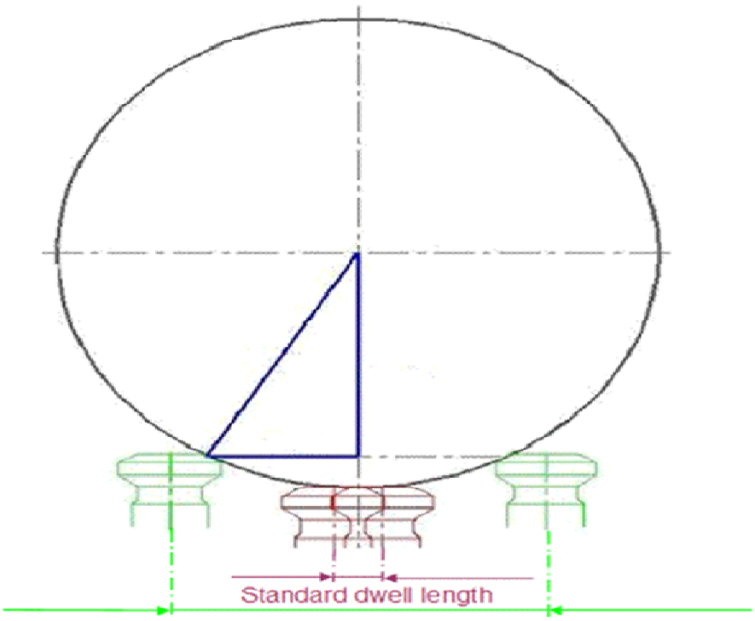

Figure 11: Dwell time phase

Moreover, in order to move to the industrial scale, an important attention should be payed to the dwell time or contact time. The dwell time is defined as the time when the punch does not move in vertical direction or the time of contact of the flat portion of the punch head with the compression roll figure (11), (94).# Dwell time is calculated according to the following equation :

$$DT = \frac{L.NS.3600000}{\pi.PCD.TPH}$$ ##Equation (8)#

where L=Length of a flat portion of the punch head (mm), NS=Number of stations, PCD=Pitch circle diameter of the turrent (mm), and TPH=Tablets per hour

1.7.5. Tablet press instrumentation

In order to ensure quality by design to the development and production of the pharmaceutical solid dosage forms, the material properties have to be characterized and the process should be well understood. Tablet press instrumentation is required in all steps of the tabletting cycle (98).

1.7.6. Systems involved for tablet press instrumentation

Different types of sensors are applied for the instrumentation of tablet presses. Tablet press sensors are mainly intended to measure applied force, compaction speed or punch displacement (99).

Strain gauges and piezoelectric transducers are mainly used in tablet presses. They are capable to measure different forces in the tablet press such as precompression,

compression, ejection and take-off forces. A strain gauge is a network of wires, through wich an electric current is passed. Under stress, the wires of the strain gauge deform and hence its electrical resistance changes. The size of the signal is proportional to the deformation, which in turn is a function of the applied force. In order to ensure signal balancing, a special arrangement of strain gauges (wheatstone bridge) is performed. Wheatstonebridge is composed of two pairs of resistors in a circle. This technique is used to increase the sensitivity of the sensors and to erase the impact of the temperature on the signal.

Piezoelectric force transducers consist of quartz crystals, which accumulate electrical charge when subjected to stress. This charge is proportioanl to the applied force, but signal drifting occurs due to charge leakage. The most precise results can be obtained if the measurement is done as close as possible to the tip of the punch (101).

1.8. Leuenberger equation

Leuenberger et al (51) has derived an expression to account for the compressibility and compactibility of powder systems based on an examination of bonding and nonbonding

contact points across a cross-sectional area of a compact. Compressibility is defined as the ability of a powder to reduce in volume under pressure, and compactibility is the ability of a powder to attain a specific strength. Leuenberger and co-workers have been proposed that deformation hardness of a tablet could be correlated with the compressive stresses during compaction. They have claimed that increasing relative density of the compact allows more particles to come into contact and increases the deformation hardness.

From a pharmaceutical point of view, it is more important to get a compact of defined strength rather than of defined volume reduction. However, the use of the Leuenberger equation is a good model where compressibility and compactibility are included:

Figure 12: Disintegration apparatus

$$\sigma_t = \sigma_{tmax} .(1–e^{-\gamma t.\sigma.\rho r}) \qquad \text{Equation (9)}$$

Blattner et al have been supposed that equation (9) can be applied using the tensile strength σ_t, the relative density ρr, and the compaction pressure σ to fit the maximum possible tensile strength σ_{tmax} at zero porosity and the pressure susceptibility γ_t.

The maximum tensile strength σ_{tmax} is a degree for the compactibility. However, the γ_t expresses the compressibility of the material. A low σ_{tmax} value corresponds to a relative poor compactibility, while high γ_t exhibits a good compressibility.

1.9. Disintegration test

The disintegration apparatus (Figure 12) consists of a basket-rack assembly containing six open-ended glass tubes with a 10 mesh screen on the bottom. The basket-rack is immersed in an 800ml of distilled aqueous medium at 37°C in a one liter beaker so that the basket-rack is never less than 2.5 cm below the surface of fluid or above the bottom of the beaker. The basket-rack is raised and lowered through a distance of 5 to 6 cm at a rate of 30 strokes per minute.

To determine disintegration time, a tablet is placed in each glass tube and a disk may be added. The disks are perforated and grooved, intended to simulate the movement of the gastro-intestinal tract. The disintegration time is the time required for a tablet to rupture and the particles fall apart through the screen until a soft mass having no palpably firm core remains on the screen. The disintegration time of a tablet is strongly dependent on the physical and chemical properties of the tablet. Moreover, disintegration time is usually connected to particle size of the tablet, which is markedly affecting the bonding behavior between the particles. Tablet disintegration can be divided in four different mechanisms that are responsible for breaking up the binding force in a tablet and thus initiating disintegration (95, 96):

- **Swelling**: particles swell and break up the bonds inside the matrix
- **Deformation recovery**: particles swell to pre-compression size when revealed to moisture. This phenomenon conducts to localized stresses followed by breaking up the matrix.
- **Wicking:** water is pulled into pores and reduces the physical bonding forces between particles.

- **Repulsion:** water is drawn into pores and particles start to repulse each other because of the resulting electrical forces.

Moreover, tablet porosity has been showed a strong influence on the disintegration time. Thus the penetration of water into a tablet is proportional to the tablet porosity. Furthermore, the porosity and permeability of tablets decrease as the applied tabletting pressure is increased, and as the porosity decreases, the disintegration time increases (97).

1.10. The choice of Pharmaceutical excipients and active pharmaceutical ingredient

Various different excipients are available to produce granules and tablets. Among those, Microcrystalline cellulose (MCC) has gained widespread acceptance according to its superior compressibility and compactibility properties.

Microcrystalline cellulose: The preparation of cellulose in a microcrystalline form was first disclosed in patents issued in 1961, 1962 and 1964 and was later described in several basic papers by Battista and Smith (77-79) of the American Viscose Corporation. The product was first commercialized in 1962 under the brand name Avicel® which is currently marketed by FMC Corporation with four different particle size grades, each with different properties. MCC 101 is one of the most used filler binders in direct compression due to its extreme good binding properties. It also works as a disintegrant and a lubricant and has a high dilution potential in tablets prepared by wet granulation, for the production of granules.

Paracetamol: or acetaminophen is widely used over-the-counter analgesic (pain reliever) and antipyretic (pain reducer). It is commonly used for the relief of headaches, other minor aches and pains.

Paracetamol is well known that it has various difficulties to compact it by direct compression and even by dry granulation, therefore, it has been decided to employ a model system of Paracetamol wet granulated, which has strong criteria for the evaluation of the physical properties of the granule as well as of the tablet, since Paracetamol powder exhibits a very poor flow and compaction behavior.

In the current work, Paracetamol was chosen as an API substance based on its properties. First Paracetamol shows a very poor compaction behaviour, it exhibits capping and lamination in direct compaction even during a low drug load, and also shows poor flowability. These reasons oblige the pharmaceutical industries to granulate Paracetamol powder before the compression and compaction step. On the other hand, Paracetamol is well know as it is cohesive material and this might be an extreme case regarding the sticking problem of the powder on the FBRM window. Therefore, the ratio

of Paracetamol was set to 68% which is considered as a high drug load to get a formulation which reflects mainly the Paracetamol properties that are mentioned above.

1.11. Design of experiment (DOE)

Increasing productivity and improving quality are important goals in any business. The methods for determining how to increase productivity and improve quality are evolving. They have changed from costly, time consuming, and trial and error searches to the powerful, elegant, and cost effective statistical methods, which is called design of experiments.

Experimentation may be defined as the investigation of a defined area with a firm objective, using appropriate tools and drawing conclusions that are justified by the experimental data so obtained. Most experiments consist of measuring the effect that one or more factors have on the outcome of the experiment. The factors are the independent variables, and the outcome is the response or dependent variable (80).

The overall experimental process may be divided into the following stages:

1. Statement of the problem. What is the experiment supposed to achieve? What is its objective?

2. Choice of factors to be investigated, and the levels of those factors that are to be used.

3. Selection of a suitable response. This may be defined in Stage 1, statement of the problem. If so, then it should be certain that the measurement of the chosen response contributes to achieving the objective.

4. Choice of the experimental design. This is often a balance between cost and statistical validity. The more an experiment is replicated, the greater the reliability of the results. However, replication increases cost, and the experimenter must therefore consider what is an acceptable degree of uncertainty.

5. Performance of the experiment: the data collection process.

6. Data interpretation.

7. Drawing conclusions.

A simple factorial desin is one in which two factors are studied at two levels : low and high. The design consists of four experiments (-1,-1), (+1,-1), (-1,+1), (+1,+1) (see figure 13) which are carried out simultaneously, using identical apparatus and the same personnel.# This is because there may be uncontrolled or even unknown factors that can affect the response. The regression equations obtained from the experiments based on factorial design are only valid for the factor space where they were calculated from. Extraplotations outside this space are not applicable. Thus, it requires knowledge of the behavior of the factos and responses to set a useful design space. In comparison to full factorial design, where all factors are examined at all levels and all possible combinations are tested, fractional design is more economical by decreasing the number of experiments. Fractional design are extremely useful in

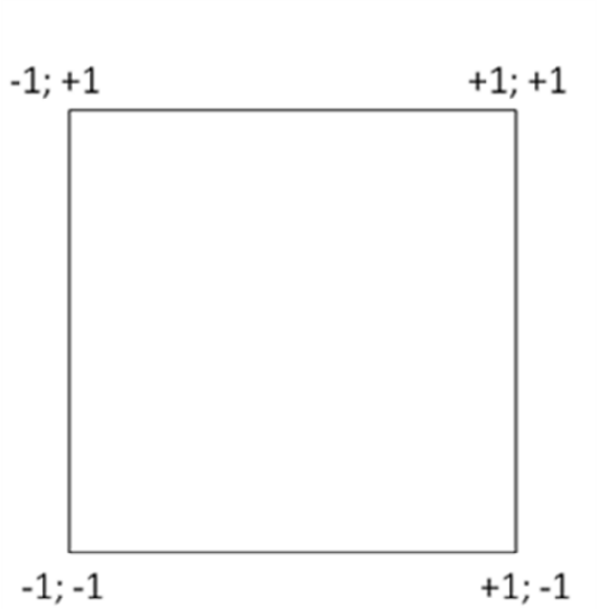

Figure 13: Full factorial design of a 2^2 design

screening experiments where many factors are considered (more than three factors). Those factors that have large effects can be identified, and these can be more throughly investigated.

1.12. Aim of the work

The main aim of the work was to investigate the performance of FBRM method as a monitoring tool of the granulation process when applying it into a fluid bed granulator. In this study, the position and location of the probe was taken into consideration in order to achieve the optimum balance between the representative fluidized particles zone and preventing sticking problems on the probe window. The FBRM method to monitor in-line the granule growth was compared with an external method, such as sieve analysis. Design of experiments was applied in order to determine the significant parameters and to optimize the experimental plan. In the second part of the work the relationship between CLDs and PSDs and the final tablet quality such as the disintegration time, breaking force, compactibility and compressiblity was investigated.

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Chapter 1: Focused beam reflectance method as an innovative (PAT) tool to monitor in-line granulation process in fluidized bed

Abstract

Fluidized bed granulation is a commonly used unit operation in the pharmaceutical industry. But still to obtain and control the desired granule size is challenging due to many process variables affecting the final product. Focused beam reflectance measurement (FBRM, Mettler-Toledo, Switzerland) is an increasingly popular particle growth analysis technique. FBRM tool was installed in two different locations inside a fluidized bed granulator (GPCG2, Glatt, Binzen) in order to monitor the granulation growth kinetics. An experimental design was created to study the effect of process variables using FBRM probe and comparing the results with the one's measured by sieve analysis. The probe location is of major importance to get smooth and robust curves. The excess feeding of binder solution might lead to agglomeration and thus to process collapse, however this phenomenon was clearly detected with FBRM method. On the other hand, the process variables at certain levels might affect the FBRM efficiency by blocking the probe window with sticky particles. A good correlation was obtained

(R^2=0.95) between FBRM and sieve analysis mean particle size. The proposed in-line monitoring tool enables the operator to select appropriate process parameters and control the wet granulation process more efficiently.

Key words: Focused beam reflectance measurement (FBRM), Fluidized bed granulation, particle size determination

1. Introduction

Granulation is an important and frequently used unit operation in industries of various fields such as pharmaceutical, agriculture, food, etc. in order to improve the properties of the starting materials. Wet granulation processes, such as high-shear granulation or fluidized bed granulation are often chosen in the manufacture of pharmaceutical granules and can be considered as critical. Since many decades formulators and operators are searching for the correct process time and the correct amount of granulating liquid addition (1-4).

Fluid bed spray granulation consists of three sequential phases; wetting and nucleation, consolidation and growth and finally attrition and breakage (5-8).

Fluidized bed granulation (FBG) has been successfully applied to produce granules with improved physical properties such as particle size, shape, density and porosity (9-18) where this improvement leads to a better compactiblity and compressibility in tableting process (16,19-21). Furthermore, the flow properties enhancement, producing a dust-

free product and the uniformity of drug content even at high drug load are other advantages to be achieved in this method (22,23).

FBG is one unit where the mixing, granulation and drying processes are carried out inside a single container. However, FBG is still not well understood with a large number of variables affecting the granule properties, these variables could stem from the apparatus or process variables. Several studies have already shown the important effect of process variables on granule growth such as spray rate (17,18,24-29), air nozzle pressure (17,18,25,30-33), and temperature (14,15,18,29,31,32,34,35). Therefore, these variables have to be controlled and optimized in order to avoid any over or under-wetting and process collapse.

A number of different technologies are commonly used for the off-line analysis of particle size; sieve analysis, image analysis and laser diffraction. However, those methods have some drawbacks such as requiring process interruption, high duration and the inability to provide real-time information. Many authors have been examining the use of NIR for at line, on-line or in-line particle size measurement during granulation

process (21, 36-41). But the temperature sensitivity of NIR spectra and the needed efforts to build calibration model are limiting the use of this method.

The United States' Food and Drug Administration (FDA) has been pushing pharmaceutical industries to employ process analytical technology (PAT) in developing and manufacturing processes (42). The main aim of implementing PAT initiatives is to ensure a final product with high quality and to prevent batch rejection.

Recently, Focused Beam Reflectance Measurement (FBRM) is being widely considered as technique for particle size analysis. FBRM provides in-line particle growth measurement even in a wide range of solid concentrations. The cylindrical shape of FBRM probe simplifies the implementation in a granulation vessel. A low-intensity laser beam rotates through a sapphire window with high velocity (up to 8 m/s) crossing the particles which pass in front of the window, and the laser beam will intersect two edges of particle. The laser light is reflected and propagated back through the window to a photo-detector in the probe. The FBRM optics are collecting the backscattered light. A correspond chord length is calculated from the reflection time, which gives information on the particle size

distribution and the proximity of particles to each other. Due to the high velocity of laser rotation, many thousands of chord lengths of particles are measured per second, which is represented in chord length bins. So far, FBRM does not directly measure particle size distribution; however the calculated chord lengths are strongly influenced by particle geometry, particle number density, and refractive index of the particle (43,44). The elimination of sampling preparation and error, simple use and measurement robustness are the main advantages of FBRM.

