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Department of Pharmaceutical Technology

DIPLOMA THESIS

Evaluation and optimisation of a granulation process on a laboratory scale fluid bed granulator

Heidelberg & Hradec Králové 2013 Jan Stoniš

I declare, this thesis is my original copyrighted work.

All literature and other resources I used while processing are listed in bibliography and properly cited. This thesis was not used for obtaining the same or another degree.

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In Hradec Králové 4. 8. 2013 Jan Stoniš

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1. Abstract

The fluid bed granulation is a well-established method how to improve such properties of powders as flowability and increase content uniformity of the tablets.

In this thesis, there was evaluated a granulation process on a lab scale fluid Glatt bed granulator and optimized for highest possible yield. Product yield in the size range of 80–90 % of granules and process reproducibility were stated as most effective. The product was analysed for its particle size distribution, the API distribution within the different particle size fractions and the flowability of the final granules. For process optimization, the most critical parameters such as spraying rate, particle size of raw materials and fluid bed pressure were identified and evaluated. As the highest-yielding dosage for the powder binder was found the spraying rate of 9 g/min. Changes in bed fluid pressure and nozzle pressure showed no significant improvement.

Different grades of caffeine were compared for their impact on the granulation properties. Sieved caffeine enhanced yield of the product and reproducibility compared to bulk or disagglomerated caffeine.

Abstrakt

Granulace na fluidním lůžku je dobře zavedenou metodou, a způsobem, jak zlepšit sypnost a obsahovou stejnoměrnost tablet.

V této práci je hodnocen a optimalizován granulační process na laboratorním fluidním granulátoru značky Glatt za účelem nejvyššího možného výtěžku (80-90%) a reprodukovatelnosti procesu. Produkt byl analyzován z hlediska distribuce velikosti částic, sypnosti finálních granulí a distribuce účinné látky v jednotlivých velikostních frakcích částic. Pro optimalizaci procesu byly identifikovány a zhodnoceny kritické parametry. Nejvýhodnější dávkování pojiva bylo 9 g/min. Změny v tlaku fluidního lůžka a tlaku v dávkovací trysce nevedly k výraznému zlepšení.

Různé stupně zpracovaného kofeinu byly porovnány vzhledem k jejich vlivu na vlastnosti granulačního procesu. Přesívaný kofein vykazoval zdokonalení výtěžku v produktu a reprodukovatelnost v porovnání k nezpracovanému a deaglomerovanému kofeinu

2. Aim of the thesis

Main task of this thesis was to evaluate a granulation process based on the given powder formulation and to optimize the process towards (with the regard to) higher reproducibility. Therefore, critical process and product parameters had to be determined and their importance for the process had to be evaluated. The goal was to achieve a stable yield around 80–90 % of granules. For this reason, final granules were analysed for particle size distribution, flowability.

Consequently, the content of active pharmaceutical substance (API) was investigated to get the information about the distribution of API in a fractions and homogeneity of produced batches.

The practical part of this thesis was carried out at the Institute for Pharmacy and Molecular Biotechnology, University of Heidelberg within the ERASMUS students exchange program.

3. Introduction

The granulation is one of the most important techniques for preparation of powder mixture in industrial tablet pressing. Granules are characterized by better flowability and content uniformity, which are perfectly suited properties for following process of tablet production. As a consequence of better flowability, it is possible to provide uniform API (active pharmaceutical ingredient) content in tablet batch and, therefore, rapidly improve quality of distribution of remedy to a patient in the very end of the line. This method reduces financial expense not only in manufacturing phase, but also during the storage phase and transportation.

Among all of the types of granulations, fluid bed granulation belongs to the group of the most used and popular in the today's pharmaceutical industry, because of the uniting the granules' production process and drying process of newly created granules. Big advantage is also equal distribution of the binder, mostly dissolved in the solution, and better control of the process.

4. Theoretical part

4.1 Tablets and tablet production

Tablets are the most widely used pharmaceutical dosage form and are advantageous both for user and manufacturer. They can be produced in much higher rate than any other pharmaceutical dosage forms while keeping greater uniformity through the batches than other medicines. They are maintaining long time stability, their shelf life can be measured in several years. Tablets are convenient for transport stability, since they contain relatively small proportions of excipients, unlike oral liquids or other solutions. From pharmacist´s point of the view, they are easy to dispense and they are versatile drug delivery system. These advantages are normally possessed, if tablets are properly formulated and manufactured according to the following qualities: permitted limit content of stated dose of drug (content uniformity), they should be sufficiently strong to withstand the stresses of manufacture, transportation, and handling. Tablets should reach a patient intact.[1]

European Pharmacopoeia[2] states that in the classification of pharmaceutical dosage forms, tablets belong into the division of solid dosage forms. As a group, they are sorted according to delivery ways (oral, vaginal etc.). In most cases the tablets are composed of one or more active pharmaceutical ingredients, but always a single dose unit. Active pharmaceutical ingredients are combined with excipients with many different functions (in most cases, they are improving flow ability and tablet compression, storage properties, releasing properties etc.). Tablets are obtained by tablet compression, single or multiple. In most cases, they have a shape of straight circular solid cylinders. Many other different shapes are also possible, for example oval, bullet, triangle, rectangle etc. End surfaces are flat or convex and the edges could be beveled. In certain cases, tablets can be moulded or manufactured by extrusion. After manufacturing, tablets are modified by coating. Often they are also left uncoated. Nevertheless, coating improves stability and physical state of tablets, especially of those connected to the appearance. Tablets may contain the following excipients: fillers, binders, disintegrating agents, glidants, lubricants etc.

The earliest reference to a dosage form resembling the tablet is possible to found in 10th century Arabic medical literature. First patent, related to tablet compression, was granted in Great Britain in the year 1843. The tablets were made by simple hammer. The term tablet was used for the first time in 1870s in the United States of America. In 1874, the first patent for a power driven press-was granted. Two most successful designs are represented until now days by both rotary and eccentric presses.[1]

All tablets are produced by compression of solids, like powder, crystals or granules etc. Generally, this process can be described as forming of solid, relatively small elements into a bigger system – tablets. These particles are contained in a die and compressed by a force of several tons. The shape of the die defines shape of tablet and the distance between punch tips determines thickness of tablet body. Eccentric press has one die and one pair of punches. Rotary press has larger number of punches and dies arranged (assembled) in the rotary turret. Tablet pressing process contains 3 phases: [1]

a) Filling of the die – although tablets are described by a weight of their body, the die is filled by a volumetric process, therefore, uniform filling is essential and appropriate fluidity of particles is required.
b) Compression is characterized by the movement of one punch against another, which resolves in progressive porosity reduction in the content of the die. Particles are forced into even closer proximity to each other. Particles are falling apart or/and are deformed. Inter-particulate forces between particles cause aggregation and forming of the tablet.
c) Ejection is an action, when tablet is pushed away from the die by lower punch. Ejection demands lack of adhesion between the tablet body and a die wall.

If a particulate solid should be transform into tablet dosage form, three key properties are needed: [1]

- Good particle flow,
- The ability of the particles to cohere under the influence of compressing force,
- The ability of the tablet to be ejected from the die after compressing force has been removed.

4.2 Direct compression method

Few powders have the properties to be compressed directly to the tablets. Some of the powders and powders' mixtures need before successful tablet pressing preliminary treatment with addition of excipients (one or more). This step is almost invariably needed.[1]

However, if a major component of the formulation already possesses the necessary degree of flowability and compressibility, granulation would be unnecessary. Such direct compression mixes must flow uniformly into a die and form a robust tablet.[3] This is the basis of tablet manufacture of direct compression. The key component here is the diluent, in direct compression theory called dry binder.[1]

The filler (dry binder) is material, which the active ingredient is mixed with. Many drugs need to be administered in doses of only few milligrams or even less.[1]
The choice of excipients is extremely critical in formulating direct compressed tablets. They must possess both compatibility and good flow.[3] It is necessary to increase the bulk of such a tablet with a diluent. It should be in ideal chemically, physiologically inert and inexpensive and be easily tableted. As examples can be taken microcrystalline cellulose and lactose.[1]

When the formulation is compressed, the sides of a tablet come in direct contact with the wall of the die. For good ejection of just made tablet, friction between side of tablet's body and die's wall has to be overcome, otherwise the friction in this area could destroy the tablet, which is removed after compression. Therefore, a lubricant is almost invariably included in tablet formulation. It is a substance, which deforms very easily when sheared between two surfaces. Between tablet side and die´s wall it provides a readily deformable film. In practice, magnesium stearate is by far the most used tablet lubricant and is extremely effective. Other possibilities are talc, PEG (polyethylene glycol) 4000 or 6000 or hydrogenated vegetable oil. Inadequate lubrication can be recognized according to the vertical scratches on the sides of the tablet or phenomenon known as picking.[1]

Additional group of materials (ingredient, excipient, substance, material) used for make direct compression easier, is called glidants. This helps to sufficiently improve the flow of particles for uniform die filling. As the best example, the

colloidal silicon dioxide can be used. This substance also bears another advantage – it is acting as a moisture scavenger, and, therefore, it is providing a drier environment for other ingredients.[1]

Strongly coherent particles are essential for the production of robust tablets. However, before they can be absorbed by gastrointestinal tract, the active ingredient has to be dissolved and a physically strong tablet is an impediment to dissolution. Therefore, formulation often includes disintegrating agent.[1] For a long time the conventional disintegrating agent was starch. Recently, so-called "super disintegrants" have been introduced, such as croscarmellose, crospovidone, polacrilin potassium and sodium starch glycolate.[1] Their low use levels allow faster disintegration of tablets, minimize softening and flow problems encountered, when high levels of starch is used. The concentration of 0,5–4 % of superdisintegrant in formulation is recommended.[3]

The most striking feature of direct compression is its simplicity and hence economy (lower labour costs, reduced processing time and lower power consumption). Very important is also no need of drying phase. Further advantage is that disintegrate tablets in smaller particles better than granular aggregates.[1]

Primary limitation is directly connected with dependency of direct compressing on the flowability and compressibility of tablet diluent. For direct compression it means that poor flow, if not prohibitive, will cause higher weight variability of a tablet and the problem gets worse as the speed of tableting increases.[3] Paradoxically, one of the key obstacles in the process of direct compression is its simplicity.[1] Meanwhile for wet granulation is typical that particles are "submerged" in the mass of a binder, and, therefore, minor changes in properties of constituents can occur. In process of direct compression each particle of every constituent remains essentially unaltered.[1] Last but not least, segregation of constituents after homogenous blend of active pharmaceutical ingredient and excipients was observed.

For this reasons, direct compression has been mostly adopted by manufacturers of the generic (non-innovative) pharmaceuticals.[1]

4.3 Granulation

According to the European Pharmacopoeia[2], granules are defined as preparations of solid dry aggregates of powder particles able to withstand handling. Very often, they are used for oral administration. They can be prepared in single or multi-dose presentation with several types of use. Classification defines effervescent granules, coated, gastro resistant granules and, last but not least, modified-release granules.

Perry's Chemical Engineer's Handbook[4] defines granulation as a process, whereby small particles are gathered into the larger, permanent masses, in which the original particles still can be identified. Granulation represents form of the powder's pre-treatment, which improves flow by increasing particle size, it is a good approach how to densify the material. Granulation increases uniformity of the drug distribution in the product. It also reduces dust. Last but not least, granulation facilitates metric or volumetric dispensing. Although the granules are primarily used for tablet manufacturing, they can be also used as filler for the hard gelatine capsules or they may become as sachet, when a large dose exceeds capacity, which can be swallowed easily.[5]

Generally, two main types can be distinguished. For wet granulation, the size of the particles is increased by creation of the bonds between single particles. These bonds are provided by a binder, in most of the cases dissolved in the solvent. As a carrier of the binder, solvent is evaporated and what is left, are granules sticking together thanks to the binder.

Second type is the dry granulation. It is the way of granules production, which can be used, when mechanical or chemical fragility does not allow to process active ingredient and filler with wet granulation methods. With dry pharmaceutical granulation processing the powder particles are aggregated, when compressed at high pressure, because of bonding forces developed by the direct contact between solid surfaces. The high pressure serves to improve contact area between the surfaces and thus the overall bonding strength. Sometimes binding agent is needed to create additional bonding strength.[6] Usually, the process is called slugging. After putting particles in one body by high pressure, these blocks are milled through sieve.

Slugging is process typical for the period from 1950s to 1970s. On the other hand, a roller compaction is well suited and preferred method for dry granulation today. Main advantages are: simplified processing, facilitated powder flow and use of minimal energy. It uses less raw materials, improves content uniformity etc. During the compaction, material goes through different stages of granules formation:[7]

1. particle rearrangement
2. particle deformation
3. particle fragmentation
4. particle bonding

There are two basic groups of materials, participating on the tablet production, which can be distinguished. Inner phase (also called as intra-granular phase) is in solid state and it is represented by powder mixture composed of active ingredient (one or more) combined with filler (again one or more). For second phase (called as extra-granular), where disintegrant, lubricant and sometimes also glidant, if needed, are included. Main difference between these two phases is, that meanwhile intra-granular phase is directly processed by granulation, extra-granular phase is added after granulation to improve flow and compress properties of granulate. As a solvent for binding agent, purified water is used most often, and because of the usage of tablets as final product, water should be also treated against anti-microbiological contamination. From other possibilities for solvent, ethanol is mentioned as an alternative to the purified water, if chosen active ingredient can be effected by hydrolysis. However, some difficulties with the usage of such solvent can occur. For example, due to increased lipophilicity it is impacting the wetting of the powder particles and, furthermore, granules properties.[8]

4.3.1 High Shear Granulation

High shear granulation is a type of the wet granulation. High shear granulator consists of a mixing bowl, three-blade impeller and an auxiliary chopper. The shape of the mixing bowl could be cylindrical or conical. The mixing bowl can be jacketed for heating or cooling of the content in the bowl. Often cooling or heating liquid is

used to maintain demanded temperature of the mixing bowl. An impeller is employed to mix and to dry the powder and spread the granulating liquid with binder. The speed for high shear granulating machines ranges from 100 to 500 rpm. The function of the chopper is to break down the wet mass to produce granules. It`s rotation speed ranges from 1000–3000 rpm. High shear granulator can be situated in vertical or horizontal direction, based on orientation and the position of the impeller. Size of the high shear granulators varies from lab scale size to the big machines for industrial usage, depending on the model. They are also equipped with an end point control. Last but not least, high shear granulators can be divided in three groups according to a specific features, for example clean in place (CIP) or wash in place (WIP) and one pot processing. CIP or WIP feature means much easier cleaning of the whole machine. One pot processing approach advantage is drying wet granules in the same bowl without additional equipment.[9]

4.3.1.1 Binders and solvents

Binder could be included to a formulation to increase adhesive and cohesive forces between particles. Consequently, this leads to better growth of particle during the process of granulation. Spreading of the hydrophilic binder on the surface of particles can also improve the dissolution of lipophilic or badly soluble active ingredients by enhancing wettability.[10] The binder should be applied in just amount to achieve a sustained and fully controlled process. If the amount of binder is too small, the particles do not show good quality (they are falling apart or the nucleation and particle growth is not running properly, on the other hand, too high spraying can result in the creation of agglomerates).

There were described five major particle interactions through the process:[10]

1. Solid bridges – they are formed due to dissolution and during the process subsequent drying of solvent during process. Another possibility of forming this interaction can be creating of chemical interaction (chemical reactions).
2. Immobile liquids – addition of special binders, which can sorb the granulating solvent, soften, deform, and adhere to a drying, and harden the structure of newly created particles.

3. Mobile liquids – liquid bridges at higher fluid levels that can create interaction in void spaces.
4. Intermolecular and long-range forces – electrostatic and Van der Waals forces.
5. Mechanical interlocking – fracture and deformation related to the mechanical stresses, that produce shape related bonding or intertwining of long fibrous particles.

Binding can be also achieved with a help of adhesion and cohesion forces in highly viscous binders.

One of the most important parameters affecting granule characteristics and size distribution is binder viscosity. Variation of binder viscosity could be achieved by either formulation changes (i. e. the type or concentration of binder) or by changes in operating temperature.[11]

Degree of drug solubility in the binder solution could affect its distribution in different granule size fractions. It was found that drugs with high solubility in the binder solution exhibited migration during drying process leading to higher drug concentration at the outer granular surfaces. High drug concentrations in fines relative to larger granules will appear with subsequent processing due to abrasion and crusts' detachments.[12]

Four key mechanisms or rate processes contribute to a granulation. Between mechanisms is included wetting and nucleation, coalescence or growth, consolidation and attrition or breakage.[10]

Wetting is highly influenced by spraying rate and fluid distribution as well as feed formulation properties in comparison to mechanical mixing. Wetting initiates nucleation from fine powder and it is first important. Often wetting agents as surfactant are carefully chosen to increase and to stabilize wetting feeds.[10]

The most common way of binder's classification is according to their chemical structure. Big influence in the matter, which type of the binder will be used, has of course the nature of used active ingredients and fillers. Compatibility between ingredients, fillers and binder is necessary, if the process should be successful. However, the knowledge about different types of binders is wide. The most popular way of choosing the binder is in many cases empirical, depending on the quantity of binder, optimization studies, previous experiences with the formulation etc. Product parameters, such as friability of the granules (and also tablets), disintegration time and

hardness are also included in the process of deciding, which binder would be the best to use:[10]

- The group of natural polymers is represented by starch derivatives and gelatine. Nowadays, their importance can be considered as traditional. Usually they are creating solutions only with warm water. Their sources are plants (wheat, maize, rice as sources of the starch) or animal tissues (gelatine).
- Family of synthetic polymers is represented by polyvinylpyrrolidone, which is also one of the most used binders. It is readily soluble in water and also alcohols. In this group also belongs methylcellulose, hydroxypropyl methyl cellulose, sodium carboxymethyl cellulose, ethyl cellulose, polyethylene glycol, polymethacrylates, polyvinyl alcohol.
- Another big group of substances used as binders, sugars, are represented by glucose, sucrose and sorbitol.
- Recently, some new natural and synthetical substances were investigated for the possibility to be used as binders. In this group belong manz gums obtained from plant sources, such as Khaya gum or Anacardium occidental gum. As new synthetic binders were examined maltrodextrines and chitosan derivatives.

4.3.1.2 Particle growth

During the growth stage (coalescence) wetter larger particles or nucleons are merging together to form granules, composed of several particles. It is important to distinguish coalescence on the beginning of the granulation – nucleation as initial coalescence of primary particles in the immediate vicinity of the larger wetting drop whereas the more general term of coalescence refers to the successful collision of two granules to form a new, larger one. As granules grow, they are consolidated by compaction forces due to bed agitation. This consolidation controls granule porosity and, therefore, final use properties of the granules, such as granule strength, hardness and dissolution.

For example, fluidized bed granulators are strongly influenced by wetting process, whereas mechanical re-dispersion of binding fluid impellers. On the other

hand, consolidation is much more pronounced in high shear method of the granulation mixing than fluid bed granulation.[9]

Compaction is a forming process controlled by mechanical properties of the feed in relationship to applied stresses and strains. Micro level processes are controlled by particle properties such as friction, hardness, size, shape, surface energy and elastic modulus.[9]

The initial distribution of binding fluid can have an evident influence on the size distribution of seed granules, or nuclei, which are formed from fine powder. Poor wetting results in drop coalescence, and in fewer, will resolve in larger nuclei with un-granulated powder and over-wetted masses, leading to broad nuclei distributions. On the start of the granulation process, initial wetting can be critical to uniform nuclei formation and often a narrow uniform product. Wide nuclei distribution can lead to a wide granule size distribution. Wetting phenomena also influence redistribution of individual ingredients within a granule, drying process and for fluidized bed granulation, re-dispersion of granules in fluid phase. Wetting at the first stage of wet granulation involves liquid binder distribution to feed the powder.

Granule growth and consolidation is, during the granulation, controlled by several mechanisms, such as wetting, nucleation and coating, granule coalescence, consolidation and of course the granule breakage. Granule growth includes coalescence of existing granules as well as layering of fine powder onto previously created nuclei or granules. They are almost immediately compacted by consolidation mechanism, which reduce internal granule voidage or porosity. If little deformation takes place during granule collision, the system is referred as a low deformability and low agitation process. Growth generally occurs at a faster time scale than overall granule deformation and consolidation. In this time interval, small particles still can be distinguished as a part of larger granule structure or “pop-corn”-type appearance, as often occurs in fluid bed granulation. Bad agitation is controlled by mechanical variables of the process, such as fluid-bed excess gas velocity or mixer impeller and chopper seed. Agitation intensity controls the relative collisional and shears velocities of granules within the process and, therefore, growth breakage, consolidation and final product density.[9] The process or formulation itself cannot define, whether it falls into low- or high-agitation intensity process.

