Table of Contents

Abbreviations and Symbols

Latin abbreviations and symbols

$\bar{x}$	sample arithmetic mean
(v/v)	specification volume by volume
(w/w)	specification weight by weight
bw	sequence of charging equipment with blue followed by white material
C	concentration
c1000	abbreviation for Cellets$^{\circledR}$ 1000 leaned on the diameter
c250	abreviation for Cellets$^{\circledR}$ 200 leaned on the diameter
c500	abbreviation for Cellets$^{\circledR}$ 350 leaned on the diameter
C_A	coefficient of variation of substance A
CFPC	critical fine particle concentration
C_R	coefficient of variation for a random mix
C_{RA}	coefficient of variation for random adhesion
C_V	coefficient of variation
D	Diffusion coefficient
ECT	electrical capacitance tomography
f	fraction
FDA	Food and Drug Administration
G	mass content per sample
gp1000	abbreviation for Glass pellets 1mm leaned on the diameter
gp250	abbreviation for Glass pellets 0.25-0.3mm leaned on the diameter
gp500	abbreviation for Glass pellets 0.4-0.6mm leaned on the diameter
H	Hausner ratio
l	distance in the direction of diffusion
M	sample weight
m	mean particle weight
m_A	mean particle mass of substance A
M_A	mean content by mass of substance A
$m_{x, y}$	mean particle weight of component x or y

n	number of samples
n_p	number of particles per sample
p	occupation probability
PAT	Process Analytical Technology
p_c	percolation threshold
q	critical exponent
rpm	rounds per minute
s	unbiased sample standard deviation
S	scaling factor
s_a	standard deviation of sample analysis method
SEM	Scanning Electron Microscopy
s_m	standard deviation of the mixing process
s_s	standard deviation of the sampling error
t	time
V_0	poured volume
V	volume after tapping 2500 times
wb	sequence of charging equipment with white followed by blue material
x	proportion of component x
X	system property
x_i	ith value of x representing a characteristic of a sample
y	proportion of component y (= 1 - x)

Greek abbreviations and symbols

ρ	density
ρ_p	poured density
ρ_t	tapped density
σ_0	theoretical standard deviation of an unmixed system
σ_r	theoretical standard deviation of a completely random mixed system
σ_{total}	theoretical standard deviation of a total mix

1. Summary

Powder mixing represents a common process with broad applications from domestic to industrial areas. In pharmaceutical technology, where active pharmaceutical ingredients must be uniformly distributed to ensure safety and efficacy, mixing represents an important process in the manufacturing of solid dosage forms. With a long and rich historical background, the scientific and economic relevance is a proved certainty. Up to today, the diversity of powders, products and applications has led to a multiplicity of mixing apparatus, mixing theories and process descriptions and therefore difficulties of generalization.

Mixing of non- interactive or interactive particles can involve diffusive, convective and shear mixing mechanisms, which can lead to incomplete random, complete random or perfect mixture qualities or even to segregation where the components do not form a mixture at all. In order to receive information about mixing, sampling is necessary. Even though the requirements for the assessment and descriptions of powder mixtures are high, only basic principles are known for best sampling results so far.

The aims of the study contained the development, construction and evaluation of a *sampling* apparatus, which included special devices for the Turbula® mixer in respect to the current sampling theory. In this context, the *dry coating process* was studied besides common mixing. This process has recently gained special interests in pharmaceutical technology in dry solids mixing. The following factors were studied: identification of the important particle properties, the mixing mechanism and the influences of mixing times upon mixture qualities. The implementation of the percolation theory to the dry coating process has led to propose a critical fine particle concentration, which corresponds to the percolation threshold.

Based on the known sampling theory, the development and construction of the sampling equipment including the sampling apparatus followed the «Golden Rules of Sampling». The sampling equipment consists of a hopper element and a sampling train with sampling vessels where the sampling train has a constant speed. The linear movement of the sampling train represents the time resolved. By disallowing structural disturbances of the mixtures and excluding affection of the received results, the simple, short and reliable procedure was evaluated by investigating separate parts of the sequential mixing and sampling procedure as well as the whole system with non- interactive mixtures to identify possible influences on the system and the emerging results. By evaluating sequentially sample analysis, impacts of sampling and handling and mixing, the obtained results showed the requested properties of the developed and constructed sampling equipment. The obtained sampling results reflected clearly the content distributions due to the flow properties of binary mixtures. The evaluation of the whole system by applying non-interactive particles in the Turbula® mixer followed by sampling with the novel determination method showed good agreement compared to theoretical calculations based on the common mixing theory. It was concluded that the developed and constructed sequential system of mixing and sampling could be applied for further investigations of various mixing processes as well as investigations of other mixture types.

Originating from the old concept of «ordered mixing », dry coating offers an application in pharmaceutical technology to produce particles with attractive properties by simply mixing. By applying the developed and constructed mixing and sampling system, different non- interactive carrier particles were used with interactive Methylene blue to analyze the mixing mechanism and the resulting particles to identify the important process parameters. Thereby, the important particle properties were identified as the density, the particle size and the surface texture on the carrier properties side. As most important, the density difference between the carriers and the guest particles is shown to assist the dry coating process. The particle size is determined to support the process as well, whereas with increasing particle sizes, the dry coating process is more productive. The surface texture has been determined to support the dry coating process whereas the density and the size differences must be considered as more important. On the guest particle side, further investigations must consider the influence of the residual moisture content to form the dry coating layer. The mixing mechanism was identified as a rolling shear mixing mechanism where the carrier particles roll the active on their surfaces supported by the three dimensional movement of the Turbula®, whereas the produced particles display a thin layer. Mixing times, identified as the only variable process parameter, has been shown as distinctively prolonged compared to non- interactive mixing whereas the

determined mixing times demonstrate clearly the necessary optimization of mixing processes supporting the general opinion of separate studies of mixing processes for all mixture types and mixture compositions. Additional investigations were carried out to investigate the mechanical stability of the produced dry coated particles where it was demonstrated that the particles were more resistant than conventionally coated particles with suspensions. By regarding the received results, it was concluded that the presented prospects of the dry coating process displayed distinctively the need of further investigations as well as the opening of interesting new application fields.

By proposing a critical fine particle concentration, the percolation theory was introduced to the dry coating process to identify impacts on mixture qualities and the saturation process of carrier particles. The existence of a saturation concentration was shown for all dry coated particle mixtures representing the basis for the assumption of the critical fine particle concentration. However, the obtained results of the estimation of the critical fine particle concentration displayed that an exact determination is not simple. Nevertheless, the existence of the critical fine particle concentration could be shown in 4 out of 6 cases. The implementation of the percolation theory to the dry coating process is therefore legitimated qualitatively whereas the critical fine particle concentration can be equated to the percolation threshold, where the behavior is expected to change abruptly. To conclude, investigations of the application of the percolation theory in dry coating must be advanced, which would support the development of robust dosage forms, their design and as a consequence reduce time to market, economic losses and most important risks to patient’s health.

2. Aims of the Study

Mixing and sampling of powders - the term powder is used to describe all dry solid fine and coarse particles as single substance from dust to granules and pellets - are two issues of critical importance in the manufacture of a wide variety of pharmaceutical solid dosage forms such as tablets or capsules. In order to receive pharmaceutical products of best quality, mixing aims for the highest homogeneity of two or more components in a powder mixture. To gain knowledge about the quality of a mixture, representative and reliable sampling is essential [1-3].

The aims of the study include the development and construction of a sampling apparatus in respect to the known sampling theory. The device should be evaluated using non- interactive binary powder mixtures and the results should be compared to the common mixing theory. Originating from the old concept of ordered mixing, the new approach dry coating has gained more interest in dry solids mixing. The study investigates furthermore the influence of mixing times on dry coated mixtures and the existence of a critical fine particle concentration and its relation to percolation theory.

3. Introduction: Theory and Development of New Concepts

3.1 Relevance of Powder Mixing

It is well known that powder mixing is an extremely important unit operation widely used in many domestic and industrial areas. Examples therefore can be found in relatively uncritical arrays such as cooking and gardening as well as in more demanding procedures involving the manufacturing of ceramics, plastics, fertilizers, detergents, glass, processed food, animal feeds, powder metallurgy, cement and pharmaceuticals [2, 4-6]. In short, this operation is almost always practiced wherever particulate matter is processed [4].

In pharmaceutical industry, solid dosage forms compose about 80% of the medicines produced [6]. Thereby, mixing powders represents an important process in the manufacturing of solid dosage forms such as granules, tablets and capsules [4]. In order to ensure safety and efficacy, the active pharmaceutical ingredients must be uniformly distributed inside the solid dosage forms and its contents must lie in specification limits [4, 7]. The importance of uniform distribution of active pharmaceutical ingredients in solid dosage forms has long been recognized. In 1981, Egermann described enormous differences of 0.25mg digoxine tablets with contents between 75.6 to 243.6% of the nominal value, even though no distinct weight variance was detected [8, 9]. In 1993, content uniformity problems received considerable attention by the US Food and Drug Administration FDA. The consequence of a court case referred to as the Barr Decision mandated the pharmaceutical industry to demonstrate the uniformity of unit dose samples of final powder mixtures [US vs. Barr Laboratories 812, F. Supp 458, D.N.J. 1993]. The need to understand, predict, monitor and control the performance of mixing processes was emphasized by the ruling of the judge and reinforced the official compendia to protect the public against active component variations in the final dosage. From past to presence, excessive dose variations in pharmaceutical products was not an uncommon occurrence and has led to massive product recalls, severe economic loses and risk to patient’s health, especially in high potency medications [6, 7].

Even though powder mixing has been carried out for many hundreds or even thousand years, the science of mixing as a part of pharmaceutical powder technology probably originated not until the 1940s [4, 10]. In 1954, Lacey was the first to finally describe mixing as one of the oldest arts, which has always been regarded as a simple and everyday operation. In many cases, mixing is only an incidental process, which is more or less adequately performed during some other operations with a different object [11]. Over past decades, pharmaceutical powder technology has undergone a transition from a processing art towards a processing science [12]. Therefore, the FDA introduced the Process Analytical Technology (PAT) initiative in order to reduce the variability of pharmaceutical processes [10]. Following this direction, it can be expected that the change of pharmaceutical powder technology including powder mixing as an essential process from «Art to Science» will be accelerated and a stronger tendency for designing quality into products will emerge.

3.2 Mixing Powders: Dry Mixing and Demixing

The development of the science of dry powder mixing began already in the last century and the scientific and economic relevance is a proved certainty. As it is displayed in the past many times, the quality of a dry powder mixture is influenced by numerous variables and many difficulties appeared up to today due to the diversity of particulate materials as well as mixing equipment and sampling [1, 5, 12]. The diversity of powders, products and applications which can be found has led to a multiplicity of mixing apparatus, numerous theories of process descriptions, mixing indices and thus to difficulties of generalization [2].

3.2.1 From Random to Total Mix: Theoretical Qualities of a Mixture

Powders as starting materials for mixtures and powder mixtures can be regarded as disperse systems whereas the solid particles of different diameters are distributed in a gas as the continuous phase [13]. Due to gravitation and particle interaction forces, the solid particles generate a mechanical network, which is more or less able to expand, but always aims towards the highest and random packing [13, 14]. The properties of powders and powder mixtures are therefore very versatile and feature characteristics from solids, liquids as well as gases [10, 15]. These properties do not only affect mixing, but also storage and handling [5, 12].

3.2.1.1 Random Mix

In order to ensure an acceptable content uniformity, powder mixing is an operation, where two or more particulate materials are scattered randomly in a mixer to aim for the best possible distribution of the particles [2, 16, 17]. Based on his first scientific work in 1943, Lacey summarized in 1954, that the most useful way of describing the quality of a mixture is by using statistical methods measuring the statistical variation of a mixture composition among samples by their standard deviation [11, 18]. In these works, Lacey developed equations, which allowed the calculation of theoretical variances σ_0^2 for completely unmixed (equation (1)) and σ_r^2 for randomly mixed (equation (2)) systems for the comparison and evaluation with real qualities of mixtures by real standard deviations. For the derivation of the equations, it was assumed that all particles have uniform size and are distinguishable only by color without particle interaction. Furthermore, the sample size was defined as the equal number of particles per sample [11, 18].

$$s_0^2 = x \times y \qquad \text{equation (1)}$$

$$s_r^2 = \frac{x \times y}{n_p} \qquad \text{equation (2)}$$

where x and y (=1-x) describe the proportions of the two mixture components and n_p the number of particles per sample. In the progress of the mixing operation starting completely unmixed, the randomization of the components in all three dimensions increases until the highest degree of disorder. Therefore, the mixing process is finished when the highest disorder of the components is reached which equals the maximum entropy. As depicted in figure 1, it is obvious that unmixed and perfect ordered binary mixtures strive towards a random mix due to entropy [4, 11, 13].

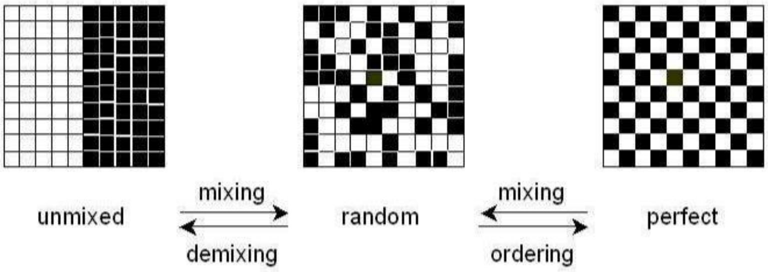


Figure 1: Schematic representation of a binary mixing system.

The randomness of particulate mixtures can never achieve a level almost as perfect as seen in liquids, but the disorderliness reaches a rough, more or less stable maximum after a certain mixing time and is not a static but dynamic state, where mixing competes with demixing [4, 11, 13].

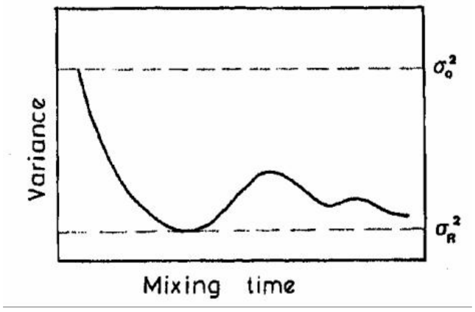


Figure 2: Example of a mixing profile where the upper and lower limits for the mixing curve are shown using the theoretical variances (σ_R^2 in the figure equals σ_r^2 of equation (2)).

The situation in powders is much more complex since powders do not only consist of single sized particles but of a range of particle sizes. Buslik provided first steps towards a solution by developing an equation dealing with the sampling of multisized materials to determine particle size distributions [19]. In 1954, Stange derived a more complex equation for the calculation of the theoretical variance of random binary mixtures based on the binominal distribution [20]. Thereby, it was shown that the quality of a random mix is dependent on the weight proportions of the two components, the sample weight, the average weight of particles and the degree of particle size uniformity and displayed good agreement to experimental results. Poole et al. simplified the equation in 1964 to obtain equation (3), which is known as the Stange- Poole equation [21].

$$s_r^2 = \frac{\frac{x \times y}{M}}{y \times m_x + x \times m_y} \qquad \text{equation (3)}$$

where	x	fraction of minor component in the mixture
	y	fraction of major component in the mixture
	M	sample weight taken from the mixture
	m_x	mean particle weight of the minor component
	m_y	mean particle weight of the major component

According to Egerman, the terms $m_{x,y}$ describe the mean particle weight as a parameter of the amount of particles per dose [22]. For spherical particles, the mean particle weight can be calculated using equation (4).

$$m = \frac{p \times r \times d_V^3}{6} \qquad \text{equation (4)}$$

wherem		mean particle weight
	d_V	diameter of a particle with a mean particle weight m
	ρ	density

The diameter d_V of the particles of each component can be obtained from the corresponding particle size distribution [22].

In 1972, Johnson introduced the coefficient of variation ({standard deviation/mean}⊙ 100%) as a degree of theoretical mixture quality. Based on the Poisson distribution, equation (5) was developed considering only the active pharmaceutical ingredient as spherical particles inside a low content binary mixture [23].

$$C_V = 100 \, \frac{p \times r}{6 \times G}^{1/2} \left(\square \, fd^3 \right)^{1/2} \qquad \text{equation (5)}$$

where	C_V	coefficient of variation
	ρ	density
	G	mass content per sample
	f	fraction of particles with diameter d
	d	diameter of particles

For the evaluation of the quality of a mixture, the coefficient of variation is a more descriptive value as the standard deviation because it shows the fluctuations of the standard deviation in relation to the mean content [22]. In the course of time, equation (5) was transformed several times and showed broad validity for up to 10% (w/w; specification weight by weight) of the active pharmaceutical ingredient inside binary mixtures (equation (6)); above 10% (w/w), it was suggested to use equation (3)[17, 22, 23].

$$C_A = \frac{100\sqrt{m_A}}{M_A}$$ equation (6)

where C_A	coefficient of variation of substance A
m_A	mean particle mass of substance A
M_A	mean content by mass of substance A

During the time of the development of the above- mentioned equations for random binary mixtures of coarse, non- interacting ingredients, equations dealing with multicomponent random mixtures were investigated also and can be found in literature, but are not parts of this work.

3.2.1.2 Ordered Mix versus Interactive Mix

The theory of random mix cannot be applied to all mixing situations in pharmaceutical powder technology where fine, interacting and not coarse, non-interactive particulate systems are most common. In 1975, Hersey introduced a new concept called ordered mix to describe mixing of fine particles not equally sized and weighted which interact due to cohesion and adhesion by increased London, van der Waals and electrostatic forces [24]. With increasing fineness of the powders, the interaction properties increase as well and lead to an ordered arrangement rather than randomization similar to the chessboard pattern depicted in figure 1. Even though it is well known that large differences in particle sizes enhance demixing, the interaction properties of fine particles can be utilized to receive better mixture qualities than calculated from random mix whereby fine particles adhere especially to coarser particles to form ordered units [5, 25]. In an equilibrium situation, all fine particles adhere to all coarse particle sites and form equal ordered units [24]. For the case that fewer fines are in the mixture, the ordered units are not equal. If there are more fines, the remaining fines mix in a random matter. As it is stated in random mix, the rate of mixing follows a first order kinetic, whereas in ordered mixing, the mixing rate is proportional to the concentration of unmixed fine particles [24].

The proposed concept of Hersey opened up a broad discussion about the mixing mechanism of ordered mixing and nomenclature. In 1980, Egermann concluded that the mechanism of adhesion cannot be ordered, but random due to the irregularities of the surface texture of the real solid particles and the binding capacities (see figure 3)[26, 27]. In addition, the number of adhering fine particles to each carrier can hardly be identical and distributed equally.

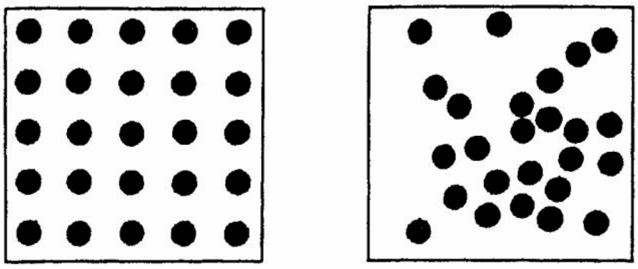


Figure 3: Ordered and random adhesion of fine particles on the surface of a coarse particle.

Following the picture of random adhesion for low dose mixture preparations of interacting fines adhering on coarser particles based on the Poisson distribution, equation (7) was derived conforming equation (6) for random mixes assuming monosized carrier particles and constant carrier surface per sample [28, 29].

$$C_{RA} = C_R = 100\sqrt{\frac{m}{G}} \qquad \text{equation (7)}$$

where C_{RA}	coefficient of variation for random adhesion
C_R	coefficient of variation for random mix
m	mean particle weight
G	mean content per sample

The existence of ordered mixtures has not been demonstrated in the past caused by an inadequate use of the Stange- Poole equation to calculate the random degree of mixing for ordered mixtures [4, 27-31]. In contrast, the highest degree of mixing was found to conform to the quality of random mixtures using equation (7) even though in real mixtures, complete adherence of even the coarsest particles may not occur [29]. In being closer to the actual situation of the mixing mechanism, the suggested nomenclature interactive instead of ordered and non- interactive instead of random appears superior [31, 32].

3.2.1.3 Total Mix

Staniforth introduced the term total mix in 1981, which accounted for real powder mixtures formed by particles, which are not totally non- interactive (randomly) distributed nor completely interactive (ordered) due to their particle size distributions [32]. The mixing mechanisms were displayed using geometrical murals from Alhambra, Spain, and are exemplary represented in figure 4.

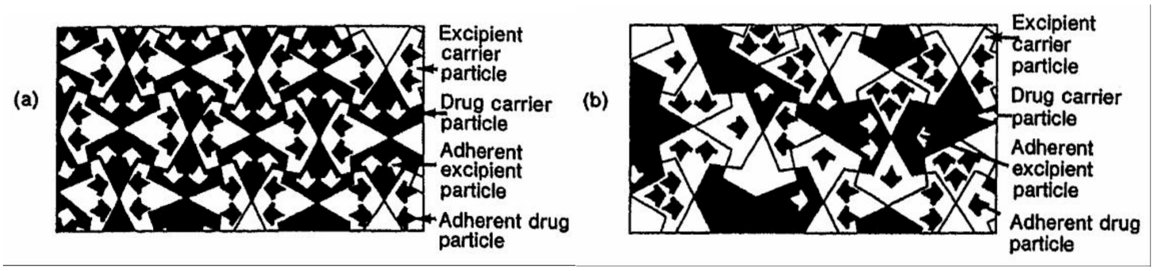


Figure 4: Illustration of the formation of a perfect interactive total mix (a) and a real total mix (b).

The theory stated that the two mechanisms, non- interactive and interactive mixing, exist in a dynamic equilibrium and are based on the gravitational and the particle interaction forces. In a non- interactive mix, the gravitational force mainly influences the particles. For interactive particles, gravity is also present but only for the ordered units. In addition, the fine particles produce adhesion and cohesion, which stabilize mixtures [32, 33]. Developing an equation for the theoretical variance of a total mix taking into account the fractions x and y, equation (8) was derived and used as a basis for further calculations of total mixes. There, the fraction of the fine component y adhering to the coarse component x is Fy, and the fraction of component x adhering to component y is Fx.

$$\sigma^2_{total} = \frac{(x + Fy - Fx)(y - Fy + Fx)}{n_p} \qquad \text{equation (8)}$$

where n_p number of particles per sample

The relevance of the term total mix was questioned by Egermann in 1989, who proposed to rather use the traditional term powder mix synonymously which appears to be more informative and clearer and does not provoke uncertainties about its actual meaning [31].

The introduction of the theory of total mix led to varying attempts of summarizing all types of mixing. Displayed in figure 5, the most advanced illustration was made by Thiel in 1984 and included all types of mixing [34]. However, the proposed nomenclature is in certain cases also not very precise.