FBRM technique has been used in various applications; crystallization and polymorphism (45-48), flocculation (49,50), and biotechnology (44,51).

Only few researchers, however, have been studying the wet granulation processes using FBRM probes (26). Nevertheless, none of them have been trying to implement the FBRM probe to monitor the particle growth in-line. The inline analyzer does not require a sampling system; it provides automatic and instant measurements. Moreover, it affords the advantage of none-perturbational analysis of a process regardless the scale of operation (42).

The aim of this study was to evaluate the use of FBRM method as an in-line tool in a fluidized bed granulator. The optimization of the probe location in the granulation vessel and identifying the critical process variables that affect the use of this technique were studied.

2. Experimental

2.1. Materials

Each powder batch consisted of 350g of Paracetamol (RHODAPAP RHODIA operations, Roussillon, France) and 150g microcrystalline cellulose MCC 101 (Pharmatrans SANAQ AG, Basel, Switzerland) was granulated, using 200g of 10 w/w % solution of polyvinylpyrrolidone (Kollidon K-30; BASF, Ludwigschafen, Germany) in distilled water.

2.2. Manufacturing process

Before granulation, the starting powder material was sieved through a 350µm screen to exclude the clumps. The granules were produced in a fully instrumented bench-scale fluidized bed granulator (Glatt GPCG 2; Glatt Air techniques Inc GmbH, Binzen, Germany). This employs a single top/centre atomized spray nozzle connected to a

peristaltic pump. A mixing phase was performed for 10 min before spraying until the required temperature was reached as specified from each experimental run. The binder solution was sprayed onto the powder bed using a nozzle assembled with 0.8mm liquid orifice and 2mm air cap. The nozzle height was set to 33cm from the distributor plate. The inlet airflow was 0.33m^3/s during mixing, and gradually increased up to 1.33m^3/s during the granulation and drying processes. The drying phase was performed at 60 °C until the final granules moisture content was below 2%. The process was performed according to the input variables of the specific run generated by design of experiments (DOE).

2.3. FBRM installation

The FBRM method was tested to be used in fluidized bed monitoring of granulation process. An in-line FBRM D600 (Mettler-Toledo Inc) probe was installed inside the granulator vessel having the probe window at the center point facing the distributor plate. Horizontal and sloped positions of the probe were tested (figure 1), where the FBRM probe was implanted in the fluid bed vessel with inclination of 90° and 45°, and

the distance between probe window and the distributer plate was 10 and 5 cm respectively. The process variables were fixed as follows; spray rate at 9.8 g/min, air nozzle pressure at 1.8 bars, temperature 41 °C.

2.4. Physical characterization of granules

2.4.1. Sieve analysis

After granulation, the particle size distribution was evaluated by sieve analysis, by using a vibrating shaker (Sieve shaker vibro, Retsch, Haan Germany) and seven standard sieves in the range of 90-1000µm with an increment of $\sqrt{2}$. The total mass of granules sample used for sieve analysis was 100g and vibrated for 15min. The test was performed in triplicate.

2.4.2. Scanning electron microscopy

In order to study morphology and shape of the produced granules, the granules were coated with gold in order to scan them with Scanning Electron Microscopy (ESEM XL 30, Philips, Netherlands).

2.4.3. Moisture content measurement

The moisture content was measured using Mettler LP 16 (Mettler instrumente AG, Switzerland). Two grams of sample was heated at 105°C for 20 min. This time setting was sufficient to reach constant mass. The percent weight loss was recorded as the moisture content.

2.5. Experimental design

A modified central-composite design was chosen by MODDE 9.0 software (Umetrics AB). This design is an excellent for the control of granulation process parameters. The examined variables were spray rate, air nozzle pressure and inlet air temperature as shown in table 1.The design has 8 corner points, 4 so called axis points and center-point performed in quadruplicate.. The set of data was evaluated by ANOVA using MODDE 9.0 program in terms of the statistical significance of the main effects and the interactions at a level of significance of ($p<0.05$). A multi linear regression was performed for data treatment. The effect of the process variables were then modeled, using a second order polynomial fitting (equations 1 and 2).

$$FBRM(Spray,Air,Temp)= a_1 \times Spray + a_2 \times Air + a_3 \times Temp + a_4 \times Spray \times Air + a_5 \times spray \times Temp + a_6 \times Air \times Temp + a_7 \times Spray^2 + a_8 \times Air^2 + a_9 \times Temp^2 + a_0$$

Equation 1

$$Sieve\ analysis(Spray,Air,Temp)= a_1 \times Spray + a_2 \times Air + a_3 \times Temp + a_4 \times Spray \times Air + a_5 \times spray \times Temp + a_6 \times Air \times Temp + a_7 \times Spray^2 + a_8 \times Air^2 + a_9 \times Temp^2 + a_0$$

Equation 2

2.6. Mathematical definitions for FBRM data processing

The following terminology is presented as a brief chronological outline to the steps of FBRM measurement:

Chord length: A straight line between any two points on the edge of a particle.

Count: A term used to describe the measure of a single chord. Each count represents a single chord of a given chord length in microns.

Channel: A bin with specific upper and lower limit in microns. Counts with a chord length between specific limits are put in a specific channel.

Chord length distribution: This distribution is comprised of 1234 channels covering the range from 0 to n*1024 µm on a linear scale where n= 1,2,3,4 for a scan speed of n*2m/s. The FBRM hardware measures each optical chord length individually then stores the counts of equivalent chord lengths in the appropriate channel.

Measurement: FBRM data were computed by iC-FBRM software (version 4.0 Mettler-Toledo AutoChem, Inc Columbia). Fifteen measurements, each of 30 seconds, were made continuously during the granulation process; the trends of measurements were then recorded and calculated over time using iC-FBRM acquisition software. The data were plotted in logarithmic scale channels, in the range 1-1024 µm. iC FBRM accumulates counts in a primary chord length distribution for an amount of time specified by the user. Once this time span is completed, the measurement is completed and the chord length distribution is passed from the FBRM hardware to the iC FBRM software. At this point, the FBRM hardware will start the next measurement. Once a measurement is saved to a file, it is referred to as a record. The record includes all

measured data, as well as all instrument configuration information relating to this measurement.

In order to normalize the count per channel, the iC FBRM software provides the number of counts n_i in each channel per second:

$$\dot{n}_i = \frac{n_i}{T_m}$$ Where T_m is the measurement duration ***Equation 3***

$$Y_i = w_i . n_i$$ ***Equation 4***

y_i is the weighted channel, the weights w_i are obtained via:

$$w_i = \frac{M_i^\gamma}{\sum_{i=1}^{N} M_i^\gamma}$$ M_i is the channel midpoint ***Equation 5***

In order to emphasize different regions of distribution separately, γ was varied from 0 to 2. When γ is 0 (no weighting) the weighting channel emphasizes the change in size distribution and count of fine particles. Whereas when γ is set to 2 (weighted channels), the weighting channel emphasizes the change in size distribution and count of coarse particles. However, if the raw weights used were $w_i = M_i^\gamma$ then the weights would

become very large for square and cube weights, which in turn would make the counts per channel and derived quantities (e.g., total counts) very large. For this reason, we have scaled the weights (not the counts) so the sum over the weights remains the same as if no weighting was chosen. That sum has to be N since each weight for ''No Weighting'' has to be 1. The operation is equivalent to normalizing raw weights W_i by their average.

The mean chord length is calculated as follows:

$$\mathbb{C} = \frac{\sum_{i=a}^{b} n_i M_i^{r+1}}{\sum_{i=a}^{b} n_i M_i^{r}}$$ Equation 4

The in-line FBRM technique provides a complete view on the changes in the kinetics of the granulation process in real-time. It offers detailed information about counts and particle size distribution for fine and coarse particles.

3. Results and discussions

3.1. The influence of FBRM probe position on the progression profile

The influence of probe position has not yet been investigated in literature. However, the optimum probe position is crucial for the performance of FBRM analysis. Two different positions were investigated and compared in terms of efficiency (as seen in figure 1) . From figure 2a it is clearly shown that the horizontal installation resulted in noisey, high scattering and non identified curves in the FBRM progression profile. The explanation of this phenomena is that the probe window was covered with powder during spraying phase. Having the probe far from the distributor plate with small distance to the air nozzle, allowed the binder solution to reach the probe window which became sticky after the evaporation of the binder solution. In contrast to this scenario, the sloped installation showed smoother and more reliable curves representing the continuous particle growth during granulation. Placing the probe with inclination angle of 45° allowed air flux to sweep away any particles that adhered to the window and kept it dry during the granulation process. In the sloped installation, the number of detected

particles was significantly higher than in horizontal installation (figure 2b). This indicated that the sloped installation kept the probe window clear and permitted the exposure to a higher population of particles sampled throughout the duration of the granulation process. Therefore, the sloped installation was chosen as a sampling position for the FBRM method in fluidized bed granulator.

3.2. Evaluation of the process profile monitored by FBRM

Figure 3 depicts a continuous particle growth which was evident during the granulation process. The kinetics profile of each batch is represented by square weighted mean chord length. As seen in figure 3, noise was evident for the first 20 min of each run, and this can be explained by the mixing phase in which the particles had high static electrical charge and thus, the window probe was covered with the powder. Once the spraying started, the window probe became clear. Moreover, the inlet airflow was keeping the probe window dry and clear by hitting and removing any particles that adhere to the probe window. When dividing the binder spraying duration into two half, it was observed that the granule growth was relatively slower in the first half than the second

one, this variety was due to the MCC which absorbs a huge amount of water before it becomes in larger particles. On the other hand, the different process parameters in each run had a significant effect on the particle growth and thus on granulation kinetics which was clearly observed in FBRM curves for run 6, which is consistent with the results describe in the work of Chew et al. (52). Several researchers have reported that using a high spray rate might lead to an excess in particle growth and therefore to collapse (53) due to the over-wetted powder which prevents the fluidizing process. The noise was clearly noticed in run 4 where the air nozzle pressure was increased to high level, the explanation of this is that the droplets of binder solution (which were atomized under high pressure) were easily reaching probe window, thus the droplets of the binder solution evaporated on the window and the binder tended to solidify, which promoted particles to stick on the probe. In run 13 similar noises were observed with lower air nozzle pressure and higher spray rate comparing to run 4. This was due to the higher amount of sprayed binder solution onto the powder bed, thus, the evaporation process was relatively slower comparing to the previous run which made the particles heavier and more difficult to fluidize. Once the count of fluidized particles above the probe

started to decrease, the probability of binder solution droplets to reach the probe window became much higher and led to an obstruction of probe window by powder particles. Nevertheless, runs 9 and 14 were good examples of FBRM results where the continuous particle growth was exhibited with less noise and no process interruption. (Figure 4a) shows a typical weighted chord length distribution (WCLD) obtained by FBRM. It is evident that the WCLD shifts to the right direction which is attributed to the particle growth and particle size enlargement during the granulation process. However; noise was clearly higher at 15 min, indicating the formation of granule clusters exceeding limited scale (>1000µm). The unweighted chord length (UCLD) as seen in (figure 4b) was decreasing which might be due to the fact that smaller particles are combining to form bigger ones which led to smaller particle counts. Moreover, a negligible increase in particle size was noticed and therefore, the UCLD was used only for the determination of particle count.

3.3. Correlation of FBRM with sieve analysis

Despite the difference in particle size measurement principle between FBRM and sieve analysis, the spherical shape of the granules enabled the comparison of FBRM method with sieve analysis. A good correlation was observed when the square weighted mean particle size measured by FBRM against the mean particle size from sieve analysis was plotted. The correlation is mostly influenced by particle geometry. The spherical shaped particles (54) give more comparable chord lengths to the average particle size than needle-like particles, which is in agreement with the findings of Barrett et al (44) (see figures 5a,b and 6). Sieve analysis measures the entire batch; however, particles having abnormal size do not affect significantly the mean particle size. On the other hand, FBRM determines the mean particle size of individual particles. The high sampling frequency (one measurement per 2 seconds) and the high number of scanned particles per measurement (up to few thousands) ensured robust and more representative profiles which corresponded to particle size measured by sieve analysis. As seen in figure 5b and table 1, batches having bigger mean particle size showed a better estimation

than those which had smaller mean particle size. Smaller mean particle size leads to presence of a higher number of fine particles. High number of fine particles contributed to higher number of particle counts. Fine particles have a higher likelihood to be detected by FBRM comparing to coarse ones. However, the fine particles tend to disperse towards the upper part of the granulator vessel which is distant from the detection zone of the FBRM probe. The coefficient of determination for the correlation between FBRM and sieve analysis measurements was 0.9019. (Figure 5 a and b) Shows that FBRM has similar error of measurement as sieve analysis which points out that the FBRM method is as usable as sieve analysis. However, the sieve analysis method measures particle size and does not take into account the shape of particles, which could lead to higher error of determination. Based on this hypothesis, the prediction of particle size by FBRM method might be improved by using more precise reference method such as laser diffraction which gives the volumetric shape of the particle.

3.4. Effect of the granulation process parameters on particle size

Model equations were generated by MODDE 9.0 software. Tables 2 and 3 show the corrected goodness of fit (Rc^2) and model validity (MV) for FBRM and sieve analysis. The obtained values of (Rc^2) and (MV) were (0.8382 and 0.9022), and (0.937 and 0.876) for FBRM and sieve analysis respectively. Having the (Rc^2) close to 1 and (MV) greater than 0.25 shows that the model fits the data well and there is no lack of fit of the model.

The effect of liquid spray rate was studied between 6.5 and 13 g/min using a 200g of an aqueous binder solution of PVP 10% W/W. The spray rate is a critical parameter in fluidized bed granulation processing (3, 4, 11, 55-57). (Figure 8) depicts that an increase of spray rate resulted in an increase of mean particle size which shows that it has strongest and most significant factor comparing it with the other factors. The excessive liquid spray, low evaporation rate and larger droplet size significantly encouraged the granule growth (58). However the decrease of contact surface between the particles and liquid droplets did not show a significant effect; this is in accordance with (55, 59-62)

who have been reported that an increase in atomizing pressure resulted in smaller spray droplet size as well as granule size.

On the other hand, the inlet air temperature variable had a profound influence on granule growth. The higher inlet air temperature and the higher evaporation rate of binder solution led to forming of smaller and weaker granules. Low inlet air temperature promoted the formation of larger granules, figure 9 showed a disproportional influence on the particle growth (63, 64). The air nozzle pressure had a negligible influence on the particle growth. Despite the important influences of the wetting phase and the mechanical force subjected to the granules, the high levels of air nozzle pressure slightly decreased the particle growth (65), (See figure 9 and 10).

Figures 9 and 10 show that the response to various granulation parameters measured with FBRM was comparable to the response measured with sieve analysis method.

4. Conclusion

The position of FBRM probe in the fluidized bed vessel was a critical one in assessing the initial usability of the method. Therefore, it is highly recommended to FBRM user to

optimize the probe position in order to keep FBRM window clear and to enable the process monitoring.

FBRM showed a continuous particle growth kinetic profile during granulation process. Binder solution spraying phase was shown to be an optimum point to start FBRM measurements. Excess of binder solution on the powder bed leads to agglomeration and therefore, the granulation process could break down. Nevertheless, the agglomeration was predicted with FBRM method which gave the possibility to adjust the process variables while the process is running and to avoid batch rejection.

The air nozzle pressure was shown to be a limiting factor for the FBRM method. High levels of air nozzle pressure allowed the binder droplets to reach the FBRM window which affected the efficiency of FBRM method. FBRM and sieve analysis results showed high correlation, although sieve analysis results exhibited positive bias. User should be careful about reporting the final average particle size. Furthermore, accuracy of FBRM results could be also determined by laser diffraction method.

The ability of FBRM to follow granulation process in-line shows the real advantage of the method for optimizing granulation process parameters and detecting process kinetics in real time.