Wet granulation then starts with loading the powder mixture, more often with

loading raw substances, including API, filler(s) and others excipients, into the mixing bowl. This can be achieved by following approaches: gravity feeding, with manual or pneumatic valve and vacuum cleaning. Next step is mixing the raw materials for short time (from 2 to 5 minutes) in a bowl at high speeds of impeller and chopper. After this period, starts the addition of liquid binder (it could be either binder solution or solvent) in the powder mixture with both chopper and impeller running on the low speed. After this procedure, granulation continues with wet massing characterized by accelerated impeller and chopper. In the end the granules are removed from the bowl and dried with appropriate technique such as fluid-bed or tray drying. As the additional part of granulation the granules are sieved. Advantages, which high shear wet granulators possesses, are, among others, short processing and relatively short manufacturing time and smaller amount of binder solution used in the process. Major advantage presents granulation of the highly cohesive materials containing e. g. hydrophilic polymers, for which the low shear granulators cannot be used. Favourable is also greater densification of product and production of less friable granules.[10]

The most important is the production of uniformly sized granules and predictable end point determination. Still, process is not immune to challenges such as production of less compressible granules and narrowed range of operating conditions. The most used technique for drying process is drying on fluidized bed. Moving product form one device to another also possesses another problem, namely exposing personnel to the toxic materials. However, this problem can be solved by single pot approach. As was mentioned above, this arrangement allows drying granules directly in mixing bowl. This can save some time. Second part of granulators does not generate such high shear as previously mentioned granulators. In this branch also belong granulators working with fluidized bed.

Except this kind of wet granulator, group also includes for example mechanical agitator granulators, which are further more divided to ribbon or paddle blenders, planetary mixers, orbiting screw granulators and sigma blade mixers. Another group of different types is called rotating shape granulator.[10]

Nevertheless, the wet granulation process still has many inherent disadvantages. Problems include choice and method of addition of the binder, and the effect of drying time and temperature on drug stability and its distribution within the sold mass.[1]

4.3.2 Batch fluid-bed granulation

Shearing of the powder bed occurs in many granulators. The low-shear granulators are granulators that, for reasons of agitator speed, sweep volume, or bed pressures, generate lower shear than high shear granulators. Fluid bed granulators are one of them. [14]

Fluidization is the unit operation by which fine solids are transformed into a fluid-like state through the contact with the gas. At certain gas velocity, fluid will support the particles, giving them freedom of mobility without entrainment.[15] With the increased gas velocity the solid particles are undergoing extremely turbulent motion. In this case, fluidized bed granulation is a process by which granules are produced in single piece of equipment by spraying with binder solution on to fluidized powder bed. This process could be named as one-pot system.

Firstly showed as an air suspension technique to coat tablets, this technique was soon applied to granulating and drying, suitable for the preparation of compressed tablets. The overall results gathered from many first studies has indicated, that fluid-bed granulator produced finer, more free-flowing and had homogenous granules, which, after compression, produced stronger and faster disintegration of tablets then the materials processed by conventional wet granulation. On the beginning, fluid-bed granulation was mostly used only for drying part of the pharmaceutical granulation process. Nowadays, it is employed routinely for drying, agglomeration, pelletization and production of modified release dosage form using air suspension coating. A typical batch fluid-bed granulation sequence consists of dry blending, wet granulation and drying steps.[16]

Fluid bed granulation requires a good understanding of the equipment functionality, theoretical aspect of fluidization, excipient interactions, and most of all identifying of critical variables that affect the process of agglomeration.

4.3.2.1 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 great enough to set them in motion. This velocity is higher than the incipient fluidizing velocity, but lower than the entrainment velocity. When the rate of flow increases the pressure drop across the bed also

increases until, at certain rate of flow, the frictional drag on the particles equal the effective weight of the bed. These conditions, and the velocity of gas corresponding to it, are termed incipient fluidization and incipient velocity respectively. At low gas velocities the bed of particles is more or less packed bed and the pressure drop is proportional to superficial velocity. As the gas velocity is increased, a point is reached at which the bed behaviour changes from fixed particles to suspended particles.[15]

The superficial velocity required to first suspend the bed particles is known as minimum fluidization velocity (u_{mf}). It sets the lower limit of possible operating velocities and the approximate pressure drop can be used to approximate pumping energy requirements. For agglomeration during the process, values normally five times or six times higher 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 cross-sectional area of the bed (W/A) (1):[15]

$$\Delta P_{mf} = W/A \text{ where } W = (1-\varepsilon_{mf})\rho_p(g/gc) \qquad (1)$$

Since the density of the gas is lower than density of the solids, it can be pictured by this equation, in which ΔP stays for pressure drop, ε equals minimum fluidization void fraction, A represents cross sectional area, W is weight of the particles ρ_p stays for density of the particles, g/gc is ratio of gravitational acceleration and gravitational conversion fraction.[15]

As the velocity rises further, the bed continues to expand and its height increases with only a slight increase in the pressure drop. The bed continues to expand and its height increases, whereas the concentration of particles per unit volume of the bed decreases. Known as entrainment, particles are carried over by the gas, which reaches entrainment velocity. When the volumetric concentration of solid particles is uniform trough out the bed all the time, the fluidization is termed as particular. When concentration is not uniform and concentrations are fluctuating through the time, the fluidization is called aggregative. According to the shape, fluidized bed gets in different velocities of air (gas) we can evaluate it and classify it to the four different types (Figure 1): [15]

1. Slugging bed is fluidized bed, in which the gas bubbles occupy the entire cross-section of the product container and divide the bed into layers,
2. Boiling bed is a fluidized bed, in which the gas forms channels in the bed

through which most of the air passes,

3. Channeling bed is a fluid bed, in which the gas forms channels in the bed through which most of the air passes,
4. Spouting bed is a fluid bed in which the gas forms a single opening through which some particles flow and fall on the outside.

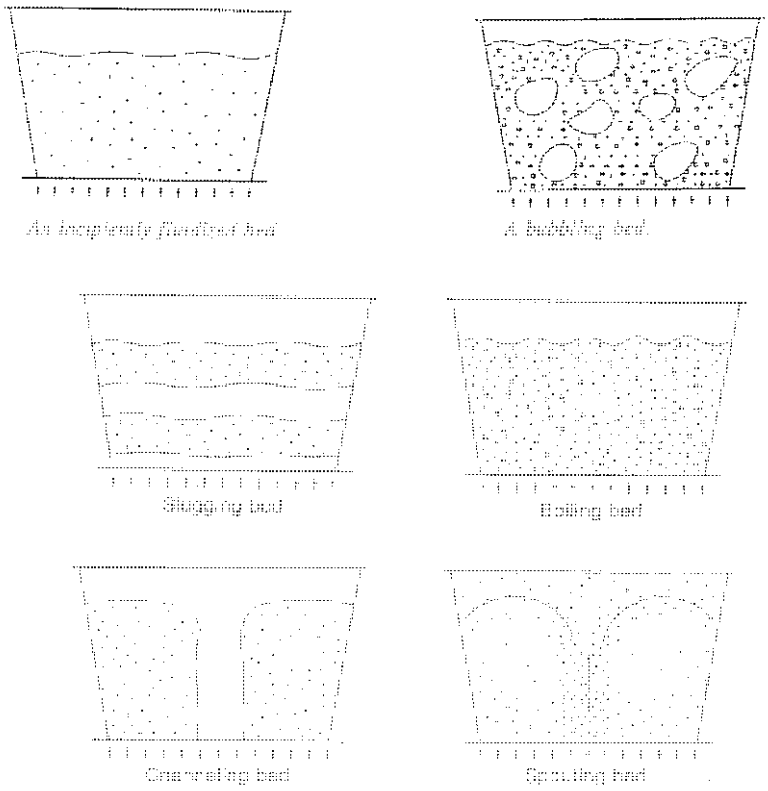

Figure 1: Various types of fluid beds [15]

When the gas velocity is higher than incipient velocity, the bubbles, which are causing mixing of the particles, are created. Mixing does not occur, if the gas velocity is low. The fluid-bed movements also have influence on heat transfer between air bubbles and particles. If there is a problem or some disadvantage of the fluidized bed, there is danger of the segregation in the fluid-bed, which can conclude in particle density differences. Main characteristic of the fluidized-bed is the relative velocity imparted to the particles, U_0, which is a strong function of the size of the particles and the gas velocity in the bed, and was shown to be given by (2):[15]

$$U_0 \approx aY^0 = 18U_b a/D_b\delta^2 \qquad (2)$$

Where a equals the average particle size, U_b is the bubble velocity, D_b is the bubble diameter, and δ is the dimensionless bubble spacing. The extent of segregation can be partly controlled by maintain in high fluidizing velocities and high bowl height-bowl diameter ratio. Therefore, there can be found standard air velocities and high bowl height-owl diameter ratio. This is calculated by using the following formula for calculating the air velocity (3): [15]

$$Velocity\ (m/sec) = Airflow\ (m^3/hr)/Area\ (m^2) \times 3600 \qquad (3)$$

Where airflow is given in cubic meters per hour (4): [15]

$$(CMH) = airflow\ (CFM)\ x\ 1{,}696 \qquad (4)$$

For drying part of the process usually velocities are low (0,8–1,4 m/sec[12]). Velocity is actually higher on the beginning of the drying, but as material loses moisture, velocity decreases. Quick particle movement and quick drying are important to prevent destroying the process during agglomeration process. Airflow velocities are normally 1,0–2,0 m/s. An indication, there is a free downward flow of the granulation at the sight glass of the drying container. However, improper fluidization can be also detected by monitoring outlet air temperature. Every product has unique heat capacity and, therefore, unique constant rate of drying. For that reason, if the outlet temperature rises more rapidly than is anticipated, it will indicate an improper fluidization and the process may have to be stopped with manual or mechanical intervention underway, which can be required to assist the fluidization.[15]

A fluid bed processor is a system of unit operations involving conditioning of process air, a system to direct it through the material to be processed, and have the same air exit unit void of the product.[15] Air preparation system includes phases for pre-filtering air, air heating, air dehumidification, re-humidification and final high-efficiency particulate air (HEPA) filtering. Because this work is focused on the topic of pharmaceutical production, the air has to be free from dust and contaminants. With various types of materials and various climatic conditions, the incoming air must be controlled very carefully.

The air, heated and moistured in the proper range, can pass through the bed of solids. The air must be introduced from the bottom of the product container, through

air inlet plenum. Proper airflow in the inlet air plenum is important to ensure that equal airflow velocities occur at every point on the air distributor plate. If air is not properly distributed before it reaches the bottom of the container, uneven fluidization can occur.[15] To facilitate the even flow of powder in the product container, conditioned air is brought in the plenum at various locations by certain manufacturers. Also proper material container volume should be chosen, such that the container is filled to at least 35–40 % of its total volume and not more than 90 % of its total volume. Typically, the container is manufactured from stainless steel with smooth inner walls.

4.3.2.2 Spraying

Spray is a splash of liquid drops in a gas and spraying is the act of breaking up a liquid into a multitude of these droplets. The general purpose of spraying is to increase the surface area of a given mass of liquid, in order to disperse it over the product area.[15] The nozzle is device, through which the liquid is forced, usually by compressed air. This can be done by one of the following methods:[15]

1. Liquid is sucked up by pressure and drop is made up over the nozzle cap after which compressed air atomizes the liquid stream by disintegrating it with air jets.
2. The compressed air operates a piston arrangement that pushes the liquid through the orifice and then lets surface tension create droplets.
3. Two pressure streams of liquid impinge upon each other and form a highly dispersed, uniform spray.

The character of nozzle device is usually represented by one of four arrangements or designs:[15]

- Pressure nozzle: the fluid under pressure is broken up by its inherent instability and its impact on the atmosphere, on another jet, or on fixed plate.
- Rotating nozzle (rotary atomizer): fluid is fed at a low pressure to the centre of a rapidly rotating disk and the centrifugal force breaks up the fluid. These types of nozzles are used mainly in a spray drying application.
- Airless spray nozzle: the fluid is separated into two streams that are brought back together at the nozzle orifice, where upon impingement, they form drops.
- Gas atomizing nozzle (two fluid nozzle): binary nozzle where the binder

solution (one fluid) is atomized by compressed air (second fluid) is the most commonly used nozzle for fluid bed granulation. These nozzles can be used as single port or multi-port device. Single ports fit for producing batches up to 100 kg. But for large size batches three port or six port nozzle devices are fitted better. When these nozzles are air atomized, the spray undergoes three distinct phases. Firstly, the compressed air or another gas expands, essentially adiabatically, from the high pressure at the nozzle to that at the fluid-bed chamber. The gas undergoes a Joule-Thompson effect and its temperature falls. In the second phase the liquid forms discrete drops. During atomization the liquid's specific surface area usually increases 1000 times. In the third phase the drops, after being formed, travel until they become completely dry or impinge on the product particles. During this phase, solvent evaporates and the diameter of the drops decreases.

Two types of spraying could be distinguished. The bottom spray design is very popular for layering of active component of coating to modify drug release, mainly due to its good film formation in such units. On the other hand, top spray has a simple set up, offers a high capacity and is typically used for either granulating powders or spray drying. The main components for a top spray processor are:[16]

1. An air-handling unit optionally equipped with humidification and dehumidification for dew point control,
2. A product container,
3. An expansion chamber,
4. A spray system containing single or multiple nozzles,
5. An exhaust system with filter and, optionally, an explosion suppression system.

The two-fluid nozzle in its simplified model is based on energy transmission as shown below:[15]

Energy + Liquid =Two fluid nozzle=Droplets + Heat

Optimum atomization is achieved by fine adjustment of their cap and atomization air pressure measured at the nozzle. The binder solution is delivered to the nozzle port through a spray lance and tubing. Peristaltic or positive displacement pump is commonly used for supplying nozzle with binder solution.[12] Nozzle ports

with openings from 0,8 to 2,8 mm in diameters are most commonly used and are interchangeable. Once the air leaves the product bed, it has to be cleaned from fine particles. They are separated from the air stream and if possible, they are returned to the product bed. Two zones are used in the fluidized bed to separate the particles from the air stream. Disengagement area is dedicated for bigger particles, which loses kinetic energy in this zone and they are falling back under the nozzle and exhaust filter.[15] By exhaust filter leaves the air or lifting gas granulation chamber of the machine. On the exhaust filter the small fine powder particles with highest velocity are caught and by counter-pressure pulses of air or another gas they can be returned to the fluidized bed.

There are several types of the exhaust filters, widely used in pharmaceutical industry or laboratory. First type is, according to the material, stainless-steel filters in the shape of the slim columns pointed down to the bed fluid. Another variant represents bags or cartridges made from various materials, mainly based or synthetic polymers. Between most used materials belong nylon, polyester, polypropylene and polytetrafluoroethylene, firstly introduced in 1980s. They are cleaned mechanically by shaking or blow back by compressed gas. Position of the exhaust filters can be vertical (provides better cleaning) or in the angle (better access and manipulation). Stainless filters are also more expensive than filters manufactured from linear polymers.

4.3.2.3 Agglomeration and particle growth

Agglomeration is provided by three mechanisms during fluid-bed granulation:[16]

1. Bridges due to immobile liquids form adhesional and cohesional bridging bonds. Thin layers with adsorption properties are formed on the surface of the fine powder particles are not mobile and can contribute to the forming of the bonds between particles.
2. If the mobile liquids are used, they are creating bonds between particles on the base of the capillary and interfacial forces are present.
3. Solid bridges formed due to crystallization of dissolved substances during drying.

According to the Newitt and Conway-Jones,[17] four types of bonds forming

approaches through four transition states are described as pendular, funicular, capillary and droplet. All of them typically happen through spray drying. Assuming a binder solution is used as the granulation fluid, which is sprayed into fine droplets, liquid bridges between particles can be viscous and adhesive. Formed solid bridges will remain after drying.[16]

If the binding forces are in excess of the breakup forces, either in the wet state or dry state, uncontrolled growth will proceed to over-wetted bet or production excessive fines, retrospectively. If the forces are balanced, the agglomeration occurs, and growth can be controlled pretty well. Formation of the granules is going through three following subsequent stages: [15]

a. Nucleation,
b. Transition,
c. Ball growth.

In practice, the liquid may not have enough time to reach its equilibrium state, due to interference from the mixing process occurring simultaneously in the granulator. The nuclei size distribution is a function of both wetting kinetics and thermodynamics. As the wetting process proceeds, the fluid penetrates into the pores of the powder surface, forms a nucleus and migrates outwards as the nucleus grows.[18]

The main difference and also advantage (maybe this property can be also called uniqueness) of the fluid-bed agglomeration process is in, how the liquid addition and drying steps are currently carried out. When the granulation liquid is sprayed into the fluidized bed, the primary particles are wetted and form together with the binder relatively loose and very porous agglomerates.[15] Drying a wet product in a fluid bed can be taken as a separate topic, but during the granulation process it becomes an integral part of the whole process. Hence understanding fluid bed drying is very important.

4.3.2.4 Fluid bed Drying

Drying is defined as the removal of moisture or solvent from the granules. Drying in every condition involves mass and energy transfer. Carrier of the heat is

evaporating liquid and mass of the liquid is transferred through the surrounding gas. Therefore, these two factors are interdependent. Drying rate is always determined by the factors affecting the heat and the mass. The transfer of the heat in the fluid bed takes place by convection. Convection means transport of the heat from one point to another within a fluid (gas, solid, liquid) by the mixing of one portion of the fluid to another.[15] Moisture, which can be removed from the granulated product in the fluid-bed granulator, is called free moisture or free moisture content and it is amount of humidity, which can be removed from the material by drying at specified temperature and humidity (5):[1]

$$M_r = M_{out} - M_{in} \qquad (5)$$

Moisture removed (M_r) during the drying process can be calculated from moisture contents of inlet (M_{in}) and outlet air (M_{out}).[16]

Rest of the moisture, moisture that remains associated with the material under drying condition, is called equilibrium moisture content. Furthermore, due to the fact that the drying step occurs simultaneously with liquid addition in fluid bed granulators, the evaporation of liquid results in an increased concentration of binder in the liquid bridges holding the particles together and consequently the liquid bridges become more viscous and immobile.[8] The evaporation of liquid film surrounding the granule being dried is related to the rate transfer by the equation (6):[15]

$$d_w/d_t = hA/H \,.\, \Delta T \qquad (6)$$

Where d_w/d_t is the mass transfer rate (drying rate), h is the heat transfer coefficient, A is the surface area, H is the latent heat of evaporation, and ΔT is the temperature difference between the air and the material surface. Because the fluid bed processing involves drying in hot suspended air, the heat transfer is extremely rapid. Improper air distribution could cause all scale of different adverse effects, such as caking channelling, or sticking.[15] Two key elements for controlling drying process are inlet air temperature and airflow.

These two factors are connected to another element; the capacity of the air (gas) stream to absorb and carry away moisture determines the drying rate

and establishes the duration of the drying cycle.

5. Experimental part

5.1 Materials

Kollidon® 30

Manufacturer: BASF - The chemical Company, Germany

Batch number: Lot 23408975L0

Description: consists of soluble and insoluble grades of polyvinylpyrrolidone (PVP), a vinylpyrrolidone/vinyl acetate copolymer and a blend of polyvinylacetate and polyvinylpyrrolidone. It is widely used in production of tablets, capsules and granules.[23] (Figure 2)

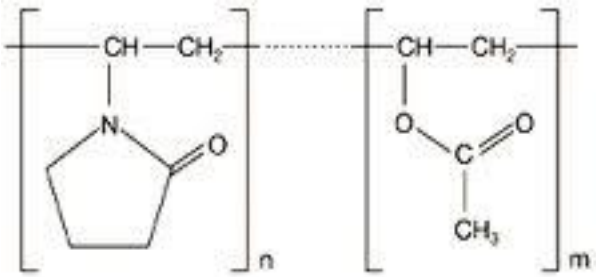

Figure 2: Chemical formula of Kollidon [25]

Pharmatose® M100

Manufacturer: DFE PHARMA, Germany

Batch number: Lot 10646055

Description: lactose is disaccharide sugar. This sieved lactose monohydrate complies with the latest editions of US Pharmacopoeia and Europian Pharmacopoeia. Often used as filler for manufacturing tablets, lactose improves compressibility. [20] (Figure 3)

Pharmatose® M200

Manufacturer: DFE PHARMA, Germany

Batch number: Lot 10690622

Description: milled lactose monohydrate. Also complies with the latest editions of US Pharmacopoeia and European Pharmacopoeia. It is used as filler for manufacturing tablets, capsules and granules. Lactose improves compressibility of mixture.[21]

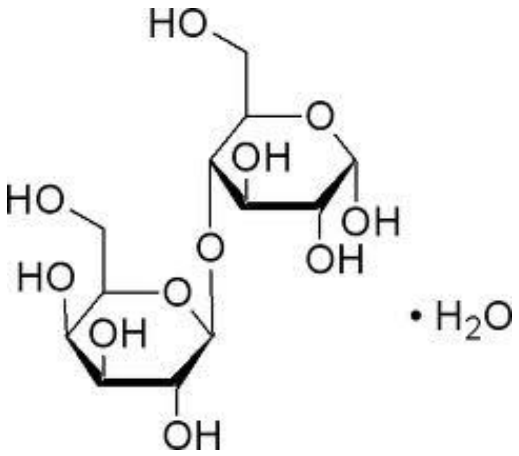

Figure 3: Chemical formula of lactose monohydrate[26]

Caffeine

Manufacturer: BASF - The chemical Company, Germany

Batch number: Lot 611

Description: Bitter, white crystalline alkaloid used as a stimulant drug and as a model API [22] (Figure 4). In experimental part of the work was used anhydrous caffeine in form of bulk, disagglomerated or sieved (three different grades and their particle size distribution are compared in Table 1).