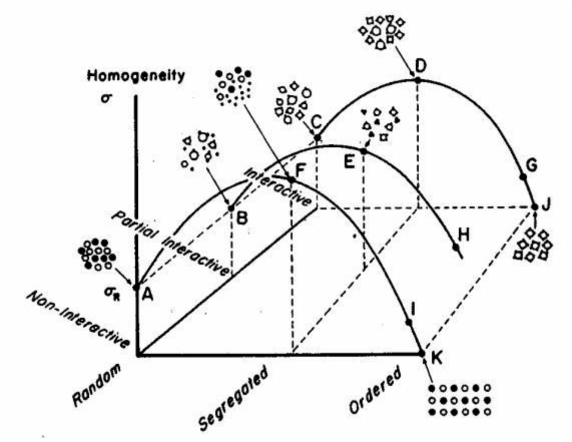


Figure 5: The quality of mixtures as a homogeneity surface for different types of mixtures.

In comparison to the complex diagram of Thiel, figure 6 will be used as a summary of powder mixing. Adapted of Harnby's engineering view and the historical developments of powder mixing, the quality of mixing is dependent on the mixing mechanism, which is controlled by the powder properties, the mixing mechanism and operating conditions [12].

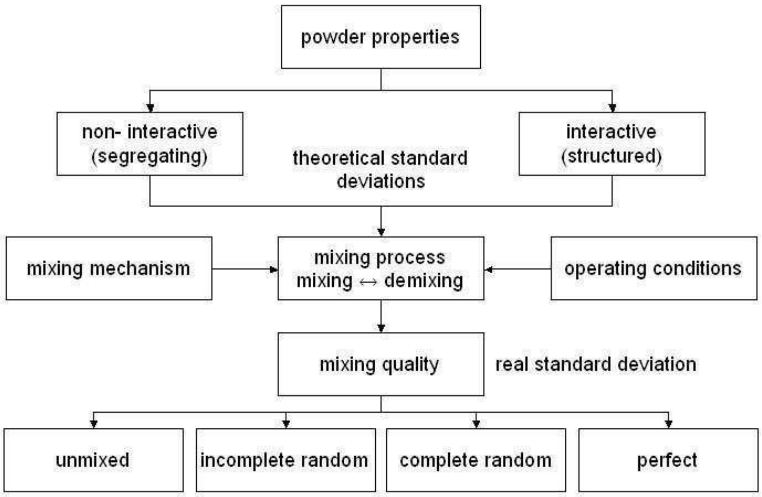


Figure 6: Summary of mixing process based on the particle properties.

The quality or output of the mixing process can be divided into unmixed, incomplete random, complete random and perfect mix whereas the goal of all real mixing operations has to be the pursuit from an incomplete random to a complete random mix as the ideal, best possible achievable mixture quality. In contrary, the perfect mix will be unattainable due to entropy already mentioned. Segregation is considered as a separation, where the main factors at a particulate level are differences in particle size, shape and density and can occur during the mixing process itself, handling, storing and transferring of powders, for example in a filling shoe of a tableting machine [17].

3.2.2 Impact of Particles and Mixing Equipment

Powder mixing is a very complex process in which many variables play an important role and influence the quality of a mixture. The influencing factors can be assorted in three major groups: powder properties, mixer properties and operating conditions.

3.2.2.1 Powder Properties

Different aspects of particle properties and their impact on mixing and demixing will be described in the following.

a. Particle Size and Particle Size Distribution

The particle size and the corresponding size distribution of the mixture components have not only an extensive influence on dissolution and absorption, but especially on the content uniformity [17]. For example in low content dosage forms, it is obvious that a sufficient number of particles must be available to supply each dose, for example tablets or capsules, adequately [35]. In using equation (5), the theoretical limiting size of equally sized spherical particles of an active pharmaceutical ingredient was calculated for a coefficient of variation of 1% and is depicted in figure 7 [23].

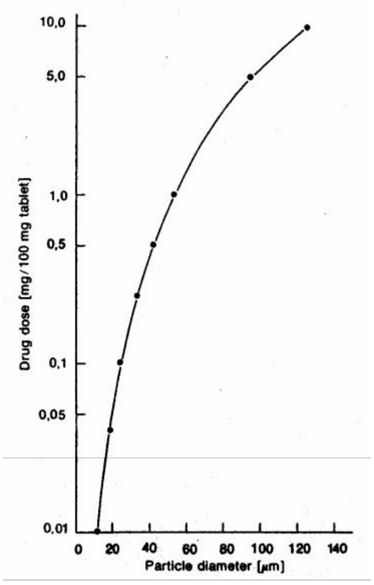


Figure 7: Limiting particle size as a function of the dose level for a C_V = 1% in 100mg tablets.

In conclusion, it would be reasonable to have as small particles as possible for best quality and reproducibility, especially in low dose preparations. However, the decrease in particle size increases the influence of cohesive and adhesive particle interaction forces, which cause agglomeration, and is followed by insufficient mixing results [36, 37]. Also, large differences between the particle size distributions of the used non- interactive components can lead to demixing or segregation where the smaller particles can slip through the voids between the larger particles (figure 8)[38].

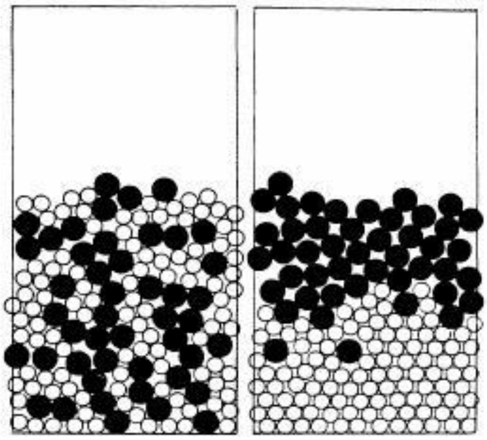


Figure 8: Size segregation: initial configuration on the left side, configuration obtained after shaking 300 times on the right.

It was discovered, that a ratio of particle diameters between smaller and larger particles of less than 1.2 is necessary to avoid size segregation [39].

b. Shape and Surface Characteristics

Spherical and smooth particles are easier to mix than irregular shaped, rough particles because no felting and sticking is possible, which would influence the mixing process [17]. In addition, round particles form smaller voids in a powder bed compared to non- spherical particles, for example angular or acicular, and show therefore less resistance to mixing [40]. Differences in terms of shape of mixing ingredients are less important than differences in particle size [41].

c. Density

With having density differences of the components inside a mixture, several problems can develop. Under the influence of the gravitational force, the more dense particles are pulled to the bottom leaving the less dense particles on top, which enhances demixing or causes segregation [16, 42]. Additionally, rather dense particles can increase mixing times [17]. In practice however, it was reported that size distribution appeals to have greater influence on mixing and demixing than the difference of densities of a ratio 1:3 [16, 43].

d. Flowability

Flow properties play an important role and must be taken into account in all powder applications such as transfer, storage, tableting, granulation, encapsulation and mixing [10]. An accurate definition of powder flowability is the ability of particles to flow in a desired manner in a specific piece of equipment [44]. Particle properties (particle size and size distribution, morphology, density), processing conditions (compression situation) and environmental conditions (relative humidity) control the flow properties and make a classification difficult [45]. The ability of air to separate particles depending on flow properties was the basis for a classification system introduced by Geldart in 1973. The work described the correlation between particle densities (difference of densities of solids and fluidizing gas) as a function of the mean particle size, which describes the ease with which materials can be fluidized [46, 47]. As displayed in figure 9, the qualitative and quantitative classification resulted in solid groups A, B, C and D, which have been described and characterized many times in the past.

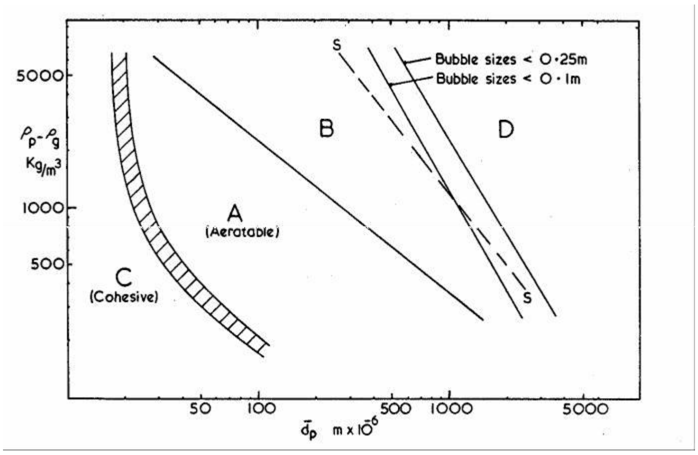


Figure 9: Geldart' s powder classification diagram based on the fluidisation properties of different solids.

Nevertheless, the determination of the necessary parameters for the classification according to Geldart is tedious and subjective and correlates empirical relating material behavior trends to only two particle properties [44, 48]. Another way of classifying powder flow is by simply observing and describing the flow behavior in a piece of equipment [44]. Thereby, differences can be seen between non-interacting, free flowing, and interactive, cohesive, powders whereas the flow properties are located between two extreme cases: mass and core flow [44, 49]. As depicted in figure 10, mass flow provides a first- in- first- out flow sequence usually seen with non- interacting powders, while core flow can be described as a first- in-last- out pattern during the discharge out of a hopper of interactive powders.

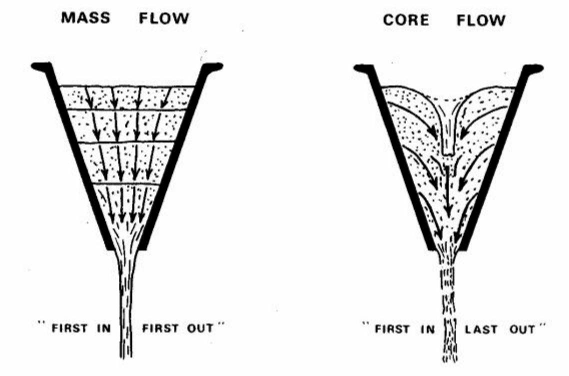


Figure 10: Schematic illustration of mass and core flow out of a hopper.

However, the barrier between non- interactive and interactive flow properties in terms of the flow patterns is diffusive but a simple differentiation is possible.

Powder mixtures can also be classified into non- interactive and interactive mixtures due to their flow patterns, but one must be aware that the flow properties of the individual components that make up a mixture cannot necessarily determine the flow properties of the mixture. The ability of individual particles to move independently is evidently an important characteristic in mixing [44]. Processing a non- interactive mixture consisting of only non- interacting powders will generally permit individual particles to move independent and fast, only with gravitation as the influencing force, which expresses in mass flow. Due to the same freedom that allows those particles to move, the disadvantage of non- interactive mixtures is demixing or segregation, whereby great care has to be taken in subsequent handling and storage depending on differences in density and particle size of the components [12]. On the other hand, interactive mixtures contain one or more cohesive ingredients, which generally underlie cohesive and adhesive forces, permitting particles to move only with an associated cluster and admitting interaction with the equipment which can be seen in core flow [5]. During the mixing process, the natural agglomerate structure has to be broken down repeatedly in order to give the individual particles the opportunity to relocate [44].

e. Moisture Content

Powders and powder mixtures are in constant water exchange with the environment depending on the relative humidity, which can exhibit in relative unstable moisture contents. The alteration of the moisture content leads to a conversion in surface forces where the increase of the relative humidity conditions expresses in liquid bridges and dominates cohesive and adhesive forces [50, 51]. Therefore, rather moist and sticky particles can retard the mixing process by particle agglomeration and adherence to the equipment [16]. Hence, it is obvious to keep materials under constant relative humidity conditions.

3.2.2.2 Mixer Properties

The basic object of powder mixing requires primarily the movement and the derangement of mixing components. Therefore, the dislocation of particles in a mixer should be three dimensional, random and fast and expresses the need for expansion of the mixtures in terms of the capacity without dead regions inside the mixer [2, 16, 17]. However, the complexity and interaction of the powder properties already mentioned precludes a universal design. Nevertheless, all mixers are based on three mixing mechanisms: diffusion, convection and shear [11].

The diffusive mixing mechanism occurs by the distribution of particles over a freshly developed surface and is caused by the movement of the mixer itself [11, 16]. Considerable amount of work has been done by describing diffusive mixing beginning in 1954, where Lacey applied the classical diffusion theory using Fick' s diffusion law, which is written in equation (9), in order to describe the relation between the degree of mixing and the mixing time in analogy to the molecular diffusion [11, 16].

$$\frac{dC}{dt} = D\frac{d^2C}{dl^2} \qquad \text{equation (9)}$$

where C concentration of the mixture
t time
D diffusion coefficient
l distance in the direction of diffusion

In mixers of the convective type, groups of particles inside the mixture are in motion. The particles are subdivided into clumps and are displaced relative to one another by movable parts inside an immobile mixer whereas the gross effect will be similar to diffusion and can be compared to the motion in turbulent liquids [2, 11, 16, 17]. In comparison, figure 11 illustrates the diffusive and convective mixing mechanisms, which operate at macroscopic scale [2]. At microscopic level, the diffusion movement is not equivalent in gas, liquids and powders whereas in the last case, there will be no relative movement of the particles without the input of energy. Besides, particle components do not have identical properties and differ in physical characteristics. The smallest element in a powder system is a particle and cannot be compared with a molecule in a liquid or gas system, which expresses in a rougher texture of the mixture [2, 10, 18]. Shear mixing can be considered as a three dimensional shuffling and occurs when grinding or rolling parts, for example blades, are involved inside the mixer and generate slipping of particle planes [2, 11, 16]. Shear is often considered as a combination of diffusive and convective mixing, but a specific mechanical action is needed [2, 11, 16, 17].

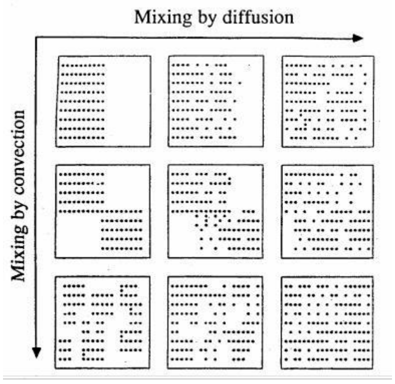


Figure 11: Schematic illustration of the diffusive and convective mixing mechanisms.

In the process of mixing, all three mechanisms function to some extent where different mixers give different predominating mechanisms and make a classification difficult [16]. Examples of different mixers are given in figure 12.

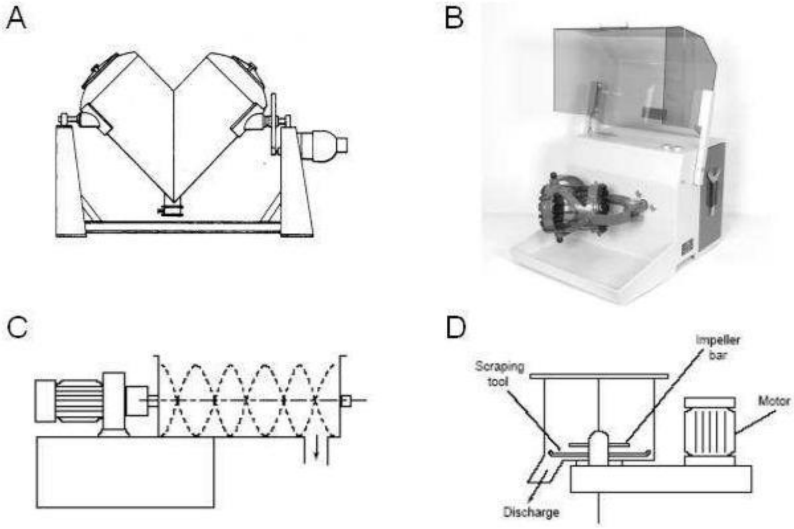


Figure 12: Examples of different mixers. Diffusive mixers: A: V- mixer and B: Turbula®; convective mixer: C: ribbon mixer; shear mixer: D: high-speed impeller.

In a diffusive mixer, non- interactive and interactive mixtures can be handled, but demixing can be caused by size and density differences. In addition, only weakly structured powders will be broken down, but small agglomerates of interactive ingredients might remain intact [5, 16, 17]. Convective mixers can be used in a wide range of processes with the advantage of minimizing demixing caused by size and density differences [12, 16]. Also, interactive mixtures mix well but dead regions inside the mixers are often present [12]. Shear mixers have the advantage of breaking down all kinds of agglomerates but dead regions inside the mixer can be found as well [12, 16]. It is obvious that a selection of a mixer is rather difficult whereas mixture quality and process requirements in terms of mixing ingredients as well as costs, operation mode and maintenance play an important role [2].

3.2.2.3 Operating Conditions

Operating conditions of powder mixtures and mixing equipment influence significantly the quality of mixtures. The weight fractions of constituents, the sequence and place of adding ingredients in a mixer as well as the pretreatment of components, for example by breaking down agglomerated particles by sieving, and mixer emptying affect the mixing result [5, 16, 52]. The filling volume of the mixer needs considerations to give the mixture the opportunity of expansion [2, 16, 17]. For several types of mixers, the ratio of mixture and mixer volume should not exceed 25 to 30% whereas in a Turbula®, a filling volume of up to 70% is possible due to its three dimensional movement [16, 53]. The mixer or agitation speed, if existent, and the mixing time have great influence depending on the materials mixed to either decrease demixing or increase agglomeration break down [6, 17]. Especially the mixing times have to be optimized for all mixers and materials and so far, no existing rule can be applied.

3.2.3 Mixing Indices and Rate of Mixing

Statistical analysis is the major tool in order to gain knowledge about the quality of a real mixture. By using samples, the distribution of an ingredient in a binary mixture can be described by the sample arithmetic mean $\bar{x}$ from equation (10).

$$\bar{x} = \frac{1}{n}\sum_{i=1}^{n} x_i$$ equation (10)

where	n	number of samples
	x_i	ith value of x which represents a characteristic of a sample such as the composition

and the unbiased sample variance s of equation (11)[2, 16].

$$s^2 = \frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x})^2$$ equation (11)

Implicating equation (11) with equations (1) and (2) for theoretical qualities of a mixture, the following inequality can be written in equation (12)[2]:

$$\sigma_0^2 > s^2 > \sigma_r^2$$ equation (12)

In order to have a single statistic description of different qualities of mixing processes, mixing indices were introduced in mixing theory to have one single figure as a rate of the mixing process relating theoretical and observed variances [54]. To characterize mixing processes, general and useful indices had to be easy to determine and sensitive [2]. Throughout the development of mixing theory, over 40 different indices have been proposed whereas examples are listed in table 1 and more exhaustive lists can be found in literature [2, 16, 55].

Table 1: Examples of mixing indices.

author	mixing index	change of index with improved mixing	ref. no.
			cited in
Kramer	$M = \frac{\sigma_0 - s}{\sigma_0 - \sigma_r}$	0 → 1	[5]
Lacey	$M = \frac{\sigma_r}{s}$	< 1 → 1	[18]
Poole, Taylor, Wall	$M = \frac{c}{c_r}$ or $\frac{s}{\sigma_r}$	>>1 → 1	[21]
Ashton and Valentin	$M^2 = \frac{\log \sigma_0^2 - \log s^2}{\log \sigma_0^2 - \log \sigma_r^2}$	0 → 1	[56]

where M is the mixing index, s the observed standard deviation, σ_0 the theoretical standard deviation in the unmixed state, σ_r the theoretical standard deviation of the random mixture and c, c_r the coefficients of variation of observed and random mixtures respectively.

In many instances however, a single figure is not sufficient to adequately describe mixing processes and more complicated methods should be used. Additionally, several mixing indices fail in terms of sensitivity and the simple standard deviations or coefficient of variations can adequately be used [54, 55].

3.4 Sampling of Powder Mixtures

For the assessment and description of powder mixtures it is necessary to observe subsets. Even though sampling and analyzing samples is often considered as expensive, time consuming and wasteful, samples are indispensable and have the obligation to characterize a whole mixture, irrespective of whether a physical or chemical assay is carried out [3, 16, 58]. In order to receive representative samples, all particles must have equal chances to be sampled without interference of the structure of the powder mixture. Additionally, the composition of the mixture must remain constant. In order to receive reliable information using a proper sampling procedure, an adequate amount of samples and a sufficient sample size is required [3, 16]. However, difficulties arise due to the characteristics of powders, such as particle size and flowability, where already simple handling and storage, including sampling with sampling equipment and operator bias, can make the mixture composition vulnerable to demixing or segregation [3, 58]. The large number of different powder compositions makes it impossible to lay down universal instructions for all sampling situations [58]. Even at the level of regulation, it is only asked to reach certain specification limits with a limited number of samples rather than trying to evaluate rigorously the quality of a mixture by proposing accurate sampling procedures [59]. So far, only basic principles are known for best sampling results. The so called «Golden Rules of Sampling» indicate t hat powders should be sampled from a moving stream and the whole stream should be sampled for short equal periods of time rather than parts of the stream for the whole time [3, 58]. These rules should be applied whenever possible and sampling methods not following these principles should be regarded as second best methods leading to errors [58]. However, differences between the mixture composition and the samples will always exist. In order to estimate these differences, studies of mixtures and mixing processes have to include details about the method and location of samples, the sample size and the number of samples [16].

3.4.1 Methods of Sampling

Many sampling methods are available from the simple use of a scoop to more complex devices. The selection of an adequate sampling technique is dependent on the characteristics of the mixing process and the powder mixture [16, 58]. Most types of sampling equipment are operated invasively by removing manually or automatically samples from a mixture after the mixing process [3]. Examples of such samplers are the sample thief, the pneumatic lance and the full- stream trough sampler, which are depicted in figure 13.

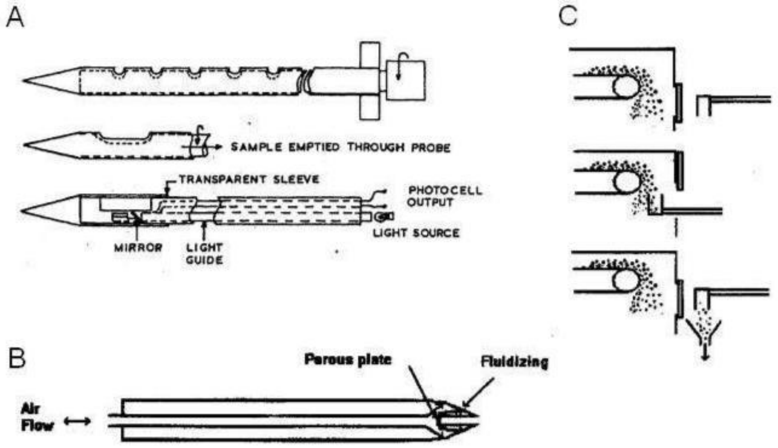


Figure 13: A: sample thiefs; B: pneumatic lance; C: full- stream trough sampler.

Results of the determination of the quality of a mixture from the application of some of the mentioned sampling devices must be regarded with caution since the original structure of the mixture can massively be disrupted, like displayed in figure 14 [54].