Tables and figures for chapter 1

Table (1): Composition of experimental design and response for different formulations

		Factor 1	Factor 2	Factor 3	Response (1)	Response (2)
Experimental region	Run	Spray rate (g/min)	Air nozzle pressure (Bar)	Inlet temperature (°C)	Mean square weight (µm)	Mean particle size (µm)
Corner	1	6.5	1	22	226.94	360.41
Corner	2	13	1	22	469.15	741.53
Corner	3	6.5	2.5	22	238.73	398.83
Corner	4	13	2.5	22	-	-
Corner	5	6.5	1	60	162.2	300.19
Corner	6	13	1	60	252.73	424.31
Corner	7	6.5	2.5	60	199.15	271.12
Corner	8	13	2.5	60	310.18	460.03
Center	9	9.8	1.8	41	214.13	368.6
Center	10	8.1	1.8	41	154.83	291.31
Center	11	11.4	1.8	41	299.94	475.93
Axis	12	9.8	1.1	41	289.99	463.67
Axis	13	9.8	2.4	41	-	-
Axis	14	9.8	1.8	30	325.28	484.11
Axis	15	9.8	1.8	50	247.41	370.35
Center	16	9.8	1.8	41	307.36	473.83

Table (2): Model equation for weighted mean chord length measured by FBRM

Parameter	Estimated	P value	Regression coefficient	Factor description
Intercept	+265.2451	0.0004	-413.8	Intercept
*s	+94.5725	0.0084	+263.3	Spray rate
*a	+21.2109	0.2764	-417.1	Air nozzle pressure
*t	-66.8955	0.0218	-16.29	Temperature
*s^2	-115.3841	0.1766	-10.92	Spray rate square
*a^2	+64.6498	0.2557	+114.9	Air nozzle pressure square
*t^2	+83.0779	0.2878	+0.2301	Temperature square
s*a	+8.5003	0.6306	+3.487	Spray rate*air nozzle pressure
s*t	-41.0721	0.0822	-0.6651	Spray rate*temperature
a*t	+3.1513	0.8558	+0.2211	Air nozzle pressure*temperature
Goodness of fit (R^2) Corrected goodness of fit (R^2_c)				0.9595 0.8382
Predictability (Q^2)				0.501
Model validity (MV)				0.937

Table (3): Model equation for mean particle size measured by sieve analysis

Parameter	Estimated	P value	Regression coefficient	Factor description
Intercept	+416.5556	0.0002	-226.1	Intercept
*s	+146.4514	0.0036	+226.2	Spray rate
*a	+21.2844	0.3309	-595.3	Air nozzle pressure
*t	-111.9395	0.0077	-3.076	Temperature
$*s^2$	-81.4036	0.3596	-7.707	Spray rate square
$*a^2$	+97.2542	0.1644	+172.9	Air nozzle pressure square
$*t^2$	+43.4498	0.5992	+0.1204	Temperature square
s*a	+17.9638	0.3994	+7.370	Spray rate*air nozzle pressure
s*t	-65.9386	0.0370	-1.068	Spray rate*temperature
a*t	-18.5153	0.3869	-1.299	Air nozzle pressure*temperature
Goodness of fit (R^2) Corrected goodness of fit (R^2_c)				0.9755 0.9022
Predictability (Q^2)				0.350
Model validity				0.876

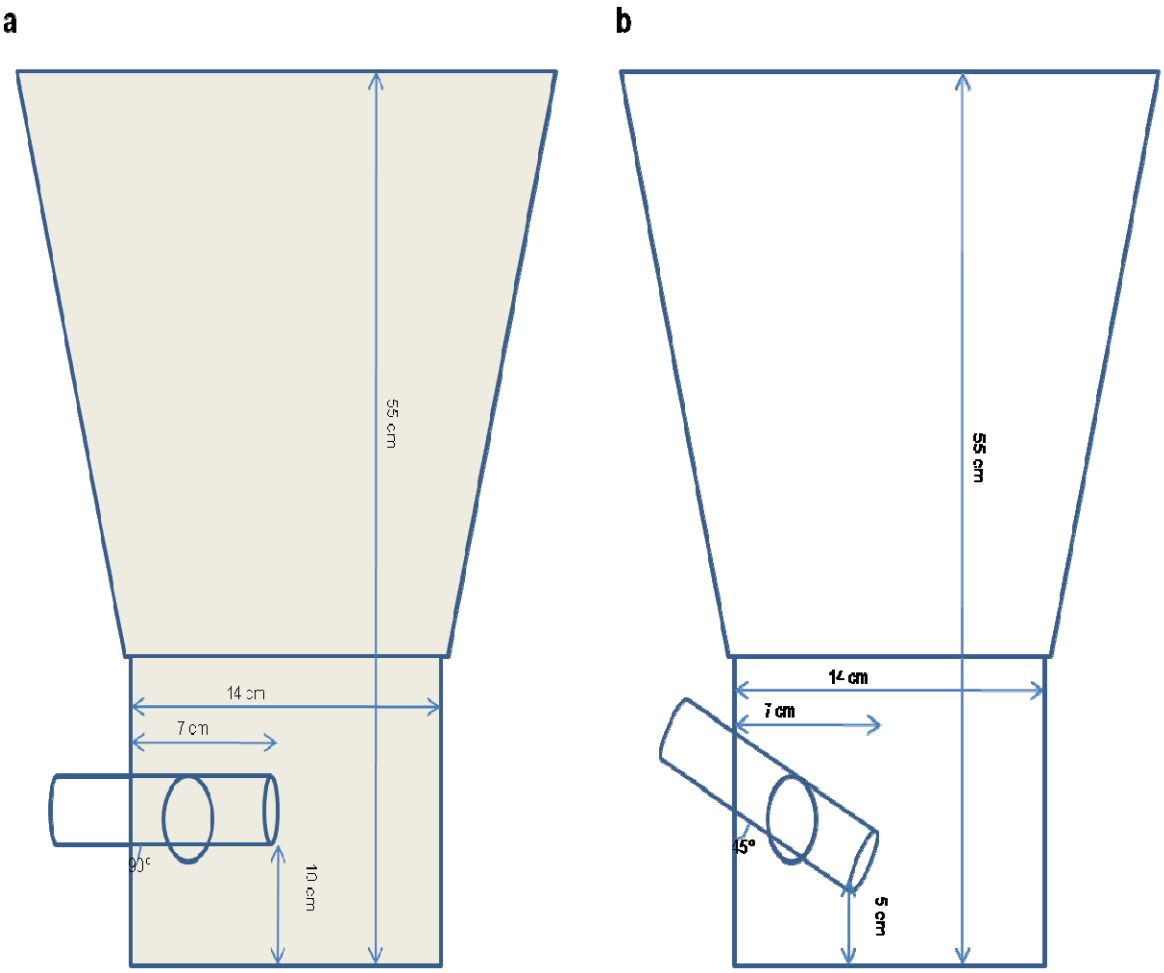
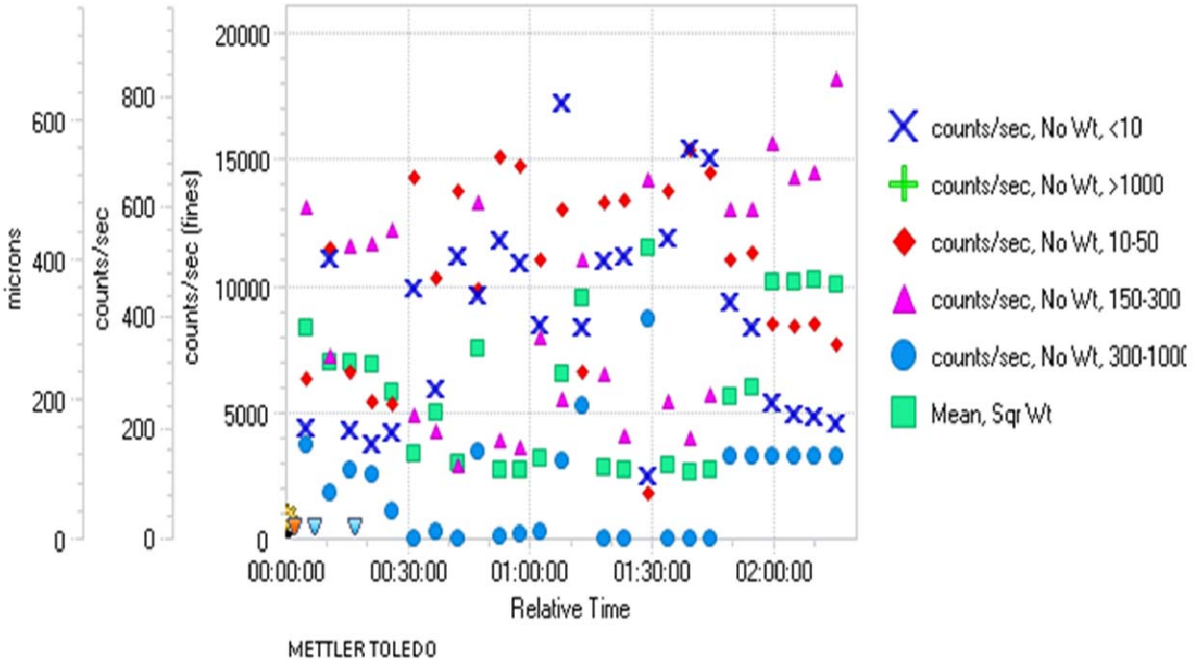
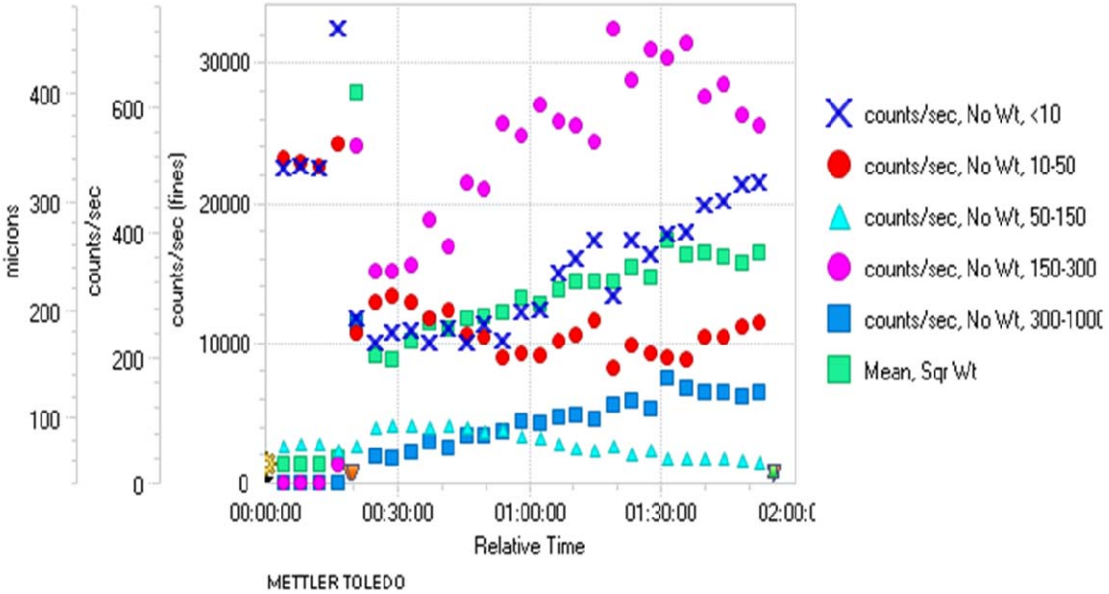


Figure (1): (a) Horizontal and (b) slopped Installation for FBRM probe inside the granulator vessel



(a): FBRM progression profile in the horizontal installation



(b): FBRM progression profile in the horizontal installation

Figure (2): Granule growth measured by FBRM detecting particle size from 10 to 1000µm for (a) horizontal and (b) slopped installation

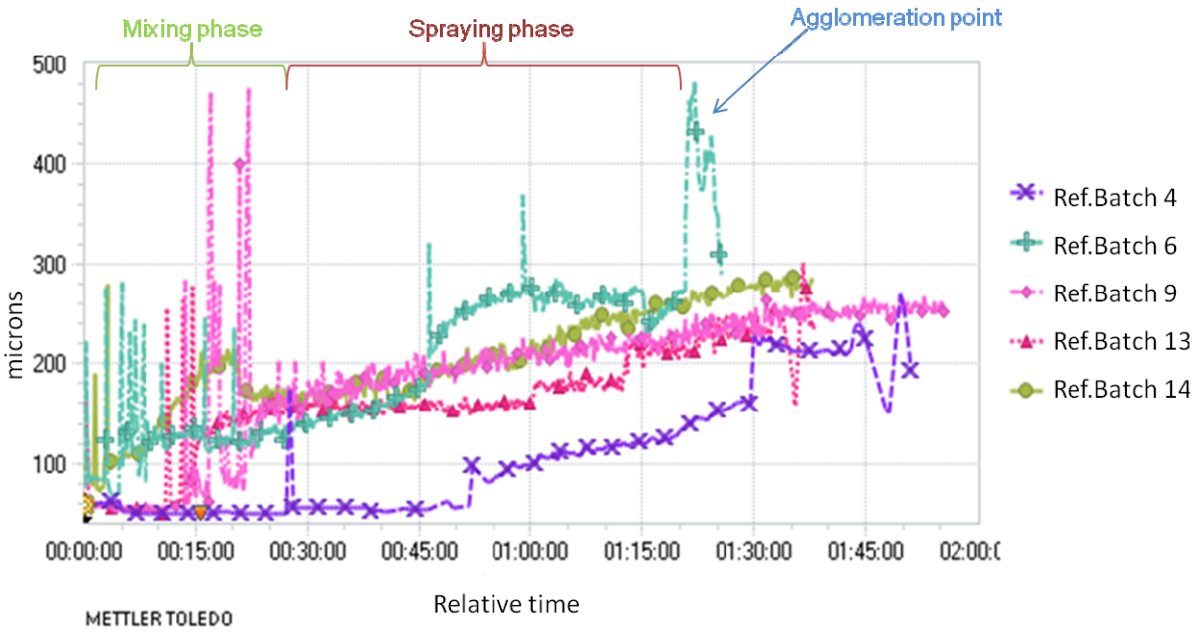
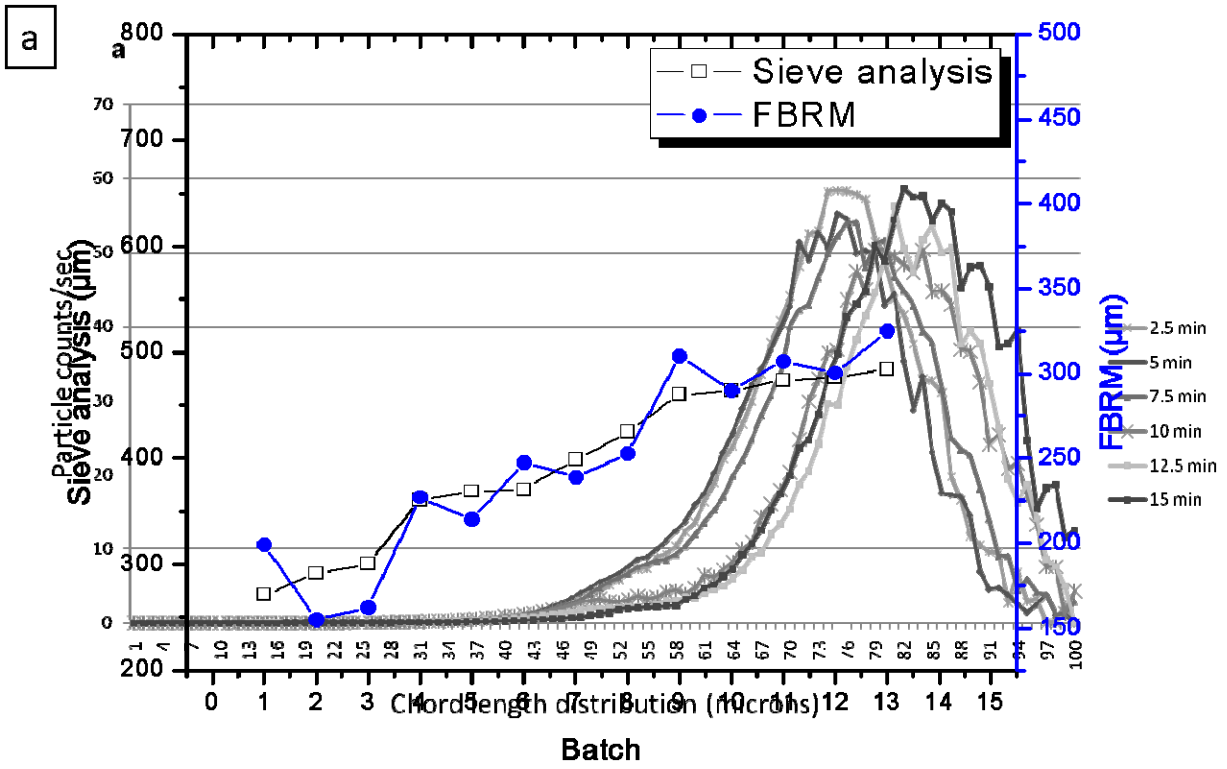