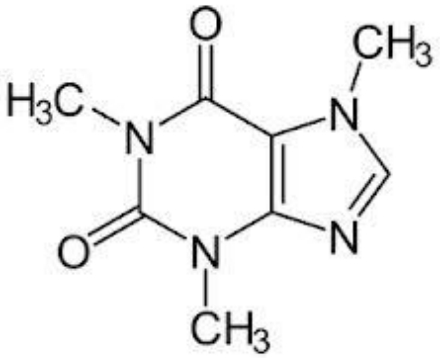

Figure 4: Chemical formula of caffeine[27]

Maize Starch

Manufacturer: Roquette, France

Batch number: E1040

Description: carbohydrate biopolymer consisting of glucose monomers connected by glycosidic bonds. Used as the filler for its insolubility. Also important is its disintegration function.[24] (Figure 5)

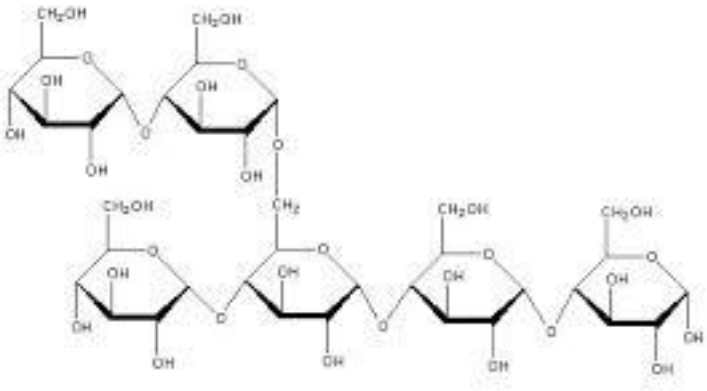

Figure 5: Chemical formula of starch[28]

5.2 Equipment & Aids

MIDI Glatt® fluid bed granulator/ spraying dryer/ coating device

Fluid bed system for batch volumes from 375 g – 1350 g

Manufacturer: Glatt, Binzen, Germany

Turbula® blender

Container volume up to 2 liters

Manufacturer: WAB, Switzerland

UV spectrophotometer Beckman-Coulter DU640

Scanning single beam spectrophotometer with internal computer.

Wavelength range: 190-1100 nm

Manufacturer: Beckman-Coulter, USA

IR moisture analyser Kern MLS®

Working range of temperatures: 50-160°C

Accuracy of moisture measuring: 0.01 – 0.001

Manufacturer: Kern, Germany

Fortuna Graduated and bulb pipettes

Used volumes 5 – 25 ml

Manufacturer: Poulten and Graf

Balance Mettler 50 AE®

Working range: 0 – 50.0000 gram

Manufacturer: Mettler Toledo, Germany

Balance Sartorius CPA series

Working range: 0 – 12000.0 gram

Device used for flowability measurements

Assembled according to the design of Dr. Pfrengle, type 3102

Manufacturer: Hans W. Schmidt

Sieving tower Fritsch®

Maximal frequency of vibrations: 50 Hz

Manufacturer: Fritsch, Germany

Magnetic stirrer Ika Combimag Ret®

Maximal temperature 350 ° C and maximal revolution rate 1100 rpm

Manufacturer: Ika, Germany

Elmasonic S 300 H®

Ultra sonic cleaning bath

Manufacturer: Elma GmbH & Co KG, Germany

Wet granulator, type not specified

Manufacturer: Erweka GmbH, Germany

Glassware (pipettes, flasks e.c.)

Manufacturers: Falcon, HBG, Costar, Gilson, Fischer

Sieves for Particle size distribution analysis

Diametr of the holes: 1400 – 40 μm

Manufacturer: Fritsch, Germany

5.3 Preparations of powder mixture and binder solution

Mixture is composed of three raw substances: Caffeine (88 g), Lactose (two grades, together 198 g) and Maize Starch (154 g).

Caffeine was API of granules and because of its state, it had to be disagglomerated manually or with a help of the wet granulator. Usual size spectra of raw caffeine after a disagglomeration should be in the interval from 800 μm to smaller than 40 μm. For manual disagglomeration a manual powder mixer or wet granulator were used. Caffeine treated with this approach should not contain agglomerates bigger than 800 μm and should be prepared for use in powder mixture. Table 1 shows particle distribution in different caffeine grades.

Lactose was an excipient in formulation of granules. Two separated grades of lactose were used in proportion 1:1. First grade of lactose was a sieved one. It`s particle size distribution, according to information given by manufacturer, should be from 80 % located between 100 μm and 1000 μm. Second grade of lactose was milled lactose. Maize Starch, used in amount of 154 g, was the second excipient in process. For answering a question of particle growth in granulation process, that was run, particle size distribution analysis on sieving tower with results.

Table 1: Comparison of different caffeine grade's particle size distribution

SIEVE (µm)	CAFFEINE GRADES		
	AGGLOMERATED	DISAGGLOMERATED	SIEVED
1400	0%	0%	0%
800	29%	1%	0%
710	3%	1%	0%
600	4%	5%	0%
500	26%	17%	0%
400	7%	32%	18%
315	15%	27%	24%
250	12%	8%	15%
125	2%	9%	23%
100	2%	0%	17%
63	0%	0%	4%
40	0%	0%	0%

Table 2: Comparison of the excipients and mixture's particle size distribution

SIEVE (µm)	MATERIALS			
	MAIZE STARCH	LACTOSE 100M	LACTOSE 200M	FINAL MIXTURE
500	0%	0%	0%	1%
400	13%	0%	0%	0%
315	11%	0%	0%	1%
250	16%	0%	2%	9%
125	16%	54%	43%	27%
100	26%	35%	32%	23%
63	8%	11%	20%	19%
40	2%	0%	3%	15%
0	9%	0%	0%	5%

For blending the granulation mixture, Turbula mixer (Figure 6) was used. After insert of a dose with freshly weighted powder mixture and fixing the dose inside the holding basket, the blending was started. Whole blending procedure lasted 10 minutes. Particle size distribution of raw materials and mixture used for granulation are shown in Table 2.

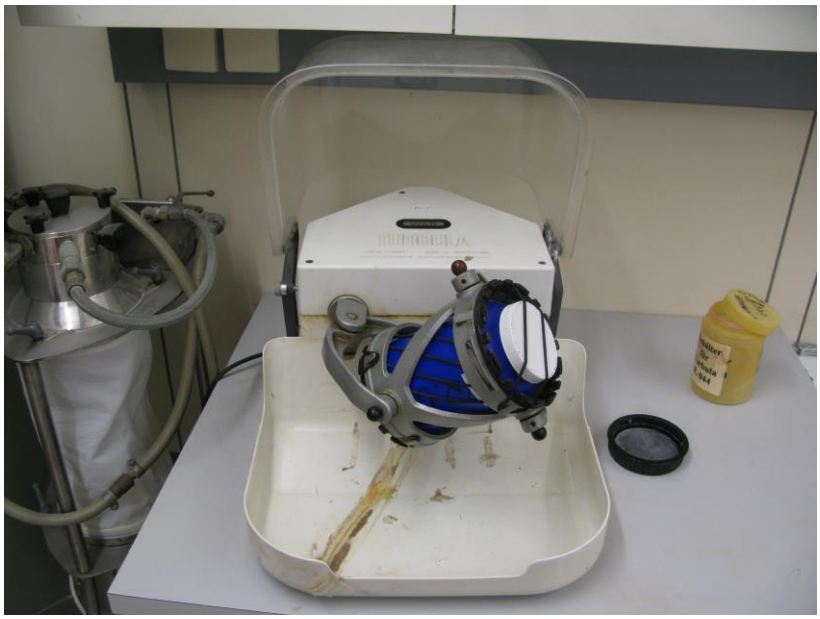

Figure 6: Turbula mixer prepared for blending procedure

Binding solution (Figure 7) is aqueous solution of poly-vinyl-pyrrolidone (concentration 10%). After weighing 216 g of demineralized water 24 g of PVP was added and dissolved in the water with a help of magnetic stirring device without using heating. Dissolving of PVP lasted from 10–15 minutes.

Figure 7: Binding solution prepared for granulation run

5.4 Fluid bed granulation

5.4.1 MIDI Glatt

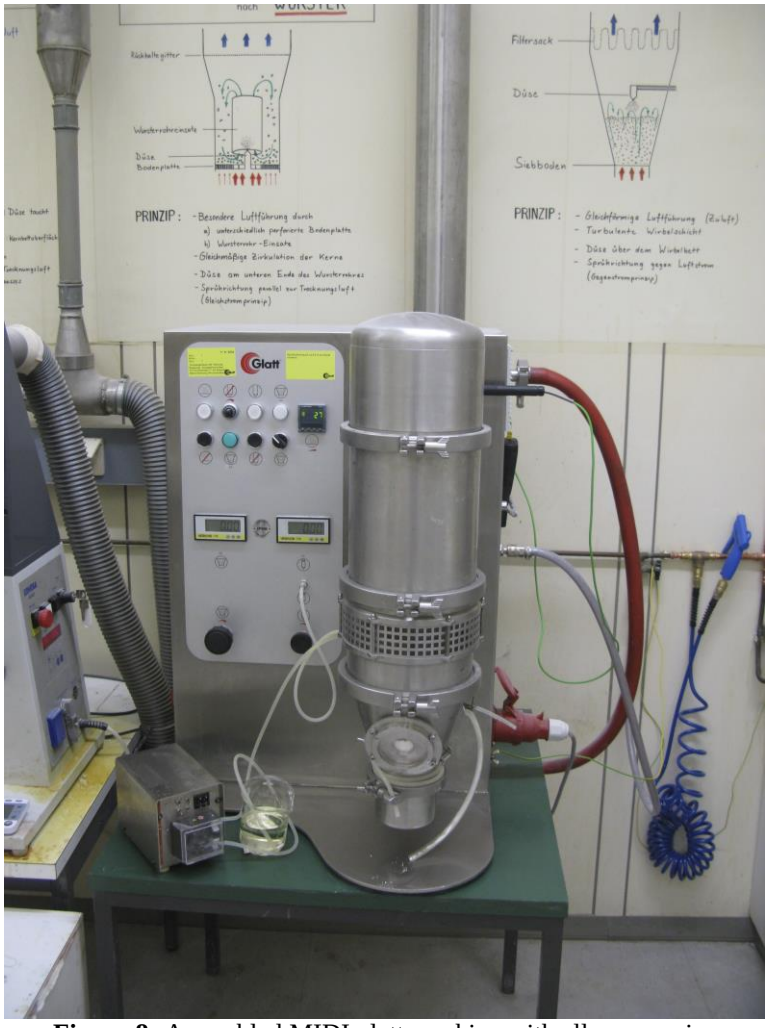

Figure 8: Assembled MIDI glatt machine with all accessories

The MIDI Glatt (Figure 8) is device of laboratory scale. Its intended use is to perform fluid-bed drying, fluid-bed continuous granulation and fluid-bed coating process.

Device is manufactured from stainless steel. It consists of two main parts: body with control panel and included air ventilation and granulation/drying/coating chamber. Spraying pump is separated. Granulation/drying/coating chamber is assembled from filter housing[25], sprayer housing[25] (equipped by plastic ring window) and material container[25]. Sealing between these parts is provided with silicon rings.

Filter housing (Figure 9) includes four products retaining tubular housing fan filters[25], which are pointed down.

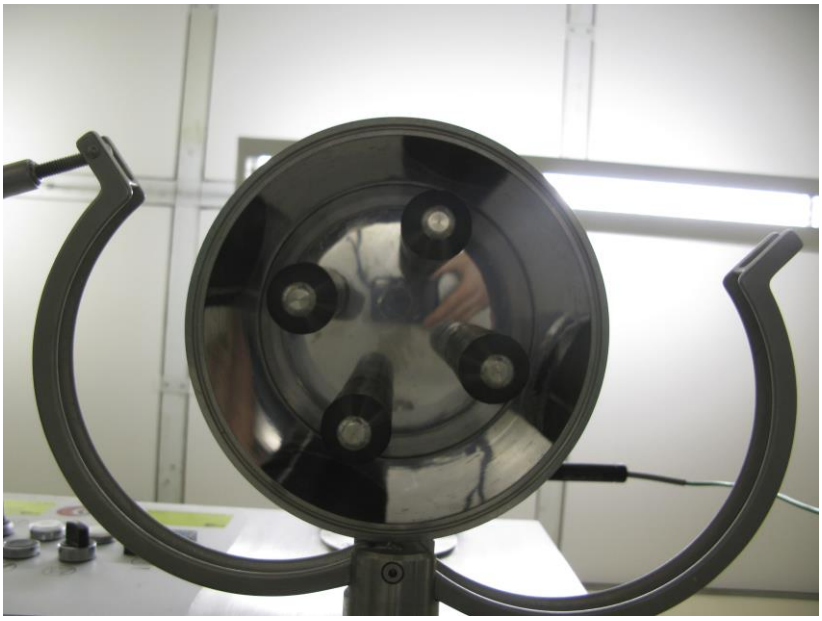

Figure 9: Filter housing with 4 product retaining tubular filters

Sprayer housing (Figure 10) holds spraying nozzle. It is situated in low distance arrangement. During the process, powder mixture is top-sprayed. Nozzle is assembled from several parts, including two tubes providing air and binding solution for the nozzle. Spray housing part of granulation chamber also includes ring window.

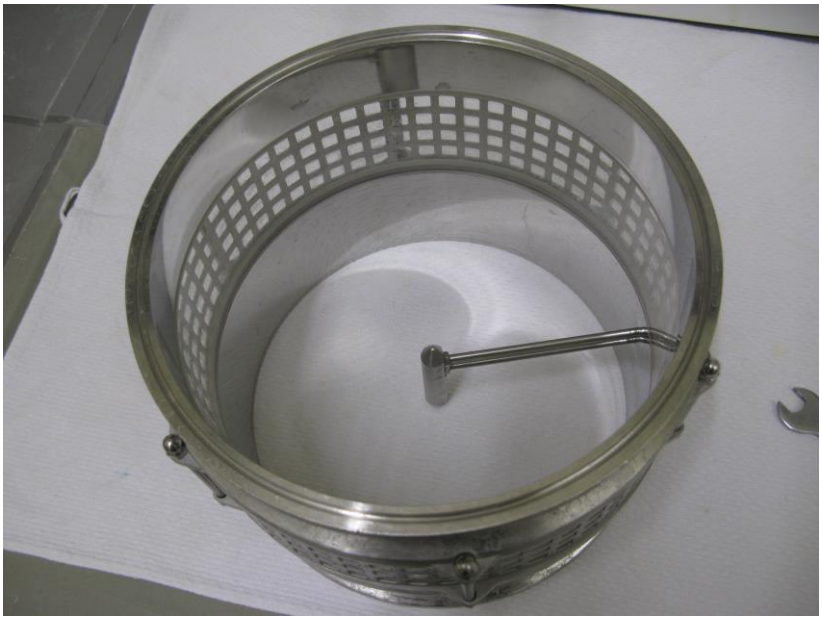

Figure 10: Spray housing part of granulation chamber with attached spraying nozzle in low distance top spray arrangement

Material container (Figure 11) has useful volume 580–2800 ml[25] (and it is equipped with tube on the bottom, where the air comes into the granulation chamber. Material container includes also round window.

Figure 11: Material Container from the side

On the top, the air leaves the body through four smaller tubes. It is filtrated and exiting MIDI Glatt. Round window is situated in middle of material container. This part also valve for taking in-line samples. The air filter is placed between the bottom part and the rest of material container.

The design of controls allows many variations of the process parameters, which can influence the product quality and quantity of the product. Between them belong:

In Tables 3, 4, 5 and 6 below can be seen the overview of important parameters of MIDI Glatt:

Table 3: Dimensions[25]

Parameter	Value
Height	900 mm
Width	700 mm
Depth	740 mm
Weight (empty)	90 kg

Table. 4: Filters[25]

Filter	Type (material)
Compressed air Filter	Preliminary filter with water trap 3 μm/100 m^3/h
Product retaining air filter in filter housing	Fibre tissue filter DIN 5338 man

Table 5: Spraying pump[25]

Type	Maximal flow rate
Watson-Marlow	100 ml/min

Table 6: Optional parameters[25]

Parameter	Scale
Fluid-bed pressure	0 – 6 bar
Spraying rate	1 rpm to 99 rpm
Temperature in working chamber	Up to 80 °C
Counter-pressure pulses interval	1 to 10 seconds
Nozzle pressure	0 – 2 bar

5.4.2 Preparations for granulation

At the beginning, the assembling and filling of the machine with a mixture needed to be done. Low arrangement of the spraying nozzle was used and the spraying nozzle was pointed down inside the material container. The spraying nozzle was connected to the source of pressurized air and hose for binding solution. This hose, supplying spraying nozzle with binding agent, went through the electric pump. The speed of the pump was crucial for the successful granulation. It was dependent on inner diameter of hose and velocity of pump. After control the phase of pre-heating was initiated. Pre-heating was procedure preparing the air used for fluid-bed process. Counter pressure, a function, which has provided cleaning of top part of granulation chamber, was set on. Counter pressure caused that light particles, which were located in the highest part of machine, has fallen down in a space under the nozzle during the process and they were able to continue to participate on the process. Especially for a beginning of the granulation was crucial to set counter pressure to the smallest

interval (with MIDI Glatt it was 1 second). During the part of pre-heating the nozzle pressure was set. Nozzle pressure was determining the area of spraying – if there was increase of the nozzle pressure, the area of spraying has spread. For examined granulation process the optimal nozzle pressure was 1.2 bar. Pre-heating lasted 5 minutes with temperature set on 80 °C. Pre-heating phase was finished by increasing of fluid bed pressure to the value of 0.08 bar. The movement of particles through the big window was seen.

5.4.3 Granulation operations

After the start of the fluid bed and initiating of spraying with spraying rate, a fluid bed pressure was set. Fluid bed pressure was 0.08 bar just for few seconds, only to make powder wetter. Temperature was over-watched and it was kept in the interval of 53–55 °C. In this phase, in lower part of the machine was placed sensor for monitoring of the temperature. It was connected to thermometer located in a tube, which took air for fluid bed in a granulation chamber of the device. Then the fluid bed pressure was raised to 0.3 bar and it was maintained for 5 minutes. After this period, for the first time the decrease of the fluid bed pressure to 0.07 bar was initiated, just to sustain a stabile fluid bed. In 30 seconds period a counter pressure was cleaning upper parts of a device. Next cleaning procedures were set for every 8 minutes.

During the 6th minute of granulation process, fluid bed pressure increased to 0.4 bar. Soon after a round window situated low should be clean and the movement of the growing particles should be visible (Figure 12).

This was considered as the sign of well running granulation. 16 minutes from the granulation's start the bed fluid pressure was increased again, this time to 0,5 bar. 3 minutes before that, another cycle of cleaning was completed. 0,5 bar was final setting of bed fluid pressure for granulation run. After 27 minutes the whole binding solution was depleted, which meant that drying of granules could start. For that process, the thermometer probe was placed in tube, where wet air from granulation chamber was leaving the granulator.

Figure 12: Particle growth over-watched through the round window of material container

Figure 13: emplacement of thermo-probe for drying part of granulation

The drying phase usually takes circa 20 minutes. The parameters for drying contained higher temperature 65 °C and lower fluid bed pressure 0.2 bar. These parameters had to be chosen carefully, because high temperature and high fluid bed pressure could result in dire destruction of newly granule particles.

Temperature was monitored by thermometer, located in tube, where used air is leaving granulation chamber (Figure 13) Starting temperature was marked and as end point value temperature was chosen starting temperature in drying process +0.5 °C. This has ensured that moisture level reached values in the interval of 1–2 %.

Still, during the drying, the fluidal movement of the granules should be visible. When the drying was finished, the machine was dismantled and the product was collected.

The process parameters together with their shifts during the process of the granulation are stated in the Table 7.

Table 7: Process parameters and their changes during granulation run

Process Parameter	Initial setup	Time - shift during the granulation
Fluid-bed pressure	0-3 bar	6th minute – 0.4 bar 16th minute – 0.5 bar 27th minute – 0.2 bar
Spraying rate	9 g/min -	Same through whole granulation
Temperature of inlet air	50 - 54 °C	27th minute – 65 °C
Counter pressure interval	Every second	In 5th minute running only with fluid-bed pressure 0,8 bar to clean the filters (since then repeated every 8th minute)
Nozzle pressure	1.2 bar	Same through whole granulation

5.5 Analysis

5.5.1 Particle size distribution of granules

For particle size distribution analysis of the product was used the device from company Retsch (Figure 14). Before whole procedure all mashes were weighted for counting down the exact mass of each fraction. As a first step, weight of the whole product with balances was measured. As a second step, sieving tower was assembled.

The product was analysed in whole. After the assembling of the sieving tower from separated sieves, the product was placed into the top mash (with size 1400 μm). Then the sieving tower was closed and secured with straps. Program for sieving of granules with permanent vibrations (strength 8 on the scale of the machine) was used. During the analysis, it was used this order of mashes: 1400, 800, 710, 630, 500, 400, 250, 125, 100, 63, 40 μm and bottom, for the rest of the product, smaller than 40 μm. Ideal time for particle sized distribution analysis was estimated to 5 minutes. After that, every mash was carefully weighted and the result was noted.