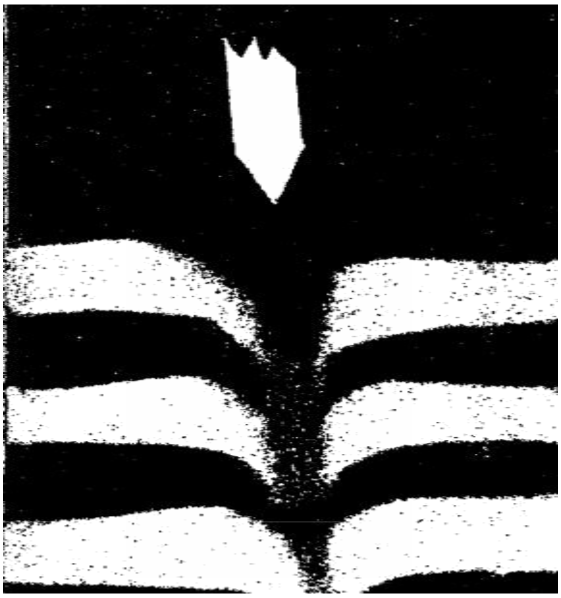


Figure 14: The disruption of the original structure of a mixture by a sample thief.

The location where samples are taken from has to be considered also in using such sampling devices. Since for example the surface region is always rich of coarse particles due to segregation, samples should never be removed from that area [58]. Sometimes, when a large amount of samples is available, sub- sampling with for example a spinning riffler or a hopper sample divider in figure 15 is necessary [2, 3]. Even though these sampling devices show superior properties compared to others, they are also vulnerable to segregation [3, 58].

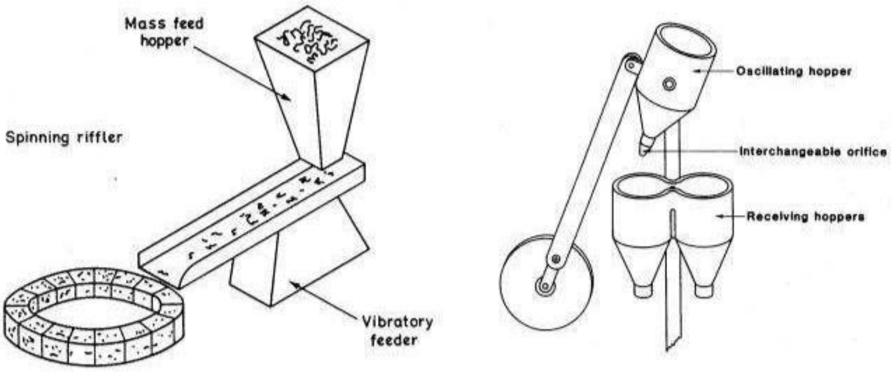


Figure 15: Spinning riffler and hopper sample divider.

In order to investigate samples or mixing processes, methods of measurement without influencing the structure of a mixture have been introduced, such as radioactive or color labeling of ingredients or freezing of a mixture with monomers [3, 16]. The improvement of technical methods nowadays leads to non- invasive online process measurements, like optical fiber systems or electrical capacitance tomography (ECT), but still a considerable amount of developments has to be done [59].

3.4.2 Sample Size

The smallest possible sample size consists of only one single particle where no information about the quality of a mixture can be obtained. The largest possible sample size is the entire mixture, which can make the quality of a mixture appear better as it actually is [16]. In summary, the ideal sample size is located somewhere in between.

The sum of samples removed from a powder mixture must be adapted to the dimensions of the material [2]. For instance, the characteristics of many tons of material cannot be assumed on analysis executed based on grams or even milligrams [58]. A rough rule indicates to remove about 5% of the mixture [16].

In terms of each sample, the nature of particles must be considered, where a small sample volume will not represent large particles and large volumes will neglect fines [2]. In addition, agglomerates of interactive powders will affect the sample size [16]. In a completely random non- interactive mixture, sample size is reported to be inversely proportional to the sample variance whereas in a completely separated mix, sample size is independent [18].

So far, no systematic method has been proposed to determine the optimal sample size and the general thoughts just mentioned must be meditated when selecting a convenient sample size [16]. In pharmaceutical technology, the final product is used oftentimes, such as tablets, whereas a tableting machine is rightly considered and frequently chosen as sampling equipment.

3.4.3 Number of Samples

To have confidence in an estimation of the quality of a mixture like the variance, the number of values must be known upon which the estimation is based on [54]. A small number of samples make the determination of the quality undetermined and not sufficiently confidential [16]. Even though a large number of samples withdrawn from a mixture result in a structural disruption, more knowledge can be obtained. To have increasing confidence in a received measurement, large numbers of samples are required as shown in figure 16, where the probability values of 5% as a function of the ratio true to estimated standard deviation is displayed [cited in 54].

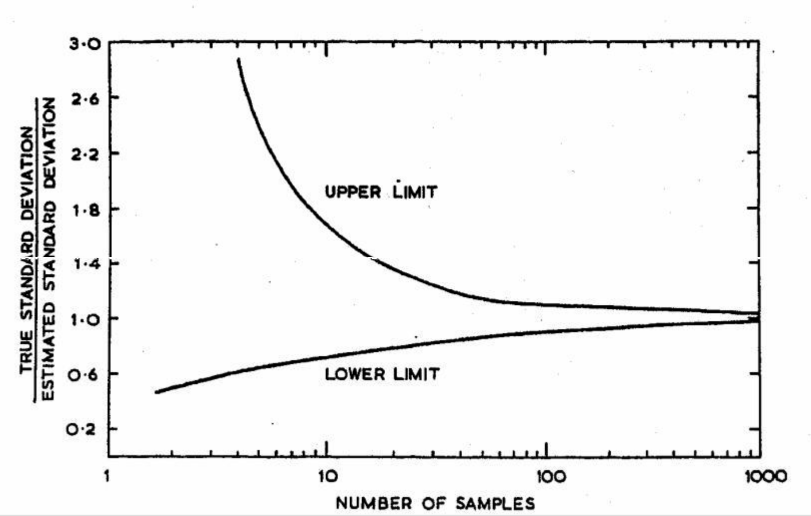


Figure 16: 95% confidence limits for the ratio
true and estimated standard deviation.

The determination of the number of samples depends primarily on the mixer and the mixture, the sampling method and the costs of sample analysis, whereas no other uniform principles or systematic methods are proposed and several numbers from 5 to 50 or more circulate [2, 16, 60].

3.4.4 Accuracy of Evaluating the Quality of a Mixture

After sampling, analyzing samples leads to an experimental measured variance, which must be considered as a combination of various variances [1, 22, 61]. The total experimentally measured variance s^2 includes the variance of the mixing process s_m^2, the variance introduced by the sampling error s_s^2 and the variance resulting from the sample analysis method s_a^2. Using the error addition law, equation (13) can be conveyed, when the errors are independent [22].

$$s^2 = s_m^2 + s_s^2 + s_a^2 \qquad \text{equation (13)}$$

It is obvious that s_s^2 is difficult to determine and dependent on the sampling method, the sample size and the number of samples [1, 61]. In ideal and skillful sampling, s_s^2 and s_a^2 can be neglected and s_m^2 is almost identical to s^2 [1, 22, 61]

3.5 Concepts for the Practical Assignments

3.5.1 Development of a New Sampling Apparatus

To produce and investigate binary mixtures of dry powders, the Turbula® was chosen which operates only on the basis of diffusive mixing without severely influencing particle properties. Furthermore, the mixer has been widely used and good mixing results can be achieved due to its three dimensional movement. It is evident that free movement is only possible if the mixing vessel is not completely filled. The degree of filling needs to be optimally 50% to 70% [53].

For the determination of the quality of the mixtures, a simple sampling method had to be developed conforming to the mixing process. Leaning on the «Golden Rules of Sampling», samples should be obtained by s ampling a whole moving stream to decrease structural disturbances of the mixtures. According to the spinning riffler, the device should be able to lead to samples reflecting linearly in time the content distribution of a vertical flowing binary mixture by simple discharge from a hopper. In other words, the sample apparatus should work like a tableting machine excluding the movement of a filling shoe and without compaction, which leaded to a device illustrated in figure 17.

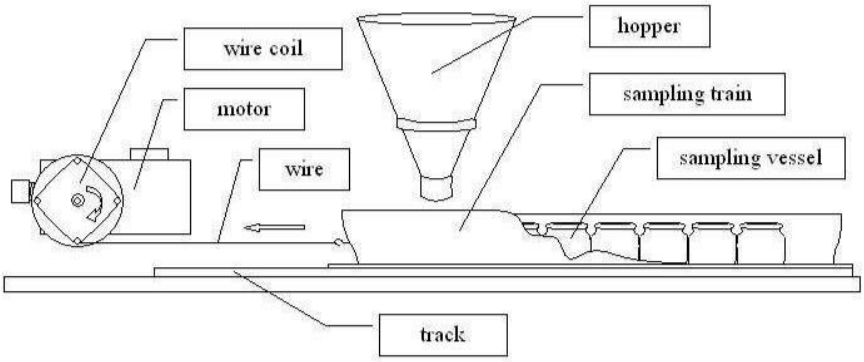


Figure 17: Illustration of the developed sampling apparatus.

3.5.2 Spontaneous Granulation or Dry Coating?

After the development of the theory of ordered mixing, various investigations studied the method of mixing coarse particles with fines to generate mixtures that result in better mixture qualities than theoretical non- interactive mixtures. In 1985, Staniforth examined interactive mixtures on stability using host particles with different moisture contents concluding in producing more stable particles using carriers containing higher moisture contents and suggesting interactive mixing rather as a spontaneous or direct granulation [62]. Granulation is considered as a process, where primary powder particles form larger, multiparticle entities irrespective of particle sizes to prevent segregation, to improve flow properties and to link or freeze active pharmaceutical ingredients to larger particles to improve distribution and increase the quality of a mixture [63]. Granulation can be divided into wet and dry methods. The wet processes involve liquids to produce granules following steps such as dry mixing, wetting, agglomeration process and desagglomeration by sieving [63]. Dry granulation processes form agglomerates under high pressure by either producing a large tablet, known as slugging, or by squeezing powders between two rollers to produce a sheet of material, known as roller compaction [64]. Both methods need additional milling steps to break down the products into suitable granules.

In comparison of regarding dry or interactive mixing as a kind of granulation process, the structure of the resulting particles consists of a layer of fines adhered on the surface of the larger particles without the aid of high pressures or liquids and reminds therefore on a process mechanism similar to coating but without applying coating suspensions [65]. Regarding the attractive possibilities of such a simple process receiving high quality mixtures with very good flow characteristics, dry mixing must rather be considered as a dry coating process where investigations must direct towards the understanding of the mechanism and the identification of the important process parameters [65, 66].

3.5.3 Application of the Percolation Theory in Dry Coating

The concept of describing the behavior of disordered systems by the percolation theory was first introduced in the 1940s to characterize gelation and the terminology of the percolation process followed based on the work of Broadbent and Hammersley in 1957 [67-69]. Since then, the percolation theory has been applied to describe a variety of phenomena also in the field of pharmaceutical powder technology introduced by Leuenberger, where the theory has been successfully utilized to describe tablet properties for the design of solid robust dosage forms [70, 71]. However, interparticle percolation has been used to explain demixing or segregation in powder mixing [5, 72].

For the application of the percolation theory in a disordered system, two requirements are necessary. First of all, it must be possible to subdivide the disordered system into subunits with an arranged geometrical order. Secondly, each subunit must be assigned to a property A or B with the corresponding probabilities p_A or p_B ($p_B = 1 - p_A$). It is obvious, that these conditions are not very restrictive and make an application of the percolation theory to manifold disordered systems in nature possible [10, 71]. The above- mentioned geometrical order is determined by lattices, which can be one-, two- or n- dimensional where the lattice sites may be arranged in different geometrical patterns, such as square, honeycomb or the Bethe-lattice. The lattice sites can either be occupied randomly with the probability p_A or unoccupied with the counter probability p_B depending on the corresponding subunit property A or B. A group of directly neighboring occupied sites is called cluster. For the case, that the probability p_A is small, a lot of small clusters can be found. Increase of the probability p_A results in a decrease of the number of clusters, whereas the size of the clusters increases. At the critical probability p_c, which is termed percolation threshold, an infinite cluster is formed penetrating the whole lattice in all directions. Other types of percolation, such as bond, site- bond, directed or continuum, are known besides the so far described site percolation. An example of site percolation in a two- dimensional square lattice is depicted in figure 18. The important aspects are discussed in more detail in the textbook of Stauffer and Ahorny [73].

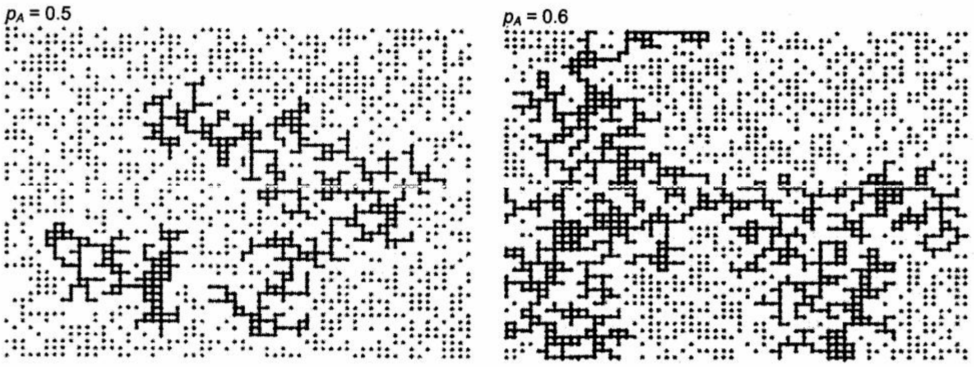


Figure 18: Square lattice of site percolation with an occupation probability below (left) and above (right) the percolation threshold, where above the critical probability, an infinite cluster percolates the system.

In the array of the percolation threshold p_c, which is dependent of the type of percolation, the type and dimension of the lattice, the behaviour is expected to change very abruptly, where the properties of the system obey the fundamental power law (scaling law), which is presented in equation (14).

$$X = S(p - p_c)^q \qquad \text{equation (14)}$$

where X system property
S scaling factor
p occupation probability (corresponding to p_A)
p_c percolation threshold
q critical exponent

In order to understand and describe the dry coating process, the percolation theory may be applied when fines are covering the surface of coarse particles to achieve high quality mixtures. A similar situation can be found in surfactant- water systems, where as soon as the surface is completely covered with surfactant molecules, micelles are formed by precipitation and change the properties of the system. The formation of micelles can be compared to the formation of fine particle clusters, which starts as soon as the surface of the coarse particles is completely covered and results in worse mixture qualities. As shown in figure 19, the existence of a critical fine particle concentration CFPC is proposed compared to the dynamic equilibrium situation of the critical micelle concentration, where below, high quality mixtures can be achieved and above, saturation of the surface of the coarse particles results in decreasing mixture qualities. In respect to the percolation theory, it is proposed, that the critical fine particle concentration is identical to the percolation threshold p_c.

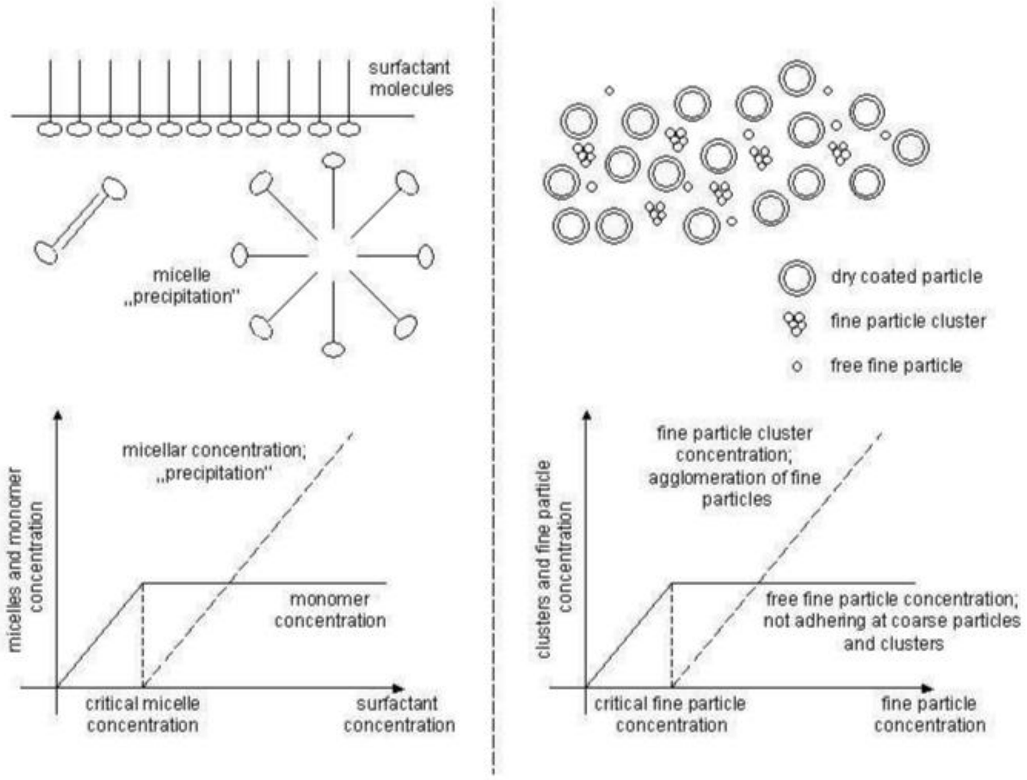


Figure 19: Comparison of the formation of micelles and fine particle clusters.

4. Experimental Section: Materials and Methods

As an overview, all used materials are listed in table 2. For visual monitoring as well as spectrophotometric studies, Methylene blue was applied as an active on coated particles, granules and in dry coating, respectively and was sieved through a 180µm sieve before characterization and mixing. Methylene blue (3, 4- Bis-(dimethylamino) phenothiazin- 5 - ium- chlorid) appears as dark green and lucent crystals highly soluble in water (1:25)[74].

Table 2: Overview of the applied substances.

substance	distributor	assignment
Methylene blue	Sigma Aldrich GmbH, Buchs, Switzerland	active for coating and dry coating
Glass pellets 1mm	B. Braun Biotech International GmbH, Melsungen, Germany	coating cores and carriers in dry coating
Lactose powder HMS	B. V. Hollandsche Melksuikerfabrik, Uitgeest, Netherlands	powder for granulation
Kollidon® K 30	BASF AG, Ludwigshafen, Germany	film former and binder
Glass pellets 0.4-0.6mm	Sartorius AG, Goettingen, Germany	carriers in dry coating
Glass pellets 0.25-0.3mm	Sartorius AG, Goettingen, Germany	carriers in dry coating
Cellets® 1000	Pharmatrans Sanaq AG, Basel, Switzerland	carriers in dry coating
Cellets® 350	Pharmatrans Sanaq AG, Basel, Switzerland	carriers in dry coating
Cellets® 200	Pharmatrans Sanaq AG, Basel, Switzerland	carriers in dry coating

Glass pellets 1mm were taken as cores for coated particles with Kollidon® K 30 (polyvinylpyrrolidon) as a film former. Lactose powder HMS was used for granulation to receive particles of 1000µm using a solution of diluted Kollidon® K 30 as a binder. The manufactured non- interactive particles were employed in the characterization of the new sampling apparatus.

Dry coating was performed using different carrier particles with similar shapes but different densities and surfaces. For these investigations, Glass pellets 1mm, Glass pellets 0.4-0.6mm and 0.25-0.3mm, microcrystalline cellulose pellets Cellets® 1000, Cellets® 350 and Cellets® 200 were used as carriers for Methylene blue.

4.1 Material Preparation and Characterization

4.1.1 Preparation of Non- Interactive Materials

4.1.1.1 Coating of Glass Pellets 1mm

To produce non- interactive binary mixing components, Glass pellets 1mm (leaned on the diameter) were coated in the Mini Glatt® fluidized bed coater (Glatt® GmbH, Binzen, Germany)(see table 3). A 10% (w/w) solution of diluted Kollidon® K 30 3% (w/w) of the final composition was used to coat 150g of the pellets. To receive blue particles, 2% (w/w) of Methylene blue was added to the coating suspension for identification by color. The obtained white and blue particles can be applied for mixing experiments.

Table 3: Coating process parameters for the Mini Glatt® fluidized bed coater.

settings	
process air pressure	0.25 bar
inlet temperature	50 - 55°C
product temperature	38 - 46°C
spray pressure	0.9 - 1.0 bar
pump rate	0.5 - 1 g/min

4.1.1.2 Production of Lactose Particles 1mm

Lactose powder HMS was granulated in the Strea 1 fluidized bed granulator (Aeromatic® AG, Berlin, Germany). To granulate 500g of the powder, a 20% (w/w) solution of diluted Kollidon® K 30 10% (w/w) of the final composition was used (see table 4). Additionally, 2% (w/w) Methylene blue was put into the granulation solution to receive blue particles whereas the received white and blue particles can be used for mixing experiments.

Table 4: Granulation process parameters for the Strea 1 fluidized bed granulator.

settings	
process air	2 m^3/min (maximum)
inlet temperature	20- 25°C
product temperature	25- 35°C
spray pressure	1 bar
pump rate	beginning 4-5g/min, later 12-13g/min

In order to achieve a narrow particle size distribution in the same range of approximately 1mm as the coated Glass pellets, the produced granular particles were fractionated for 5 minutes with a sieve tower using the fraction between sieves 1000 and 1400µm (Retsch GmbH, Haan, Germany) at amplitude 1mm and a frequency of 50Hz.

4.1.2 Characterization of Mixing Components

4.1.2.1 Storage

Methylene blue, Glass pellets 1mm (cores and coated particles white and blue), lactose particles white and blue 1mm, Glass pellets 0.4-0.6mm, 0.25-0.3mm, Cellets® 1000, Cellets® 350 and Cellets® 200 were stored for at least 7 days at 20-25°C and a relative humidity of 43% ± 5% over a sat urated solution of potassium carbonate (K_2CO_3, Haenseler AG, Herisau, Switzerland) before characterization or mixing [75]. Temperature and relative humidity were controlled with a hygrometer (HygroPalm 1 with Hygro Clip S, Rotronic AG, Bassersdorf, Switzerland) to avoid irregularities due to environmental influences.

4.1.2.2 Particle Size Measurements

Particle size distributions were measured by using a laser scattering based particle sizer (MasterSizer X Long Bed, Malvern Instruments, Worcestershire, UK) with a 1000mm range lens for dry measurements or a 300mm lens for wet measurements, respectively. The dry measurements were performed using the sample preparation unit (MSX64- Manual Dry Powder Feeder, Malvern Instruments, Worcestershire, UK). The sample preparation unit introduced an adequate amount of material (approximately 3 to 5g) with a dispersion of air pressure of 2bars into the air cell (sample cell), which has an active beam length of 10mm. This procedure was used for the Glass pellets 1mm (cores and coated particles white and blue), lactose particles white and blue 1mm, Glass pellets 0.4-0.6mm, 0.25-0.3mm, Cellets® 1000, Cellets® 350 and Cellets® 200.