Fig (3): FBRM progression profile during granulation process shows that no measurements were able to obtain during mixing phase, run 3 and 13 show a noise due to the agglomeration occurred the fluidizing process which was nearly blocked, run 2 shows an extreme particle growth and noise due to the poor fluidizing process, runs 9 and 14 show continuous particle growth with no troubles



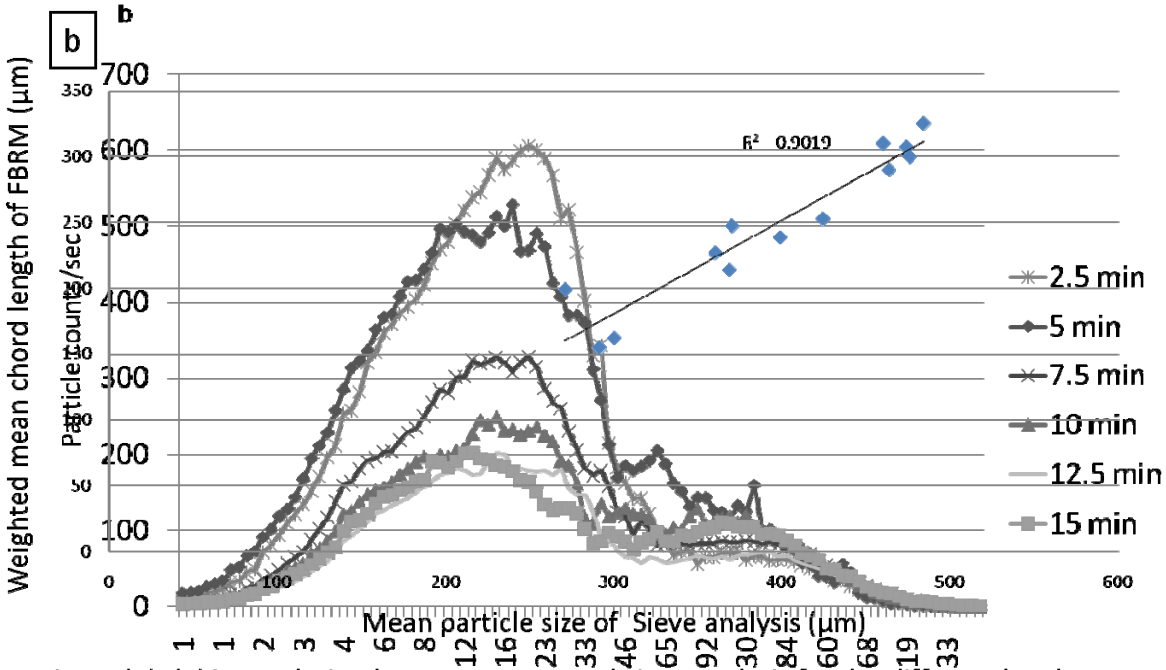


Figure (5): (a)Λ correlation between FBRM and sieve analysis for the different batches (b) FBRM mean chord length against mean particle size of sieve analysis

Fig (4): (a) Weighted shows a shifting to right side due to particle growth and (b) Unweighted chord length distribution for run 2 shows the decrease particle counts due to the increase of particle growth

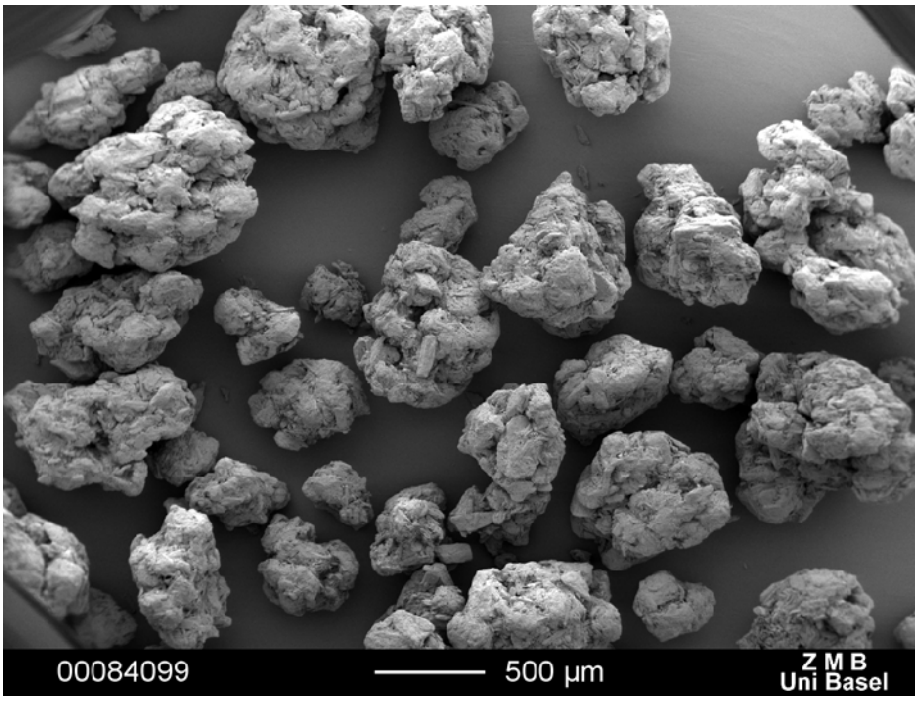


Fig (6): SEM image of final granules in run 3 shows a nearly spherical shape

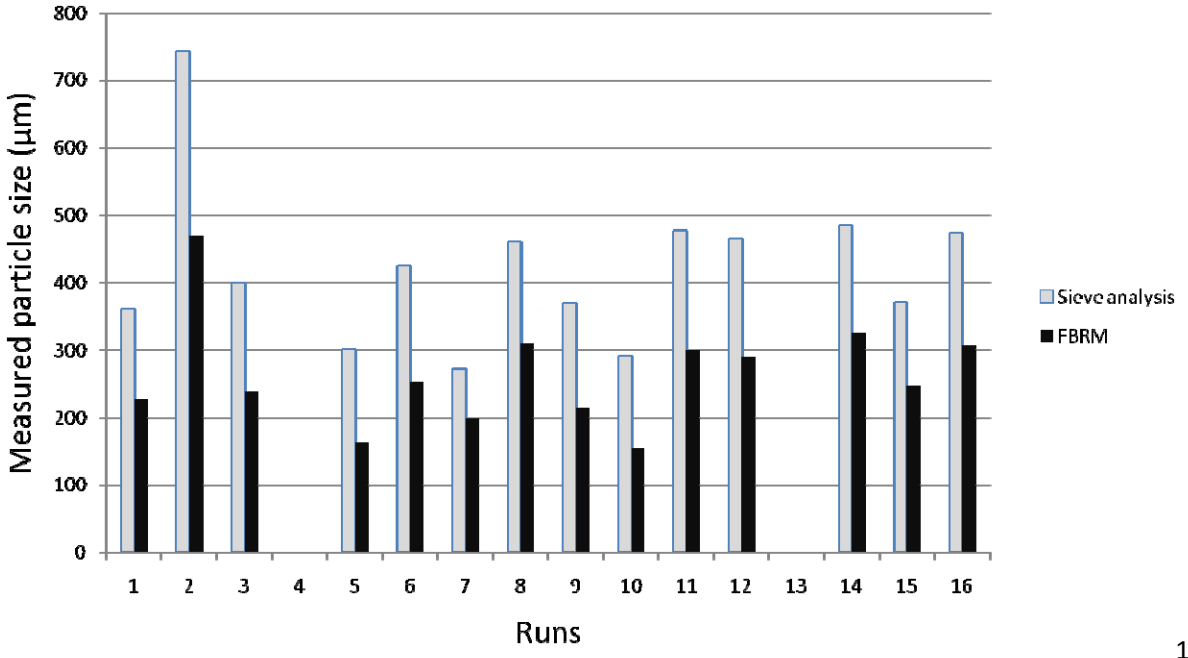


Fig (7): Mean particle size of dried granules measured by FBRM and sieve analysis, Data show that prdicted values for FBRM are smaller than those for sieve analysis. No measurements for runs 4 and 13 due to the agglomeration occourred during process

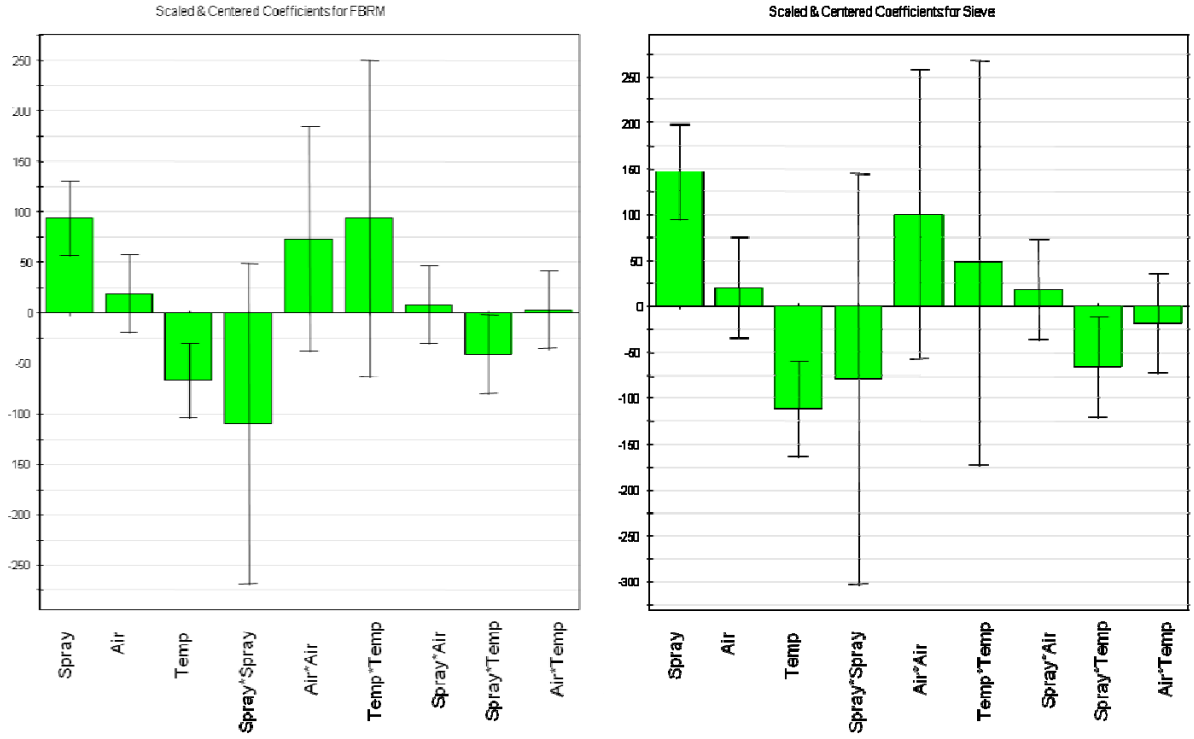


Figure (8): Coefficient plots of process variables for the responses FBRM and sieve analysis with confidence intervals

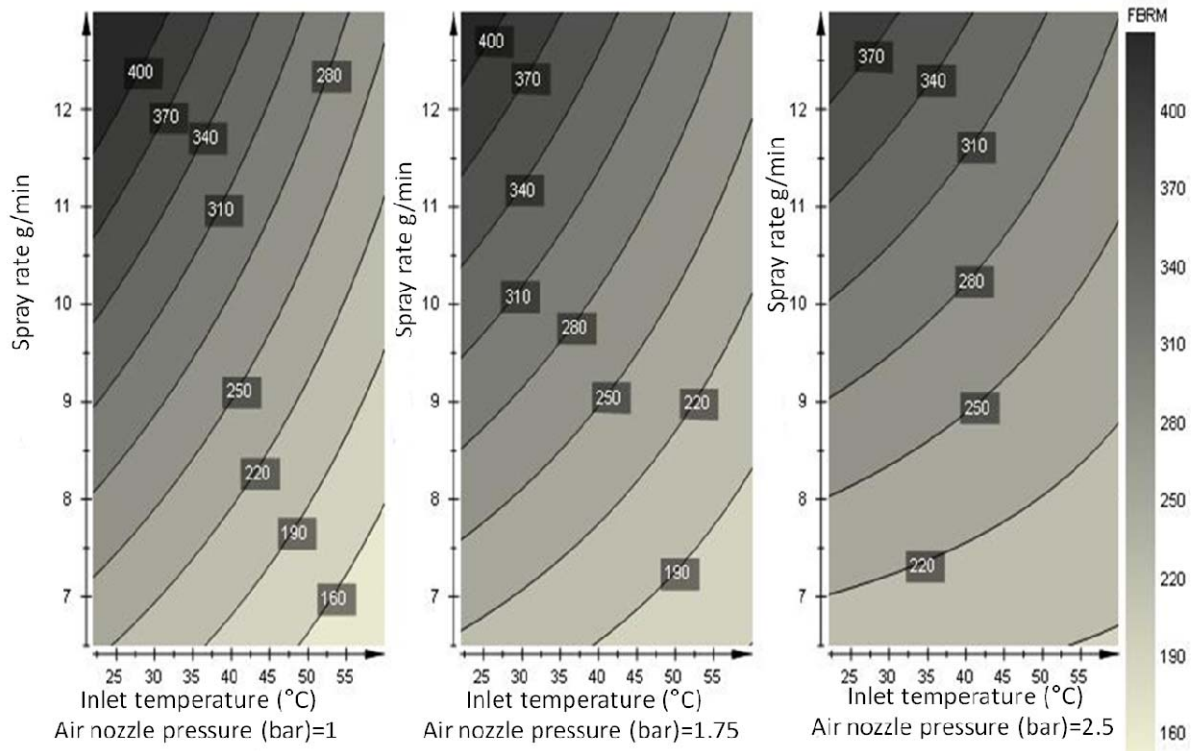


Figure (9): Granule size measured by FBRM; 4D contour showing the effect of process variables; spray rate and inlet temperature each at air nozzle pressure of 1.0, 1.75, and 2.5 respectively.