Figure 14: Sieving tower Retsch used for Particle size distribution analysis

5.5.2 Flowability

For the flowability analysis, it was used 100 g of product (raw granulate with all fractions from 800 micron and smaller). There were run three measurements with one specimen with machine designed for flowability measurements (Figure 15). The hole was held closed in bottom of conical part of machine with one finger and the hole on bottom was opened after filling. In the same moment, the stopwatch was activated.

When the granulate was not leaving the machine smoothly, it was used the steering device to improve its flow. Once the conical part was empty, time measuring was stopped and followed by measuring height and diameter granulate body's base.

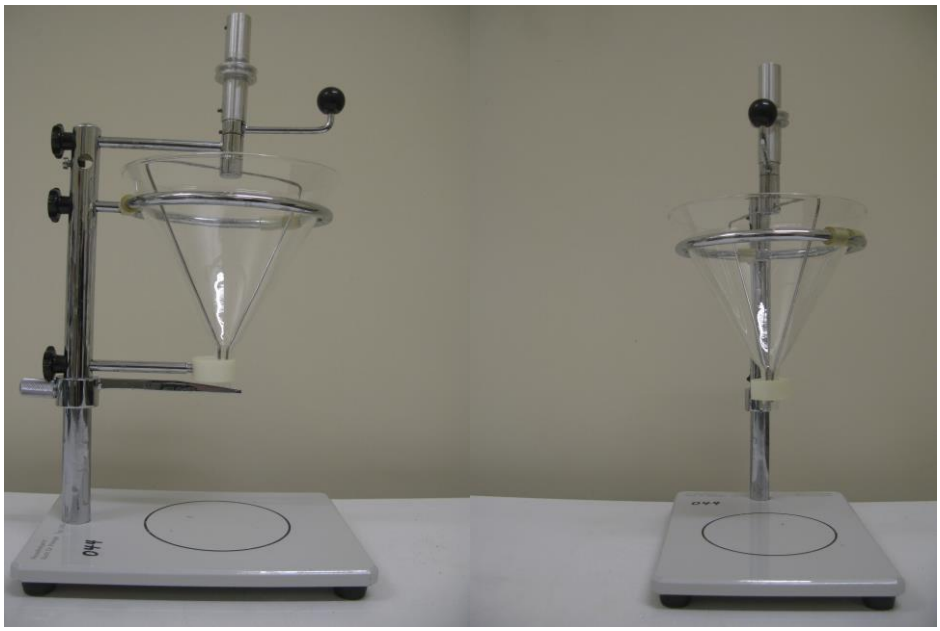

Figure 15: Device used for flowability measurements

5.5.3 UV Spectroscopy

Calibration curve

After creating a stock solution (stock was put in a sonic bath for at least 5 minutes, no heating) with a concentration 200 microgram per millilitre, the solution was diluted ten times and additionally, it was diluted another time in this pattern (Table 8):

Table 8: Dilution of caffeine stock solution (concentration 200 µg/ml)

Concentration (µg/ml)	Stock (ml)	Water (ml)
20	0.5	9.5
16	0.5	12
10	0.2	7.8
8	0.2	9.8
4	0.1	9.9

Measuring of Caffeine content in samples

For each batch, nine samples were prepared and they were examined. Than 100 milligram were taken directly from these samples and were dissolved in 50 ml of water. To save a time during dissolution of samples, every single sample was put for two hours in sonic bath with proper shaking after one hour. This was also done, so as much as possible amount of caffeine could be analyse in UV. After this step, each sample was filtered with membrane filter with using syringe. From filtrated solution, 2 ml were taken to dilute it ten times and right after that four times. Samples prepared in this way were taken to Spectrophotometer Beckmann (Figure 16) and measured in UV (wavelength 272 nm, 274 nm or both, referred to water). Samples were measured with wavelength 272 nm in glass cuvettes and water was used as reference.

Figure 16: UV Spectrophotometer Beckman-Coulter Du® 640

6. Results

6.1 Evaluation and optimization of the fluid-bed granulation process

Granulation process was evaluated according to the information gathered from batches produced during Phase I, II, III. The name Phase I was used for set of batches produced during the first half of November 2012. As Phase II was called the set of batches produced in the second half of November. Phase III was created from the batches produced in December of the same year. Main criteria for evaluation of the process were the properties of the product: size of the yield in percentage, particle size distribution and flowability of the product.

The yield was defined as particles between 500 micron and 125 micron. Above this interval, particles were classified as agglomerates. Particles smaller than this interval were classified as fine. The perimeter between yield and fine was represented by particles with size between 250 and 125 microns. It was classified as part of yield. As appropriate fluidity of the granules, values around 30 degrees are considered as a good result. For evaluating process parameters, three of process parameters were taken and their changes and influence of these changes to the product were examined. This was done for spraying rate, fluid-bed pressure and nozzle pressure.

Yield is highly dependent on spraying rate. In Phase I, spraying rate was 5 g/min and yield was less than 50 % on these runs (Figure 17). In Phase II, the spraying rate was increased to 7.5 grams per minute. In this Phase, yield was around 50–70 % of the product (Figure 18). For later granulation runs (Phase III) the spraying rate was raised up to 9 g/min and this change resulted in achieving yields of 80–90 % and from there on, it was fixed at 9 g/min (Figure 19). The yield increased up to 80 % of granules. No other process parameters were altered.

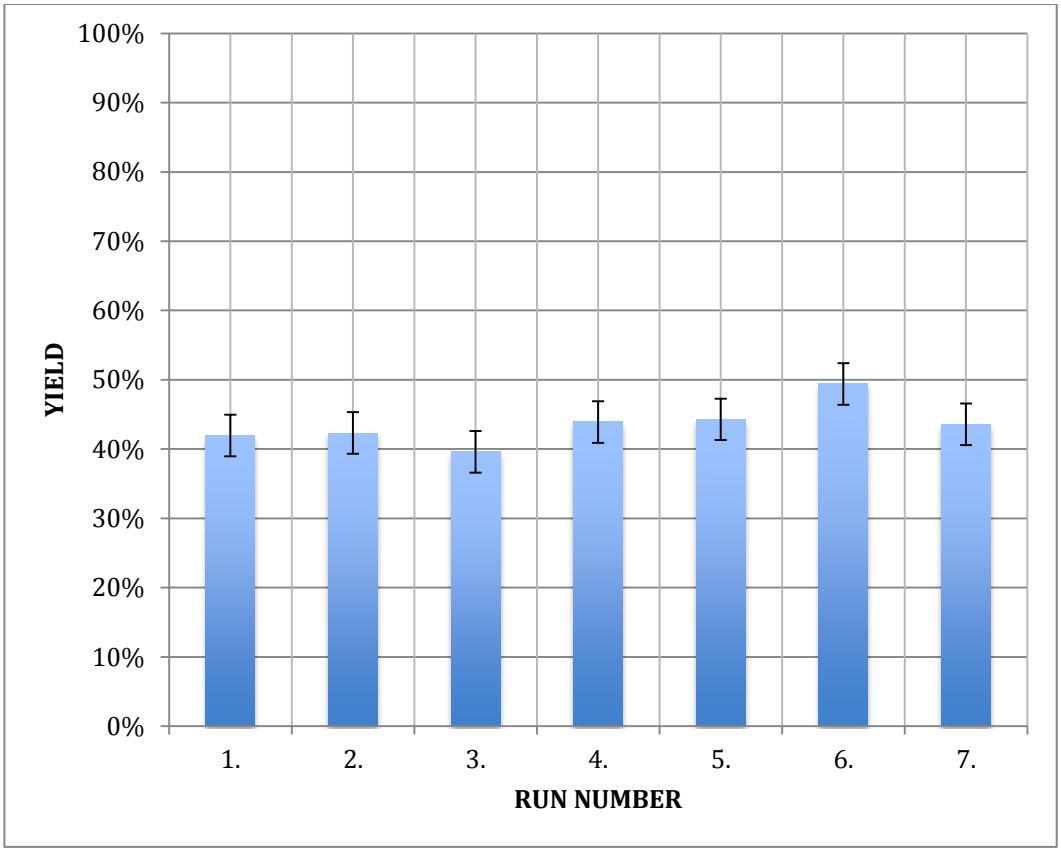

Figure 17: Yield progression during Phase I (spraying rate 5 g/min)

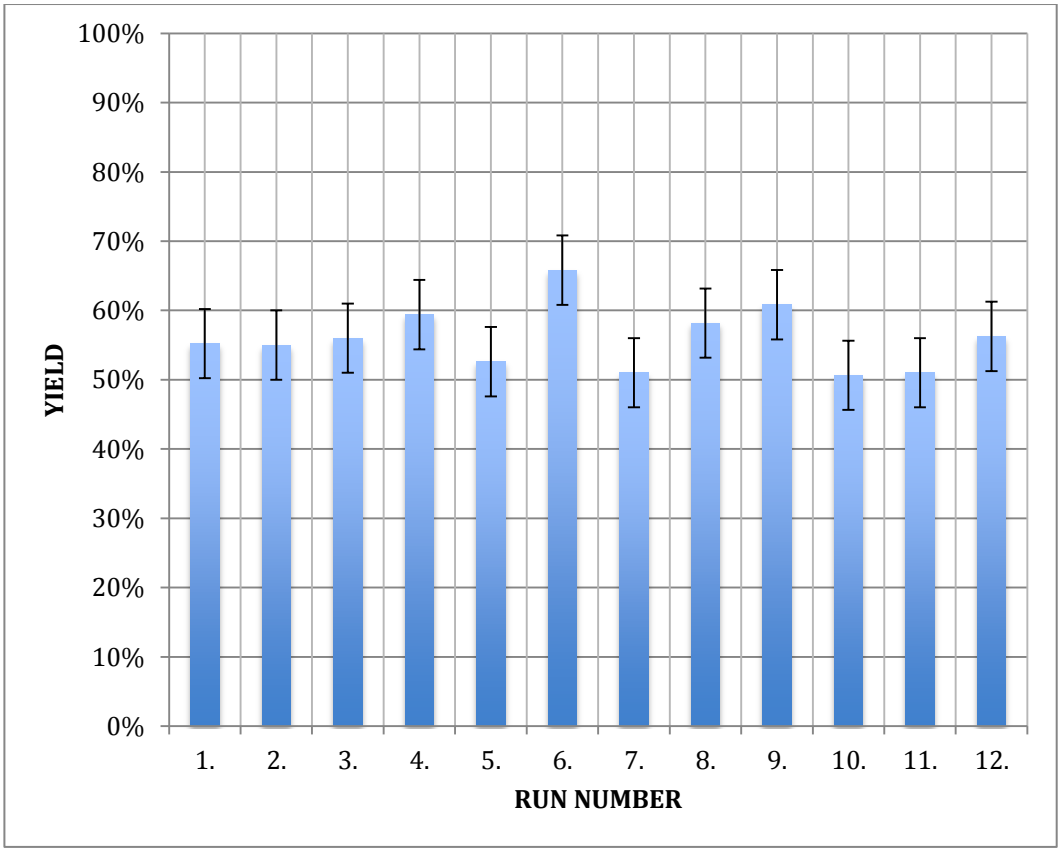

Figure 18: Yield progression during Phase II (spraying rate 7.5 g/min)

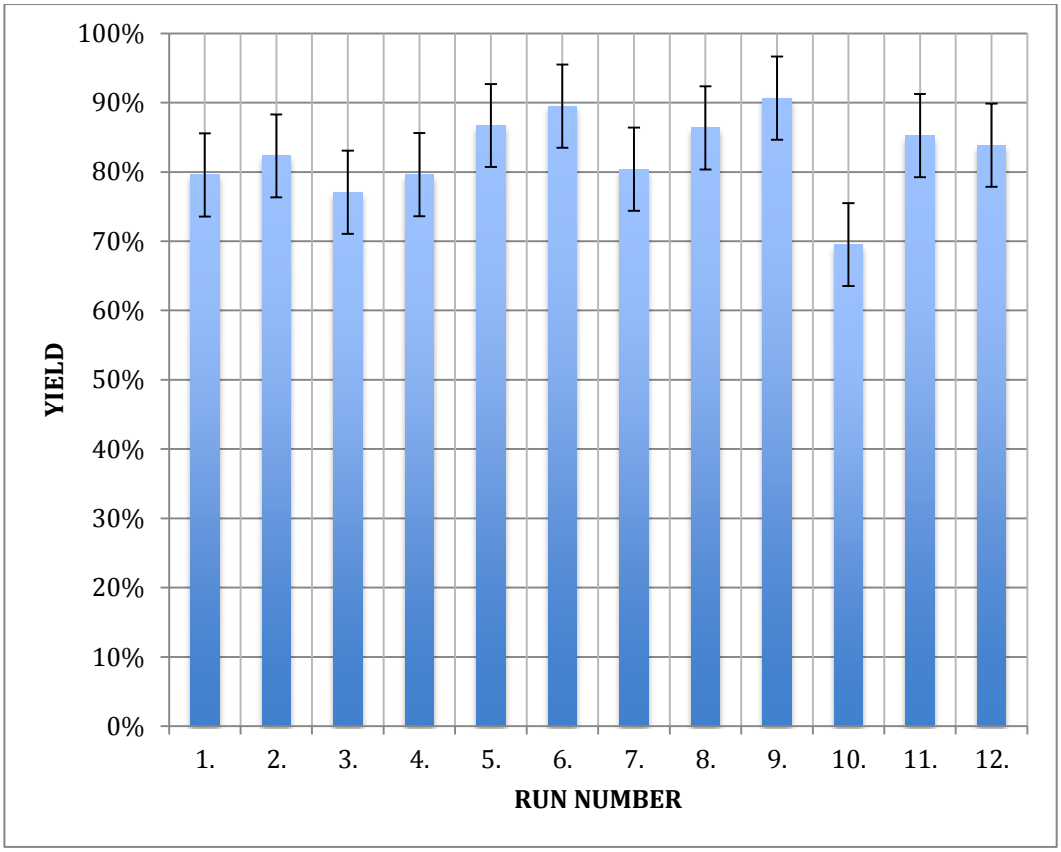

Figure 19: Yield progression during Phase III (spraying rate 9 g/min)

Spraying rate was further examined to evaluate, whether smaller changes in the spraying rate could result in an improvement of the yield. For these runs, sieved caffeine was used instead of bulk caffeine and because of this, in comparison to the previous runs, the yields are higher.

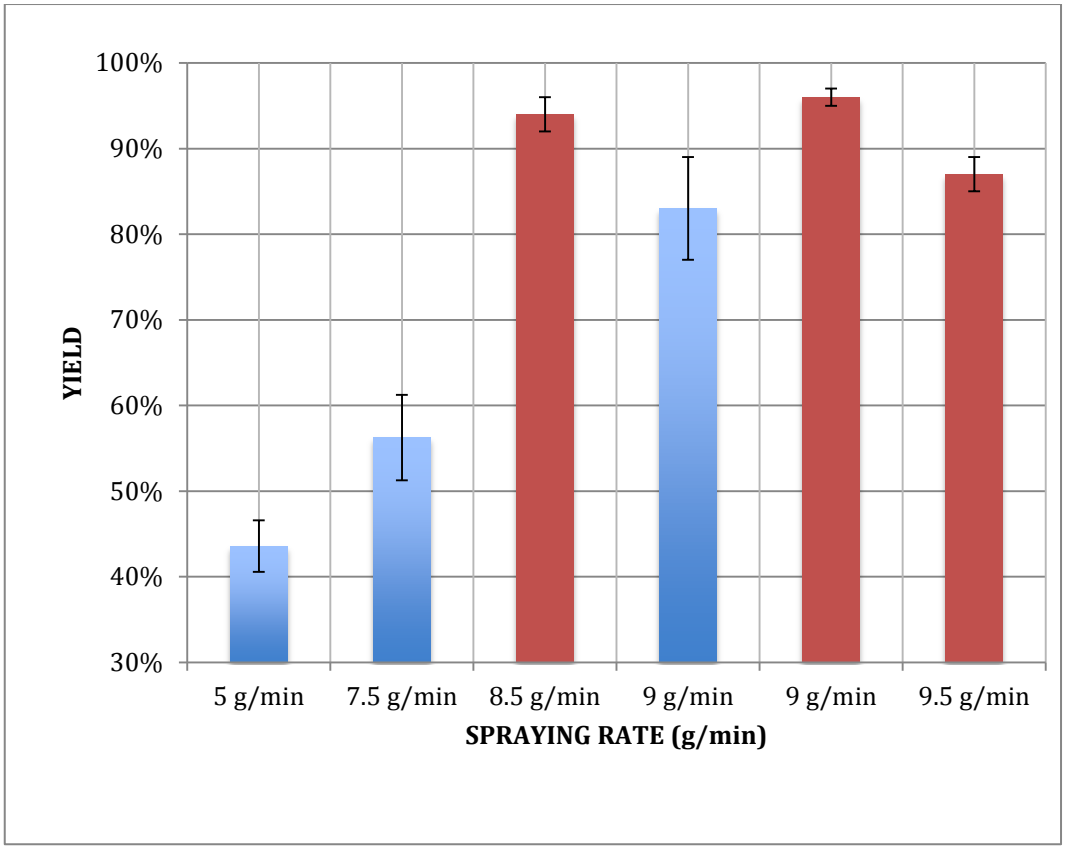

Figure 20: The relation between yield and spraying rate. Red color represents sieved caffeine and blue color represents bulk caffeine

Small changes in the spraying rate (changed up and down for 0,5 g/min) have led to the lower yield (Figure 20). The runs made with sieved caffeine have better yields and their standard deviations were smaller than in the case of the runs, where bulk caffeine was used. In both cases (bulk and sieved caffeine), the best results were achieved with spraying rate 9 g/min.

Increasing spraying rate up to 9.5 g/min caused a decrease in yield from 96 % to 88 %. A further increase of spraying pressure was not examined because of highly presumable destruction of the granulation process with the spraying rate 10 g/min and due to over-wetting the system. With higher spraying rate in unchanged temperature conditions the water was not evaporating quickly enough and particles were getting heavier and stickier. From certain point the airflow was not strong enough to lift them sufficiently and they were staying on the bottom of the chamber, creating chunks and destroying the process by jamming supply of air in the worst case and consequently preventing the proper fluid bed.

Particle size distribution has also changed with spraying rate. With increased spraying rate an increase of all fractions between 500 and 125 was observed. Some fractions were increased up to 20 %. Most reproducible batches according to Figure 21 were produced with sieved caffeine and with a spraying rate 9 g/min. Reproducibility of the process was highly improved, by using sieved caffeine and improved machine handling.

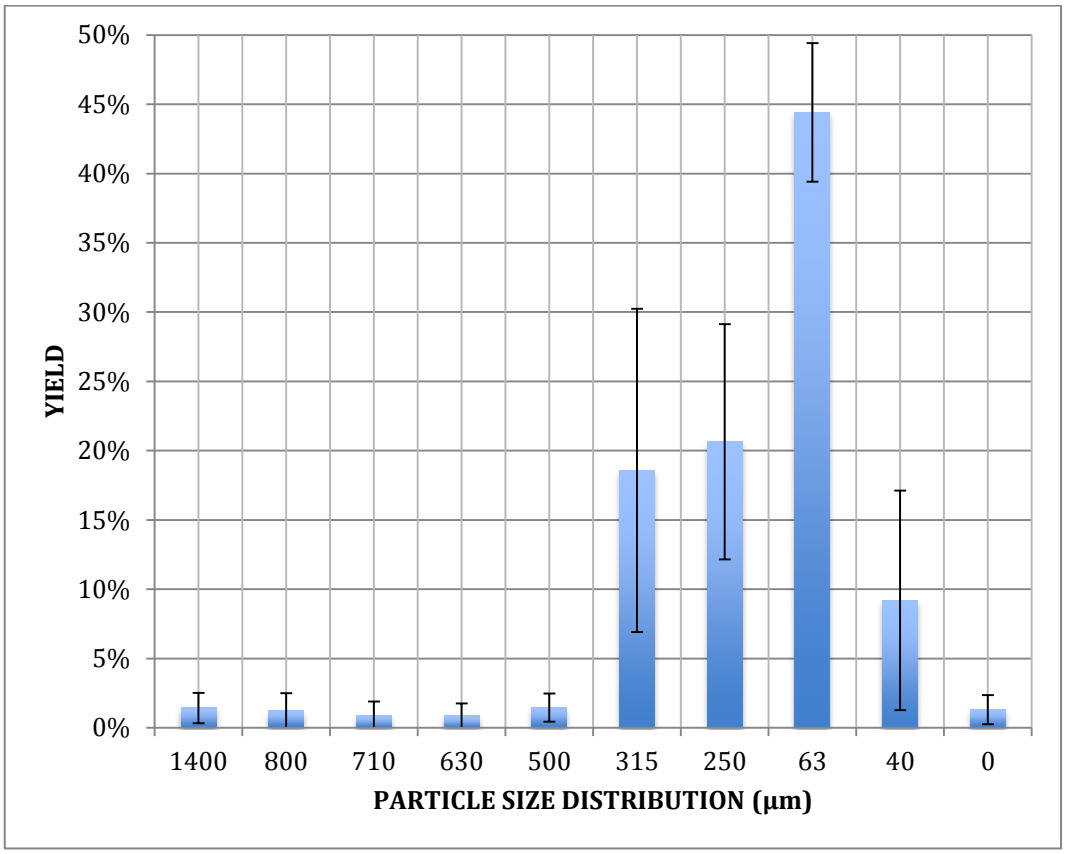

Figure 21: Average particle size distribution of product, that was produced with spraying rate of 5 g/min and bulk caffeine. (Fraction 0 represents particles smaller than 40 micron.)