Methylene blue was dispersed in diethyl ether (Fluka Chemie AG, Buchs, Switzerland) to perform the wet measurements. The MSX1 dispersion unit (MSX1-Small Volume Sample Preparation Unit, Malvern Instruments, Worcestershire, UK) pumped the dispersion through the circulating flow- through system including the sample cell, which has an active beam length of 2.4mm.

The software Mastersizer X v2.19 (Malvern Instruments, Worcestershire, UK) controlled the measurements and used the data collected to calculate the particle size distributions using the Fraunhofer scattering theory, which requires no assumptions of the particles optical properties. Derived parameters from the measurements were the mean diameter (from the volume distribution, D[4, 3]) and the median (D[v, 0.5]).

4.1.2.3 True Density

A gas displacement pycnometer AccuPyc 1330 (Micromeretics Instrument Corporation, Norcross, USA) was used to measure the true density of all mixing materials with a nominal cell volume of 10ml and helium as a gas. In order to achieve results with good accuracy, the sample volume was chosen to be at least 70% of the nominal cell volume for all used materials.

4.1.2.4 Hausner Ratio *H*

For the determination of the bulk and tapped density, an appropriate apparatus (Type STAV 2003, Engelsmann AG, Ludwigshafen, Germany) was used and the test conditions were held to the conditions according to the USP 28 NF 23 and the European pharmacopoeia 5. edition. The weight of the tested materials was in every case 100g and the used cylinder had a volume of 250ml (readable to 2ml). The experiments were performed by noting the volumes at the beginning (poured, V_0) and after tapping 2500 times (V_{2500}). The Hausner ratio H was then calculated according to equation (15) for Methylene blue, Glass pellets 1mm (cores and coated particles white and blue), lactose particles 1mm white and blue, Glass pellets 0.4-0.6mm, 0.25-0.3mm, Cellets® 1000, Cellets® 350 and Cellets® 200 [76].

$$H = \frac{\rho_t}{\rho_p} = \frac{V_0}{V_{2500}} \qquad \text{equation (15)}$$

where ρ_t tapped density
ρ_p poured density

4.1.2.5 Flowability

The experimental setup of the flowability measurements carried out is illustrated in figure 20.

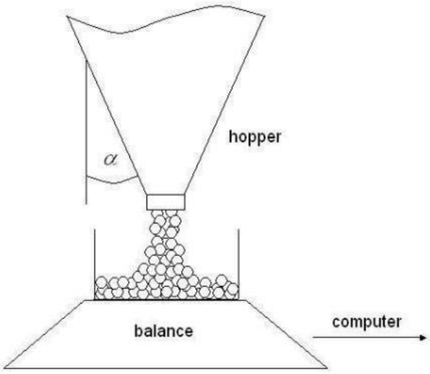


Figure 20: Experimental setup for the flowability measurements.

To investigate the influences of hopper shape and hopper material on the flow properties of the used materials, three different hoppers were tested. A regular pharmacopoeia hopper according to the European pharmacopoeia 5. edition, consisting of Plexiglas with a half centered angle of 17° (α), was compared with the two developed hopper inserts, one out of glass (Glastechnik Rahm, Muttenz, Switzerland), one out of stainless steel (Glatt® GmbH, Binzen, Germany), respectively. The sampling elements (glass and metal) were attached to the sampling bracket as shown in figure 19. The weight of 50g of the material discharged from the hoppers was recorded by a balance, which transmitted the data to a connected computer. The orifices of all used hoppers were 7mm. The measurements were performed with the Glass pellets 1mm (cores and coated particles white and blue), lactose particles 1mm white and blue, Glass pellets 0.4-0.6mm, 0.25-0.3mm, Cellets® 1000, Cellets® 350 and Cellets® 200.

4.1.2.6 Residual Moisture Content

The residual moisture content was determined gravimetrically by an infrared balance (Mettler Toledo Type LP 16M, Mettler Instruments, Naenikon- Uster, Switzerland). Samples of approximately 1g to 1.5g of all mixing materials were measured after storage (see chapter 4.1.2.1) for 20 minutes with a temperature of 105°C presenting the result as the loss of moisture in percent by weight.

4.1.2.7 Content

Additional characterization of the content after storage (see chapter 4.1.2.1) was performed for the blue non- interactive coated glass pellets 1mm and the blue lactose particles 1mm. Therefore, 10 samples of each batch were measured with the UV/Vis spectrometer Perkin Elmer Lambda 20 (Perkin Elmer, Schwerzenbach, Switzerland) with the corresponding software Perkin Elmer Lambda 20 UV- Winlab 2.8 (Perkin Elmer, Schwerzenbach, Switzerland). For the determination, 5 samples were balanced and 5 samples were prepared by balancing 100 particles. The measurements were carried out at 666.7nm for Methylene blue.

4.1.2.8 Scanning Electron Microscopy (SEM)

The shape and surface texture of Methylene blue, Glass pellets 1mm, Glass pellets 0.4-0.6mm, 0.25-0.3mm, Cellets® 1000, Cellets® 350 and Cellets® 200 were examined in a scanning electron microscope (Philips XL ESEM, Philips, Eindhoven, Netherlands). The samples were attached with carbon adhesive on aluminium stups, sputtered with 20nm of platinum (MED 020 Modular Coating Unit, BAL- TEC, Balzers, Principality of Liechtenstein) and photographed at an acceleration voltage between 5kV and 10kV.

4.2 Preparation of Mixtures and Sampling

4.2.1 Binary Mixture Preparation and Mixing

Non- interactive coated glass pellets 1mm white and blue and the lactose particles 1mm white and blue were used to manufacture binary mixtures to compare the discharge from a regular pharmacopoeia hopper with the two developed and constructed hopper inserts in flowability profiles. Therefore, the Plexiglas hopper was installed in a rack and locked with a metal plate. The sampling glass or metal elements were assembled without the cap to the sampling bracket, locked by the flexible sealing arm. With different ratios 50, 1 and 0.1% (w/w) of blue diluted in white particles and different experimental setups (sequence of charging) the discharge of the non-interactive materials from the above- mentioned hoppers were analyzed in respect to the mixing quality. Particles were balanced according to the dilution ratio and poured directly into the hoppers in regard of not having more than 50% of filling volume inside the sampling equipments (possibility of changing the hopper and mixing inserts). The inserted amount of material was 20g for the coated glass pellets 1mm mixtures, for the lactose granulate particles 1mm 10g, respectively.

Handling experiments were also executed with the non- interactive materials mentioned above and with the same amounts of material. Particles for mixtures in the Plexiglas hopper were balanced and put inside a 50ml mixing glass vessel dependent on the sequence of charging. Material used for the experiments with the developed mixing parts were balanced and poured inside the glass or metal body part equipped with the corresponding carrier and the cap. Subsequently, the glass or metal mixing elements were assembled by mounting the mixing inserts with the carrier to the corresponding body parts as shown in figure 21.

Figure 21: Example of the assembled metal mixing ®

The mixing glass vessel (cap upwards), the glass or metal mixing element (cap downwards) including the mixtures of ratios 50, 1 and 0.1% (w/w) of blue and white particles were inserted in a Turbula® Type T2C mixer (W. Bachofen, Basel, Switzerland) and immediately removed. To analyze the handling effects using the mixing glass vessel, the Plexiglas hopper with the orifice upward was put on top of the opened mixing glass vessel, quickly turned 180° and installed in a rack on the track. After removing the mixing elements out of the Turbula®, the mixing inserts were exchanged with the hopper inserts including the hopper insert carrier. The assembled sampling glass or metal elements were also turned quickly 180° and mounted to the sampling bracket on the track.

In order to evaluate the new sampling equipment by comparing the received results to the calculations based on the common mixing theory, the non- interactive materials coated glass pellets 1mm white and blue and the lactose particles 1mm white and blue were employed to establish mixing kinetics with the Turbula®. The preparation of the mixtures followed the same procedure as described above by assembling the glass or metal mixing elements after balancing the white followed by the blue particles inside the corresponding body parts. Mixing was processed for different mixing times with a Turbula® speed of 21 rounds per minute (rpm) using 20g of coated glass pellets 1mm white and blue and 10g of lactose particles 1mm white and blue each as 50% (w/w) mixtures. Exchange of the mixing element with the sampling element and subsequent handling followed the same procedure as described above.

Dry coated mixtures were produced using Methylene blue and Glass pellets 1mm, 0.4-0.6mm, 0.25-0.3mm, Cellets® 1000, 350 and 200 as carrier particles. At first, experiments were set up to ascertain differences between the glass and metal mixing elements producing mixtures using 0.1% (w/w) of Methylene blue to stay clearly below the saturation concentration and Glass pellets 1mm in the Turbula® at a speed of 21 rpm. Mixing was processed for different times to obtain mixing kinetics. Ideal mixing time experiments and experiments to find the surface saturation concentration of Methylene blue were prepared according to the description above. Methylene blue was used in a 0.1% (w/w) concentration to find the ideal mixing time for all carrier materials in the Turbula® at a speed of 21 rpm. Different concentration levels of Methylene blue were applied in mixtures to find the saturation concentration of all carrier materials at the determined ideal mixing time. The total mixture weight for the Glass pellets 1mm and 0.25-0.3mm was 20g, for the Glass pellets 0.4-0.6mm, the Cellets® 1000, 350 and 200 15g, respectively. Depending on the experiment, some mixtures used for the saturation experiments were sieved using a sieve tower with sieves 180 and 90µm (Retsch GmbH, Haan, Germany) for 1 minute at an amplitude 1mm and a frequency of 50Hz. After mixing, the preparation for sampling followed the description above.

4.2.2 Sampling

Sampling of all mixture preparations described above was executed equally. The locked Plexiglas hopper in the rack, the sampling glass or sampling metal element including the sampling bracket was placed on the track. At the end of the track, the sampling train with 32 sampling vessels was in its starting position. The sampling train was connected with a wire to a motor (Heidolph Type RZL 50L) with a coil (diameter 8cm). By launching the motor, the coil winded up the wire connected to the sampling train, which started the sampling procedure. The orifice of the Plexiglas hopper was unlocked manually as soon as the first funnel compartment was below the orifice. The orifices of the glass or metal hopper inserts were unlocked as soon as the flexible sealing arm stroke the rail and started the sampling automatically. During the discharge of the mixtures from the hoppers, the sampling train divided the whole mixtures into samples, which were collected inside the sampling vessels. The speed of the motor was adjusted to the flowability and weight of the produced mixtures in respect of receiving at least 25 samples (table 5).

Table 5: Motor speeds and total mixture weight.

	motor speed [rpm]	total mixture weight [g]
coated glass pellets 1mm	83	20
lactose particles 1mm	51	10
Glass pellets 1mm	83	20
Glass pellets 0.4-0.6mm	127	15
Glass pellets 0.25-0.3mm	94	20
Cellets® 1000	44	15
Cellets® 350	69	15
Cellets® 200	83	15

Further specifications of the mixing and sampling equipment and the sampling apparatus can be found in Appendix A.

4.3 Characterization of Mixtures and Mixing Processes

4.3.1 Mixture Contents and Mixing Process Evaluations

All contents and process evaluations of mixing are summarized in figure 22.

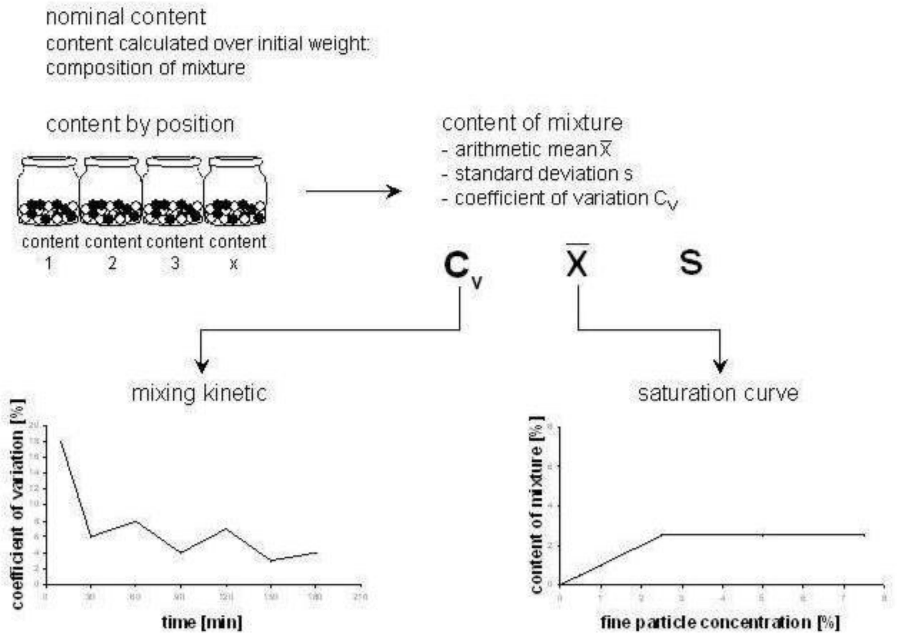


Figure 22: Description of all measured and calculated contents and mixing process evaluations.

To measure the content of each collected sample, the particles inside the sampling vessels were balanced according to their appearance in the sampling train beginning with the first, transferred separately into appropriate flasks and dissolved in water. Following the sequence of sampling vessels, the content by position of Methylene blue was subsequently measured using the UV/Vis spectrometer Perkin Elmer Lambda 20 (Perkin Elmer, Schwerzenbach, Switzerland) with the corresponding software Perkin Elmer Lambda 20 UV- Winlab 2.8 (Perkin Elmer, Schwerzenbach, Switzerland). The measurement of the content by position was performed for all mixtures using the wavelength 666.7nm for Methylene blue.

To receive the contents of the mixtures, the arithmetic mean, standard deviation and coefficient of variation ({standard deviation/mean}⊙ 100%) was calculated from the content by position measurements to obtain a declaration of the quality of the mixture. Calculations of the respective parameters followed equations (10) and (11).

The coefficient of variation C_V of non- interactive and dry coated mixtures was used to estimate the ideal mixing times by the received mixing kinetics. Using the content of mixtures of different nominal content concentrations, saturation curves of different dry coated carrier particles were established to find the saturation concentrations for the distinct carrier materials.

4.3.2 Weight Balance

For process monitoring and additional knowledge about the disposition of Methylene blue during the production of dry coated particles, the residual amount of Methylene blue on the glass or metal body part, corresponding mixing and hopper inserts were measured by rinsing the parts with water. The maintained Methylene blue solutions were quantified with the UV/Vis spectrometer Perkin Elmer Lambda 20 (Perkin Elmer, Schwerzenbach, Switzerland) with the corresponding software Perkin Elmer Lambda 20 UV- Winlab 2.8 (Perkin Elmer, Schwerzenbach, Switzerland) at 666.7nm. The obtained value is defined as hopper content. In order to receive weight balances for mixing kinetics, the converted amount of the contents of mixtures and the hopper contents were calculated in respect of the initially applied amount of Methylene blue (in % of initial Methylene blue weight in %).

During the production of mixtures used to evaluate the saturation concentrations of different carrier particles in dry coated mixing, several mixtures were sieved prior to the content analysis. The sieves used to remove fines were also rinsed whereas the maintained Methylene blue solutions were quantified resulting in a value defined as sieve content. The weight balances were assembled by using the converted amounts of the contents of mixtures, the hopper contents (received by the procedure described above) and the sieve contents. By adding the amounts, the received sum can be compared to the initially applied amount of Methylene blue.

4.3.3 Dissolution

Samples of approximately 1g of dry coated particles were taken to investigate the dissolution and stability of Methylene blue from different carrier particles. The dissolution was performed using a dissolution apparatus (Sotax AT7, Sotax AG, Basel, Switzerland) equipped with paddles. The paddle speed was set to a constant speed of 100 rpm. As dissolution medium, 500 ml distilled water at 24°C ± 2°C was applied, if not other mentioned. After inserting the samples of dry coated mixtures samples, 10 ml of dissolution medium was removed after 0.25, 1, 2.5, 5, 15, 30, 60 and 120 minutes and instantly substituted with medium to obtain the primary medium volume. The concentration of Methylene blue was quantified with the UV/Vis spectrometer Perkin Elmer Lambda 20 (Perkin Elmer, Schwerzenbach, Switzerland) with the corresponding software Perkin Elmer Lambda 20 UV- Winlab 2.8 (Perkin Elmer, Schwerzenbach, Switzerland) at 666.7nm. Sink conditions (drug concentration in the medium below 10% of the solubility) were maintained throughout the entire experiment.

4.3.4 Mechanical Stability Test

Mechanical stability tests were enforced to evaluate the mechanical strength of the interaction between carrier particles and Methylene blue after the dry coated mixing process. Therefore, a sieve tower (Retsch GmbH, Haan, Germany) was used at agitation amplitudes 1 (weakest), 2 and 3mm (strongest) assembled with a bottom plate to collect not adhering Methylene blue and the sieves 90, 250µm and 8 more sieves to gain weight to reach all amplitudes. 2g of coated glass pellets 1mm blue (standard), 0.1% (w/w) dry coated mixtures of Methylene blue with Glass pellets

1mm, 0.4-0.6mm, 0.25-0.3mm, Cellets® 1000, 350 and 200 were put on the 90µm and agitated for 1 hour at a frequency of 50Hz. Afterwards, the bottom plate and the 3 bottom sieves were rinsed carefully with distilled water. The collected solution of Methylene blue was quantified with the UV/Vis spectrometer Perkin Elmer Lambda 20 (Perkin Elmer, Schwerzenbach, Switzerland) with the corresponding software Perkin Elmer Lambda 20 UV- Winlab 2.8 (Perkin Elmer, Schwerzenbach, Switzerland) at 666.7nm.

4.1.5 Scanning Electron Microscopy (SEM)

Samples of all dry coated mixture particles and coated glass pellets 1mm blue were prepared and examined according to the procedure described in chapter 4.1.2.8.

5. Results and Discussion

5.1 Evaluation of the Mixing and Sampling System

The investigation of the qualities of mixtures using the developed and constructed sampling apparatus and mixing equipment must follow a procedure as simple, short and reliable as possible in order to disallow structural disturbances of the mixtures and without affecting the results. After balancing and filling the mixing components inside the mixing equipment and charging the Turbula®, the actual mixing process takes place before removing the mixtures from the mixer followed by prearrangement of sampling, sampling and analysis of the samples and can be considered as a sequential processing system as shown in figure 23.

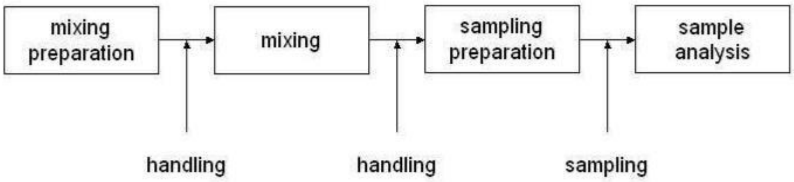


Figure 23: Illustration of the sampling and mixing system procedure.

Certain parts of the system can be regarded separately and must be analyzed in respect of their impact upon the system and the emerging results, such as influences of the analysis and sampling method and impact of handling and mixing.

5.1.1 Influence of the Analysis and Sampling Method

5.1.1.1 Accuracy of Sample Analysis

According to equation (13), the accuracy of the sample analysis s_a^2 can be estimated separately to evaluate its influence on experimentally measured mixing results. Therefore, 30 samples in total from six aqueous stock solutions each measured five times from accurately weighted Methylene blue after storage were examined with the UV/Vis spectrometer. To determine the value of s_a, the coefficients of variation calculated from the standard deviations of the analyzed samples were summarized resulting in a mean of 0.6614% ± 0.1052%. Therefore, the value for s_a^2 is 0.44%, which can be considered negligible like similar slightly higher values found in the past [22, 61].

5.1.1.2 Impact of Sampling on the Quality of Mixtures

The developed sampling method and corresponding equipment follows the «Golden Rules of Sampling», which means the quality of sampling is dependent on flowability. Figure 24 displays the developed and constructed sampling equipment for the powder mixtures and the additional developed and constructed mixing devices for the Turbula® including the corresponding carriers.

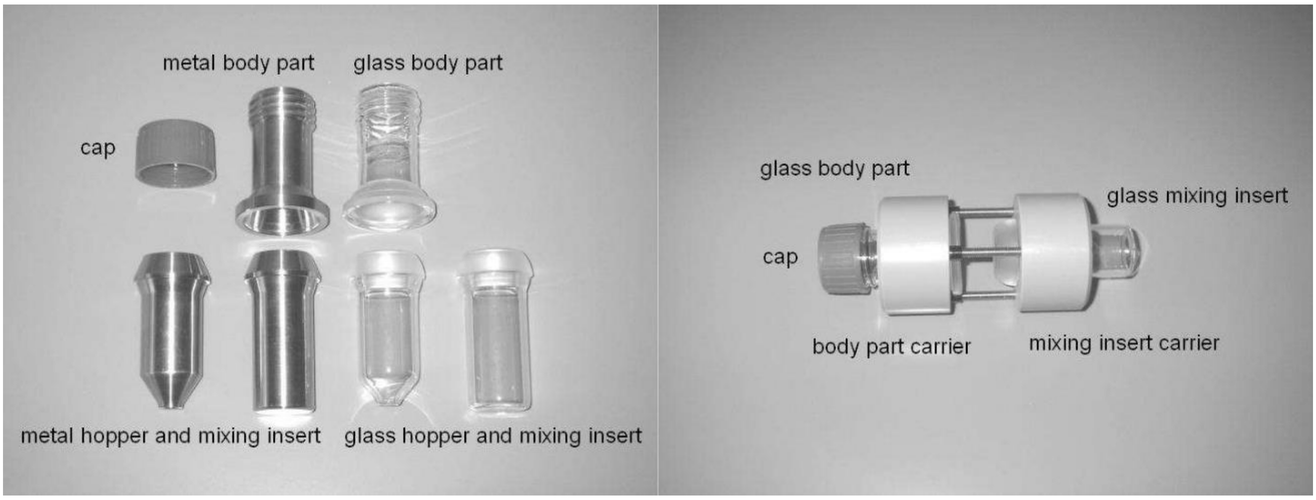


Figure 24: Sample and mixing devices without (left) and with corresponding carriers for sampling and mixing in the Turbula® (right).

For the investigations, the glass or metal body parts with the corresponding hopper inserts were assembled with the body part and the hopper insert carrier and mounted to the sampling bracket as depicted in figure 25 (left) without the cap. Additionally, figure 25 shows the developed and constructed sampling train with the sampling vessels. To have as less influence on the structural appearance of mixtures due to flowability as possible, mass flow is desired and can be analyzed in the linear content by position measured with the UV/Vis spectrometer of vertical discharged unmixed mixtures divided in the sampling vessels. In order to compare a standard Plexiglas hopper with the developed sampling elements of different shape and material (glass, metal), different sampling setups by means of sequence of charging may be used to evaluate qualitatively and quantitatively the sampling error s_S^2 of equation (13).