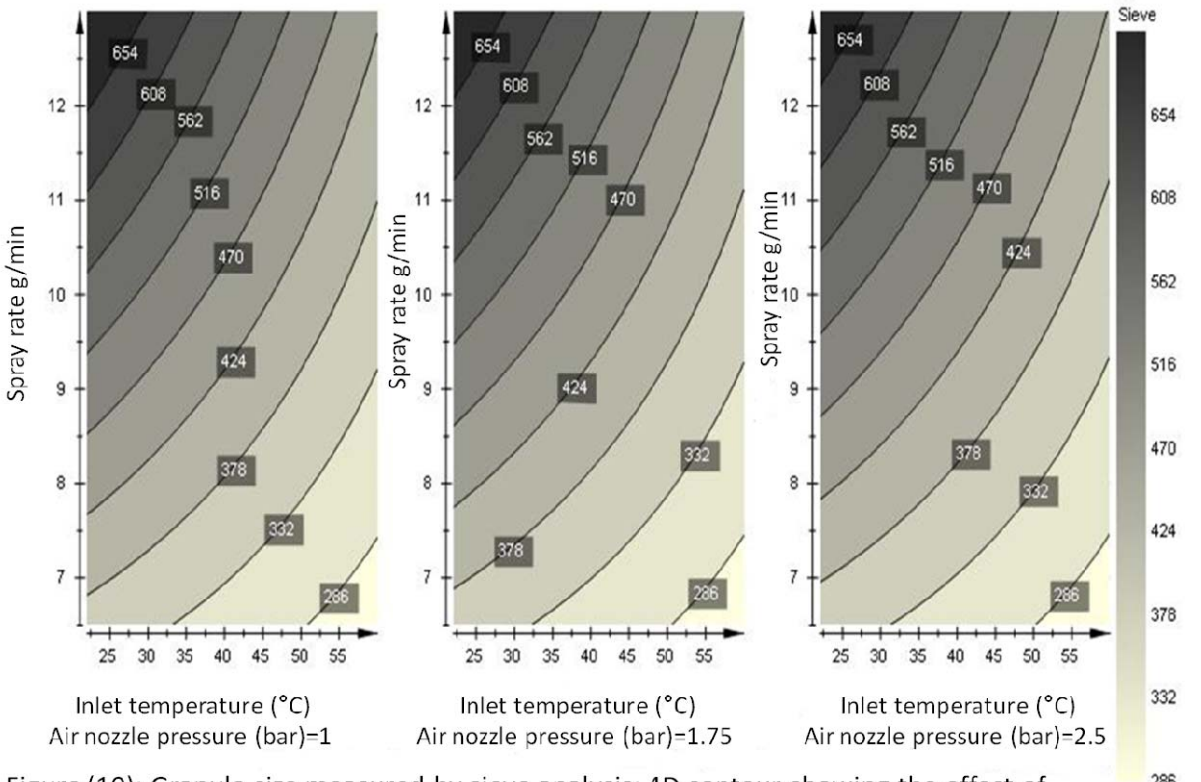


Figure (10): Granule size measured by sieve analysis; 4D contour showing the effect of process variables;Spray rate and inlet temperature each at air nozzle pressure of 1.0, 1.75, and 2.5 respectively.

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Chapter 2 : Investigation of the relationship between granule particle size and final tablet quality using fluid bed granulation process monitored by Focused beam reflectance measurement (FBRM) method

Abstract

Fluid bed granulation is a dominant method used to produce granules in the pharmaceutical industry. However, controlling the various process parameters is still challenging and granule product quality has further impacts on the tabletting process and final tablet quality. Focused Beam Reflectance Measurement (FBRM) was implemented inside the vessel of a fluid bed granulator as a tool for monitoring in-line the particle growth during granulation process. Fifteen granulation experiments were performed under different process parameters in order to vary the dimension of the granules. After granulation, the mean granule size was measured using sieve analysis. Then, the granules were compacted using an instrumented compaction simulator in order to simulate high speed tabletting conditions. The breaking force, disintegration time, compactibility and compressibility of the tablets were analyzed. The results showed that granule size has a powerful influence on the physical properties of the final

tablets, thus on the quality of the tablets. However, the prediction of those properties exhibited its dependency on the method used to determine particle size.

Key words: Focused beam reflectance measurement (FBRM), particle size determination, Breaking force, Disintegration times, Leuenberger equation.

1. Introduction

Wet granulation is a process widely used in pharmaceutical industry in order to agglomerate the powder particles into permanent aggregates by pendular or funicular bridges, in which the original particles can still be identified, using a liquid binder sprayed onto the fluidized powder (1-3). Among different techniques of wet granulation, fluid bed granulation FBG is the unique method by which the granules are produced and dried successively in a single piece of equipment. Three phases can be distinguished in the granulation process: (I) wetting and nucleation (II) consolidation and growth, and (III) breaking and attrition (4-7). FBG process offers various advantages, such as producing particles with modified physical properties (size, shape, density, porosity) (8-15) and further controlling those properties has a strong effect on the flowability behavior since the small mean particle size leads to less significant gravitational forces, whereas adhesive forces such as electrostatic and van der Waal's forces become dominant (16,17). Moreover, the mean particle size distribution has a powerful influence on the outcome of the compressibility and the compactibility of the tablets produced (11, 18-20). Further advantages are clearly noticed when using fluid bed granulation, such as

providing a better control of drug content uniformity at low drug load as well as for high drug contents, reducing the manufacturing process steps that shorten the manufacturing time (21, 22). However, FBG is a complex and dynamic process. The main challenge using FBG is to obtain a stable regime carefully balancing the different inter-related process variables, such as spray rate, the amount of liquid binder (3,15,16,23,24), air nozzle pressure (3,15,25), inlet air humidity, and temperature (13,14,26). Therefore, it has been shown that those variables have an influence on the mean granule size, which is one of the most important key characteristics of granulated products that strongly affect the tablets behavior during the compression phase (11, 18-20). A group of investigators have been shown the influence of mean granule size distribution on tablet characterizations quality such as tablet breaking force (27-29), flowability (30-32), disintegration (33), compressibility and compactibility (27,34-38). In the early eighties, H. Leuenberger has developed the Leuenberger equation, which describes the compressibility and compactibility properties of a powder system. When describing those two terms; the compressibility shows the ability of a powder to decrease in

volume under pressure, whereas the compactibility defines the ability of the powder to be compressed into a tablet of specified breaking force (51).

The postulation of Leuenberger equation is when taking a cross-sectional area of a cylindrical tablet; thus a number N_+ of bonding contact points and a number N_ of non-bonding contact points can be distinguished in this area which is described by the following equation:

$A = N_0 a = (N_+ + N_-).a \quad with \quad N_0 = N_+ + N$ ***Equation 1***

Where A is the cross-sectional area, a is the unit area per bonding point.

It is also assumed that a proportional relationship between the breaking force (P) and the number of bonding points N_+ which is shown in following equation:

$P = \lambda.N_+ = \lambda.(N_0 - N_-)$ ***Equation 2***

Furthermore, when assuming that the relative decrease in the number of non-bonding points dN_-/N_- leads to proportional changes to the applied compression pressure σ_c and influences the relative density $d\rho_r$, the following equation is reached:

$dN\_/N\_ = -\gamma.\sigma_c.\, d\rho_r$ **Equation 3**

Where γ = proportionality factor

By considering some additional physiochemical powder technology rules and after several mathematical equations the Leuenberger equation is obtained. However, it was proposed (52) that Leuenberger equation can be applied using the tensile strength σ_t, the relative density ρ_r and the compaction pressure σ to fit the maximum possible tensile strength σ_{tmax} at zero porosity and the pressure susceptibility γ_t as following:

$\sigma_t = \sigma_{tmax}.(1-e^{-\gamma.\sigma.\rho r})$ **Equation 4**

The maximum tensile strength σ_{tmax} is a degree for the compactibility. However, the γ_t expresses the compressibility of the material. A low σ_{tmax} value corresponds to a relative poor compactibility, while high γ_t exhibits a good compressibility (51).

Determination of granule size during the FBG process is mainly performed by off-line techniques such as sieve analysis, image analysis and laser diffraction. However, those methods are time consuming and efforts are needed for sample preparation. Further, the process has to be interrupted and no in-process information is obtained. The United

States Food and Drug Administration FDA introduced the process analytical technologies (PAT) initiative in modern drug development and manufacturing processes (39). The aim of the PAT initiative is that the operator should be able to completely control the manufacturing process, hence constantly ensuring predefined end product quality. Accordingly, in order to fulfill the PAT implementation in the FBG process, suitable PAT tools are needed such as modern process analyzers which may allow increasing process control and understanding, shorten the production time and reduction of the rejected and reprocessed batches. A few researchers have reported about the implementation of near-infrared spectroscopy (NIRS) in the fluid bed granulators detecting the changes in particle size of powder and granule mixtures as a rapid non-destructive method (20, 40-44). Nevertheless, the temperature sensitivity of NIR spectra and the needed efforts to build calibration models are limiting the use of this method. In recent years, Focused Beam Reflectance Measurement (FBRM) has become increasingly interesting as particle size analysis technique (45-48). FBRM was developed by *Lasentec*© and marketed by Mettler-Toledo AutoChem in order to monitor particle growth in the range of 1-1000 µm. FBRM is easily implemented inside the granulator vessel thanks to its cylindrical

shape. A low-intensity laser beam rotates through a sapphire window with high velocity (up to 8 m/s), when the beam hits a particle it is reflected and back propagated through the probe window. Hence the corresponding chord length is calculated based on the duration taken to determine the distance between two edges of the particle detected and the beam velocity. Due to the high velocity of laser rotation, many thousands of chord lengths of particles are measured per second providing a robust measurement sensitive to the change in size or number of particles. Thus, the results of FBRM are presented in the form of chord length distributions (CLDs) rather than particle size distributions (PSDs). The CLDs are distributions of chord rates, reporting how frequently chords of a certain length are detected depending on the PSD and the particle geometry (49). A relationship between particle size and chord length distribution in FBRM was reported by Hu and coworkers (24). However, Hu et al have been performed their study on FBRM at line in order to prove that CLDs are identical to particle size distribution that were measured by sieve analysis. A correlation was noticed in spite of different measurement mechanisms. However, this method exhibited different limitations such as, sample preparation, process interruption and relatively low reproducibility when

comparing this method with in line FBRM installation. The investigation of our previous work (50) showed a better and more reliable correlation between the FBRM and sieve analysis method. Moreover, when the FBRM probe was mounted inside the granulator chamber, although it was shown the effect of the probe position and location on the efficiency and reproducibility of the particle measurement. In that study, no sample preparation is required, representative measurements by eliminating sampling errors and operator variability is obtained and complete process information is provided in order to handle the control of finished product quality.

The aim of the present work was to investigate the relationship between the FBRM in-line measurements of granule growth with the results of physical characterization of the compacted granules (Tablets). Acquiring in real time information that is representing the granulation kinetics can help the user to handle the process in a simple way and to optimize the fluid bed process parameters in respect to final tablet quality. Therefore, achieving the desired granule properties means achieving a high standard tablet quality.

2. Experimental

2.1. Materials

A powder batch of 350g Paracetamol (RHODAPAP RHODIA operations, Roussilon, France) and 150g microcrystalline cellulose MCC 101 (Pharmatrans SANAQ AG, Basel, Switzerland) was granulated, using 200g of 10 w/w % solution of Polyvinylpyrrolidone (Kollidon K-30; BASF, Ludwigschafen, Germany) in distilled water.

2.2. Granulation process

In order to eliminate any clumps from the batch formulation, the powder raw materials were sieved through a 350µm screen prior the process. A fully instrumented bench-scale fluidized bed granulator (Glatt GPCG2; Glatt Air techniques Inc GmbH, Binzen; Germany) was used for manufacturing the granules. The granulator possesses a single top/center atomized spray nozzle connected to a peristaltic pump. A mixing phase was initiated for 10 min until attaining the required temperature inside the vessel; afterwards the spraying phase began with spraying the binder solution onto the powder bed using a nozzle assembled with 0.8mm liquid orifice and 2mm air cap. The distance between the nozzle and the distributor plate was set to be 33cm. An in-line FBRM D600 (mettle-Toledo Inc) probe was installed inside the granulator chamber having the probe window

at the center point facing the distributor plate. The FBRM probe was implemented inside the chamber with inclination of 45°, the distance between the probe window and the distributor plate was 5cm. During the mixing phase, the inlet air volume was adjusted to be 0.33m^3/s and gradually augmented up to 1.33m^3/s during the spraying and drying phases. The drying phase was executed at constant temperature (60°C) until the product moisture content was not more than 2% RH for all the runs. Fifteen batches were granulated according to the input variables of the specific run generated by design of experiments (DOE) (see table 1).

2.3. Characterization of granules

2.3.1. Mean particle size measurements

The mean granule size was examined using two methods, FBRM and sieve analysis. In the case of FBRM, a measurement was performed each two seconds during the whole process. The mean of fifteen measurements was recorded. The average of the weighted mean chord length of the last three measurements of the process was considered as representing value of the granule growth. After the granulation process, granules were evaluated by sieve analysis using a vibrating shaker (sieve shaker vibro, Retsch; Hann, Germany) consisting of seven standard sieves in the range of 90-1000 µm with an increment of $\sqrt{2}$. The total mass of granule samples used for sieve analysis was 100 g and vibrated for 15min. The test was performed in triplicate.

2.3.2. Moisture content measurement

Mettler LP 16 was used to check the moisture content. Two grams of sample was heated up to 105°C and temperature was kept for 20 min. This time setting was sufficient to reach constant mass. The percent weight loss was recorded as the moisture content.

2.3.3. Bulk and tapped density

Bulk and tapped densities were tested according to Eur.Ph. using an apparatus STAV 2003 (Engelsmann, Germany). All measurements were performed in triplicate.

2.3.4. Hausner ratio

The Hausner ratio was calculated based on the bulk and tap densities (ρ_{bulk} and ρ_{tab}) in accordance with Eur.Ph. as follows:

Hausner ratio (HR) = ρ_{tab}/ρ_{bulk}

2.4. Tablet compaction

The physical properties of the thirteen batches were studied (excluding batches 4 and 13 due to the collapse that occurred during the process and thus the product was agglomerated, see table 1) after producing tablets using a compaction stimulator (Presster™, Metropolitan Computing Corp., NJ, USA) in order to simulate the compaction process under industrial production conditions of a rotary press Korsch® PH336 (36 stations). The compaction rolls used were 300mm in diameter. A granule mass of 220mg was compressed using flat-faced punches with a diameter of 10mm. A range from 0.5 to 24 kN of compression force was used for tablet manufacturing in order

to calculate σ_{tmax} and γ_t from leuenberger equation. The granules were manually fed. The tableting speed was constant for all the experiments 1.1m/s.

2.5. Characterization of tablets

2.5.1. Tablet dimensions

The diameter and thickness of the tablets were measured individually using a digital caliper (Mitutoyo Co., Japan) immediately after the manufacturing process.

2.5.2. Breaking force

The breaking force values were determined by measuring the load to fracture the compacts across the diameter using the tablet hardness tester (Tablet tester 8M, Dr. Schleuniger Pharmatron AG, Switzerland). The breaking force test was performed for tablets compacted under three different compression pressures (140, 190 and 280 Mpa). Tensile strength was calculated using equation 5:

$$\text{Tensile strength} = 2P/\pi DT \qquad \textbf{\textit{Equation 5}}$$

Where P = the breaking force, D = Tablet diameter, and T = Tablet thickness.

2.5.3. Disintegration test

The disintegration time of six tablets with a relative porosity of 20 ± 0.5 was determined. The disintegration test was carried out in 800mL distilled water at 37 ± 0.5°C (Sotax DT2, Sotax, Switzerland). The time duration which was needed until the disintegration of the last tablet was considered.

2.5.4. Porosity

The porosity of tablet (ε,%) was determined from the tablet weight (M, g), tablet volume (V, cm^3), tablet thickness (cm) and true density of the raw materials (ρ, g/cm^3) using the following equation 6:

$$\varepsilon(\%) = [1-(M/V\rho)] \times 100 \qquad \textbf{Equation 6}$$

2.6. FBRM data processing

The FBRM method involves the use of a rotating focused laser beam at fixed velocity. As the beam crosses the surface of a particle, light from the beam is backscattered into the probe. The duration of each reflection is multiplied by the velocity of the laser beam in order to deduce the chord length which represents a straight line between two edges of

the particle. Chord length distribution is determined by considering the whole measurement range (0-1024 µm). A more detailed description of FBRM data processing is provided in our previous study (50).

3. Results and discussions

3.1. True density and particle size distribution of powder components

Table (2) shows the true density of the raw materials used for granulation. MCC 101 showed a significant higher true density than Paracetamol. Based on those values, the true density of different batches of granules was calculated. The compression pressure applied and the dimensions of the tablets are shown in table (3).