In Figure 21, 63 µm fraction was the biggest fraction with share over 40 % on the product. 315 µm and 250 µm were reaching around 20 % of yield. Other fractions did not reach 5 %, except 40 µm. This fraction had a share almost of 10 % in the mass of the whole product.

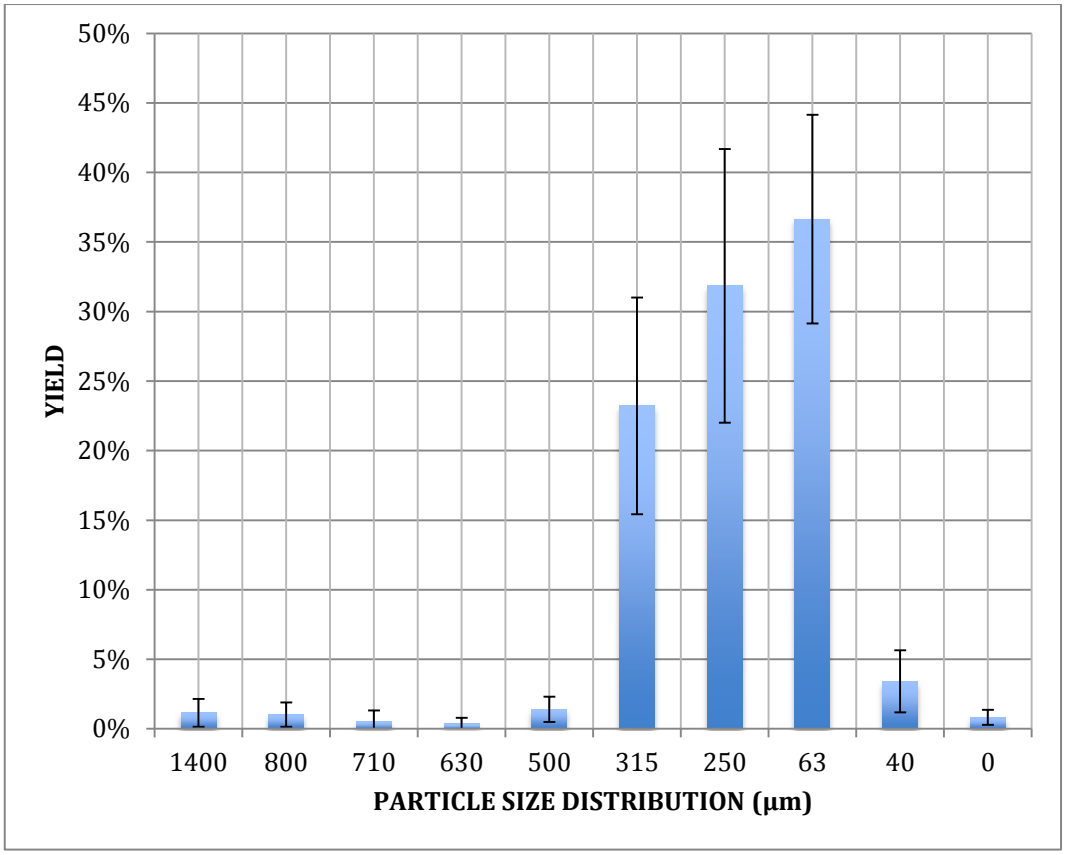

Figure 22: Average particle size distribution of product, that was produced with spraying rate of 7.5 g/min and bulk caffeine. (Fraction 0 represents particles smaller than 40 micron.)

In the runs carried out with spraying rate 7.5 g/min (Figure 22), higher spraying rate has resulted in increased amount of fractions with size 250 and 315 µm. They were representing more than 50 % of the product. On the other hand, the 63 µm fraction decreased, as well as the fraction with size of 40 microns. 63 µm fraction represents 35 % of the product.

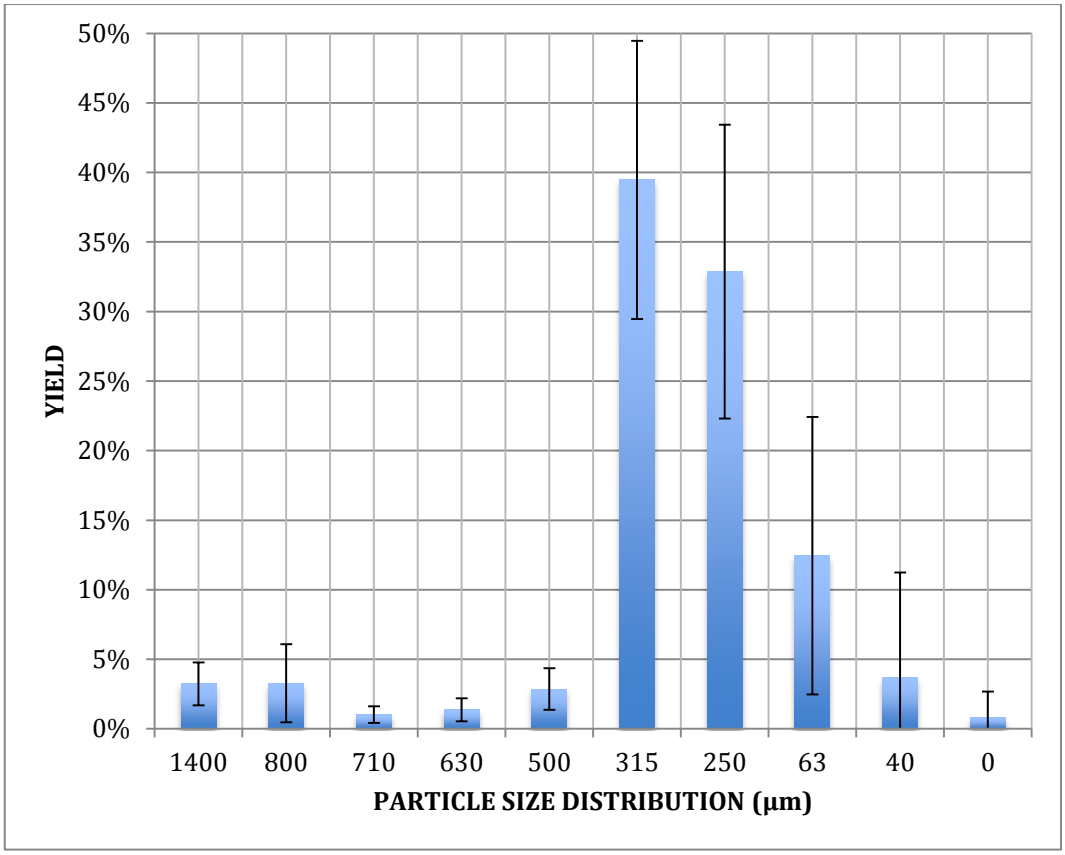

Figure 23: Average particle size distribution of product, that was produced with spraying rate of 9 g/min and bulk caffeine. (Fraction 0 represents particles smaller than 40 micron.)

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In Figure 23**,** the fraction with size 315 µm represents the biggest part of the product – 40 %. Second biggest is 250 µm – these two fractions were representing 2/3 of the product. In comparison to the batches produced with 5 g/min, there was observed a decrease of 63 micron fraction in runs produced with 7.5 g/min spraying rate.

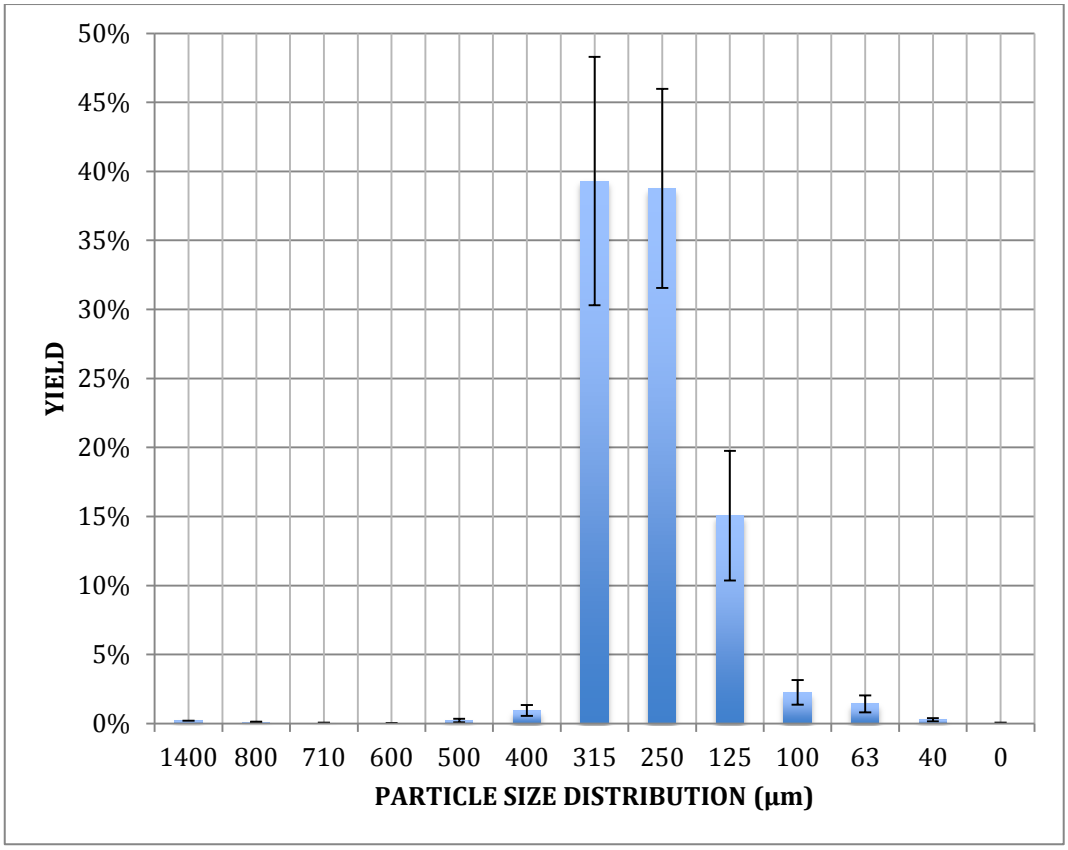

Figure 24: Average particle size distribution of product, that was produced with spraying rate of 8.5 g/min and sieved caffeine. (Fraction 0 represents particles smaller than 40 micron.)

The different arrangement of sieving tower was optimised for sieved caffeine. To obtain more precise information about particle size distribution in the range between 250 and 40 microns, there were added additional mashes of 400, 125 and 100 microns.

With this approach was discovered, that almost 80 % of the product is created by fractions 315 and 250 µm. 125 µm fraction's share was almost 15 %. Other fractions haven't crossed 5 % share in product. (Figure 24)

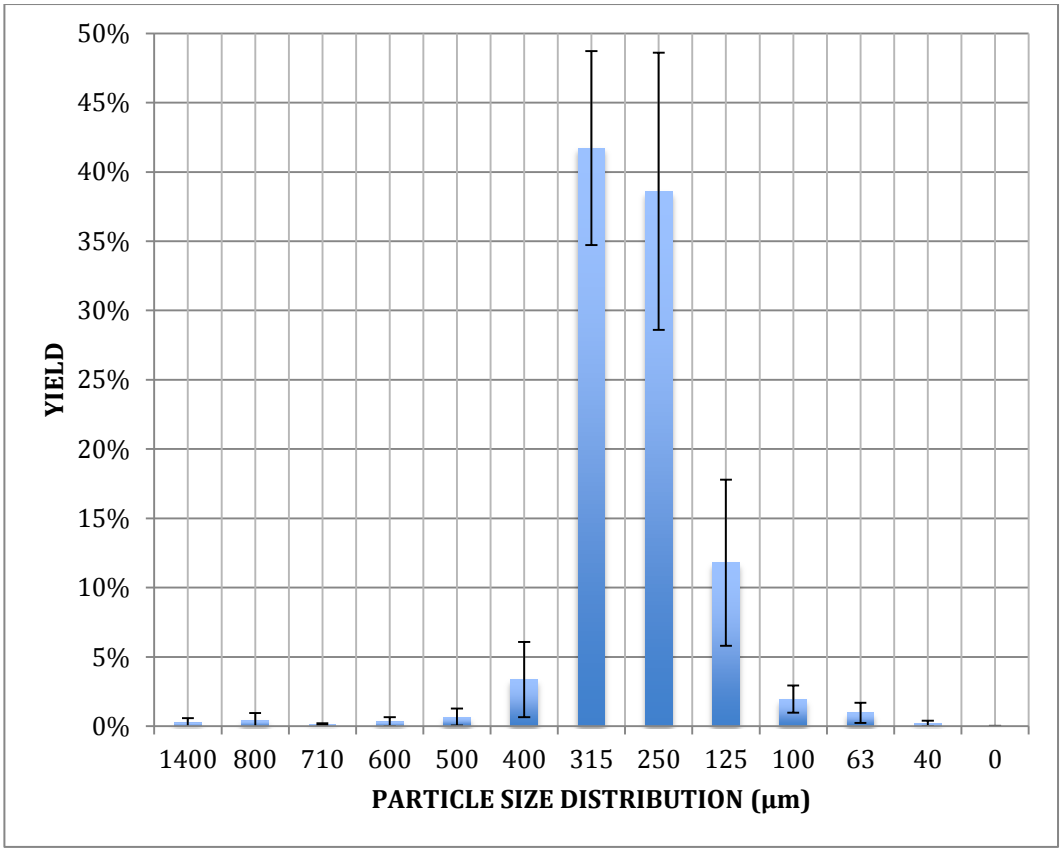

Figure 25: Average particle size distribution of product, that was produced with spraying rate of 9 g/min and sieved caffeine. (Fraction 0 represents particles smaller than 40 micron.)

Runs produced with spraying rate 9 g/min. 315 µm fraction was higher than 40 %. 400 µm fraction also increased to 3 %. A decrease was observed in 125 µm fraction. It is shown in Figure 25.

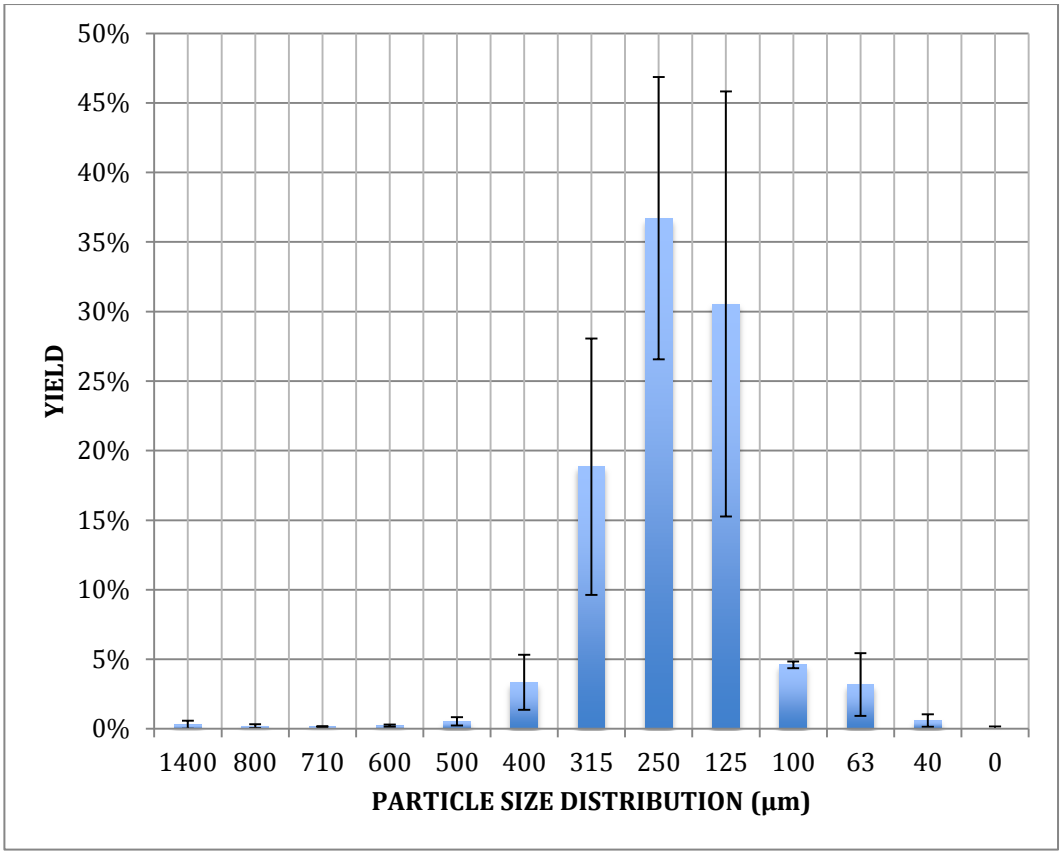

Figure 26: Average particle size distribution of product, that was produced with spraying rate of 9.5 g/min and sieved caffeine. (Fraction 0 represents particles smaller than 40 micron.)

In comparison to two previous runs, the amount of 125 µm fraction has more than doubled its size. 315 µm has showed decrease under 20 %. After adjustment of the spraying rate yield has increased to almost 40 % (Figure 26)

As next process parameter, the influence fluid bed pressure was examined. Fluid bed pressure factor was investigated for a suspicion that powder mixture, especially on the beginning of the process, was lifted too much by pressurized air. Therefore, the particles weren't wetted properly, which could lead to the lower yields.

Following earlier granulation experiments, the initial fluid bed pressure values were chosen as described in chapter 5. The fluid bed pressure was decreased from 0.3 bar at the beginning of process to 0.2 bar. This alteration didn't show a change in the yield bigger than 5 %. Through the granulation process, also other values of bed fluid pressure (in 6th minute 0.4 bar and in 16th minute 0.5 bar) were also decreased by 0.1 bar (in 6th minute to 0.3 bar and in 16th minute to 0.4 bar).

Table 9: Changes in yield caused by alternation of the fluid bed pressure.

Fluid bed pressure set up (value on the start of the process – (bar)	1st run (0.2 bar)	2nd run (0.2 bar)	3rd run (0.2 bar)	1st run (0.3 bar)	2nd run (0.3 bar)	3rd run (0.3 bar)
Yield (%)	42%	42%	40%	44%	44%	49%
Standard Deviation	0.01	0.01	0.01	0.03	0.03	0.03

As can be seen in Table 9, the setup with higher fluid bed pressure had higher yield but also higher standard deviation (0.3 bar). The yield and particle size distribution did not show bigger changes than 5 %, what was classified as no important change in yield.

Yield of granules has showed only 5 % change. Particle size distribution of the granulation run with higher operational bed fluid pressure has showed that with these process parameters, there was slight decrease in fraction of 63 microns. Given information could be considered as advantageous. Decreased bed fluid pressure was applied on three granulations processes. These were compared to three ordinary runs with similar parameters. These runs were carried out with spraying rate 5 g/min. The following table and chart show the average of fractions from three trial runs each:

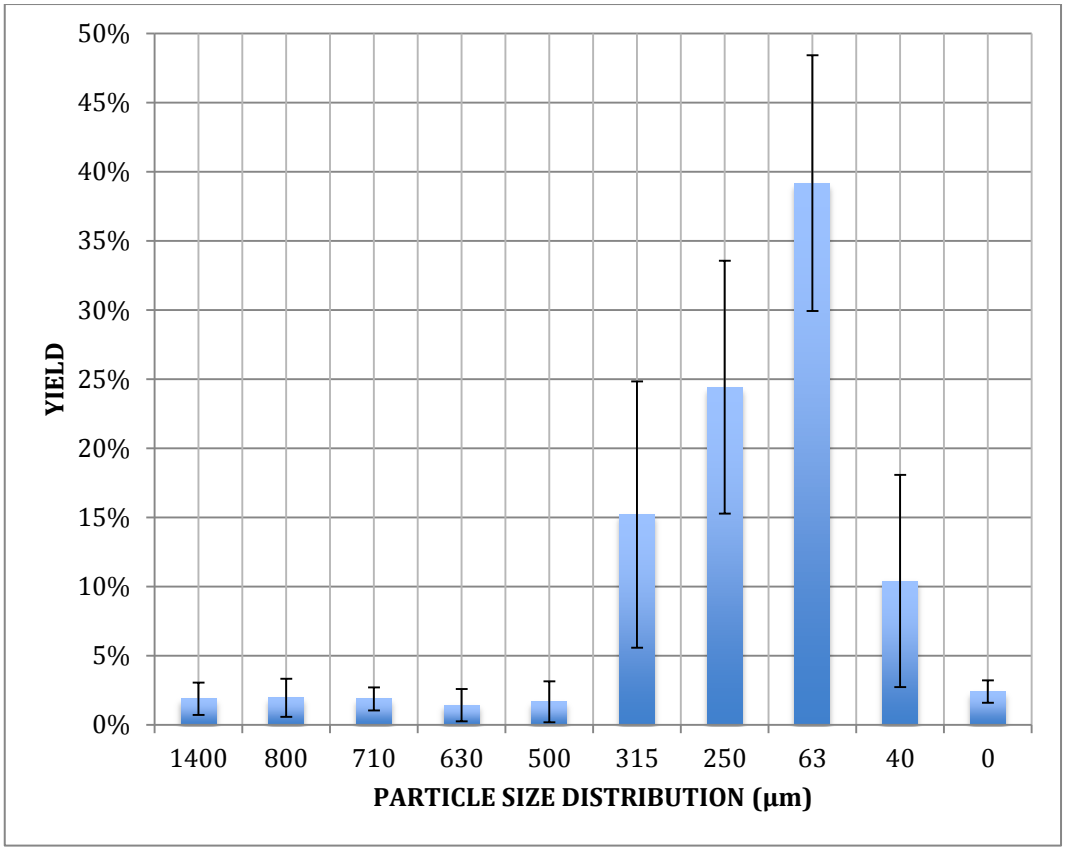

Figure 27: Average particle size distribution in a product produced with decreased fluid bed pressure setup. (starting point 0.2 bar). (Fraction 0 represents particles smaller than 40 micron.)