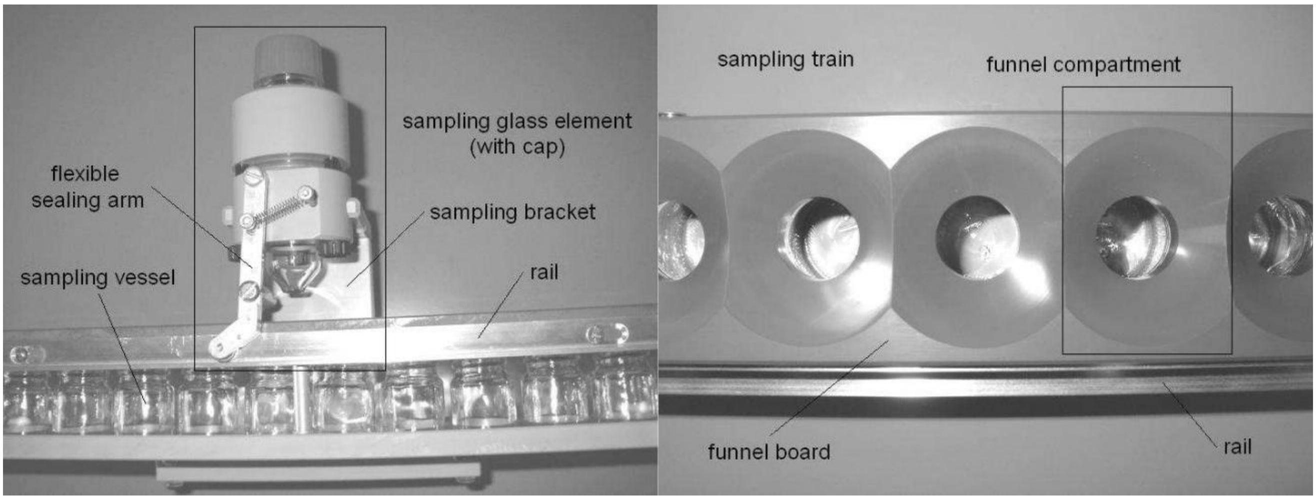


Figure 25: Illustrations of the sampling element and the sampling train.

The investigation of flowability and its impact on sampling was performed utilizing materials, which do not interact among each other and the equipment to have flowability only as a possible disturbance of the mixtures. Table 6 displays the properties of the experimentally applied coated glass pellets 1mm and lactose particles 1mm white and blue after storage.

Table 6: Properties of coated glass pellets 1mm and lactose particles 1mm.

	coated glass pellets 1mm		lactose particles 1mm	
	white	blue	white	blue
particle size [m](n = 5)				
- mean	1278.3 ± 10.9	1252.9 ± 19.1	1292.0 ± 11.8	1282.0 ± 37.3
- median	1237.7 ± 11.1	1235.2 ± 8.4	1262.3 ± 15.8	1262.6 ± 34.7
true density [g/cm^3] (n = 5)	2.3689 ± 0.0016	2.4013 ± 0.0145	1.4993 ± 0.0013	1.5012 ± 0.0026
Hausner ratio *H* (n = 3)	1.01 ± 0.02	1.04 ± 0.01	1.06 ± 0.01	1.07 ± 0.01
flowability [g/s](n = 5)				
- Plexiglas hopper	7.08 ± 0.03	6.60 ± 0.08	2.06 ± 0.03	2.00 ± 0.14
- glass element*	7.61 ± 0.09	7.16 ± 0.04	2.51 ± 0.04	2.32 ± 0.15
- metal element*	6.52 ± 0.02	6.07 ± 0.06	1.95 ± 0.02	1.79 ± 0.12
residual moisture content [%](n = 5)	0.98 ± 0.13	1.05 ± 0.09	2.44 ± 0.12	2.36 ± 0.24
content [%](n = 10)	-	0.7461 ± 0.0985	-	1.0400 ± 0.0448

* abbreviation for sampling glass or sampling metal element

The properties of the spherical coated glass pellets 1mm and non- spherical lactose particles 1mm white and blue mixture components demonstrate only small differences in particle sizes, densities and particle size distributions (see figure 26), which will result in reduced demixing tendency or segregation. Additionally, the particle sizes are distributed in a small range where the produced particles can be regarded as monosized.

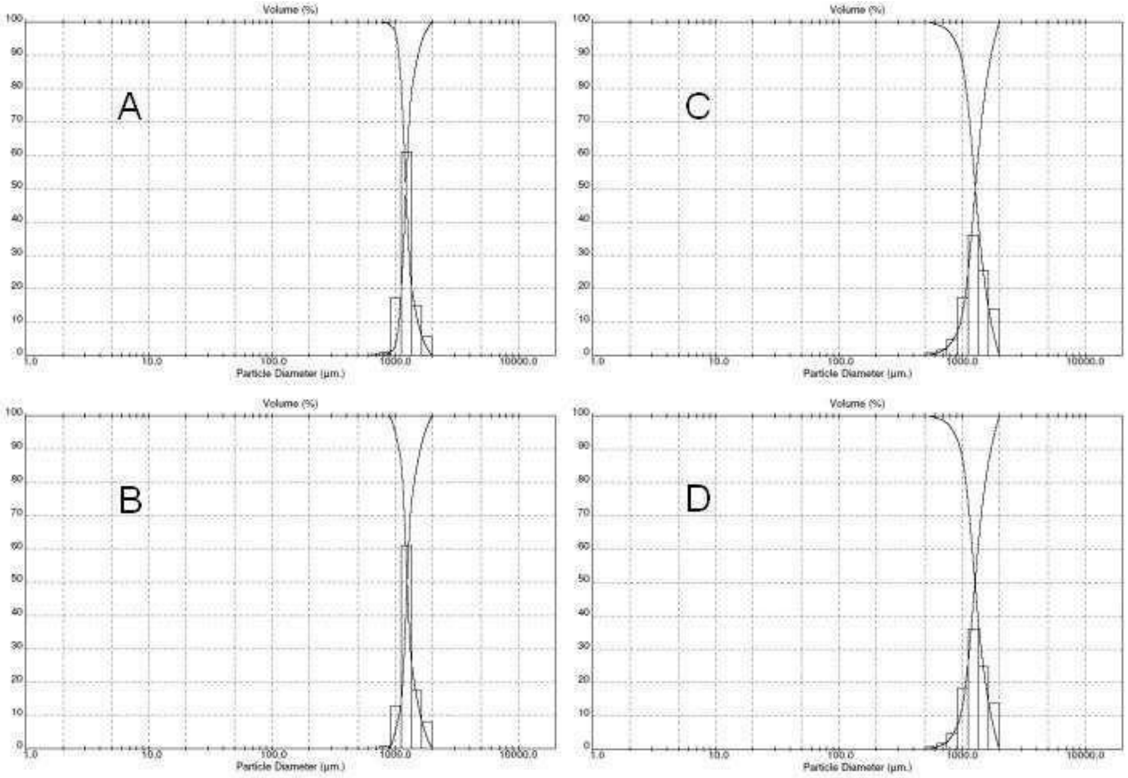


Figure 26: Examples pf particle size distributions of produced non- interactive particles glass pellets 1mm white (A) and blue (B) and lactose particles 1mm white (C) and blue (D).

Also, only small differences of the Hausner ratio *H* between the white and blue particles as mixture components show dense packing before and after mechanical treatment disallowing segregation, having robust handling mixtures and resulting in good flowability [77]. As requested, the regular patterns of flowability display small differences of all used equipments for all components as well, where it can be summarized, that particle size, shape and density play a more important role on demixing or segregation than flowability [16, 39, 41, 43]. The influence of the hopper material is shown as material surface dependent, where the sampling glass element performs fastest discharge having a rather smooth surface and the sampling metal element the slowest for all cases. The similar measurements of the residual moisture contents evidence no stickiness of moist particles retarding sampling due to particle agglomeration or adherence to the equipment. The content of the respective blue mixing components is needed to calculate nominal contents based on the weight ratios of total mixture weights. Differences between the two particle types coated glass pellets 1mm and lactose particles 1mm can only be found on shape, surface, density and flowability, where the lactose particles discharge less fast than coated glass pellets due to their properties.

Using the above- presented particles for mixtures only varying in color with marginal demixing or segregation tendencies, mixtures were prepared in different weight ratios 1:2, 1:10 and 1:100 of blue diluted in white particles to gain knowledge about the qualitative sampling effect by the degree of mass or core flow with increasing dilutions. The Plexiglas hopper mounted in the rack, the sampling glass or metal element mounted to the sampling bracket was placed on the sampling track before filling the mixtures inside the sampling equipment. The sequence of charging the sampling equipment nominating the material primarily introduced and therefore discharged first can be divided into blue- white (bw), white- blue (wb) random, wb eccentric and wb centric patterns as depicted in figure 27. For sampling, the total mass of the mixtures were determined in respect of the 50% total filling volume of the developed sampling equipment in order to allow the exchange of mixing to sampling parts without material losses. The total mixture weight, coated glass pellets 1mm mixtures of 20g and lactose particles 1mm mixtures 10g, was sampled to obtain at least 25 samples.

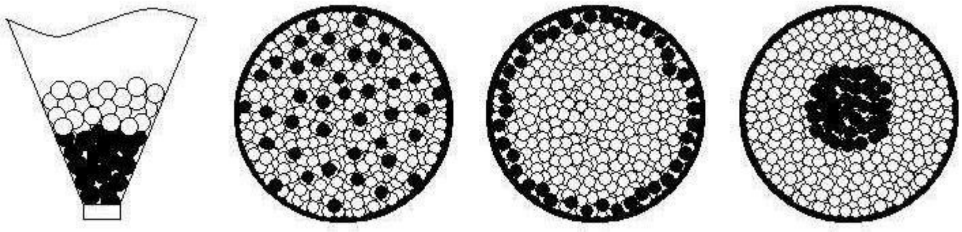


Figure 27: From left to right: longitudinal section through a hopper illustrating the charge of blue followed by white, cross sections of charging white followed by random, eccentric and centric arrangement of blue particles.

When charging the sampling equipment with blue particles first, a certain low quality of mixture level represented by the coefficient of variation should be reached and can be considered as a standard level. In general, receiving high values for coefficients of variation means less mixing effects due to flowability and therefore better sampling. For the case of mass flow, similar values of these qualities should be expected when charging white followed by blue particles, especially in the cases of eccentric and centric arrangements. Also, the flowability profiles received when displaying the contents of samples as a function of the sample position should appear similarly for all sequence of charging patterns.

The content of mixture of two mixtures prepared in the Plexiglas hopper with coated glass pellets 1mm bw and wb random diluted 1:2 with a nominal content of 0.3162% is shown in figure 28. The contents of the two mixtures derived from equations (10) and (11) are 0.2912% ± 0.2869% (w/w) for the bw and 0.3088% ± 0.2845% (w/w) for the wb random mixture resulting in coefficients of variation of 98.5% and 92.1% respectively, whereas the mean shown in figure 28 is derived from the mean of the contents of the two mixtures.

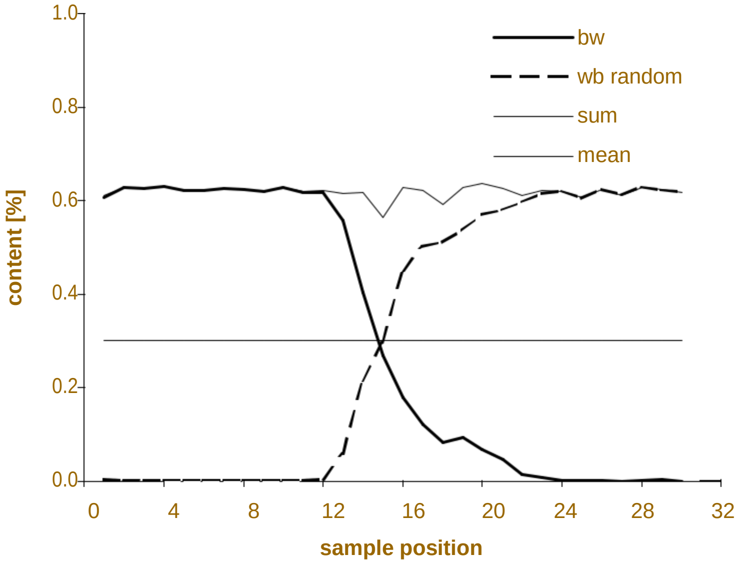


Figure 28: Flowability profile of mixtures of glass pellets 1mm charged bw and wb random in the Plexiglas hopper.

At the beginning of discharging charged bw particles, high contents by position around 0.61% (w/w) are obtained from sample positions 1 to 12 by having only blue particles inside the sample vessels. Followed by a fast increase of appearing white particles in the sample vessels, the contents by position are reduced from sample positions 13 to 23 whereas after position 23, no blue particles can be found inside the sample vessels obtaining no contents. By sampling the wb random mixture, only white particles appear in the sample vessels from sample positions 1 to 12 followed by a subsequent increase of blue particles with the corresponding contents by position from sample positions 13 to 30, whereas no white particles can be found after sample position 24 with contents around 0.61% (w/w). The similar curves of both mixtures are reflected in the similar coefficients of variation of the two prepared mixtures conformed by the fairly linear sum curve of added contents of mixture and the similar maximum levels of contents by position.

Table 7 shows all coefficients of variation for mixtures prepared in the Plexiglas hopper, the sampling glass and metal elements and all sequences of charging of the glass pellets 1mm and lactose particles 1mm mixtures.

Table 7: Coefficients of variation [%] for sampled mixtures.

mixtures*	bw		wb random		wb eccentric		wb centric	
	glass	lactose	glass	lactose	glass	lactose	glass	lactose
Plexiglas hopper								
- 1:2	98.5	87.0	92.1	89.9	-	-	-	-
- 1:10	281.3	263.6	166.1	162.9	193.1	200.5	156.6	144.3
- 1:100	520.6	457.7	210.7	209.3	340.2	236.7	209.8	243.8
glass element**								
- 1:2	85.3	66.9	89.5	69.4	-	-	-	-
- 1:10	217.3	186.7	169.5	171.8	179.9	171.5	127.7	158.2
- 1:100	511.4	514.3	223.8	163.9	281.8	216.4	286.3	279.5
metal element**								
- 1:2	90.6	79.2	88.5	84.6	-	-	-	-
- 1:10	240.1	218.6	184.8	193.5	201.7	195.4	137.8	164.6
- 1:100	548.6	569.7	245.4	236.5	265.6	279.2	227.7	294.2

* mixture abbreviation: glass for coated glass pellets 1mm mixtures and lactose for lactose particles 1mm mixtures

** abbreviation for sampling glass or sampling metal element

As predicted, the increase of the dilution rates from 1:2 to 1:100 increases the coefficients of variation for all mixtures in all sampling equipments due to the decreasing number of blue particles according to table 8, whereas mixtures prepared in the 1:2 ratios show similar coefficients of variation and flowability profiles regardless of charging bw or wb for both materials caused by the high number of blue particles per mixture.

Table 8: Calculation of number of blue particles per mixture.

mixtures	total mixture weight [g]	weight of 1 particle* [g]	total number of particles -	number of blue particles per mixture -
glass pellets 1mm				
- 1:2	20	$2.53 \cdot 10^{-3}$	7900	3950
- 1:10	20	$2.53 \cdot 10^{-3}$	7900	790
- 1:100	20	$2.53 \cdot 10^{-3}$	7900	79
lactose particles 1mm				
- 1:2	10	$1.67 \cdot 10^{-3}$	5971	2986
- 1:10	10	$1.67 \cdot 10^{-3}$	5971	597
- 1:100	10	$1.67 \cdot 10^{-3}$	5971	60

* calculated according to equation (5)

Regarding the higher dilutions of 1:10 and 1:100, the discharge of blue particles charged bw results in a small number of sample positions at first with high corresponding contents by position and fast decreasing contents down to 0% (w/w). In case of charging wb, the blue particles appear towards the end of the sampling train but without obtaining the same maximum content by position levels as received in the bw arrangement, which is reflected in lower coefficient of variation levels. Two examples of summarized flowability profiles 1:10 dilutions of mixtures sampled with the sampling glass element using glass pellets 1mm mixtures and the sampling metal element discharging lactose particles 1mm mixtures are depicted in figure 29. The reduction of the coefficients of variation of bw compared to wb arrangements can additionally be seen in the 1:100 dilutions for both materials, where the number of blue particles is reduced once more.

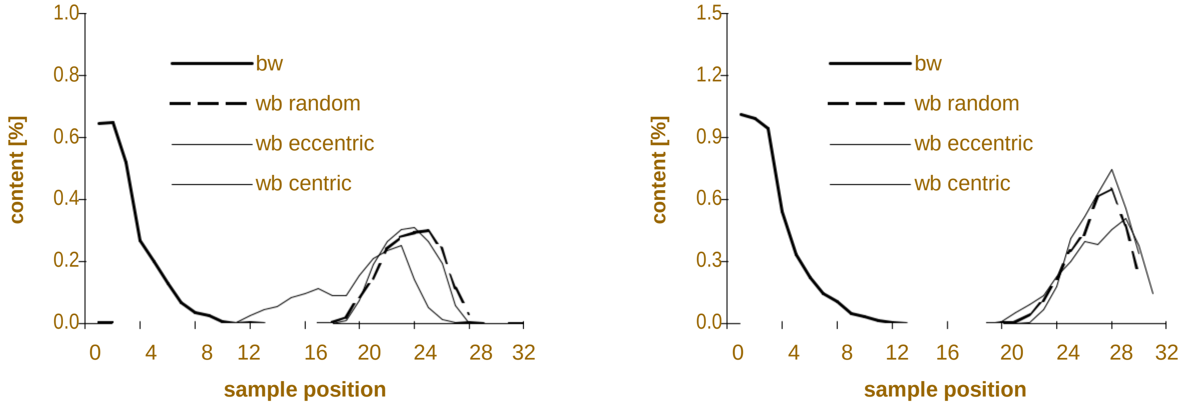


Figure 29: Examples of summarized flowability profiles of left: discharging glass pellets 1mm mixtures diluted 1:10 from the sampling glass element and right: lactose particle 1mm mixtures 1:10 from the sampling metal element.

Flowability profiles exemplarily displayed in figure 30 using the sampling glass element and the Plexiglas hopper as sampling equipment show the decreasing number of sample positions containing blue particles with the corresponding contents by position. The difference between the bw and wb arrangements is shown to be more obvious by the increasing number of sampling vessels containing blue particles in the wb arrangements compared to the bw filling patterns.

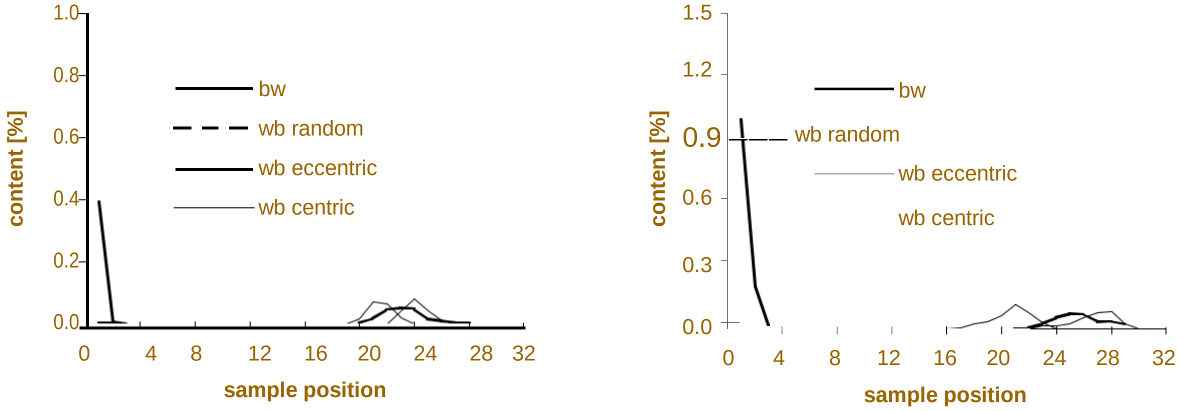


Figure 30: Examples of summarized flowability profiles of left: discharging glass pellets 1mm mixtures diluted 1:100 from the sampling glass element and right: lactose particle 1mm mixtures 1:100 from the Plexiglas hopper.

In case of the required mass flow to avoid structural disturbance of the mixtures, the wb eccentric and centric arrangement of 1:10 and 1:100 dilutions should result in similar values of the coefficients of variation and appearance of the flowability profiles. Figures 29 and 30 underline accurately the differences of the coefficients of variation for all sampling equipments by the eccentric and centric arrangements for both materials by displaying higher numbers of sample vessels including blue particles than bw and differences in the positions of the aforementioned arrangements at the rear end of the flowability profiles. So far, the shown results display only a qualitative approximation of the influence of flowability on mixture qualities, where a value for s_S^2 cannot be estimated quantitatively. Corresponding flowability profiles of all mixtures sampled can be found in Appendix B.

The materials applied as unmixed mixtures in the Plexiglas hopper, sampling glass and metal elements for the evaluation of the sampling error s_S^2 show all similar coefficients of variation and flowability profiles, independent of dilution ratios and sequence of charging. The predictions of increasing dilution rates leading to higher coefficients of variation can be confirmed due to the lower numbers of blue particles per mixture and the size of used particles. Regarding the flowability profiles, it can be concluded that the developed sampling glass and metal elements show similar properties as a standard pharmacopoeia hopper all tending to core flow with the respective materials rather than the desired mass flow. Additionally it must be concluded, that the discharge velocity of the different sampling equipment materials (Plexiglas, glass, metal) has no influence on the qualities of mixtures with the used materials where no hopper shows superior properties. Furthermore, the preferable sequence of charging for intended experimental work has to be blue followed by white particles whereas the blue particles are not given enough time during the discharge from the sampling equipment for mixing. A quantitative estimation of the sampling error s_S^2 of the developed sampling equipment remains difficult and it can be assumed, that the sampling error according to equation (13) can be neglected as it has been done in the past [22, 61]. The results support the image of unmixed mixtures tending towards a complete random mixture quality. The introduction of a small amount of energy to the system in form of flowability leads already to a large increase of the entropy, as shown by the reductions of the coefficients of variation. Thereby, the increase of mixture qualities caused by charging white followed by blue particles giving the latter more time for mixing during the discharge shows similar outcomes to results of past investigations with diffusive motionless mixers [78, 79].

5.1.2 Mixing of Non- Interactive Material

5.1.2.1 Impact of Handling on the Quality of Mixtures

At certain steps during the sequential procedure of mixing and sampling, handling operations are required, which can be investigated separately on their impact on mixture qualities. The steps include careful mixture preparation by balancing and pouring the components in the mixing equipment, charging the Turbula® with the mixing equipment followed by removal after mixing, sampling preparation and sample analysis. In order to reduce handling operations and increase reproducibility before and after mixing, mixing devices displayed in figure 24 were additionally developed. The sampling preparation has to be carried out in order to change from mixing to sampling equipment and includes one 180° turn of the mixtures inside the sampling equipment, where turning the mixtures 180° can be regarded as a single convective mixing step. To finish, the sampling equipment has to be attached to the corresponding sampling racks dependent on the applied sampling equipment on the sampling track before sampling and sample analysis. The procedure can be run through without the actual mixing process to evaluate the influence of handling on mixture qualities. Theoretically, the impact of handling should result in qualities of mixtures and flowability profiles similar to the results obtained in the investigation of the sampling procedure at best or at least in a small difference, which would mean rather high coefficients of variation demonstrating small handling influence.