3.2. Particle size measurement of granules

The particle size measurement of the granules was established using two methods; sieve analysis as traditional off-line method and FBRM, which gave mean particle size and mean chord length respectively as particle dimension. Three measurements were performed in sieve analysis, while in FBRM; the average of the last three measurements during 30 seconds was taken. Table (4) shows the results of particle size measurement of different runs for different granulation process parameters. The sieve analysis method

showed a wider range of standard deviation comparing to the one of FBRM method. The explanation of this result is that FBRM method is measuring a few thousands of chord lengths of the granules in an interval of two seconds and then the FBRM software gives the average of 15 measurements (30 seconds) as one mean result, which was performed in triplicate. It is important to note, depending on the orientation and position of the granules, the sieve analysis method does not measure the biggest diameter of the particle if they are not spherical; it measures the second biggest diameter of the particle. Due to this measurement mechanism; the accuracy of sieve analysis method might decrease especially when the particles have irregular shape (or not completely spherical), which is often the case in granules.

3.3. The relationship of FBRM and sieve analysis results with the breaking force of the final tablets

Tablets were produced from thirteen different granule batches prepared with different granulation process parameters and particle sizes (see table 1). Tablets were compacted under three different compression pressures (140, 210 and 280 Mpa). Figure (1) demonstrates a proportional correlation between the particle size of the granules and

the breaking force showing that an increase in particle size led to weaker breaking force, those findings were in agreement with (27-29, 53). The explanation is that when increasing the particle size of the granules then the surface area of contact points between the granules is significantly decreasing. Therefore, the opportunities for forming bonds between the granules are less and results in lower tablet strength.

FBRM and sieve analysis gave satisfactory results regarding the relationship between particle size and breaking force of the tablet. However, FBRM method showed better prediction accuracy (R^2=0.9538) whereas sieve analysis gave a correlation of (R^2=0.9011) when compression pressure was (140 Mpa). This was due to the robustness of FBRM method, which detects and measures few thousands of particles a second and therefore the results are very near to reality. Moreover, the method of sieve analysis depends only on the weight of the particles, for this reason, the smaller particles (or powder fines) were almost negligible when measuring them by sieve analysis. However, FBRM method does not depend on the weight of particles, which is an advantage. The FBRM fractions are representing the chord length of the particle counts whether they are fines or coarse. Table (2) illustrates the results of different compression pressures, which shows

that increasing the compression pressure to produce tablets result in an increasing error of prediction. The reason for this error is that when increasing the compression pressure of the tablets then the homogeneity of the particle distribution becomes more important, affecting the bonding behavior inside the tablet. Thus, the variation in homogeneity led the breaking force to behave unexpectedly.

3.4. Evaluation of the FBRM and sieve analysis measurement versus the disintegration time

Disintegration is the process by which a solid dosage form breaks up when it comes in contact with an aqueous medium. In order that a tablet can disintegrate, the bonds, which are formed during compaction have to be crushed. Figure (2a,b) illustrates that there was quite a linear relationship found between the particle size and the disintegration times. It was further shown that an increase in the granule growth kinetics resulted in a diminution of the disintegration times, those results were in correspondence with Ferrari and coworkers (33). This relation occurred due to decreasing number of bonds between the particles and thus decreases the bonding

capability due to surface activation as described earlier by Hüttenrauch and coworkers (54), saying that liquid penetration is stimulated into the tablet structure and separates the tablet into small pieces. Despite the different mechanisms and conditions of FBRM method, it showed similar results compared with sieve analysis method. However, FBRM method showed a better linearity (R^2=0.91) when comparing it with sieve analysis (R^2=0.85); the reason for that is the same as mentioned earlier in section 3.3, that FBRM results are based on the number of counts of the particles where the results of sieve analysis are depended on the weight of the particles. Consequently the main factor, which influences the disintegration time are the bonds between particles and those are proportionally correlated with the number of particles. All the results of disintegration time were in the accepted range (<15mins); this was due to the formulation containing microcrystalline cellulose (MCC). MCC exhibits extremely fast aqueous penetration due to the interaction with the hydrogen bonds and therefore contributes to a widening of the pores in the particles (55).

3.5. Investigation of the flowability, compressibility and compactibility of the granules and tablets with regard to the particle size measurements

Flowability of the granules was examined for each run using the Hausner ratio. Figure (5 a,b) demonstrates that an increase in mean particle size of the granules corresponded to lower values of Hausner ratio, which means a better flowability was achieved. This is in accordance with (30-32) who reported that large particles show a better flow than small ones due to the higher density of particles and less contact friction between the particles themselves. It was clearly seen that there is a relationship between FBRM and sieve analysis and Hausner ratio. However, when comparing those two methods with each other, it was noticed that FBRM method got a better linearity (R^2= 0.9735) than the one from sieve analysis (R^2=0.9127). This variation might be due to the irregular shape of the granules, since the shape is one of the most important factors affecting the flowability. Sieve analysis measures the second biggest diameter of the particles in case of non-spherical dimensions; moreover it gives always the same mean particle size even when the particles have different width. Moreover, when using sieve analysis method the particles, which have the same width but different shape will be considered as they have the same size. In contrast, FBRM method does not consider only the dimension of the particle, but also the shape of it, due to the mechanism of measurements which detects

the distance between two edges of the particle and performed up to few thousands measurements in one second. Furthermore, thanks to the high number of fractions (1000 fractions) which FBRM method has in the range of (1-1024µm), this method assures the accuracy of the measurements and further harmonizes the fractions of granules even when having irregular shapes.

Compactibility of a tablet can be defined as the capacity of the starting material to be transformed into a tablet of specified strength under the effect of compaction pressure (51). When looking at figure (6 a,b), the results for σ_{tmax} from leuenberger equation showed that small particles which are measured by FBRM method as well as for sieve analysis method, a low σ_{tmax}, which means relatively poor compactibility was obtained. This was due to the presence of a large number of contact points per unit area of granules contributing to increase the friction and the cohesive forces between the particles during the compaction cycle. However, σ_{tmax} showed a dramatic increase when the granule growth was progressed until it reached a certain point where the big mean particle size did not show an influence on the σ_{tmax} (or on the compactibility behavior).

This effect might be explained that MCC showed its plasticity behavior with the particles that have smaller mean particle size, those findings were in agreement with (34-35, 38). The elasticity behavior of Paracetamol for bigger mean particle size was dominant, similar results were shown by Pater et al (37), although an increase in fragmentation propensity might be noticed when increasing the mean particle size which is attributed to the increase of shape irregularity of the particles. Those results were in agreement with (56). When looking at FBRM and sieve analysis results, they were almost comparable. Nevertheless, the FBRM method revealed a better correlation with σ_{tmax} than sieve analysis. This could be due to highlighting of the fine particles performed by FBRM which have a major influence on the tableting properties, whereas those particles were not emphasized due to their small weight, see also Figures (3) and (4).

The pressure susceptibility γ_t for the granules was determined using Leuenberger equation. Figure (7 a,b) showed the FBRM and sieve analysis results correlated with the pressure susceptibility $\gamma_{t.}$. The γ_t was markedly increasing with the increase of granule growth till a certain point. This could be contributed to the decreased inter-particulate

interaction due to the reduction in contact points per unit area (36-37, 56). On the other hand, when the particle growth exceeded 250µm for FBRM or 425µm for sieve analysis measurements, then a turning point was noticed and the γ_t showed a disproportional response with the size of the granules. It was hypothesized that the plastic effect of MCC was more dominating than the elasticity behavior of Paracetamol in the formulations containing smaller particle fractions. However, when comparing both methods FBRM and sieve analysis; it was clearly seen the similarity between the curves, nevertheless, when looking at sieve analysis profile, the bigger particle fractions was showing a poor relationship with the $\gamma_{t.}$ which was due to the shape irregularity of the granules that occurred when the granules became bigger. However, this inconvenience was not faced when performing FBRM method due to the inclusion of shape parameters of the particles.

4. Conclusion

Regarding particle size measurement, the FBRM and sieve analysis results were competitive; however the FBRM method approved its robustness and sensitivity to any changes in particle dimension regardless the particle shape. In addition of that, FBRM

measurements were performed and analyzed in real process time. These are the two important advantages of the FBRM method.

Regarding the final tablet quality the following relationships were found. The breaking force of tablets was strongly influenced by the mean of the granule size. Therefore, a strong predictability of tablet breaking force (R^2=0.9538) was observed when using the FBRM method and is suggested before sieve analysis. A strong relationship between the in-line FBRM parameters can allow the operators to react during the process, thus guaranteeing a predefined end product quality. In the case of applying extreme high compression forces, homogeneity rearrangement of the particles was a dominant factor affecting the tablet breaking force in comparison with the influence of the mean particle size of the compressed granules. Looking at the disintegration time results of the tablets in relationship to granule particle size, FBRM method gave a better linearity due to the measuring principle. The limitation of sieve analysis in respect to particle shape of the granules, showed weaker prediction models for all investigated tablet parameters. FBRM method proved its high sensitivity to particle counts, shape and size, which is an ideal

opportunity for in-line characterization and prediction of the final physical properties of the tablet even during the early stages of manufacturing cycle. The use of FBRM method is a promising method for better understanding and controlling effectively the granulation phases as well as the tabletting step.

Tables and figure for chapter 2

Table (1): Composition of experimental design and response for different formulations

	Factor 1	Factor 2	Factor 3	Response (1)	Response (2)
Run	Spray rate (g/min)	Air nozzle pressure (Bar)	Inlet temperature (°C)	Mean square weight (µm)	Mean particle size (µm)
1	6.5	1	22	226.94	360.41
2	13	1	22	325.28	484.11
3	6.5	2.5	22	238.73	398.83
4	13	2.5	22	-	-
5	6.5	1	60	162.2	300.19
6	13	1	60	252.73	424.31
7	6.5	2.5	60	199.15	271.12
8	13	2.5	60	310.18	460.03
9	9.8	1.8	41	214.13	368.6
10	8.1	1.8	41	154.83	291.31
11	11.4	1.8	41	299.94	475.93
12	9.8	1.1	41	289.99	463.67
13	9.8	2.4	41	-	-
14	9.8	1.8	30	307.36	473.83
15	9.8	1.8	50	247.41	370.35

Table (2): Characterisation of the powder

Powder	True density (g/cm^3) ± SD	Mean particle size (µm) ± SD	Deformation behaviour
Paracetamol	1.2211 ± 0.144	82.78 ± 5.79	P astic/ɔrittle
MCC 101	1.4795 ± 0.092	83.35 ± 2.31	Viscoclast˙c/brittlc

Table (3): Properties and dimensions of compacted tablets for different runs

Run	Tablet weight (mg) ± SD	Compression pressure (Mpa) ± SD	Thickness (mm) ± SD	Diameter (mm) ± SD	Friability (%) ± SD
1	219.4 ± 0.34	140.1 ± 0.5	2.38 ± 0.02	10.13 ± 0.01	0.75 ± 0.03
2	218.7 ± 0.5	140.5 ± 0.21	2.58 ± 0.04	10.12 ± 0.00	0.83 ± 0.05
3	218.9 ± 0.21	139.5 ± 0.52	2.49 ± 0.01	10.13 ± 0.01	0.65 ± 0.07
5	218.8 ± 0.73	140.4 ± 0.77	2.48 ± 0.08	10.11 ± 0.02	0.91 ± 0.02
6	219.5 ± 0.42	140.1 ± 1.1	2.5 ± 0.02	10.11 ± 0.01	0.72 ± 0.09
7	219.6 ± 0.13	139.8 ± 0.9	2.49 ± 0.04	10.13 ± 0.02	0.52 ± 0.03
8	220.4 ± 0.24	139.6 ± 0.62	2.47 ± 0.01	10.12 ± 0.01	0.65 ± 0.07
9	220.1 ± 0.28	140.2 ± 0.46	2.51 ± 0.07	10.1 ± 0.03	0.72 ± 0.04
10	220.3 ± 0.52	140.1 ± 0.6	2.53 ± 0.02	10.12 ± 0.00	0.88 ± 0.06
11	220.8 ± 0.36	140 ± 0.71	2.55 ± 0.05	10.09 ± 0.01	0.94 ± 0.02
12	220.6 ± 0.41	139.9 ± 1.1	2.57 ± 0.01	10.1 ± 0.01	0.79 ± 0.01
14	220.9 ± 0.27	140.3 ± 0.45	2.54 ± 0.04	10.11 ± 0.01	0.41 ± 0.05
15	220.4 ± 0.4	139.8 ± 0.9	2.51 ± 0.01	10.13 ± 0.02	0.61 ± 0.04
Powder	219.4 ± 0.81	140.2 ± 0.52	2.43 ± 0.05	10.12 ± 0.01	0.86 ± 0.08

Table (4): The breakage force of the tablets under different batchs and different compression pressure

Run	Weighted mean chord length (µm) FBRM	Mean particle size (µm) Sieve analysis	Compression pressure =140 Mpa ± SD	Compression pressure =190 Mpa ± SD	Compression pressure =280 Mpa ± SD
1	226.94 ± 4.9	360.41 ± 10.5	124 ± 1.25	131 ± 3.38	140 ± 5.37
2	325.28 ± 7.23	484.11 ± 16.1	85 ± 2.5	110 ± 4.17	125 ± 6.25
3	238.73 ± 6.21	398.83 ± 14.5	122 ± 2.22	129 ± 5.04	146 ± 6.78
4*	-	-	-	-	-
5	162.2 ± 4.74	300.19 ± 11.1	145 ± 1.93	143 ± 4.62	151 ± 7.15
6	252.73 ± 3.32	424.31 ± 30.52	118 ± 3.11	124 ± 6.81	138 ± 9.48
7	199.15 ± 8.71	271.12 ± 22.4	138 ± 2.96	139 ± 5.28	150 ± 6.86
8	310.18 ± 5.84	460.03 ± 17.52	101 ± 2.44	113 ± 7.36	131 ± 8.52
9	214.13 ± 7.64	368.6 ± 14.22	128 ± 1.9	139 ± 4.08	146 ± 7.16
10	154.83 ± 2.48	291.31 ± 19.92	142 ± 2.51	146 ± 3.55	149 ± 6.37
11	299.94 ± 1.94	475.93 ± 22.28	96 ± 3.26	106 ± 6.43	134 ± 6.06
12	289.99 ± 6.52	463.67 ± 13.33	106 ± 1.83	117 ± 6.32	128 ± 7.28
13*	-	-	-	-	-
14	307.36 ± 5.11	473.83 ± 20.84	89 ± 2.22	113 ± 5.48	124 ± 5.37
15	247.41 ± 4.47	370.35 ± 16.11	119 ± 1.65	132 ± 7.65	141 ± 8.54
R^2 for FBRM measurements			0.9534	0.9337	0.8684
R^2 for sieve analysis			0.9011	0.8994	0.8375

* Experiments 4 and 13 were not able to be measured because a collapse occurred during granulation process and therefore the product was agglomerated.