63 µm fraction was dominant in mass of product and in the same time, the mass of particles bigger than 500 µm wass also increased (Figure 27).

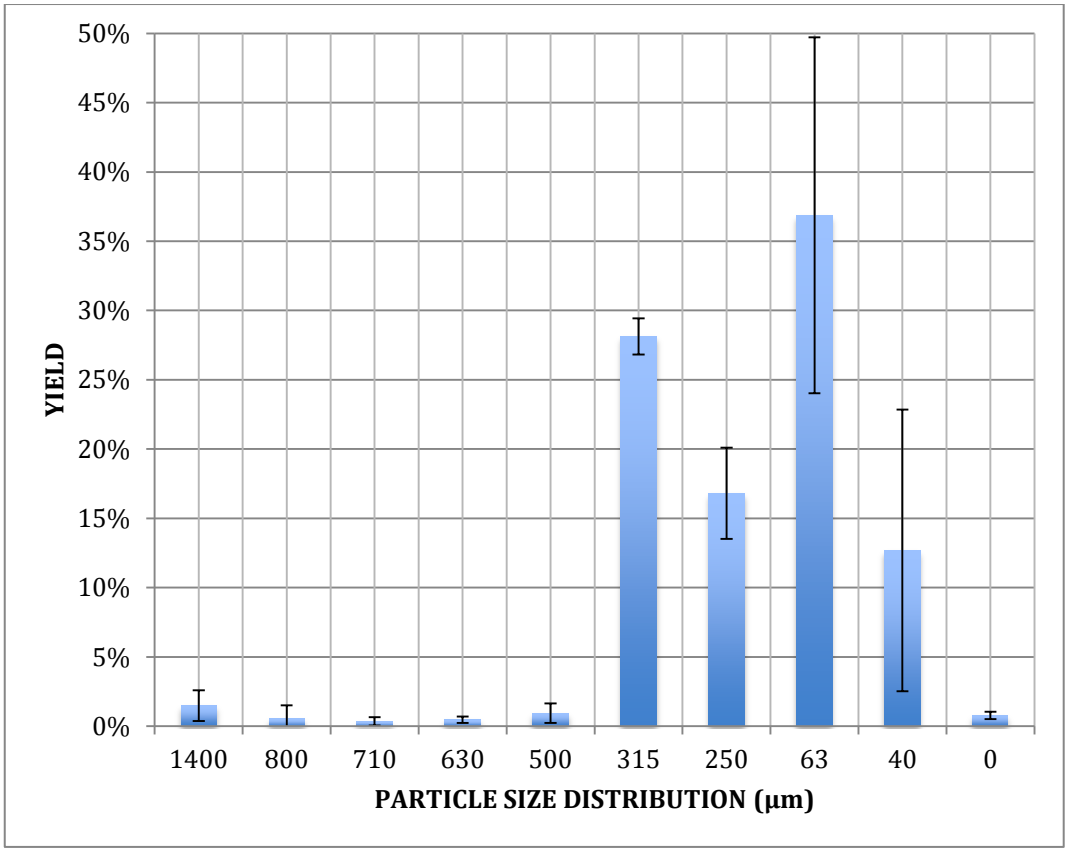

Figure 28: Average particle size distribution in a product produced with increased fluid bed pressure setup. (starting point 0.3 bar). (Fraction 0 represents particles smaller than 40 micron.)

Figure 28 shows, that for higher fluid bed pressure, original fluid-bed pressure setup (starting on the 0.3 bar) had achieved slightly better results in particle size distribution. Reducing the fluid bed pressure did not lead to significant change in yield. In yield, lower fluid bed pressure led to the higher amount of 250 microns fraction.

The last process parameter, that was chosen to investigate, was nozzle pressure. It was tested, whether higher values of nozzle pressure could increase spraying area and number of sprayed particles. First, 1.2 bar pressure in nozzle given from previous experiments as original setup, was used. Then, subsequently nozzle pressure was increased to 1.35 bar and 1.4 bar.

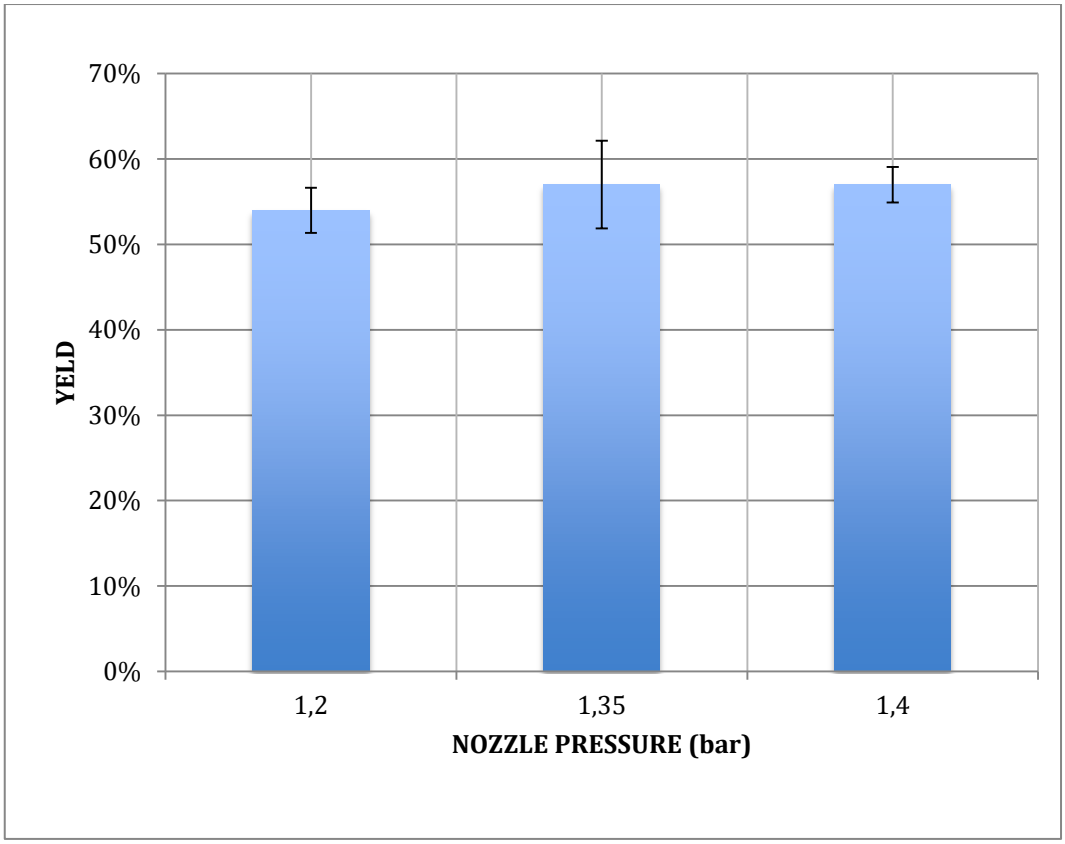

Figure 29: Average yields of batches produced with different nozzle pressure.

In Figure 29, batches produced with 1.35 bar and 1.4 bar nozzle pressure had bigger yield. Average yield of 1.35 bar shows the highest standard deviation.

Nozzle pressure has no big influence on the yield. With increased nozzle pressure, the change in yield is smaller than 5 %.

Particle size distribution for trial runs with 1.2 bar shows that the biggest part of product was divided between 250 µm and 63 µm. Each of them is representing almost 40 % of yield separately. (Figure 30)

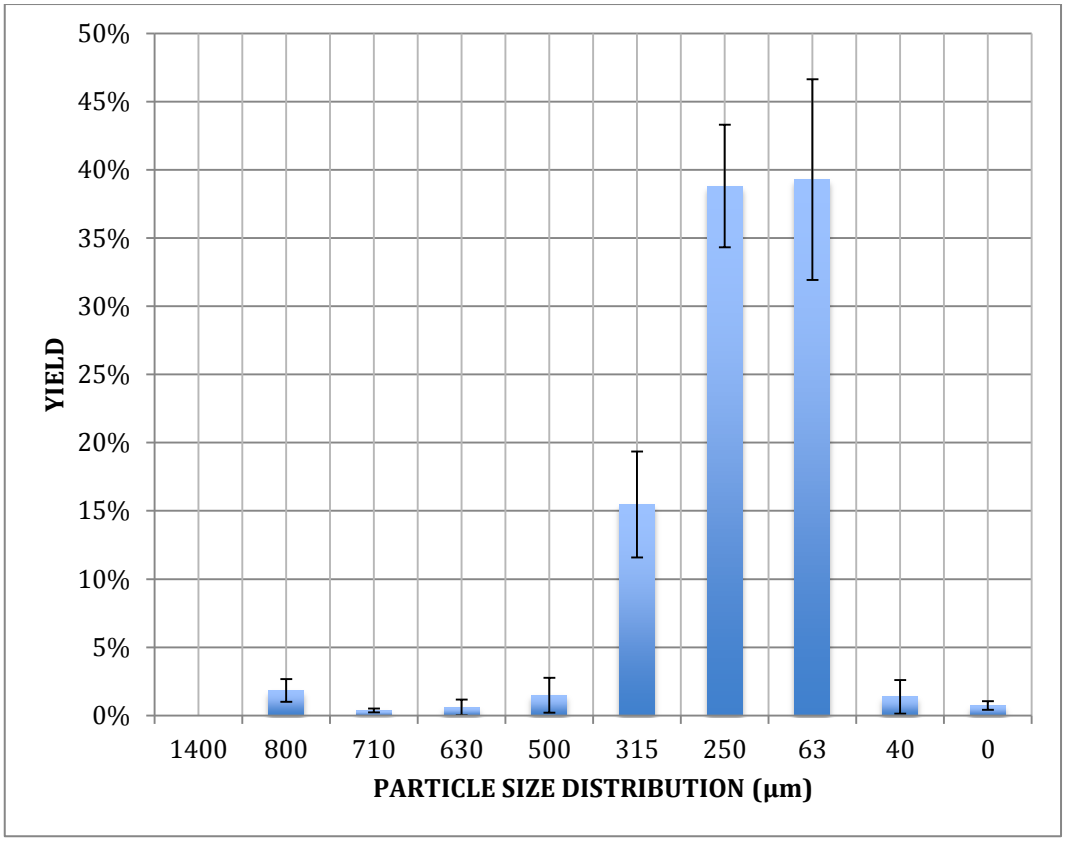

Figure 30: Average particle size distribution of batches produced with a nozzle pressure of 1.2 bar. (Fraction 0 represents particles smaller than 40 micron.)

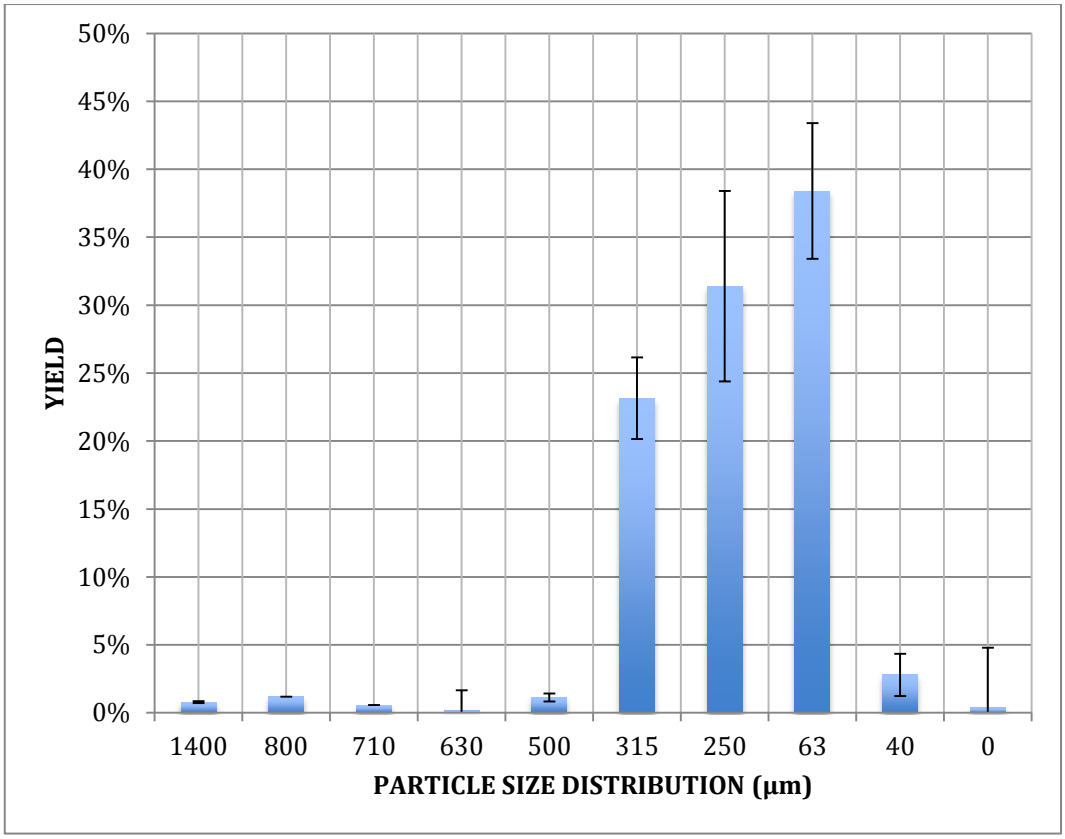

Figure 31: Average particle size distribution of batches produced with nozzle pressure 1.35 bar. (Fraction 0 represents particles smaller than 40 micron.)

For next three trial runs nozzle pressure was raised to 1.35 bar and that led to an increase of the 315 µm fraction (more than 20 %) and a decrease of 250 µm (Figure 31).

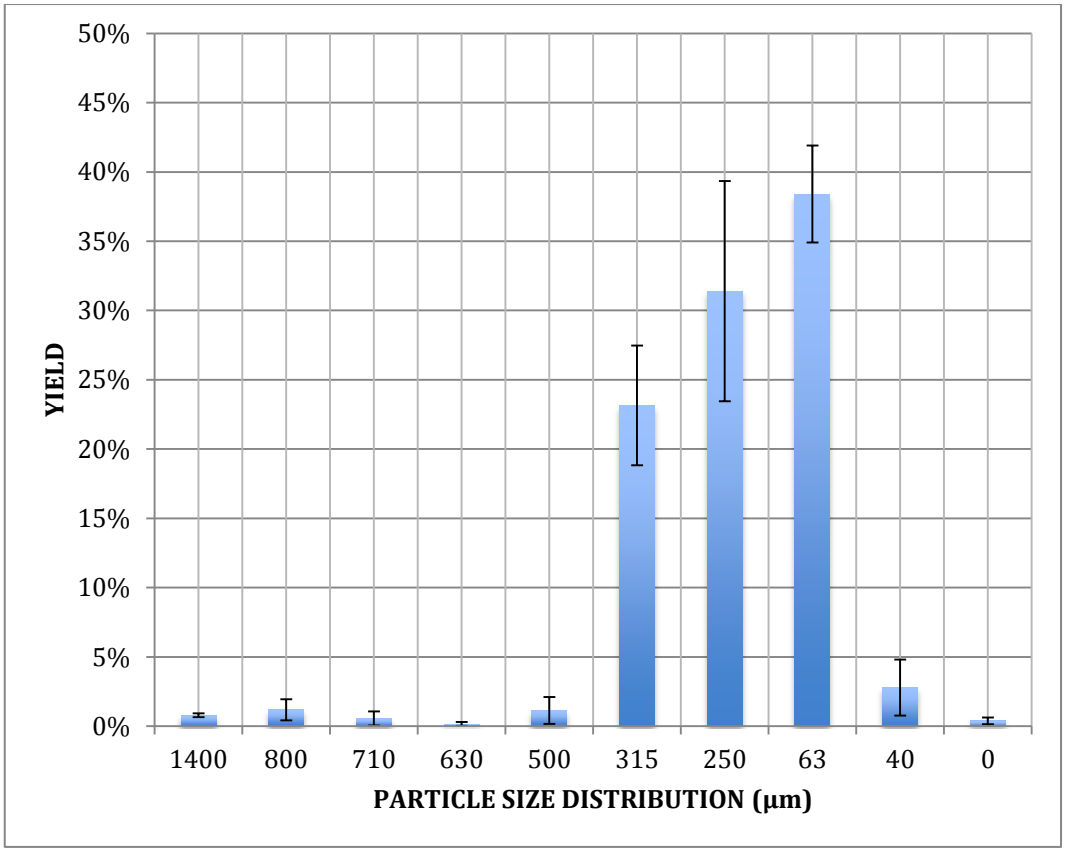

Figure 32: Average particle size distribution of batches produced with nozzle pressure 1.4 bar. (Fraction 0 represents particles smaller than 40 micron.)

For the last three runs, the nozzle pressure was increased to 1.4 bar (Figure 32). Results were almost the same as in the case of the three runs performed 1.35 bar. Change of nozzle pressure did not lead to the improving the process or high change in the yield.

For granulation with fine share bigger than 50 % of the product is typical that the angle of repose value was close to 40 degrees. In the case that fine powder represents 60 % of the product, angle of repose was near to 45 degrees. This was applied especially for granules from Phase I (spraying rate 5 grams per minute). In Phase II (spraying rate 7.5 grams/min) were also located near 40 degrees or its angle of repose was located near 35 degrees – their flow ability was classified as intermediate.

Third group of results was formed from results of Phase III. Their values were typically located near 30 degrees. According to literature, they were classified as good granules. Only batch that was measured and had angle of repose smaller than 30

degrees, was first batch of day 13. 12. 2012. This flow ability was described as excellent.

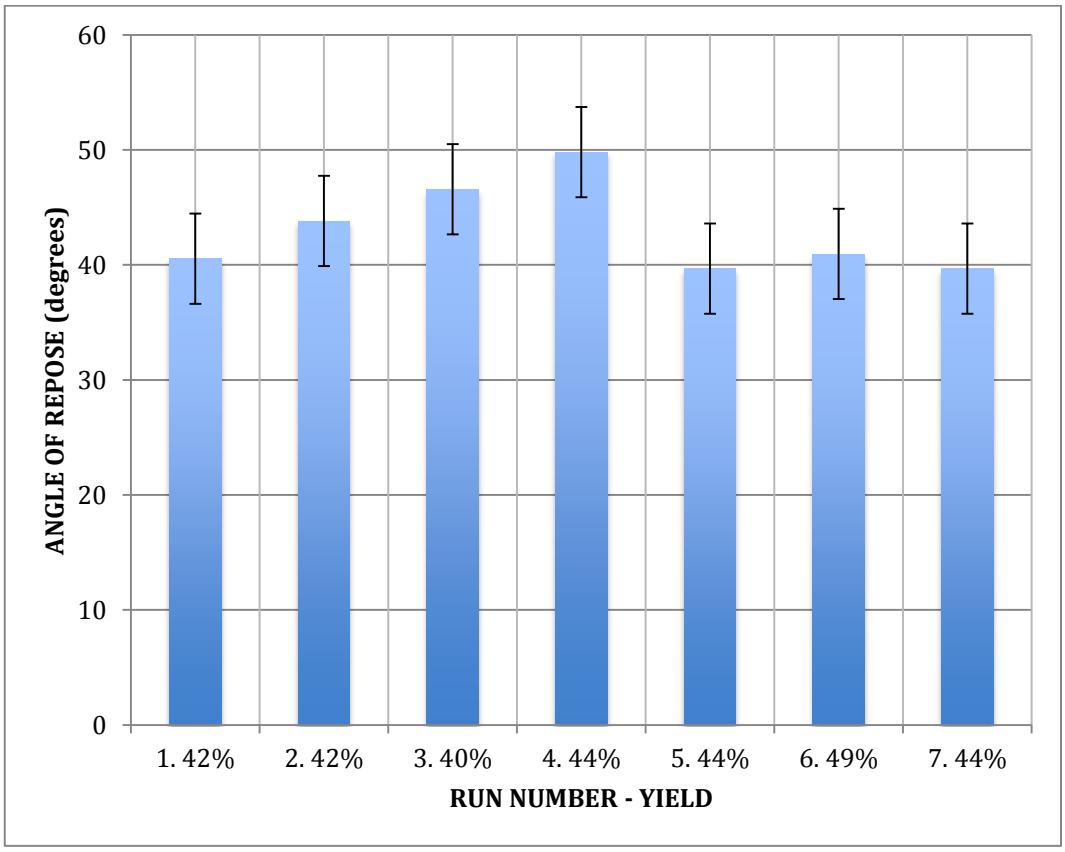

Figure 33: Angle of repose during Phase I.