For the investigation, the above characterized non- interactive materials coated glass pellets 1mm and lactose particles 1mm white and blue (see table 6 and figure 26) were used by applying the same total mixture weights of 20 or 10g, respectively. Directed from the conclusions of the impact of sampling, the favorite sequence of charging mixture components for sampling is blue followed by white particles. The sequence of charging the mixing equipment must therefore be inverse in order to retrieve the blue- white particle arrangement after turning the mixtures 180°. To evaluate the influence of handling and com paring the results to the values of the sampling evaluation, dilutions of 1:2, 1:10 and 1:100 were prepared and analyzed for all mixing and sampling equipments. The flowability profiles of two mixtures diluted 1:2 of coated glass pellets 1mm handled in the 50ml mixing glass vessel and sampled with the Plexiglass hopper and lactose particles 1mm handled with the metal mixing element and sampled with the sampling metal element are shown in figure 31 with nominal contents of 0.3986% (w/w) and 0.5061% (w/w), respectively.

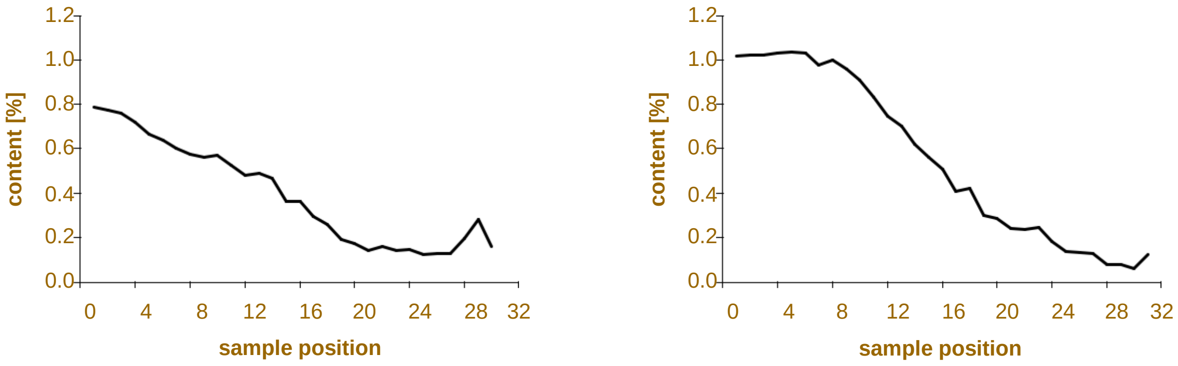


Figure 31: Examples of flowability profiles of mixtures using (left) coated glass pellets 1mm sampled with the Plexiglas hopper ratio 1:2 and (right) lactose particles 1mm sampled with the metal mixing element ratio 1:2.

According to equations (10) and (11), the contents of mixture are 0.3964% ± 0.2296% (w/w) for the coated glass pellets 1mm mixture and 0.5501% ± 0.3626% (w/w) for the lactose particles 1mm mixture resulting in coefficients of variation of 57.9% and 67.7%. The flowability profiles reflect that in all sampling vessels, blue particles can be found from sample position 1 to the last of both materials operated in both mixing and sampling equipments without massive difference. In the higher dilution rates, the results can be confirmed as exemplary displayed in figure 32.

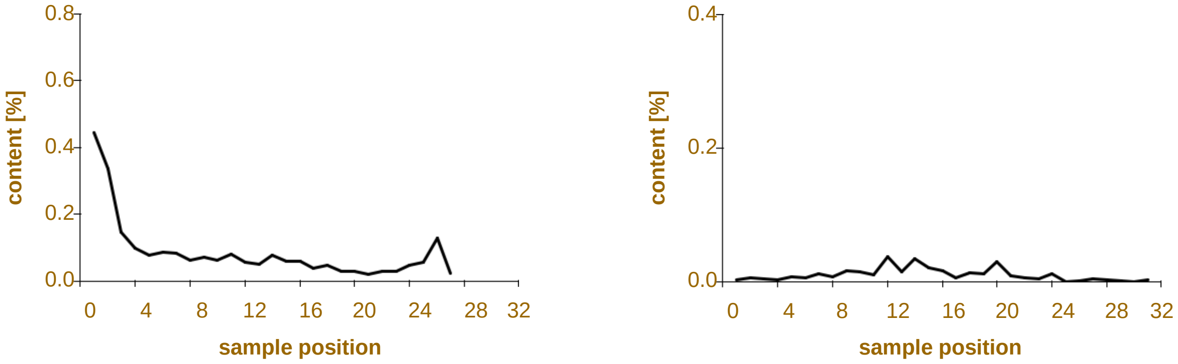


Figure 32: Examples of flowability profiles of mixtures using (left) coated glass pellets 1mm sampled with sampling glass element ratio 1:10 and (right) lactose particles 1mm sampled with the metal mixing element ratio 1:100.

The shown example of coated glass pellets 1mm mixture diluted 1:10 handled with the mixing and sampling glass equipment feature a nominal content of 0.0797% (w/w) and results in a content of mixture of 0.0861% ± 0.0941% (w/w) and a coefficient of variation of 109.3% after sampling and sample analysis. The nominal content of the lactose particles 1mm mixture 1:100 operated with the metal mixing and sampling equipment is determined 0.0102% (w/w) and shows a content of mixture of 0.0098% ± 0.0096% (w/w) and a coefficient of variation of 97.8%. Further flowability profiles of all mixtures operated with the three mixing and sampling equipments are presented in Appendix C.

A summary of coefficients of variation for both mixture materials operated with the 50ml mixing glass vessel, metal and glass mixing elements and the corresponding sampling equipment are shown in figure 33 compared to the unmixed mixture qualities of bw- arrangements.

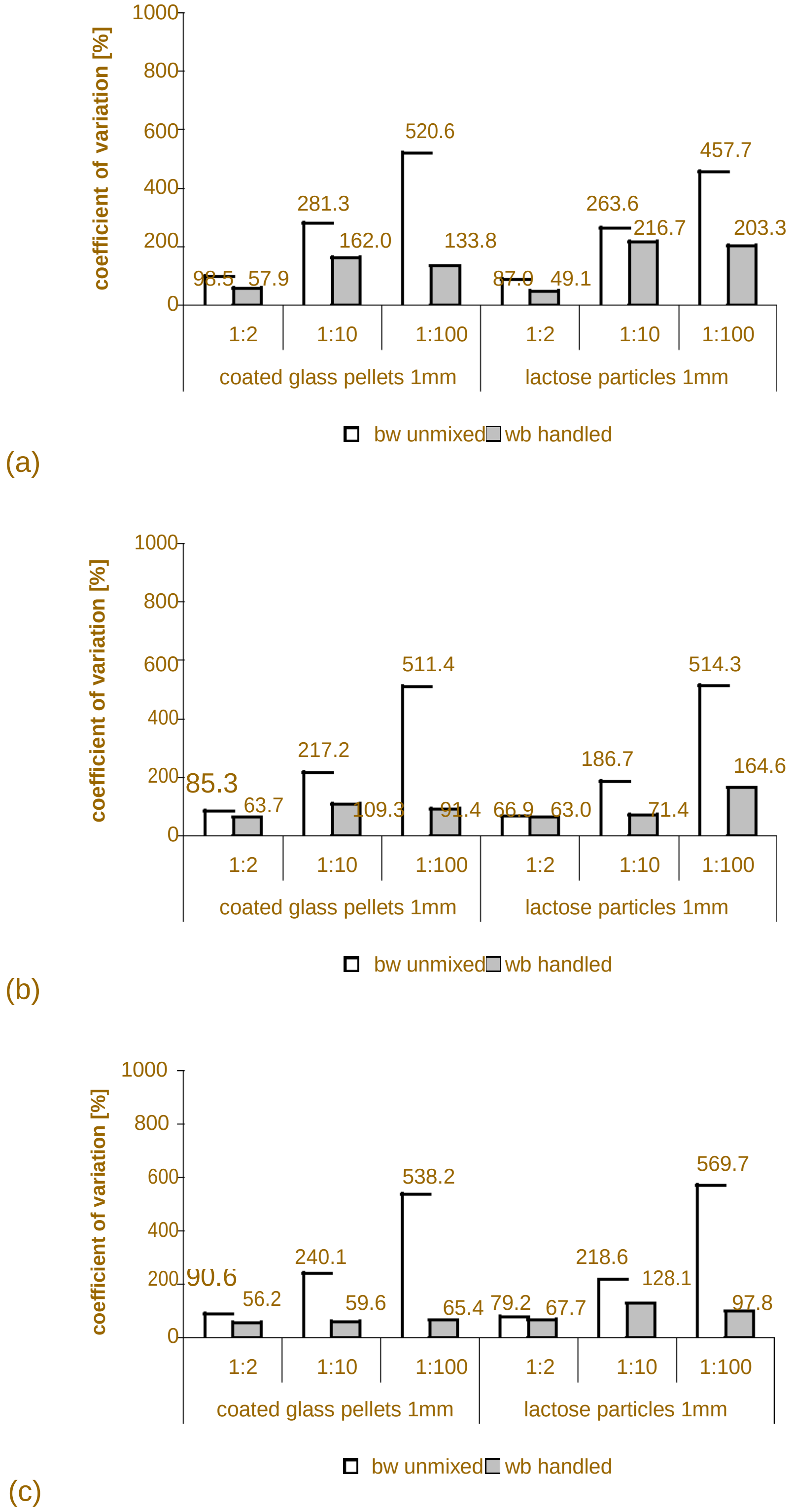


Figure 33: Comparison of bw unmixed and wb handled coefficients of variation of mixtures sampled with (a) the Plexiglass hopper, (b) the sampling glass element and (c) the sampling metal element.

The coefficients of variation of the 1:2 dilutions show only a slight improvement compared to the coefficients of variation of the bw- arrangements due to the large number of blue particles per mixture. In the higher dilution rates, the advanced distribution of the lower number of blue particles caused by the single convective motion before sampling results in an improvement of the qualities of the mixtures.

Differences between the coefficients of variation of unmixed and handled mixtures show no specific pattern towards one material used for the whole system and is shown to be in the same range. Nevertheless, handling throughout the whole mixing and sampling system is massively easier and especially more reproducible with the developed mixing and sampling equipment. The handling procedure, which includes one single convective motion, results in enhanced qualities of mixtures by reducing the coefficients of variation once more compared to the results obtained by sampling only. By dedicating a small amount of energy, the mixtures tend again towards a completely random arrangement driven by a further increase of the entropy. Following the picture of mixing kinetics, where the mixture quality is a function of mixing time, a rather fast increase of the qualities of mixtures can be estimated especially at the beginning of the curve when using non- interactive materials of larger sizes. Therefore it can be concluded, that influences of handling as well as sampling during the developed procedure with the developed equipment can be considered as beginning of a mixing kinetic investigation (mixing time equals 0 minutes) and further investigations may be executed with the developed mixing and sampling equipment.

5.1.2.2 Mixing and Sampling

The evaluation of the developed and constructed mixing and sampling equipment can be completed by including the actual mixing process to the mixing and sampling procedure which therefore will contain all steps from mixing preparation to sample analysis. To evaluate the procedure, mixing kinetics (coefficients of variation as a function of mixing times) can be generated and compared to the common theory of non- interactive mixing. Applying spherical particles, equation (3) from Stange- Poole can be used to predict theoretical qualities of mixtures for dilution rates above 10% (w/w)[17, 22, 23].

Using the above- presented non- interactive materials (see table 6 and figure 26), the total weight of mixtures was again determined 20g for the coated glass pellets 1mm mixtures and 10g for the lactose particles 1mm mixtures, respectively. Dilution rates of 1:2 were used to follow the requirements for the application of equation (3). Mixing and sampling was performed with the mixing and sampling glass or mixing elements by charging the mixing elements white followed by blue particles. Mixing was carried out using the Turbula® mixer, which will not affect particle properties due to its diffusive mixing mechanism. Sampling was carried out to achieve at least 25 samples of the mixtures.

Figure 34 displays three mixing kinetics of coated glass pellets 1mm mixtures mixed and sampled with the mixing and sampling glass elements including the value for a wb handled arrangement. Mixtures were prepared and mixed for 0.5, 1, 2.5, 5, 7.5 and 10 minutes each before sampling and analyzing.

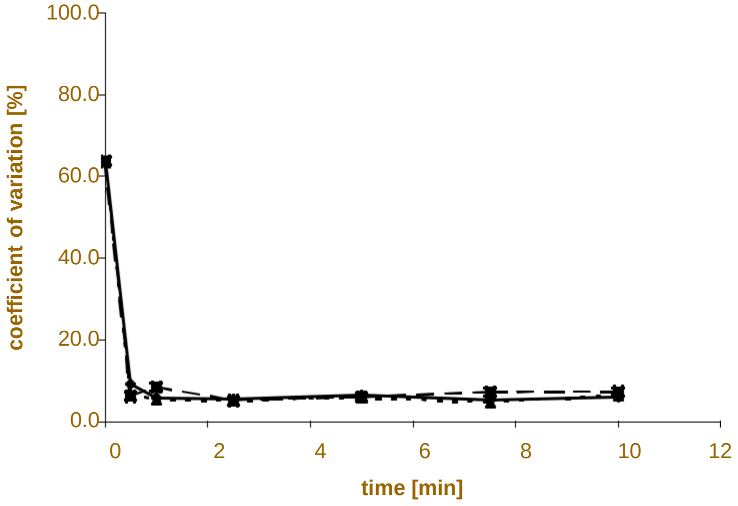


Figure 34: Mixing kinetics displaying the coefficients of variation as a function of mixing time of coated glass pellets 1mm mixtures mixed and sampled with the mixing and sampling glass elements.

Already after one minute of mixing, the coefficients of variation decline distinctively compared to the value obtained from the bw arrangement resulting in an improvement of the mixture qualities. The enhancement continues throughout the three curves as shown in even levels of the coefficients of variation after the different mixing times. By taking the mean and standard deviations of the coefficients of variation of each mixing time, the three mixing curves can be summarized to one curve. The application of equation (3) delivers a theoretical value for the standard deviation and must be converted to the theoretical coefficient of variation by using the nominal content of the mixtures. Figure 35 shows the summarized amplification of the mixing curves of coated glass pellets 1mm and lactose particles 1mm mixtures mixed and sampled with the mixing and sampling glass elements.

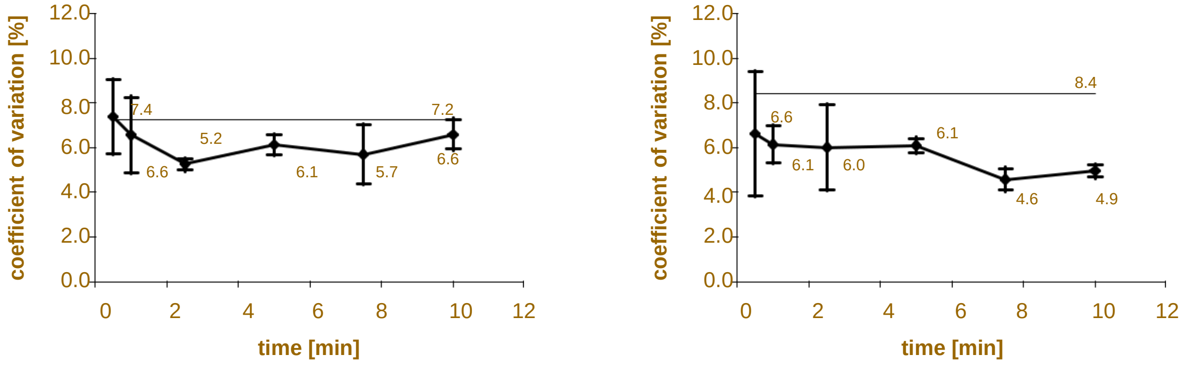


Figure 35: Summarized amplifications of mixing kinetics of (left) coated glass pellets 1mm mixtures and (right) lactose particles 1mm mixtures mixed and sampled with the mixing and sampling glass elements.

The spherical, monosized particles coated glass pellets 1mm mixtures display good agreement of received mixture qualities compared to the derived value of equation (3). An explanation for the marginal differing lower values of above 70% difference in the best case (5.2% mean compared to the derived value of equation (3)) can be found by the slightly differing sample weight of particles in the sampling vessels and the calculation of the particle weight from the particle size measurements. Low means of coefficients of variation with small corresponding standard deviations indicate good qualities of mixture and high reproducibility. Therefore, good mixture qualities can be achieved with the Turbula® between 2.5 and 5 minutes with the non-interactive particles including a high reproducibility indicating a stable mixing process. The mixing kinetic received by mixing lactose particles 1mm mixtures demonstrates clearly a higher difference to the derived value of equation (3) caused by the broader particle size distribution and the shape of the particles. Even though the process seems to need longer mixing times for good qualities of mixtures and high reproducibility, the values differ around 50 to 70% from the derived Stange- Poole value. In figure 36, a mixing kinetic of lactose particles 1mm mixtures is displayed mixed and sampled in the mixing and sampling metal element (n = 1). There, it is obvious that the course of the curve shows a similar pattern as the corresponding results of the mixing and sampling glass element indicating no difference between the two equipments. The difference of the achieved results is located in the same range between 50 and 80% of the derived value of the Stange- Poole equation. The increasing values of the derived Stange- Poole equation over the three shown mixing kinetics can be explained by the decreasing mean of the sample weights, where the sampled coated glass pellets 1mm mixtures show the highest, and the lactose particles 1mm mixtures mixed and sampled with the mixing and sampling metal elements show the lowest value.

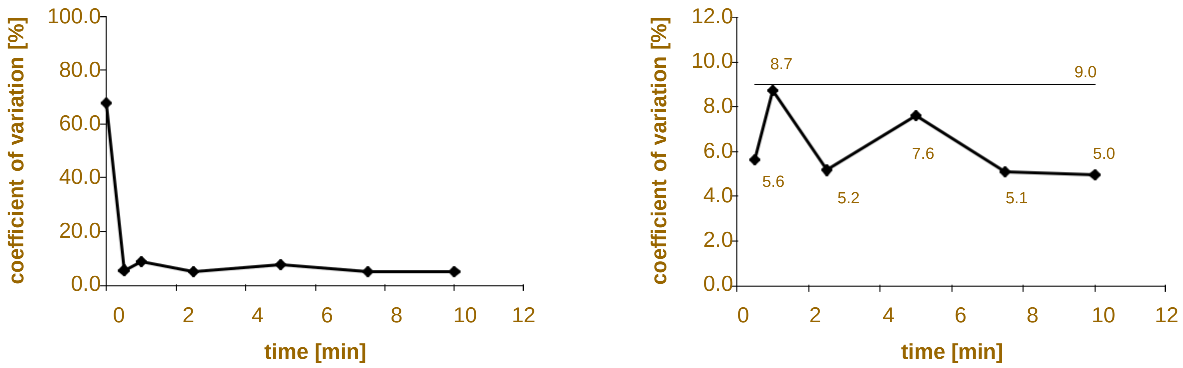


Figure 36: Mixing kinetics of lactose particles 1mm mixtures mixed and sampled with the mixing and sampling metal element (left) including the value for the corresponding wb handled arrangement and (right) the amplification of the values in comparison to the value calculated with the derived Stange- Poole equation.

The obtained results of mixing non- interactive particles correspond to the common mixing theory. Predictions of theoretical values of mixture qualities show good agreement to the received mixing results with spherical, monosized particles. Lower values of qualities of mixtures compared to theoretical values can be achieved with non- spherical particles indicating completely random mixture qualities by a wrong application of the Stange- Poole equation, which confirms investigations of the past [27-31]. The Turbula® mixer delivers fast and particularly reproducible mixing results combined with the developed and constructed mixing elements, whereas the mixing elements show no considerable difference. Additionally, no altering of particle properties was observed due to the preservative mixing mechanism. The results show distinctively the adjustment of a balance of mixing and demixing after short mixing times. Therefore, the mixing and sampling procedure with the developed equipments can be used to investigate non- interactive and interactive mixing processes with reliable results.

5.2 Dry Coating

Dry coating, originating from the old concept of ordered mixing, has gained more interests as an application in dry solids mixing in pharmaceutical technology. The resulting particles consist of a layer of interactive fines adhering to coarser non-interactive carrier particles. By simply mixing, the process generates particles with attractive properties such as good flowability and high content uniformity. Investigations must direct towards an understanding of the mixing mechanism as well as the identification of the important process parameters. Therefore, the evaluated sequential mixing and sampling system will be applied to study dry coated particles.

5.2.1 Basic Investigations for Studying the Dry Coating Process

5.2.1.1 Properties of Guest and Carrier Particles

Before studying the dry coating process, the properties of guest and carrier particles must be determined. Methylene blue powder was used as interactive guest particles due to its color for visual observation of the produced particles, the excellent measurability with the UV/Vis spectrometer and high solubility in water. The Glass pellets 1mm, 0.4-0.6mm and 0.25-0.3mm were applied as monosized non-interactive carrier particles of spherical shape with smooth surfaces and high true densities to evaluate impacts of particle size on the dry coating process. In contrast, Cellets® 1000, 350 and 200 were used as monosized and spherical non- interactive carrier particles with rougher surface textures and lower true densities.

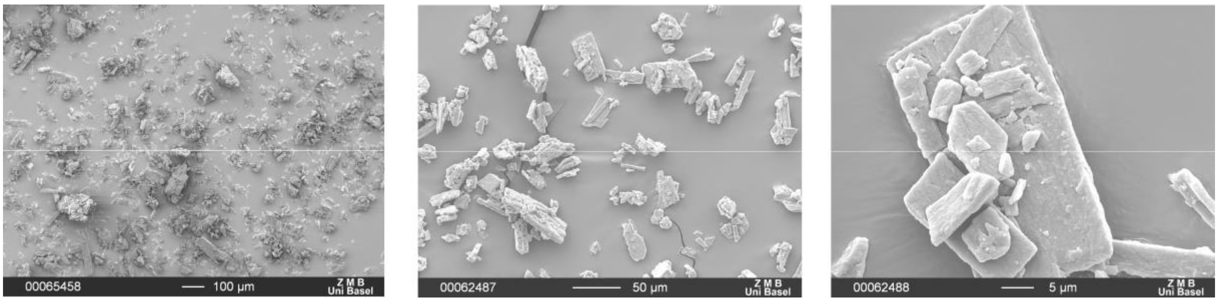
Table 9 displays the properties of the Glass pellet carriers of all particle sizes in comparison to the properties of Methylene blue. The determinations of the properties were performed after storage (see 4.1.2.1), whereas Methylene blue was sieved prior to the characterization through a sieve of size 180 m.

Table 9: Properties of Glass pellets compared to the host particles.