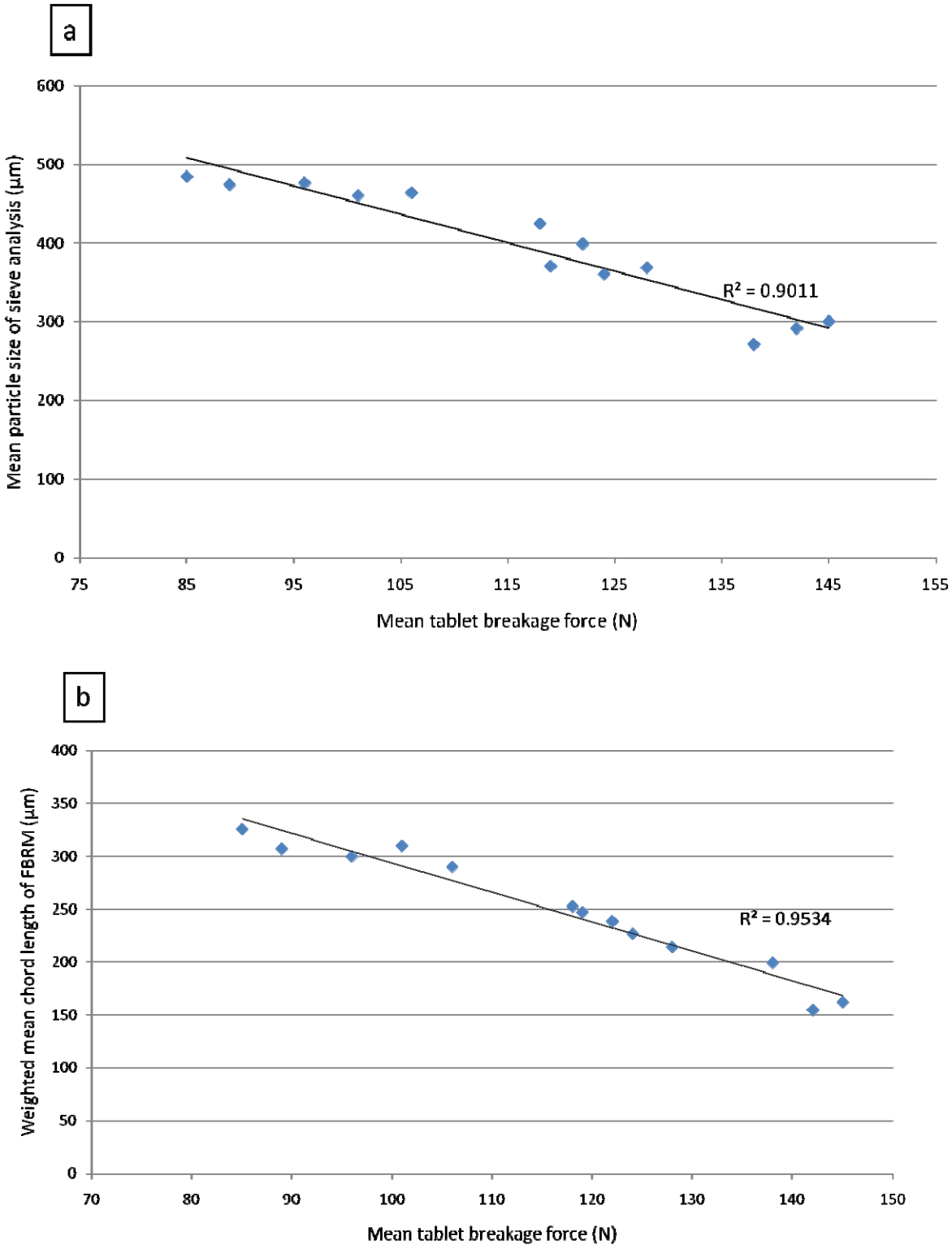
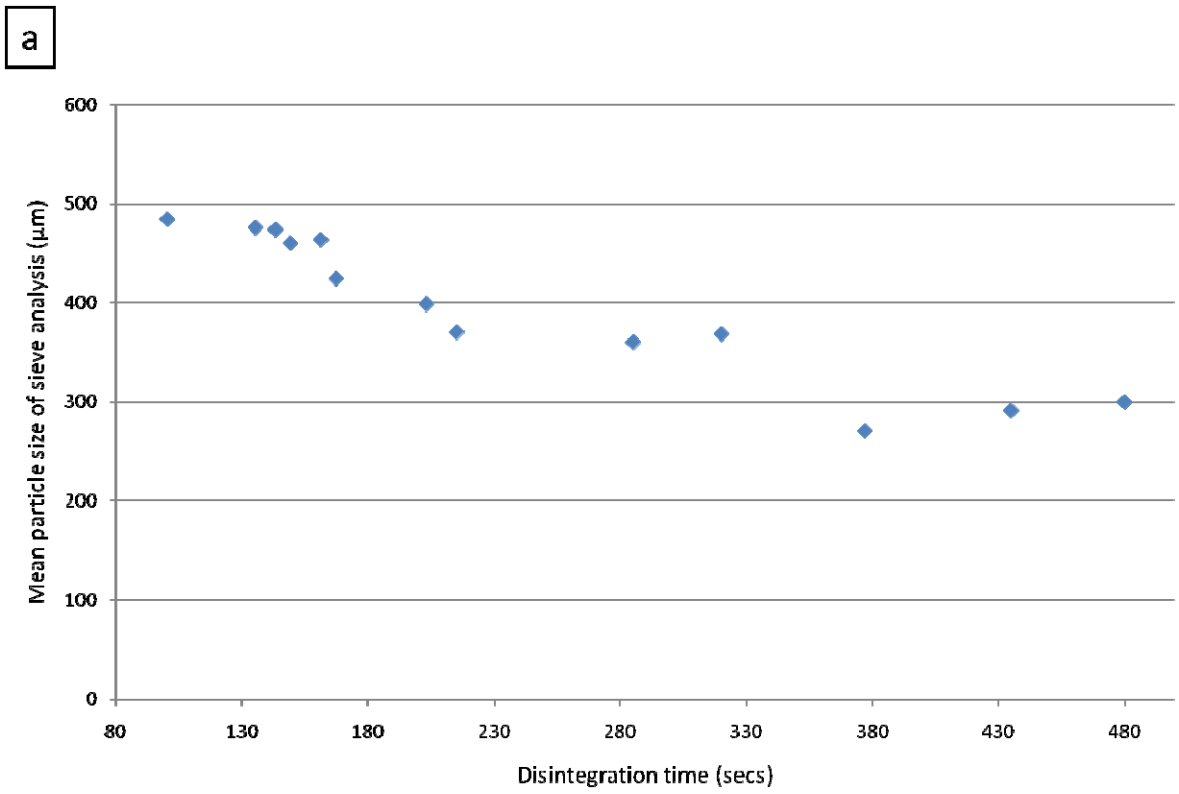


Figure 1: (a) Mean particle size of sieve analysis, (b) Weighted mean chord length of FBRM versus mean tablet breakage force for a tablets compacted under 140Mpa.



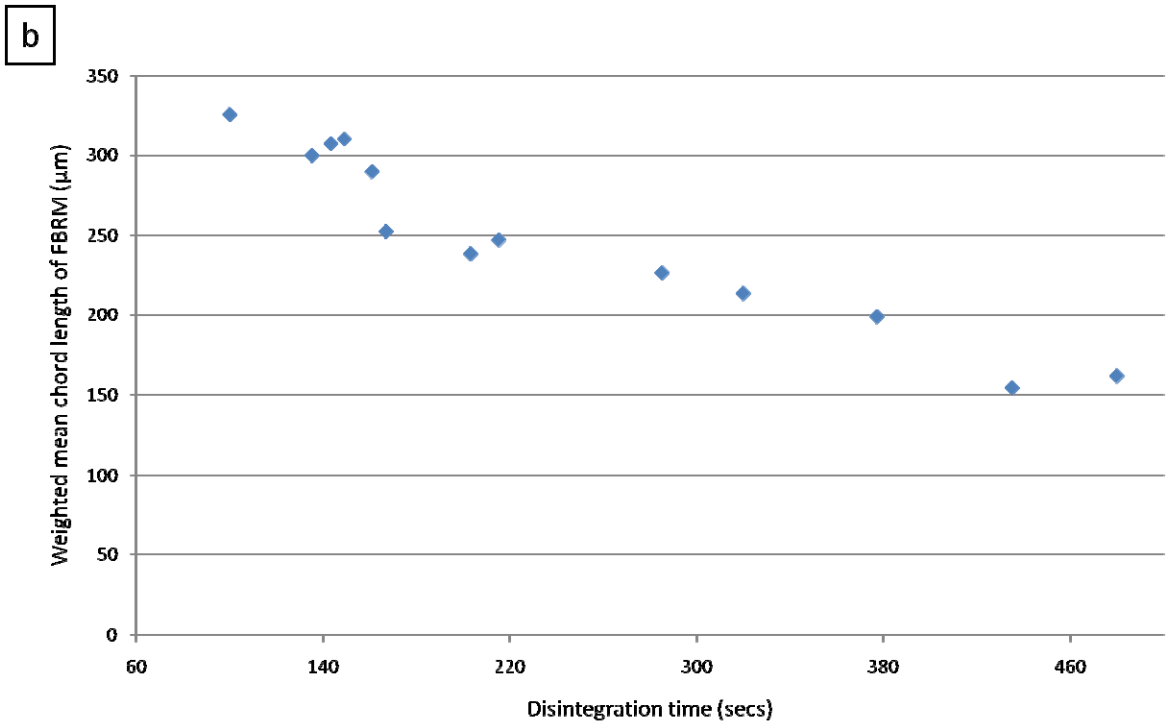


Figure 2: (a) Mean particle size of sieve analysis, (b) Weighted mean chord length of FBRM versus the disintegration time

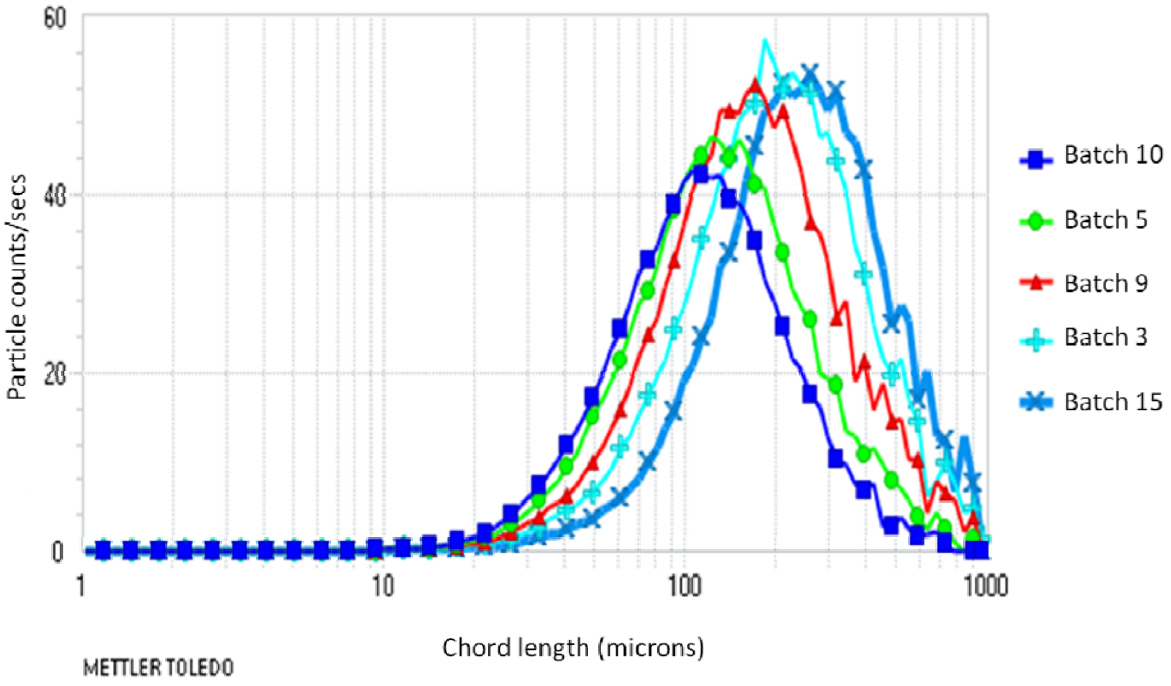


Figure 3: In-line FBRM square weighted chord length profiles for different runs of different process parameters the shifting of the curve to right side representing the enlargment of the granules

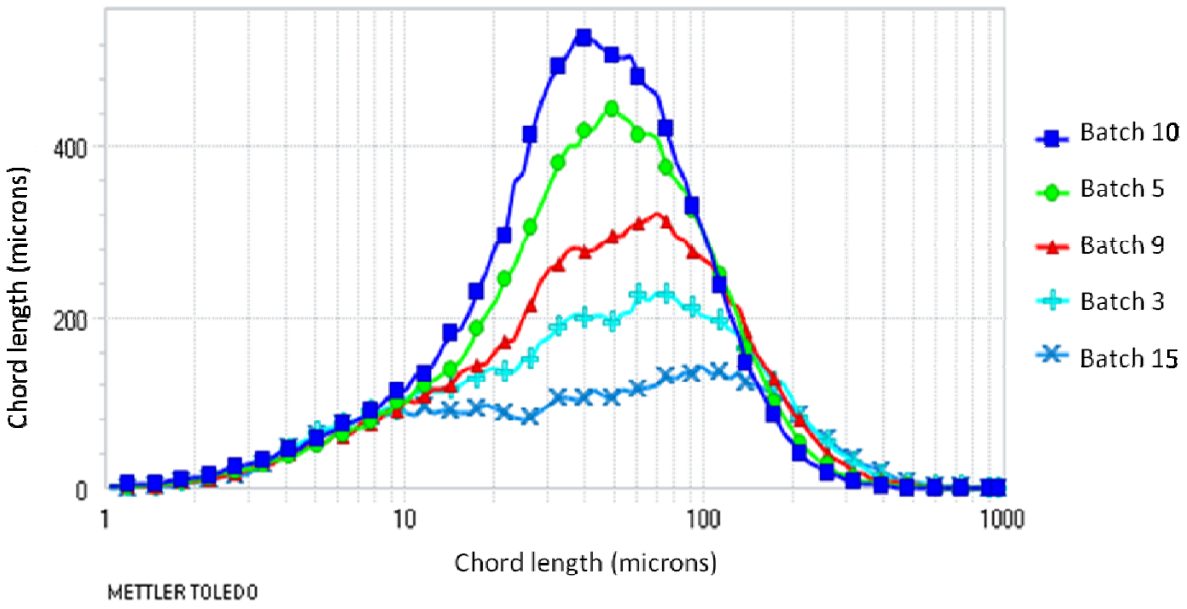


Figure 4: In-line FBRM unweighted chord length profiles for different runs of different process parameters which shows the decrease of particle counts when the particle size is bigger

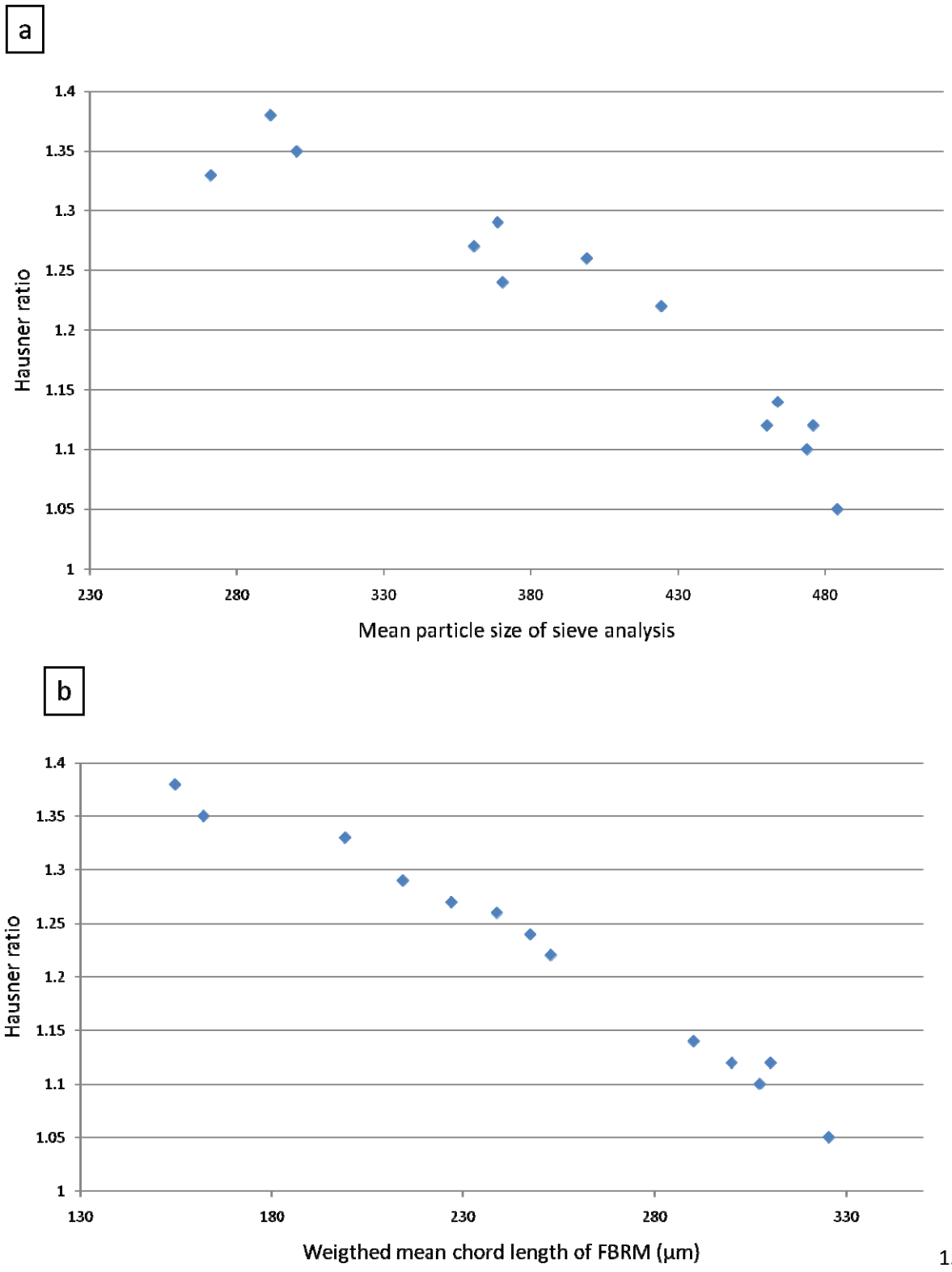


Figure 5: (a) Mean particle size of sieve analysis, (b) Weighted mean chord length of FBRM versus the huasner ration of the granules