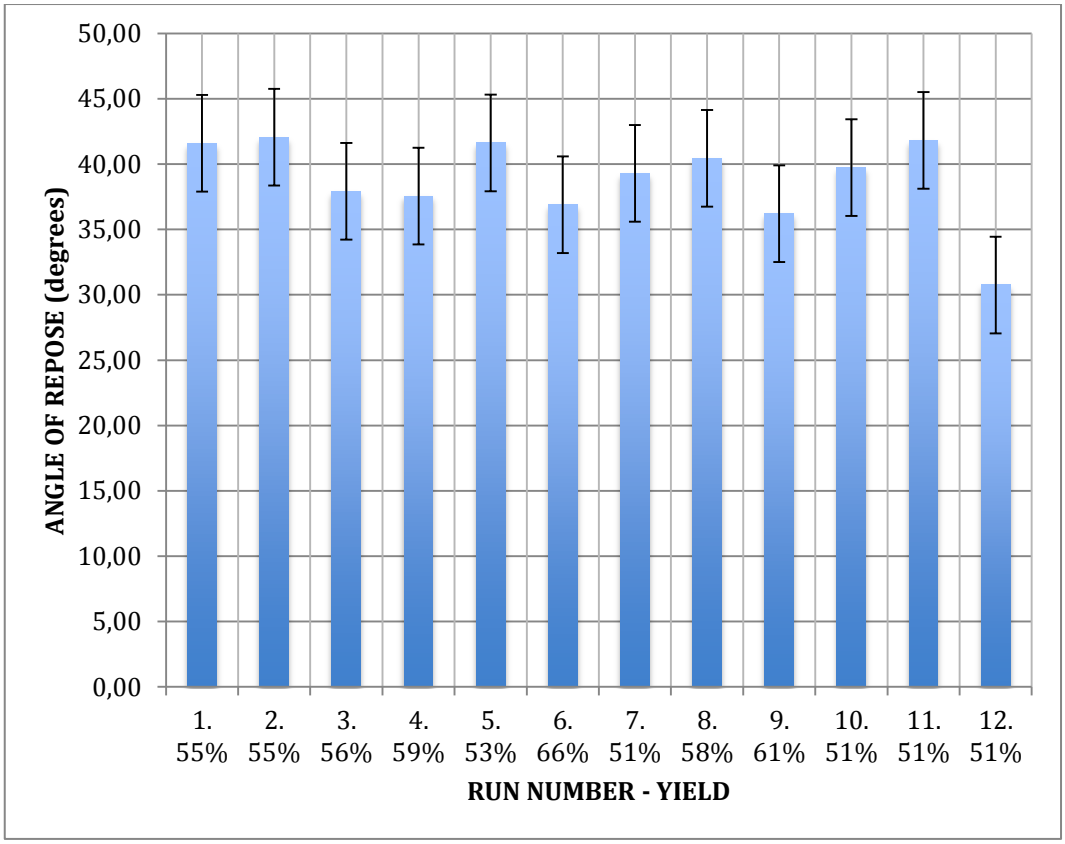

Figure 34: Angle of repose progression during Phase II

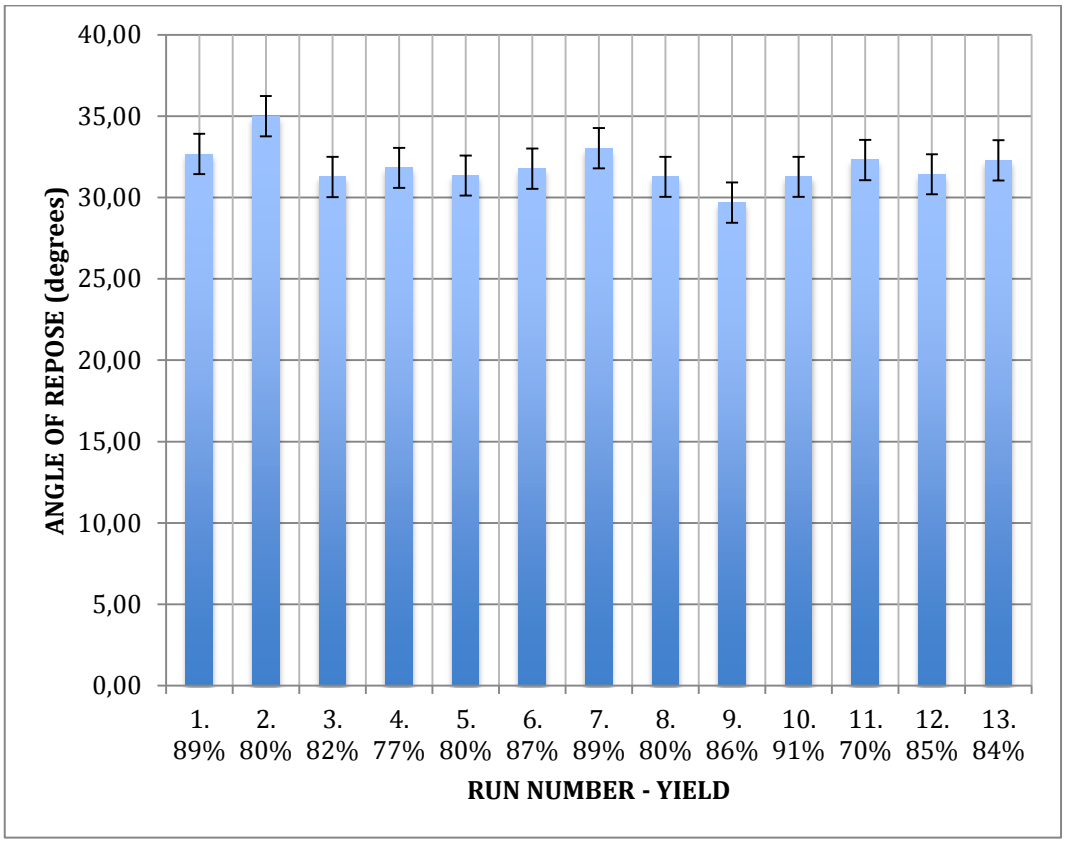

Figure 35: Angle of repose progression during Phase III

Figures 33, 34, 35 show relation between angle of repose and yield. With an increase in yield, the angle of repose was dropping. Relationship between share of the yield in product and flowability can be described as nonlinear.

The same Figures, show that with growing yield the flowability was decreased. Therefore, a relation between flowability and spraying rate can be also found. That is caused by direct relation between spraying rate and yield – increased spraying rate concludes in higher yield and high yield means low angle of repose.) where can be observed that with increased spraying rate the angle of repose was decreasing, which again led to improved flowability. All data is summarized in the tables and charts down below.

For the runs with spraying rate 7.5 g/min flowability properties can be classified the frontier between core flow and mass flow. Stirring device was not used during measurements, but samples were still showing core flow during measurements. For spraying rate 9 g/min mass flow was observed, the stirring device was not used. By comparing flowability with particle size distribution, it can be observed that with increased spraying rate, flow behaviour was improved. (Particle size distribution data for spraying rates 5 g/min, 7.5 g/min and 9 g/min are showed in Figure 21, 22 and 23.)

6.2 Granular active pharmaceutical ingredient concentration research

API (caffeine) concentration in powder mixture before the granulation was 20 %. Batches of Phase I, II, III were made with bulk caffeine. Measurements carried out with using UV spectroscopy have revealed that the distribution of caffeine in different fractions was highly fluctuating and, therefore, ways of suitable proper were researched. In the Figure 36 below, the averages of caffeine concentrations within different fractions are shown.

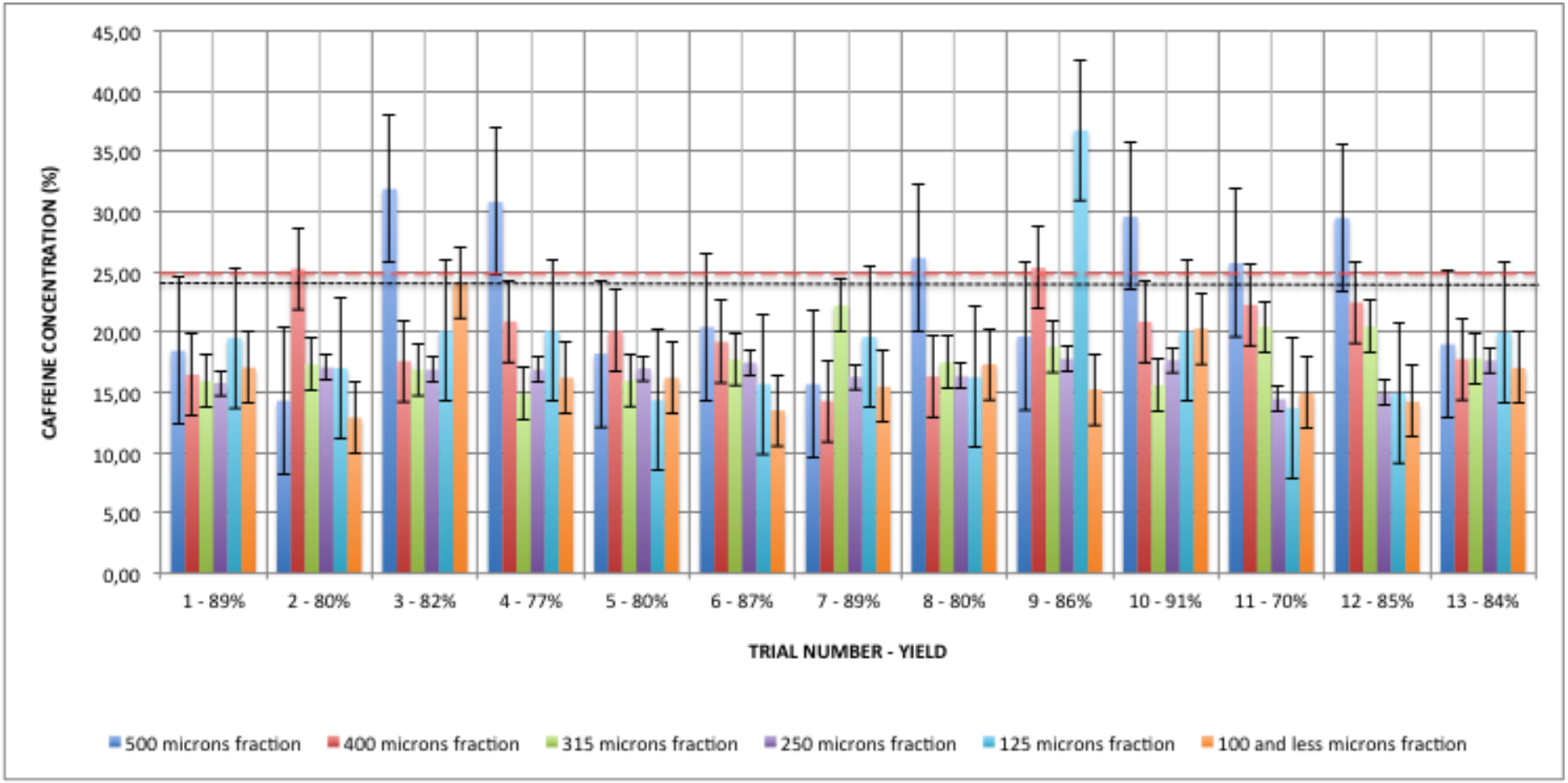

Figure 6.2.1: Caffeine concentrations of 6 selected fractions from Phase III. (Red line marks the target concentration - 20%. Black line marks average value of all fractions – 18.83%.)

There were taken only runs with a yield over 70 % for analysis. Batches with lower yield (40–70 %) were not considered as successful trial run. Concentrations of caffeine between fractions in one batch were different. As well as between batches, the differences can be seen in fraction`s caffeine concentration (Figure 37, 38, 39). Analysis made on runs has revealed that caffeine concentration in the product depends on the caffeine grades (particle size distribution of different caffeine grades is showed in Table 1). There were used three different grades were examined (bulk, disagglomerated and sieved through 500 micron mash).

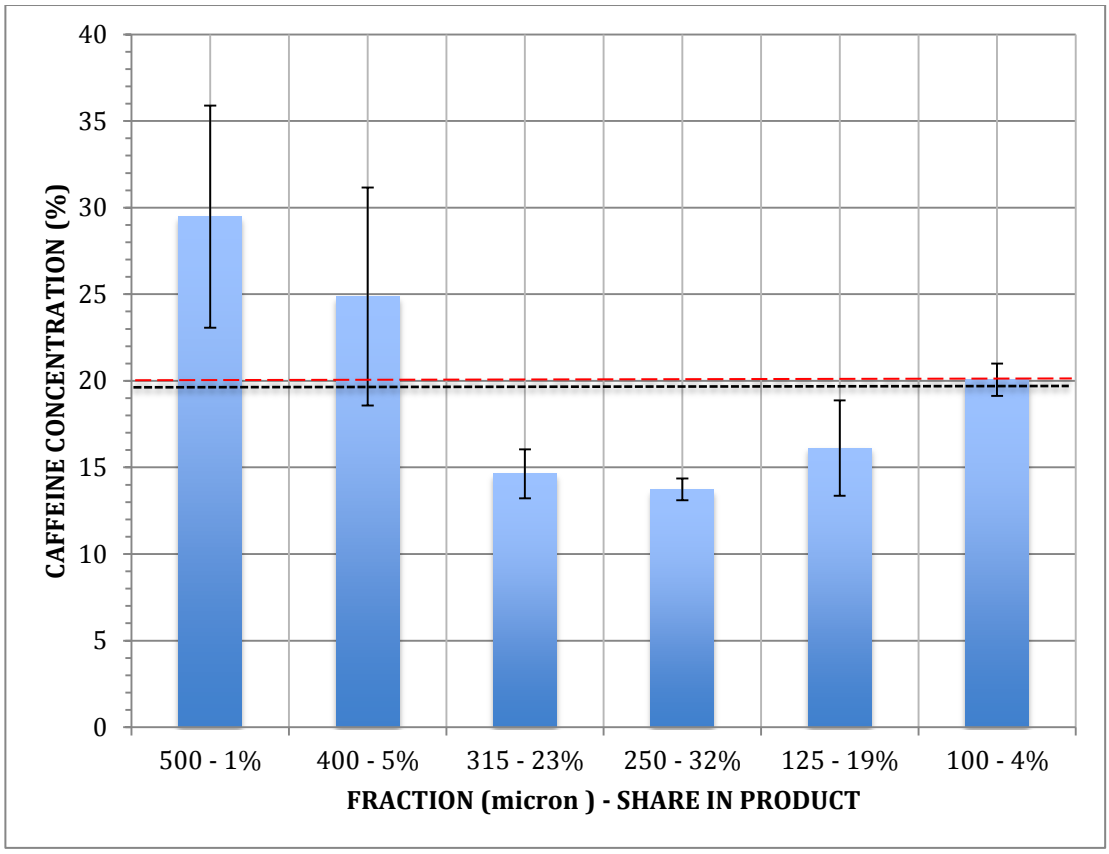

Figure 37: Average caffeine concentration in fractions. Batches were produced with bulk caffeine. Red dashed line represents ideal concentration (20%). Black dashed line represents average concentration (16.83%).

From six measured fractions, only fraction of 100 µm (fine) hits the intended amount of caffeine (20 %). 500 and 400 µm fractions contained more caffeine (29 % and 25 %) than intended amount. 315 µm, 250 µm fractions are under 15 % of caffeine content. 125 µm reaches 16 % of caffeine content. (Figure 37)

In the case of disagglomerated caffeine (caffeine was disagglomerated with the purpose to achieve smaller caffeine particles and, therefore, different granulate fractions was more balanced in comparison to the trials with bulk caffeine (Table 1).

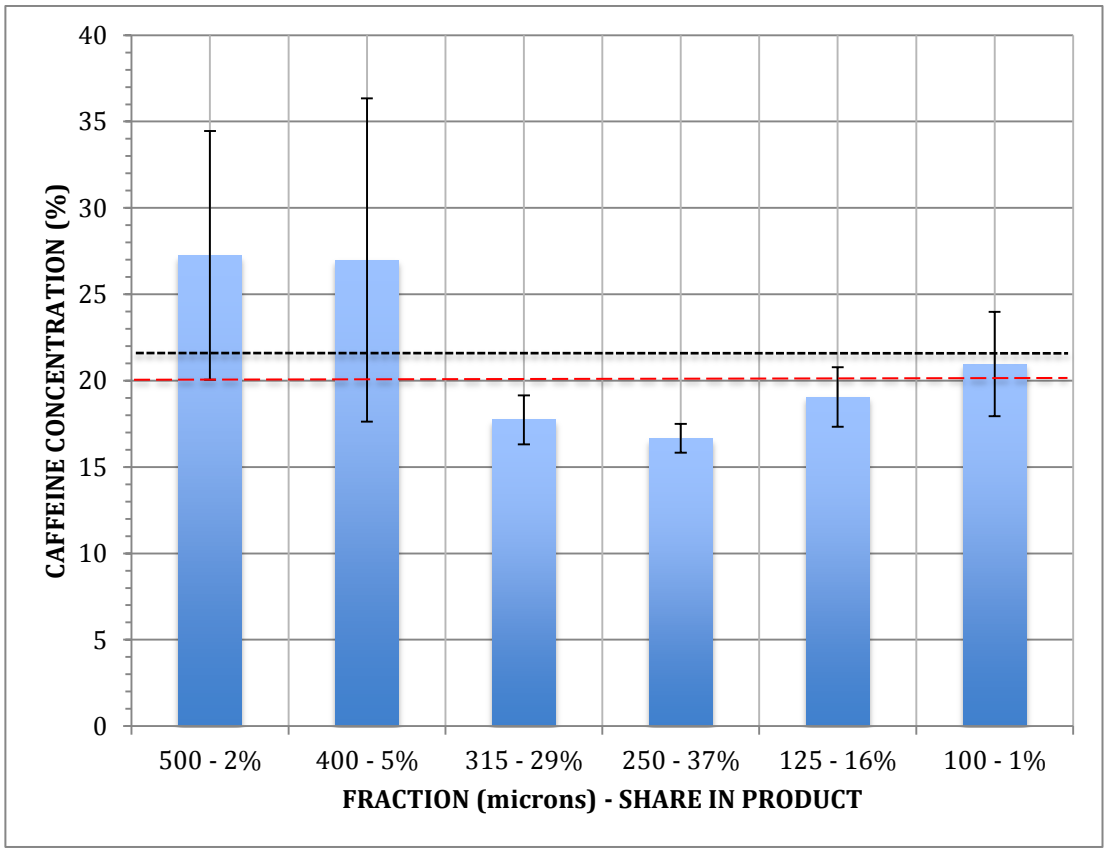

Figure 38: Average caffeine concentration in fractions. Batches were produced with disagglomerated caffeine. Red dashed line represents ideal concentration (20%). Black dashed line represents average concentration (21.44%).

500 and 400 µm fractions were both in the same range. The 100 µm fraction was slightly higher than limit of 20 % of mass. 315, 250 and 125 µm fractions were below the limit. (Figure 38)

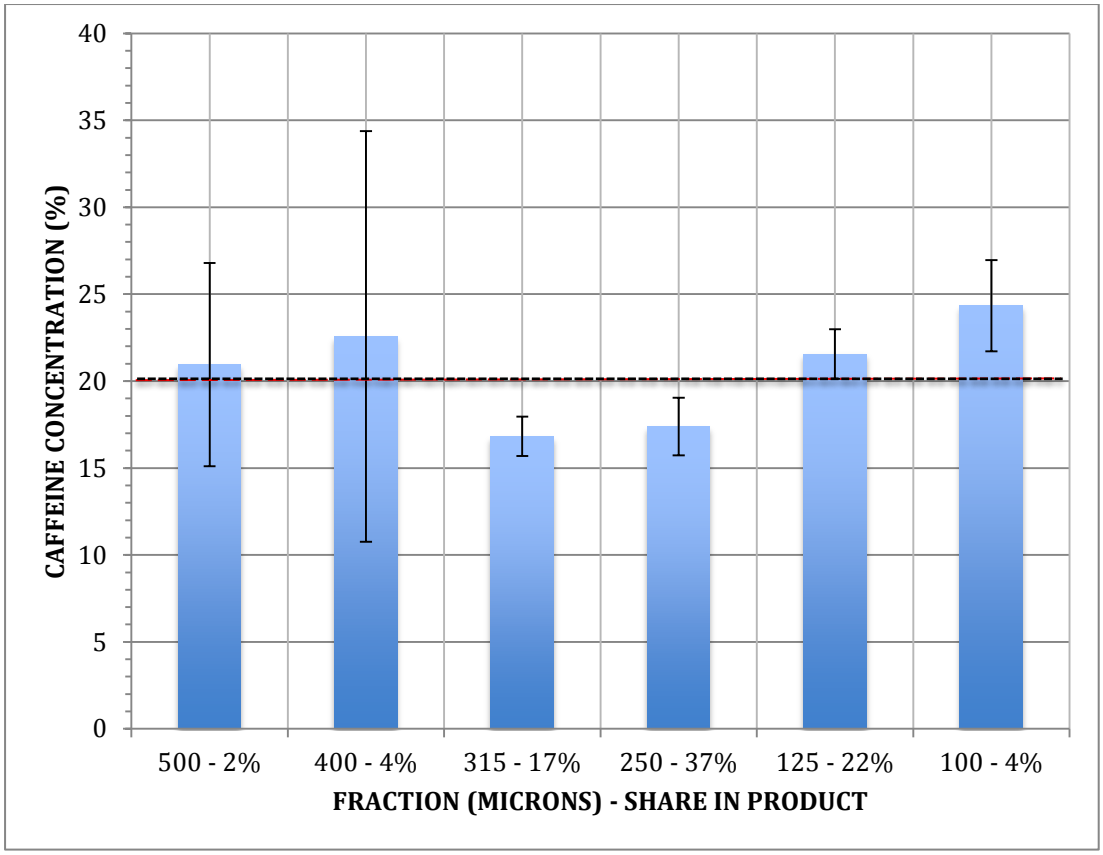

Figure 39: Average caffeine concentration in fractions. Batches were produced with sieved caffeine. Red dashed line represents ideal concentration (20%). Black dashed line represents average concentration (20.60%).