	Methylene blue	Glass pellets		
		1mm	0.4-0.6mm	0.25-0.3mm
particle size [m](n = 5)				
- mean	37.8 ± 7.7	1204.3 ± 22.8	510.6 ± 12.0	274.9 ± 1.7
- median	34.1 ± 7.5	1180.2 ± 11.5	489.9 ± 4.2	268.4 ± 0.9
true density $[g/cm^3]$ (n = 5)	1.3602 ± 0.0070	2.4989 ± 0.0004	2.4746 ± 0.0008	2.4692 ± 0.0013
Hausner ratio *H* (n = 3)	1.29 ± 0.02	1.01 ± 0.02	1.01 ± 0.01	1.12 ± 0.02
flowability [g/s](n = 5)				
- glass element*	no flow	10.53 ± 0.02	13.45 ± 0.07	13.23 ± 0.07
- metal element*	no flow	8.82 ± 0.02	10.89 ± 0.03	10.27 ± 0.03
residual moisture content [%](n = 5)	10.60 ± 0.57	0.23 ± 0.10	0.06 ± 0.07	0.37 ± 0.13

* abbreviation for sampling glass or sampling metal element

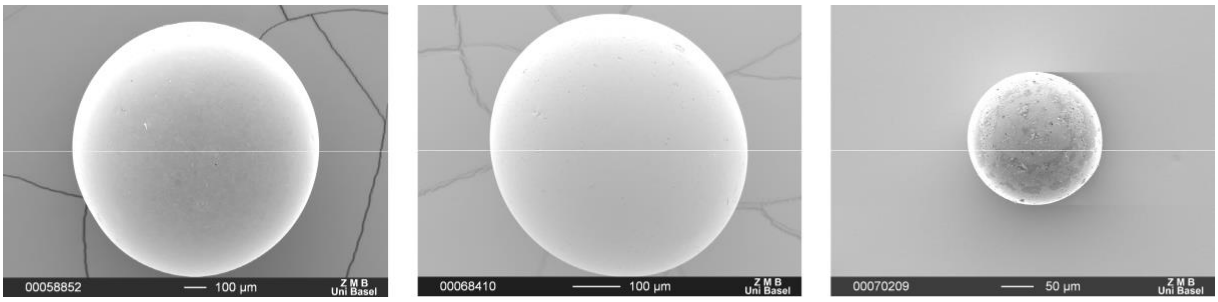
The ratios of particle sizes of Methylene blue compared to the Glass pellets are increasing from Glass pellets 1mm (gp1000; leaned on the diameter determined by the particle size measurement) 1:32, Glass pellets 0.4-0.6mm (gp500) 1:14 to the Glass pellets 0.25-0.3mm (gp250) 1:7, respectively. Comparing the true densities of Methylene blue to the Glass pellets of the different particle sizes, a ratio of 1:2 can be determined. The Hausner ratio *H* measured for Methylene blue declares an insufficient flowability compared to the values for the Glass pellets indicating good flow properties and dense packing before and after mechanical treatment [77]. As indicated by the results of the Hausner ratio, Methylene blue is not discharging neither from the sampling glass nor metal element whereas the Glass pellets of all particle sizes discharge faster using the sampling glass element compared to the values obtained with the sampling metal element. Residual moisture contents show large differences due to the properties of glass. Figure 37 displays the shapes and surfaces of interactive Methylene blue particles compared to the non- interactive Glass pellets of different sizes.



Methylene blue magnification: 70x

Methylene blue magnification: 300x

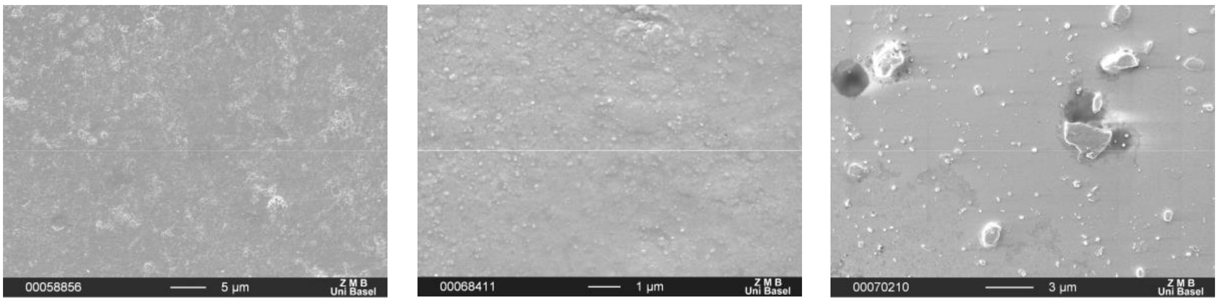
Methylene blue magnification: 2000x



gp1000 magnification: 70x

gp500 magnification: 150x

gp250 magnification: 200x



gp1000 magnification: 2200x

gp500 magnification: 10000x

gp250 magnification: 5000x

Figure 37: Examples of SEM photographs of Methylene blue guest particles compared to the Glass pellet carrier particles. The photograph of a gp250 magnification 5000 displays contamination of the surface due to improper sample preparation.

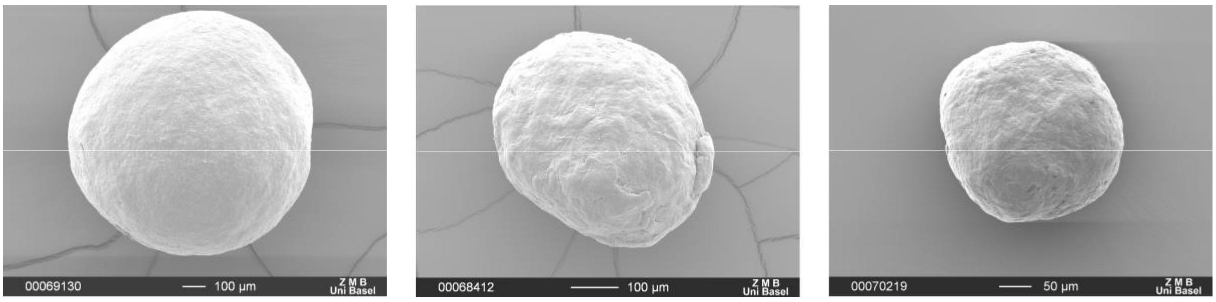
The SEM photographs show distinctively the different sizes and shapes of the Methylene blue particles. In comparison, the Glass pellets indicate spherical shapes with smooth surfaces. The properties of the non- interactive Cellets® of all particle sizes are shown in table 10 compared to Methylene blue determined after storage (see 4.1.2.1).

Table 10: Properties of Cellets® compared to the host particles.

	Methylene blue	Cellets®		
		1000	350	200
particle size [m](n = 5)				
- mean	37.8 ± 7.7	1256.5 ± 3.7	442.8 ± 5.8	283.0 ± 2.2
- median	34.1 ± 7.5	1219.0 ± 2.6	439.6 ± 5.5	278.2 ± 1.9
true density [g/cm^3] (n = 5)	1.3602 ± 0.0070	1.3649 ± 0.0013	1.4291 ± 0.0005	1.4459 ± 0.0006
Hausner ratio *H* (n = 3)	1.29 ± 0.02	1.04 ± 0.01	1.04 ± 0.01	1.06 ± 0.01
flowability [g/s](n = 5)				
- glass element*	no flow	4.86 ± 0.05	5.99 ± 0.09	4.96 ± 0.19
- metal element*	no flow	3.81 ± 0.05	4.88 ± 0.01	5.63 ± 0.08
residual moisture content [%](n = 5)	10.60 ± 0.57	2.81 ± 0.52	4.38 ± 0.26	4.46 ± 0.34

* abbreviation for sampling glass or sampling metal element

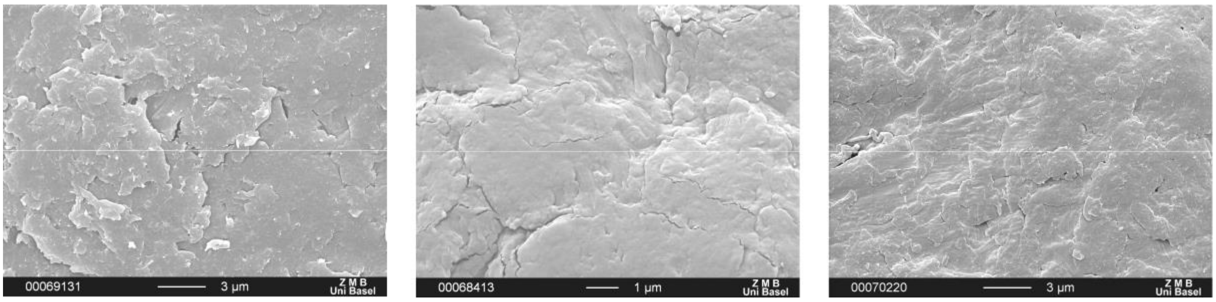
Comparing the ratios of particle sizes of Methylene blue with the Cellets®, increasing values can be found from 1:33 for the Cellets® 1000 (c1000), 1:12 for the Cellets® 350 (c500) to 1:7 for the Cellets® 200 (c250) whereas the true densities of the three powders can be considered identical. The determination of the Hausner ratios *H* for the Cellets® indicates good flow properties with dense packing before and after mechanical treatment [77]. Using the sampling glass and metal elements for the determination of the flowability, the sampling glass element enhances the discharge compared to the values obtained from the sampling metal element by showing higher values for flowability except for the c250. Only a small difference of the residual moisture contents can be observed between the materials. The shapes and surfaces of the Cellets® are shown in figure 38.



c1000
magnification: 70x

c500
magnification: 150x

c250
magnification: 200x



c1000
magnification: 5000x

c500
magnification: 10000x

c250
magnification: 5000x

Figure 38: Examples of SEM photographs of the Cellets® as carrier particles.

The photographs display that the shape of the Cellets® can be regarded as non-spherical. Additionally, the surface texture exhibits angular shapes with cavities and cannot be considered as smooth, but rough.

Comparison of the particle size ratios of the non- interactive carrier particles Glass pellets and Cellets® indicates similar proportions to the guest particles Methylene blue. Additionally, figure 39 depicts the particle size distributions of all materials used for the investigations of the dry coating process. Methylene blue exhibits a rather broad particle size distribution where the Glass pellets and the Cellets® feature narrow, monosized and similar distributions of the corresponding particle sizes, which can be considered equal.

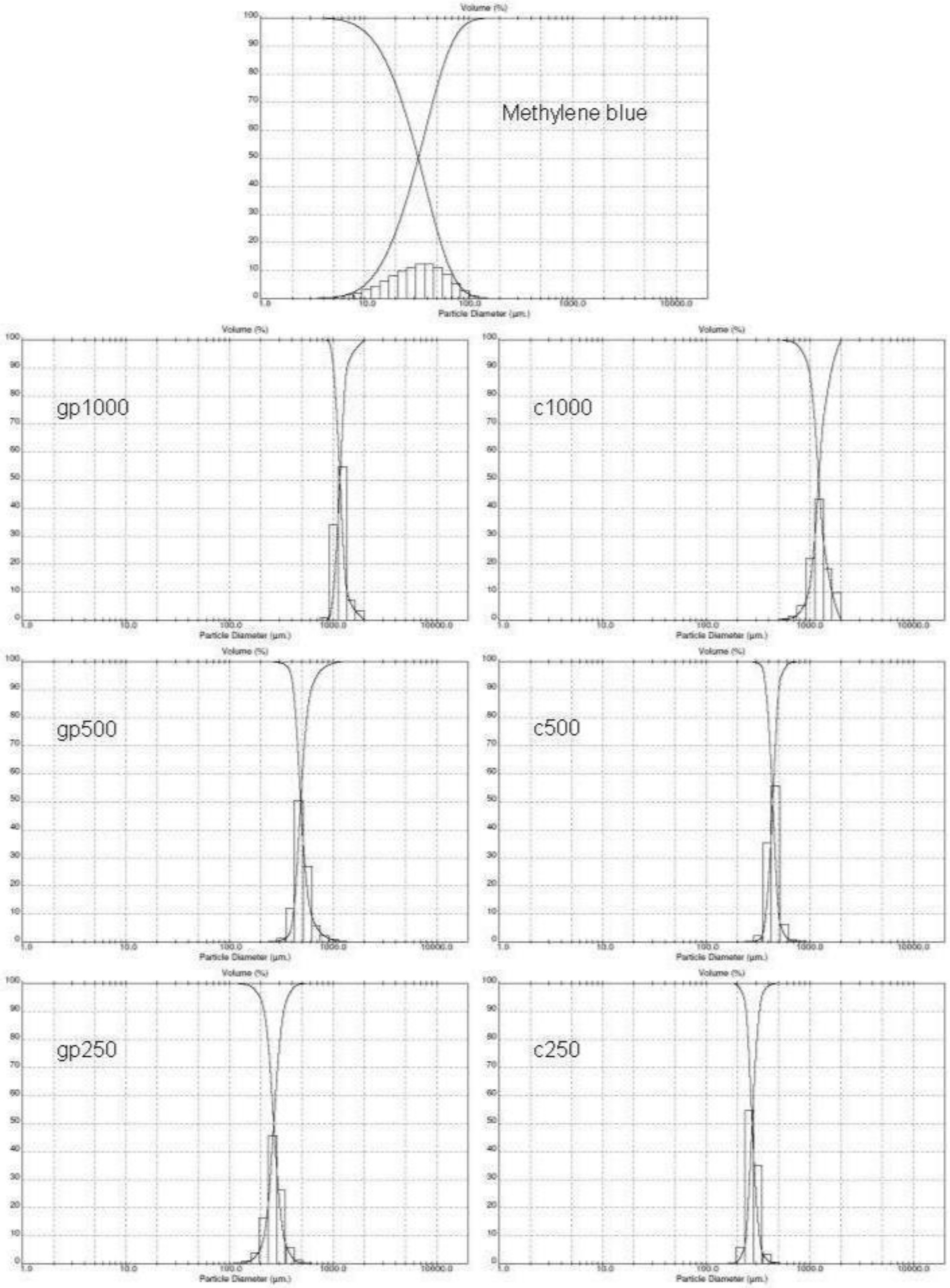


Figure 39: Examples of particle size distributions of the guest particles Methylene blue and the carrier particles gp1000, gp500, gp250, c1000, c500 and c250.

True density differences of the Cellets® compared to the heavier Glass pellets result in a ratio of approximately 1:2. The determinations of the Hausner ratios *H* show similar values for all carrier materials with a slight inclining value for the c250. The Glass pellets carrier particles exhibit faster flow velocities due to their higher densities compared to the Cellets®, where the flow pattern for the c250 determined by discharging from the sampling glass element show irregularities, as depicted in figure 40. The Glass pellets discharged from the sampling glass and metal element show linear and therefore regular flow patterns apparent from the coefficients of correlation of the curves with values of 1.000. Analyzing the Cellets®, values of coefficients of correlation of 1.000 can be found by using the sampling metal element also. By applying the sampling glass element, the coefficients of variation decrease with decreasing particle sizes of the Cellets® from 1.000 for the c1000, 0.9999 for the c500 to 0.9948 for the c250, respectively. Additionally it can be observed, that the c250 particles accumulate at the orifice of the glass hopper insert indicating unrequested electrostatic charging of the particles due to interparticle friction and derogated conductivity of the sampling glass element material. The residual moisture content of the carrier materials show both a massive difference to the value received by the guest particles, which results from the property of glass and microcrystalline cellulose, respectively. The Glass pellets show spherical shapes with smooth surfaces in comparison to the Cellets®, which demonstrate less spherical shapes and a distinctive rougher surface textures.

It can be assumed that Methylene blue particles show typical properties of interactive particles necessary for the production of dry coated particles due to its high value of the Hausner ratio *H*, the missing flowability and the high value of residual moisture content conveying additional adhering forces. The Glass pellets and the Cellets® of all particle sizes both present the necessary properties as carrier particles with high particle sizes and corresponding narrow particle size distributions as well as regular, linear flow patterns. Determination of flowability of the Cellets® particles with the sampling glass element shows irregular flow patterns due to unrequested electrostatic charging influencing sampling of the particles and must be investigated in terms of influences of the mixing and sampling glass elements upon the mixing process.

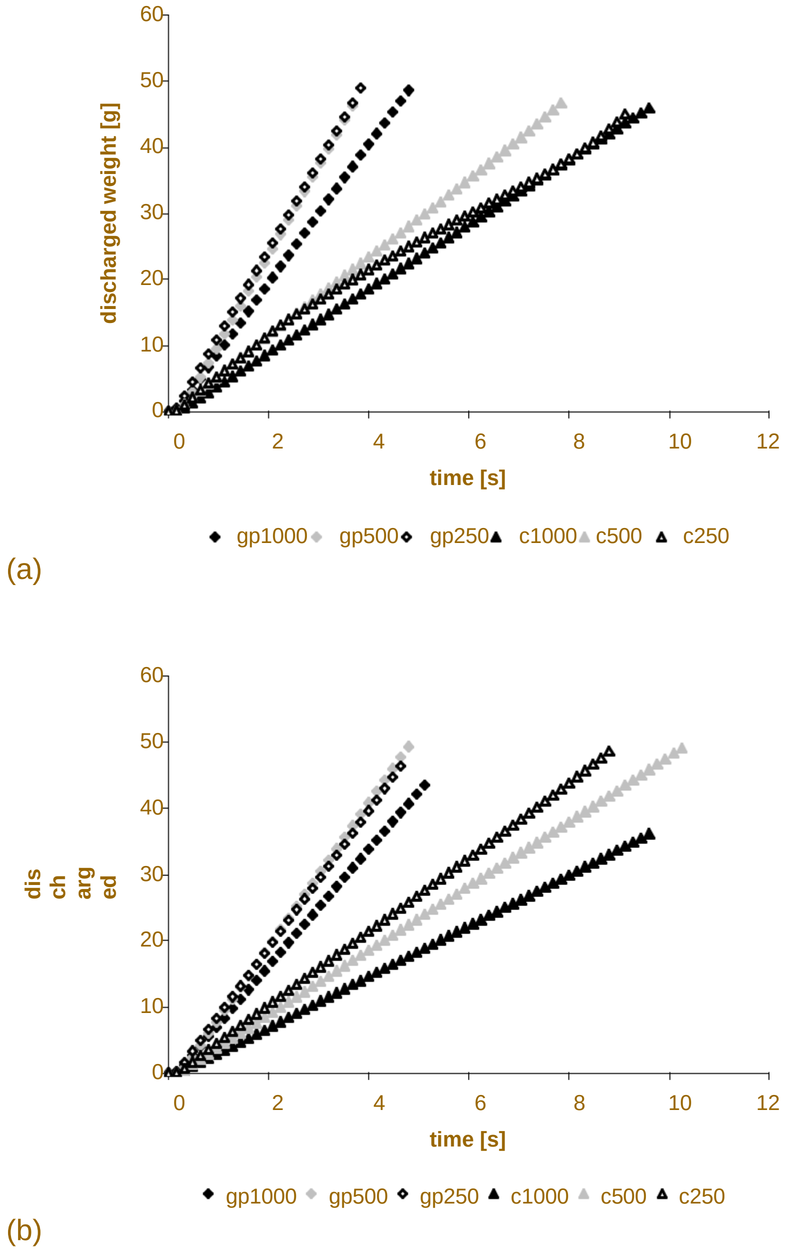


Figure 40: Examples of flow patterns of the carrier particles analyzed with (a) the sampling glass element and (b) the sampling metal element.

5.2.1.2 Comparison of the Mixing and Sampling Elements

The previous results obtained from the characterization of the material properties indicated unrequested influences of the sampling equipment upon the materials and the sampling process due to electrostatic charging. Comparing the mixing and sampling glass and metal elements in dry coating mixing processes may assess possible differences to support the previous findings and determine the degree of influence of glass and metal equipment materials.

In order to evaluate the mixing and sampling glass and metal elements, the gp1000 were chosen as carrier material having a large particle size featuring regular flow patterns applied in both equipment types. Mixtures were prepared with nominal contents of 0.1% (w/w) of Methylene blue of 20g total mixture weight to stay clearly below the saturation concentration of Methylene blue in water for the sample analysis. For each mixing time, one mixture was prepared, mixed in the Turbula® at 21 rpm and sampled to receive at least 25 samples for sample analysis.

Mixing kinetics obtained with both sampling and mixing glass and metal elements are shown in figure 41. Mixtures were mixed for 0 (according to the wb handling sequence of charging experiments), 10, 30, 60, 90, 120, 150 and 180 minutes.

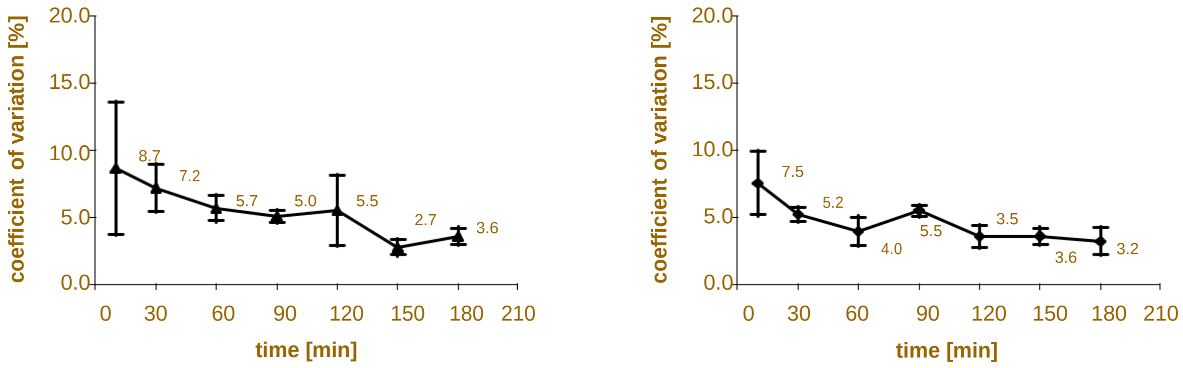


Figure 41: Comparison of mixing kinetics received with (left) the glass equipment and (right) the metal mixing and sampling elements (n = 3).

The mixing kinetic received by using the sampling and mixing metal elements shows lower values of the means of the coefficients of variation right from the beginning of the mixing process. Additionally, the standard deviations of the means of the qualities of mixtures indicate more reliable mixing results. For further illustration, a weight balance was calculated from the mixture and hopper contents in relation to the initial weight of applied Methylene blue and is displayed in figure 42. Apparently after 10 minutes of mixing, the initial weight of Methylene blue can be recovered as shown by the constant levels of the sum of the contents of mixture and the hopper contents with both glass and metal mixing and sampling equipments. The contents of mixture received by using the metal mixing and sampling equipment though shows more active on the carrier particles with lower corresponding hopper contents compared to the values obtained with the glass equipment. With hopper contents below 20% of the applied initial Methylene blue weight, the sum curves indicate furthermore only a small amount of material losses due to sampling, however again with slight advantages of the metal equipment especially with longer mixing times. By repeating the measurements, the standard deviations show lower values using the metal equipment than the values received with the glass equipment indicating a more stable, unaffected and reliable mixing process. With increasing standard deviations and including the results of the mixing kinetics, 120 minutes can be estimated as the ideal mixing time using the metal mixing and sampling equipment whereas the glass equipment offers the less requested properties already with the large carrier particles.