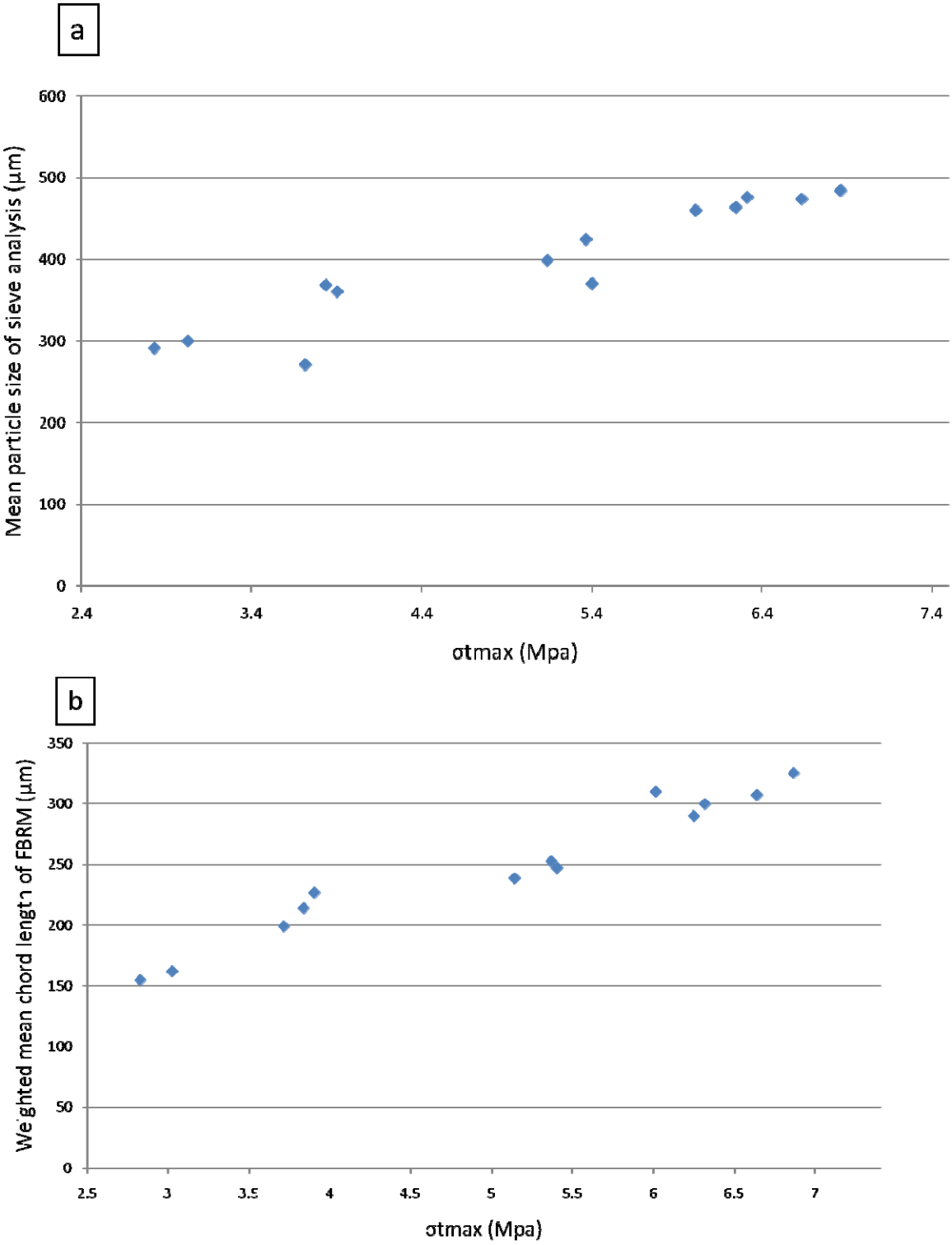


Figure 6: Comparaison of a) sieve analysis method b) FBRM method with the prediction of the Compactibility behaviour.

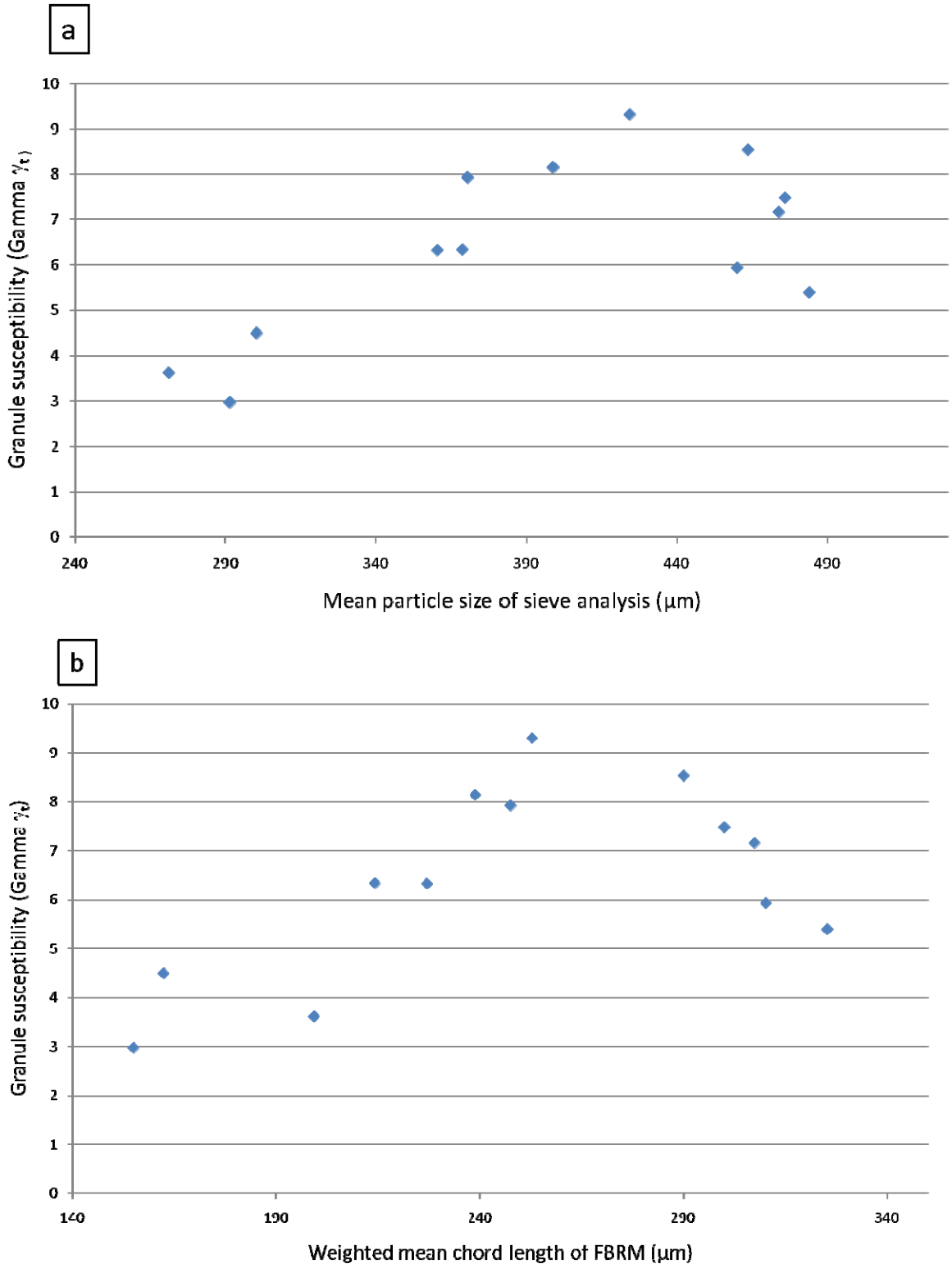


Figure 7: Comparaison of a) sieve analysis method b) FBRM method with the prediction of the Compressibility behaviour.

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Conclusion and outlook

In this study, FBRM probe was implemented inside the fluid bed granulator in order to monitor the particle growth of the granules. First of all, the probe position and location had to be investigated in order to find the optimum position. Two positions were studied, thus the results showed that placing the probe as close as possible to the distributor with an inclination of 45° prevented the probe window from being clugged by sprayed droplets. Further, this position allowed to place the probe in a zone where the number of fluidized particles is high thus ensuring representative results.

Since the fluid bed granulator has a high number of process variables that are markedly influencing the granules quality and property, a design of experiment was needed to perform a series of experiments (16 experiments) at different levels of different process variables that were spray rate, air nozzle pressure, and inlet air temperature. The aim of the first part was to measure in-line the kinetic changes of particle growth during the granulation process using FBRM as PAT tool, and furthermore to study the influence of each factor on the granule growth hence comparing the results with a traditional

method (sieve analysis). The FBRM method provided in real time the kinetics of particle counts as well as kinetics of chord length distribution. As the process was progressing, the FBRM profiles showed a decrease in particle counts and increase in chord length distribution indicating that the particles are gathering together and getting bigger in size. FBRM results showed that air nozzle pressure exhibited the strongest positive effect on the granule growth where the inlet air temperature was the weakest one. These findings were were confirmed by the results obtained with sieve analysis And in agreement with the literature. Comment please add literature references. The FBRM and sieve analysis results were compared, and a good correlation (R^2=0.9019) was obtained. However, a bias has always to be considered between the values of each method. The FBRM method was very promising and succeeded to monitor in-line the granulation process in fluid bed granulator without the need for sample preparation and process interruption.

Using the granules that were previously manufactured for producing tablets by a compaction simulator was the second part of this work. The aim was to examine the influence of the mean particle size that was measured in-line by FBRM on the physical

properties of the tablet. It was evident in respect to breaking force results that an increase in granule growth and thus particle size contributed to a decrease in the breaking force of the tablet. However, when correlating FBRM and sieve analysis results with the breaking force, it was noticed that the FBRM method showed a better correlation (R^2=0.9538) than the sieve analysis one (R^2=0.9011). Regarding the disintegration test, the big granules were restricted somehow to obtain enough number of bonds because of the diminution of the bonding capability due to the surface activation; thus resulted in faster liquid penetration inside the tablet and shorter disintegration time. The ability of FBRM method to determine the particle counts allowed this method to predict the disintegration time more accurately than the traditional method. Applying the Leuenberger equation gave the opportunity to evaluate the compactibility and compressibility of granules. The poor compactibility and poor compressibility were observed when compressing a material of small mean particle size. Moreover, the FBRM and sieve analysis results were comparable when correlating them with compactibility and compressibility values. However, the sieve analysis method was less precise due to two reasons; first sieve analysis is incapable to highlight the

importance of fine particles, and second the irregularity of the particle shape limited this method to give reproducible measurements.

As PAT tool, the portable and non-invasive in-line FBRM method can be applied to fluid bed granulators. However, further studies could be performed to investigate the application of this technique to other granulation techniques, such wet granulation in a high shear mixer.

Curriculum Vitae
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Education

Since 2008- present PhD student-Pharmaceutical Technology-University of Basel

Basel-Switzerland (expected graduation November 2011)

''Monitoring in-line the granulation process in fluid bed and investigating the relationship with final tablet quality by applying FBRM as innovative PAT tool''

2007-2008 Master of medicaments science: Pharmaceuticals engineering

Faculty of Pharmacy, Louis Pasteur University

Strasbourg - France

2002-2007 BSC of Pharmacy sciences (excellent)

Yerevan State Medical University

Yerevan - Armenia

2001- 2002 High school certificate – Almaamoun School

Aleppo - Syria

Conferences and events

- International Granulation Workshop, Luasanne, Switzerland (20-22 June/2011)
- Pharmaceutical sciences for the future of medicines, Prague, Czech Republic (13-17 June/2001)
- World Congress on Particle Technology 6, Nüremberg, Germany (26-29 April 2010)
- International Conference on Drug Discovery and Therapy 2, Dubai, UAE (2-7 February 2010)

- Experimental Design and Analysis with STAVEX Part A and B AICOS
- Granulation & Tableting (TTC) Technology Training Center, Glatt
- Fluid bed processing (TTC) Technology Training Center, Glatt
- Multiparticle Dosage Forms (TTC) Technology Training Center, Glatt
- Challenges and solutions for the formulation of classical and biological drugs (Ifiip GmbH, Pharmatrans SANAQ AG)
- Essentials in Drug Development & Clinical Trials

Experience and Employment

- Teaching assistant-Pharmaceutical Technology university of Basel 2008-2010
- Since 01/02/2008 stage in the laboratory of chemically enzymology and bioactive molecules delivery. industrial project : improving fabrication and compression of the tablets, protection the hygroscopic drugs by using fat coating, cooperation with Mr Thierry Vandamme
- 01/03/2006 – 01/06/2006 University special courses of medical marketing, cooperation with Mr. Armen Hakobian at YSMU
- 01/10/2005 – 20/11/2005 stage in the field of pharmacognosy cooperation with Mrs. naira chichoyan, campus in Dilijan , Armenia
- 2002-2006 (summer) stages, at Aleppo Pharmaceuticals industries (ALPHA) , in the department of quality control laboratory (HPLC , GC and UV spectrophotometer), and in the microbiological laboratory (sterility analysis)

Research experiences

- Wet granulation instruments, process monitoring.
- Drug product development, process optimization, validation and scale up
- Instrumentation of tabletting machines, compaction physics

- Liposomes, Gels and hydro gels, Bopadhesion
- Freeze drying, sterile dosage forms
- Statistics, Design of experiments

Publications

- Investigating the effect of particle size and shape on high speed tableting through radial die-wall pressure monitoring. Sameh Abdel-Hamid, Firas Alshihabi, Gabriele Betz., Int J Pharm 413, 29-35.
- Focused beam reflectance method as an innovative (PAT) tool to monitor in-line granulation process in fluidized bed, Firas Alshihabi, Thierry Vandamme, Gabriele Betz., Pharm Dev Tech, Accepted, August 2011.
- Investigation of the relationship between granule particle size and final tablet quality using fluid bed granulation process monitored by Focused beam reflectance measurement (FBRM) method Firas Alshihabi, Thierry Vandamme, Gabriele Betz. J Drug Delivery Sci Technol, Submitted, October 2011.

Skills

- Computer and software competency : word, excel , power point and computer general maintenance
- Travelling , reading and sport as swimming
- EU Driving license

Languages

- Arabic (native language)
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References

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