For sieved caffeine it was observed, that none of the fraction had a bigger caffeine concentration than 25 %. The highest concentration of caffeine in granules was found for sieved caffeine grade 100 micron`s fraction.

Comparing Figures 37, 38, 39 the sieved caffeine provides the best results (average value of all fractions was very close to target caffeine concentration value).

Also homogeneity of whole raw yield was examined. Again, only runs with yield higher than 70 % were taken. Each of runs was measured three times (sample 1, 2 and 3). (Figure 40)

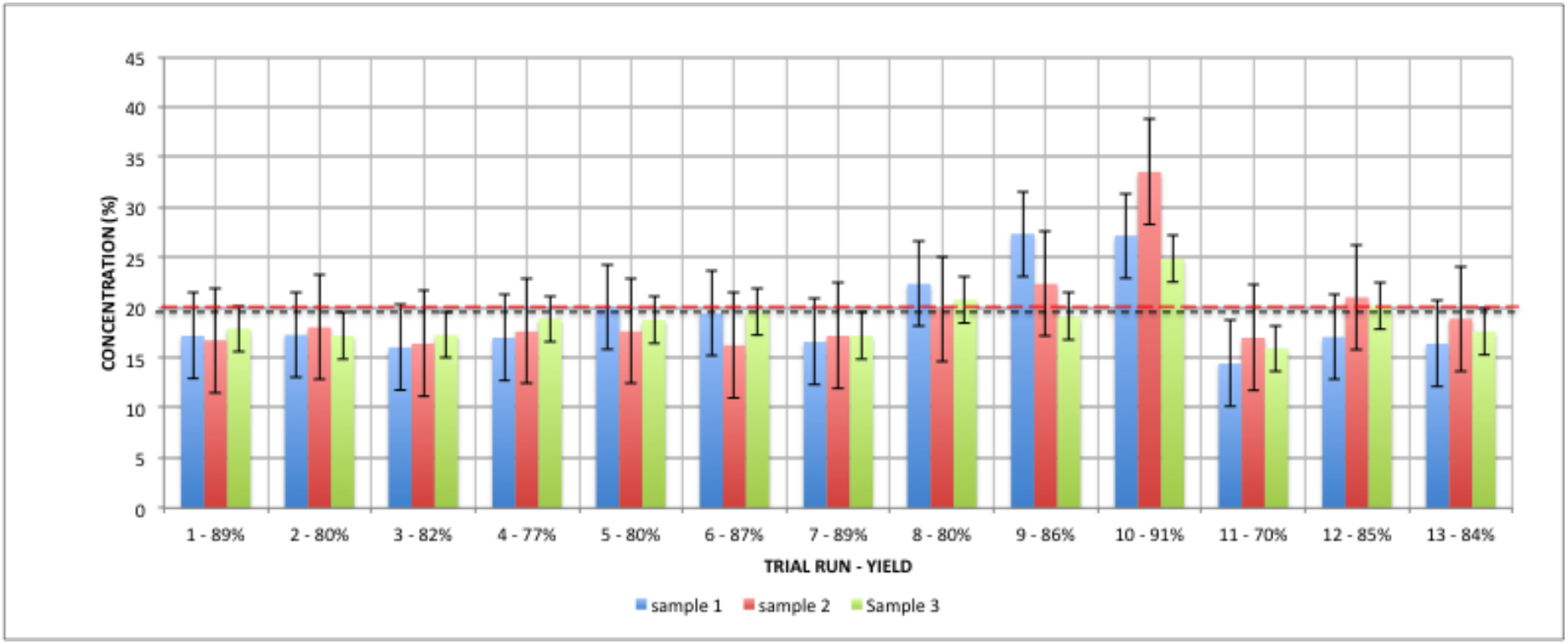

Figure 6.2.6: Caffeine homogeneity in phase III. 3 samples were taken for one batch. Red dashed line marks ideal concentration (20%). Black dashed line marks average value calculated from all values.

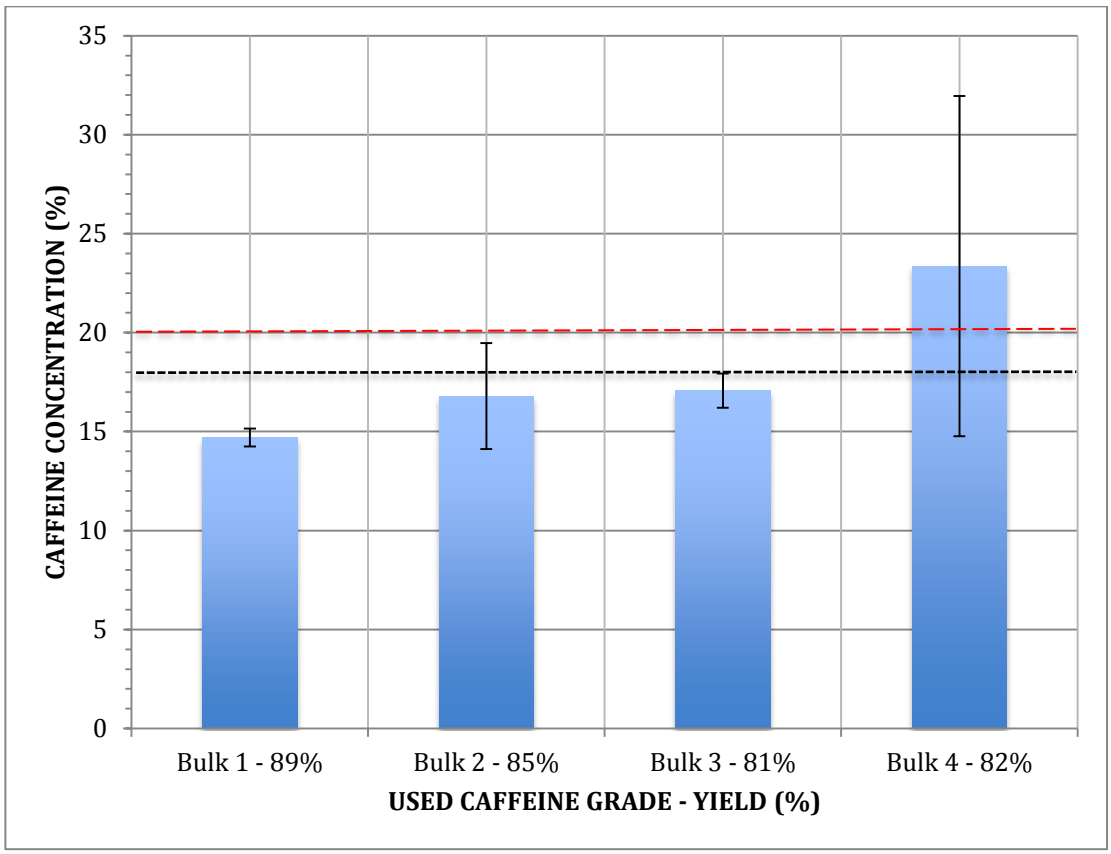

Figure 41: Caffeine homogeneity of batches produced with bulk caffeine. Red dashed line marks target caffeine concentration – 20%. Black dashed line represents average concentration of all 4 runs (18.00%).

The highest value of caffeine concentration was found on run 4 (23 %). Other runs were lower than 18 %. As there can be seen, between batches with bulk caffeine can be found high fluctuation in caffeine concentration homogeneity (Figure 41).

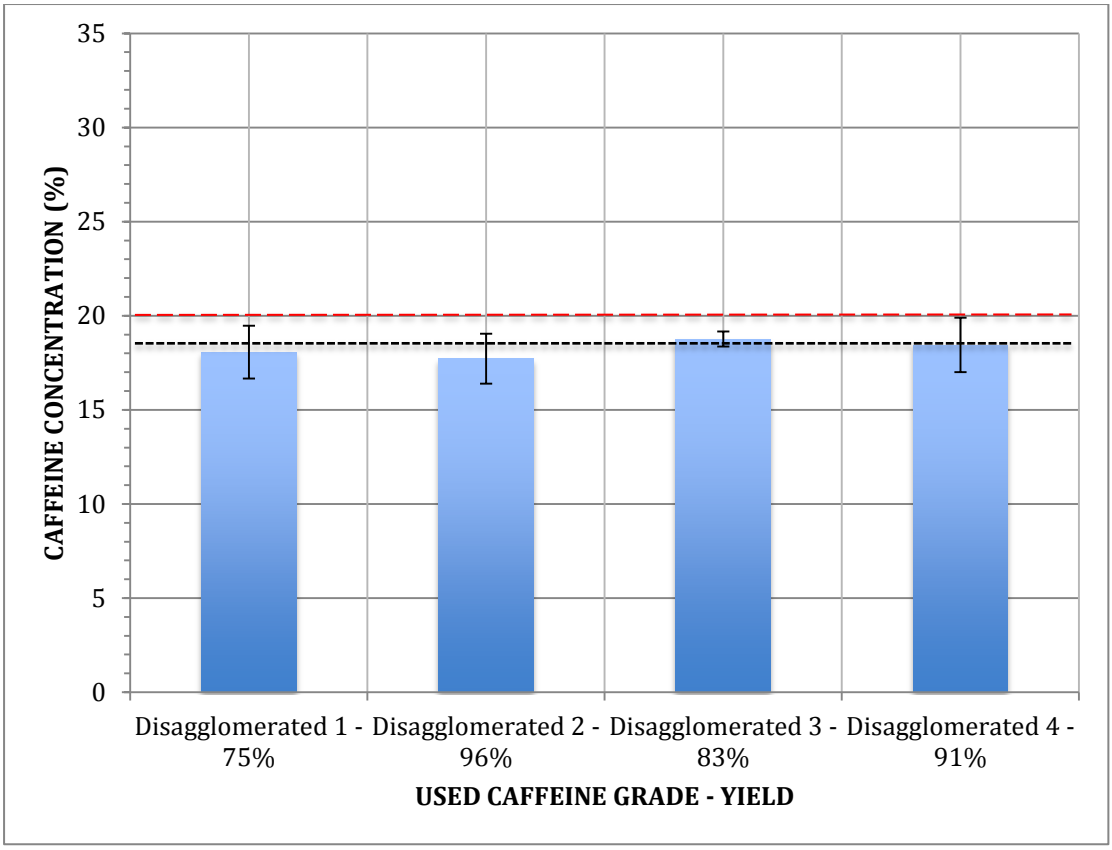

Figure 42: Caffeine homogeneity of batches produced with disagglomerated caffeine. Red dashed line marks target caffeine concentration – 20%. Black dashed line represents average concentration of all 4 runs (18.25%).

Disagglomerated 1 and 2 were reaching caffeine concentration of 18 %, meanwhile disagglomerated 3 and 4 has crossed this value. Batches produced with disagglomerated caffeine showed lower fluctuation than bulk batches (Figure 42).

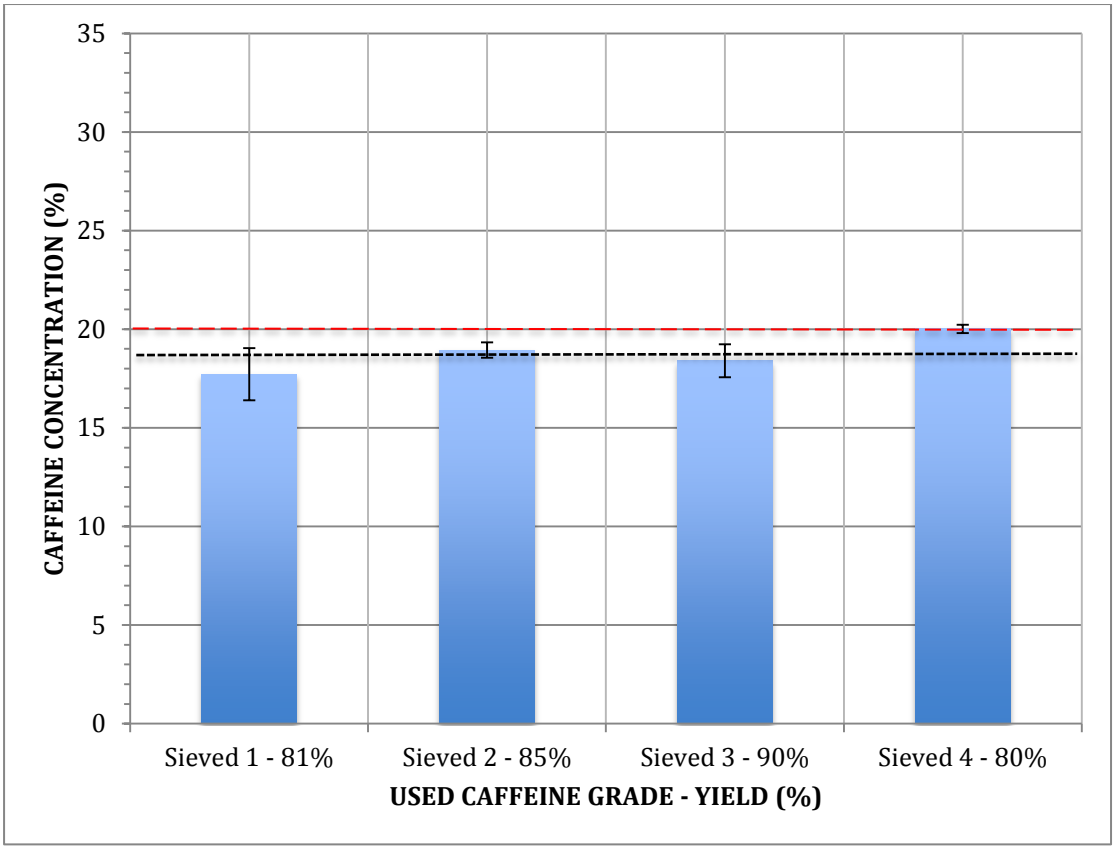

Figure 43: Caffeine homogeneity of batches produced with sieved caffeine. Red dashed line marks target caffeine concentration – 20%. Black dashed line represents average concentration of all 4 runs (18.77%).

Run, that was named as Sieved 4, has reached target value of 20 %. Batches called Sieved 2 & 3 have both higher caffeine concentrations than 17 %, meanwhile run called Sieved 1 is below 17 % (Figure 43).

7. Discussion

7.1 Evaluation and optimization of the fluid-bed granulation process

The experimental work started with establishing a granulation process based on previous workers experience. After achieving a working granulation process, attention has focused on evaluation and optimization of the process parameters, in a purpose to achieve higher yields and better reproducibility. It was decided to focus on searching of the most critical process parameter, which affect the yield more than 10 %. Three process´ parameters were identified as critical parameters: spraying rate, fluid bed pressure and nozzle pressure.

The trial experiments that were run during Phase I to Phase III revealed, the spraying rate has the biggest impact on quality of the yield. With 9 g/min was achieved acceptable and also the biggest yield between 80–90 %. In this part, bulk caffeine was used. Smaller changes in spraying rate were carried out with sieved caffeine and concluded in smaller yield. This yield was around 80 %. The yield has increased again up to 93 % after using original spraying rate 9 g/min.

In the case of using lower spraying rates than 9 g/min, low yields could be caused by quick evaporating of binding solution. Therefore, the binder did not have enough time to create a stable bond between two particles.

When the spraying rate was equal or higher than 10 g/min, agglomerates were created. With too much solution sprayed in fluidized bed, particles got over-wetted. Eventually they were too heavy to be lifted by air stream. These over-wetted, sticky particles stayed on the bottom of the granulation chamber and sticking to each other. They have created agglomerates.

Except of the change in yield, spraying rate was directly affecting particle size distribution of the product. Main growth was observed in fractions of 250 and 315 micron, meanwhile decrease of the fine powder share of product (size of particles under 250 micron) was achieved.

As consequence of increased spraying rate the flowability of the runs has changed in the way of decreased angle of repose from 40 degrees to 30 degrees. This was mainly caused by increased average particle size in runs produced with ideal spraying rate in a comparison to much bigger fine fraction in product of the runs

carried out with lower spraying rate. Generally, yields of phase I and II had worst flowability because of imperfect surface of the particles and because of bigger shares of fine in products. Runs produced with lower spraying rate have higher angle of repose. For runs with lower spraying rate was typical core flow. Runs performed with ideal spraying rate were characterized by mass flow. Mass flow would be much more appropriate for tablet pressing. Smaller changes in angle of repose were caused by different particle size distribution of different runs.

Next trial experiments were focusing on the fluid-bed pressure. Fluid-bed pressure setup represents an important parameter. It was investigated, whether smaller setup of fluid-bed pressure, combined with lower spraying rate, can increase share of yield in a product. Starting value of fluid-bed pressure was set 0.2 bar (original setup starting with 0.3 bar). Although there was improvement in the yield, change in the yield was never bigger than 10 %, so it was decided not to change the operation schematics of the granulation. Changes of particle size distribution and flowability were marginal. Original fluid-bed pressure led to a good yield, if the other process parameters were chosen in a right way. In this case fluid bed pressure has no further potential to be improved, it is already set in the suitable range. Still, fluid bed pressure represents critical process parameter for whole process of fluid-bed granulation.

For nozzle pressure, three values were examined (given original setup 1.2 bar and two increased setups 1.35 and 1.4 bar). Nozzle pressure was investigated for an idea that with higher nozzle pressure the area of spraying will be bigger and amount of sprayed particles would be enlarged. However, increased nozzle pressure has not showed big influence on the quality and quantity of the product, nor any big impact to the flowability values and particle size distribution. It has not showed potential to improve. With original nozzle pressure, good yields were gained, if the other parameters were chosen right. Nozzle pressure does not belong to critical process parameters.

7.2 Caffeine content investigation

Experiments have proved that caffeine concentration in different fractions of yield is highly fluctuating. As the distribution of caffeine's particles size got narrower, also the differences in caffeine concentration fractions between fractions

got smaller. Fractions were also closer in caffeine content to average caffeine concentration. Best results were achieved with sieved caffeine. Sieved caffeine also has showed a pattern in caffeine distribution between different fractions.

In the end can be stated that the best results in caffeine distribution and homogeneity has the caffeine sieved through the 500 micron mash, as well as from the point of the view of measured concentrations. They are situated in really narrow range. In the opposite from the bulk caffeine and disagglomerated caffeine results, sieved caffeine also shows trend in distribution of API in the fractions, which can be useful for future prediction and planning of the process. Since the working with a bulk and disagglomerated caffeine had irreproducible results, sieved caffeine represents only way, how to produce granules with satisfying uniformity of caffeine content. Sieving the caffeine is worth of investing time and money, so the better fraction homogeneity would be achieved.

This topic still holds a lot of potential for a deep research. Due to time constraints and unbalanced distribution of caffeine could not be done further investigations.

8. Conclusion

Fluid bed granulation is a complex process with many parameters, which have to be established, determined and also monitored carefully, if the reproducibility between different batches would be maintained. This puts lot of responsibility on the designer and operator of the process. Operator has to be skilled in work with a granulator device (if it is operated manually). Designer has to be aware of influence of human factor, characteristics of the machine, raw materials and conditions during the granulation process.

For successful fluid-bed granulation, the most important parameters of the process are temperature, spraying rate of binding solution and fluid-bed pressure. From point of view of this thesis, spraying rate is set on 9 g/min – increasing or decreasing of this value will result in drop of yield. The highest yield is provided with sieved API. With the increase of spraying rate and with decrease in area of fine powder and particles bigger than 500 μm (indirect effect), the angle of repose is also decreasing, which leads to a better flowability.

Sieved API has showed the best results in homogeneity of yield in API distribution and also it proved a pattern in API distribution through fractions in one batch. Still, caffeine content of the granules is not perfectly balanced. On the other hand, the bulk and the disagglomerated caffeine were spread more in values of concentrations in the case of fractions. The biggest concentration was found in the fractions of 500, 400 and 100 microns. 315 microns and 250 are in opposite in average of 17 % of caffeine.

This work should light some of many obstacles that can occur on the path to develop a successful fluid-bed granulation performed on MIDI Glatt. Findings should also give a look inside about importance of some major and minor process parameters. Key condition for developing and performing successful granulation is careful over-watching of whole process and monitoring of process parameters. In the case of changing of any of parameter, it is favourable to change them precisely, so the reproducibility between different runs would be as high as possible. For producing granules in laboratory conditions, the best solution is to use raw materials with narrow particle size distribution. It improves reproducibility of process and it is also better for balanced composition of final granules. These findings should help to design the process with high yield, reproducibility, which is easy to control, and sustain.

Closures of this work are also worth for laboratory scale of fluid-bed granulation, as well as for industry.

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