Mixing and sampling of the applied large material as carrier particles indicates already differences using the sampling and mixing glass or metal elements with slight advantages of the metal equipment showing a regular, faster and more reliable mixing process. By extrapolating these findings to the smaller particles with smooth and especially with the rougher surface textures, it can be assumed that the difference between the two equipments increases with decreasing particle sizes. In conclusion including the results obtained from the characterization of the materials, the sampling and mixing metal elements show superior properties due to the properties of metal without electrostatic influences upon material and sampling. Therefore, further investigations of the dry coating process should be executed applying the mixing and sampling metal elements only.

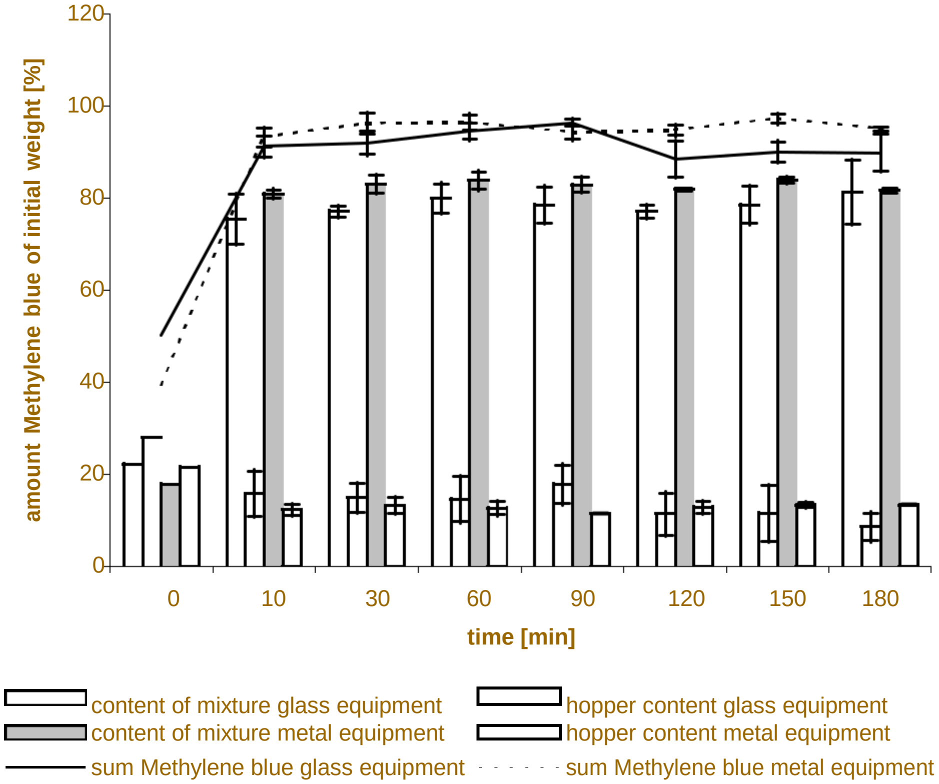


Figure 42: Mass balance as comparison of the glass and metal mixing and sampling equipment. The sum means the addition of the content of mixture and the hopper content and should equal 100% of initial Methylene blue weight (n = 3).

5.2.1.3 Dissolution

To receive accurate and reliable values for mixture qualities produced with dry coating of the Glass pellets and the Cellets® as carrier particles, sample analysis must be inspected. Since Cellets® consist of microcrystalline cellulose not soluble in water with an additional capability of swelling, possible deviations of the contents can be discovered by performing dissolution tests with the Glass pellets as a standard for comparison [74, 80, 81].

Particles were produced by using the mixing metal element in the Turbula® mixing for 120 minutes according to the mixing time determined above. Mixtures were prepared as 0.1% (w/w) dilutions of Methylene blue with total mixture weights of 20g for the Glass pellets and 15g for the Cellets® mixtures, respectively. As solvent, water was chosen at room temperature to simulate sample preparation and sample analysis and dissolution samples were taken after 0.25, 1, 2.5, 5, 15, 30, 60 and 120 minutes. With particles of each material, three dissolution tests were performed using 1g of dry coated particles.

The dissolution of Methylene blue in water from the gp1000 dry coated particles is depicted in figure 43. In comparison to the content of mixture, Methylene blue shows already a complete dissolution up to a constant level of 100% after a short dissolving time, which approves no influence of the carrier particles upon the sample analysis. The Cellets® dry coated particles exhibit a distinctive loss of Methylene blue already at the beginning of the dissolution measurement of around 30%. With preceding dissolution times, the values decrease additionally indicating massive influence of the carrier particles on the content of the mixtures disturbing sample analysis. By swelling of the microcrystalline cellulose in contact with water, Methylene blue diffuses inside the carrier particles causing a loss of content additionally observed by a distinctive blue coloring of the particles. Therefore, water is inappropriate as a solvent for Methylene blue with Cellets® as carrier particles for analysing samples.

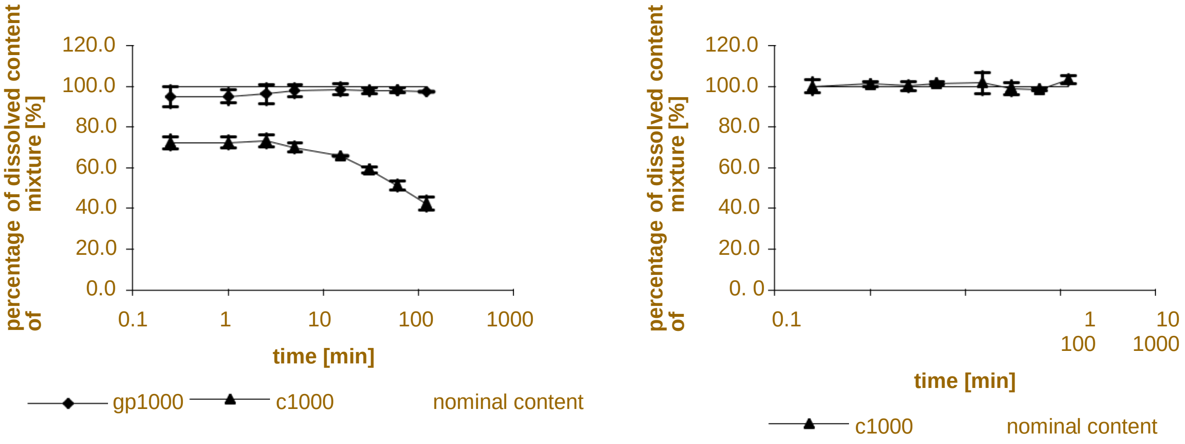


Figure 43: Dissolution of mixtures of Methylene blue 0.1% (w/w) with (left) gp1000 and c1000 carrier particles measured in water and (right) c1000 measured in a 10% (v/v) aqueous solution of acetic acid.

A suitable solvent of Methylene blue must avoid the swelling of the Cellets® to detain the diffusion inside the carrier particles. It is known that acetic acid prevents swelling of microcrystalline cellulose [74, 80, 81]. By applying a 10% (v/v; specification volume by volume) aqueous solution of acetic acid (Sigma Aldrich Chemie GmbH, Buchs, Switzerland), complete dissolution can be reached up to 100% compared to the content of mixture at the beginning of the measurements. As depicted in figure 43, the diffusion is stopped by using the solvent as indicated by the constant dissolution levels with stability of Methylene blue in the acid over the total performance of the dissolution measurements. Investigations of the dissolutions of dry coated particles with smaller particle sizes show the same results whereas the use of acetic acid avoids swelling, diffusion and the disturbance of the measurements. For completeness, further dissolution profiles can be found in Appendix D.

To conclude, Glass pellets as carriers with Methylene blue as guest particles can be analysed using water as solvent for sample analysis whereas the Cellets® must be prepared in 10% (v/v) aqueous solution of acetic acid to avoid distraction and adulteration of the measurements of mixture qualities.

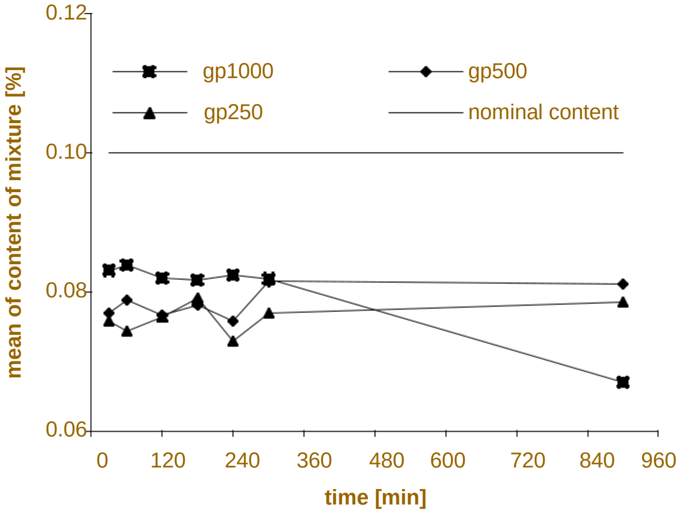
5.2.2 Estimation of Ideal Mixing Times

In dry solid mixing processes, no general rule exists for ideal mixing times [5, 16, 17]. The countless mixture components including their properties and various mixer types make an optimization of the mixing time for each mixture and mixing process indispensable. In dry coating processes, the only variable parameter as part of the operating conditions is the mixing time compared to processes in pharmaceutical technology with more and complex parameters such as coating or tableting. Therefore, the quality of dry coated mixtures must be studied in regards of the mixing time as the important process parameter followed by drawing of conclusions based on the applied materials and mixer properties including the mixing mechanism. The original mixing mechanism of the Turbula® is considered as diffusive. Applying the Turbula® as a dry coating mixer, the mechanism might change and must be investigated on the properties of the obtained particles.

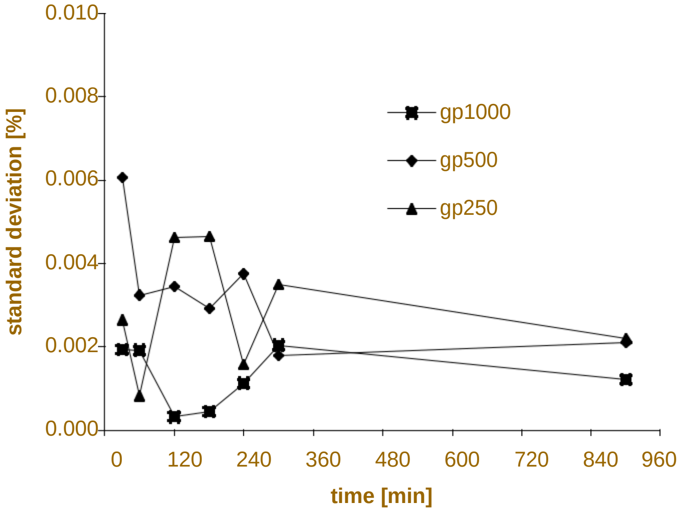
The properties of the applied materials for the estimation of the ideal mixing times have been shown in the previous chapter including the required details for sampling and sample analysis with the developed and constructed mixing and sampling metal equipment. The Glass pellets and the Cellets® were used as carriers with Methylene blue as guest particles in mixtures of 0.1% (w/w) to stay clearly beneath the saturation concentration for the active. The total mixture weights of the applied materials of all sizes can be gathered from table 5 whereas each mixture was prepared by the preferred wb sequence of charging of the mixing element for each mixing time. The qualities of the mixtures were determined after 30, 60, 120, 180, 240, 300 and 900 minutes of mixing in the Turbula® at 21 rpm. Mixtures produced for 900 minutes were investigated to identify possible tendencies. Sampling was carried out to receive at least 25 samples for sample analysis.

5.2.2.1 Process Investigations of Mixtures with Glass Pellet Carriers

The dry coating process can be described and monitored by the contents of mixtures after different mixing times to receive information about the quality of the produced dry coated particles. In addition by repeating the mixing process, the corresponding standard deviations of the mean contents for each mixing time can be used to gather information about the reproducibility of the process. Demanded properties of mixing processes are therefore contents of mixtures with values close to the value of the nominal content as well as low values of standard deviations. Figure 44 shows the mean contents of mixtures (a) calculated according to equation (10) of three mixtures produced for each mixing time with the corresponding standard deviations (b) following equation (11) of the dry coating process of applying the spherical Glass pellet carriers 1000, 500 and 250 with Methylene blue as guest particles. The mixtures using gp1000 as carrier particles feature contents of Methylene blue of around 0.0830% (w/w) at the beginning of the mixing process whereas the contents decrease with proceeding mixing times to 0.0670% (w/w), especially shown by mixing 900 minutes (15 hours). The contents of the used gp500 and gp250 as carriers display slight increase of the contents of 0.0769% (w/w) to 0.0812% (w/w) for the gp500 and 0.0758% (w/w) to 0.0785% (w/w) for the gp250 with a relative stable progression of the gp500 and an irregular course for the gp250 mixtures with increasing mixing times. Highest contents can be achieved using the gp1000 particles as carriers whereas with decreasing particle size, the contents decrease as well. Nevertheless, the contents are located approximately in the same range of 75 to 80% of the initial applied Methylene blue with the exception of gp1000 carriers mixed 900 minutes. Comparison of the standard deviations shows lowest values and therefore highest reproducibility of approximately 0.0013% (w/w) when applying gp1000 carrier particle mixtures and an increase of the values for decreasing particle sizes of 0.0033% (w/w) for the gp500 and 0.0029% (w/w) for the gp250, respectively. With proceeding mixing times, the reproducibility grows as shown by the decreasing standard deviations for all particle sizes. The difference between the standard deviations is not too large compared to the content values resulting in coefficients of variation calculated from the mean of the contents and the corresponding standard deviations of 1.6% for the gp1000, 4.3% for the gp500 and 3.8% for the gp250 resulting in good reproducibility of the three mixing processes.



(a)



(b)

Figure 44: Dry coating process description and monitoring of binary mixtures of gp1000, gp500 and gp250 with Methylene blue as guest particles. (a) depicts the mean of the contents of mixtures and (b) the corresponding standard deviations (n = 3).

Figure 45 displays the weight balance of the described processes for the gp1000, 500 and 250 as carrier particles for monitoring and control of the distribution of the initially applied Methylene blue confirming the slight decrease of content of mixtures with decreasing particle sizes of 80.3%, 78.4% and 76.3%.

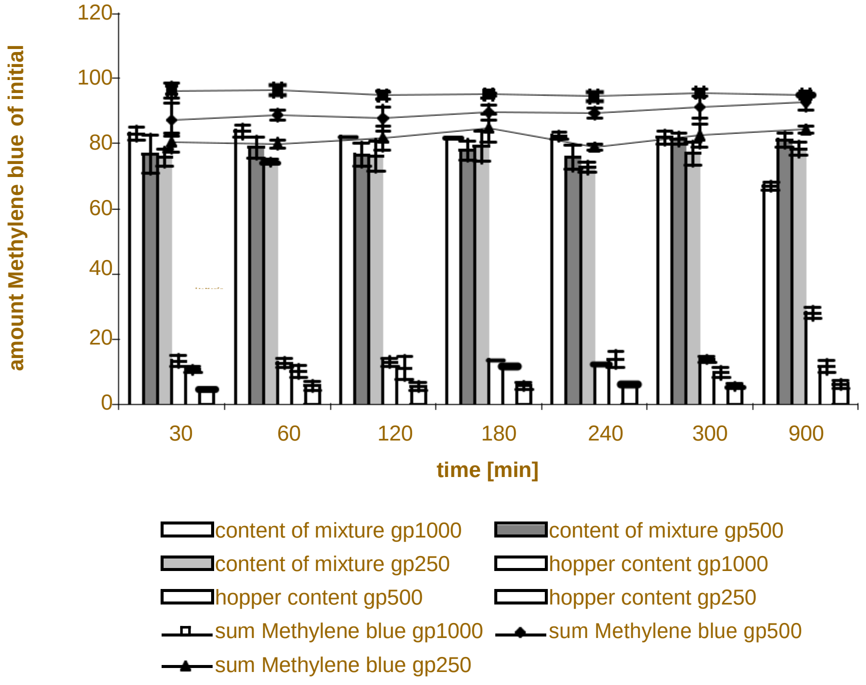


Figure 45: Mass balance of applied Glass pellets 1000, 500 and 250 as carrier particles in dry coating mixtures with Meythlene blue.

Also, the decrease in particle sizes causes a decrease of the hopper contents from 15.1%, 11.2% to 5.6%. The larger the particle, the more Methylene blue is distributed on the carrier particles and the equipment approved by the curves of the sum of initial applied Methylene blue. The decrease of particle size causes a loss of Methylene blue of around 4.6% for the gp1000, 10.5% for the gp500 and 18.2% for the gp250 carrier particles, respectively. The amount of Methylene blue not recovered can be found on the sampling train, inside the sampling vessels and in the mixture as single or agglomerated fines. Even though the total surface area is increasing with decreasing particle sizes of the carriers disposing more active to adhere on the surface, the increase of the loss of Methylene blue can be explained by the decrease of particle size. The single particle is loosing the power to roll Methylene blue on the surfaces of the carrier particles and the mixing and sampling equipment. Table 11 displays the calculation of the total surface area per mixture.

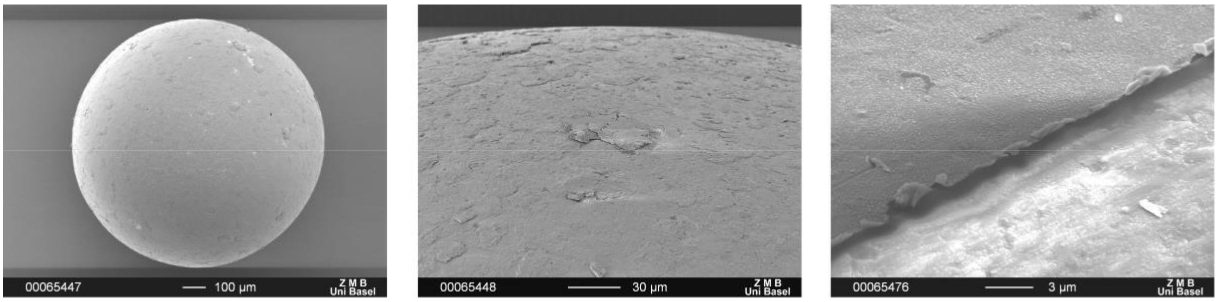
Table 11: Calculation of the total surface area per mixture.

carriers	total mixture weight [g]	weight of 1 carrier* [g]	total number of carriers per mixture -	surface area of 1 carrier [cm^2]	total surface area of carriers [cm^2]
gp1000	20	$2.29 \cdot 10^{-3}$	8743	0.0456	398.4
gp500	15	$1.72 \cdot 10^{-4}$	86876	0.0082	711.6
gp250	20	$2.69 \cdot 10^{-5}$	743128	0.0024	1765.5

* calculated according to equation (5)

Examples of SEM photographs of dry coated gp1000, 500 and 250 particles with Methylene blue are depicted in figure 46. The original structure of size and shape of Methylene blue disappears due to the rolling mixing mechanism occurring in the mixing equipment inside the Turbula® from particles to a thin layer on the carriers as indicated by the examples of the SEM photographs.

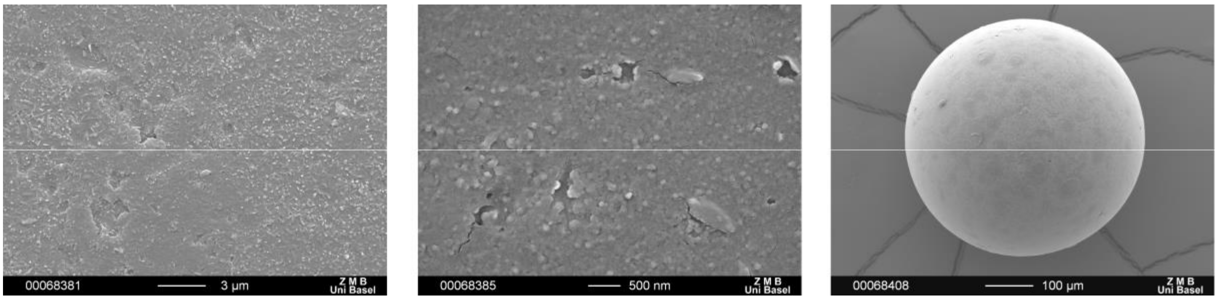
The process investigations indicate no explicit estimation of the ideal mixing times for the Glass pellet carrier particles. Nevertheless, high values of the contents of the guest particles on the carriers show good recovery with only small losses of the applied active, even for prolonged process times. Even though the gp1000 show decreasing content tendencies, the standard deviations keep the low values. Therefore, the processes can be considered stable and reliable in dependence of mixing time. With decreasing particle size, it should be expected to have better distributions of the guest particles on the surface of the carriers due to the increasing total surface area resulting in longer mixing times and better qualities of mixtures. However, the decreasing particle sizes applied in the different mixing processes result in decreasing contents. The produced particles must be considered as coated by rolling the guest particles on the carrier surfaces. The guest particles loose their initial shape and size due to a shear mixing mechanism of the carrier particles in the mixing equipment used with the Turbula® as discovered in previous investigations [82, 83, 84].



gp1000; mixing 30 minutes
magnification: 70x

gp1000; mixing 30 minutes
magnification: 550x

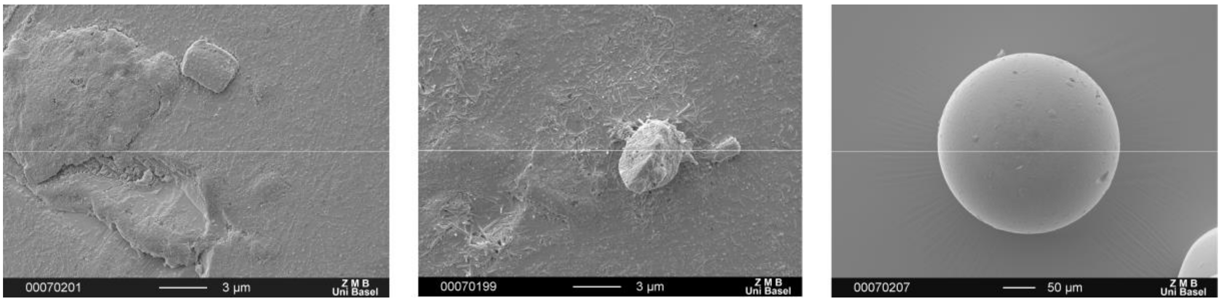
gp1000; mixing 180 minutes
magnification: 5000x (scratch)



gp500; mixing 60 minutes
magnification: 5000x

gp500; mixing 180 minutes
magnification: 20000x

gp500; mixing 300 minutes
magnification: 150x



gp250; mixing 240 minutes
magnification: 5000x

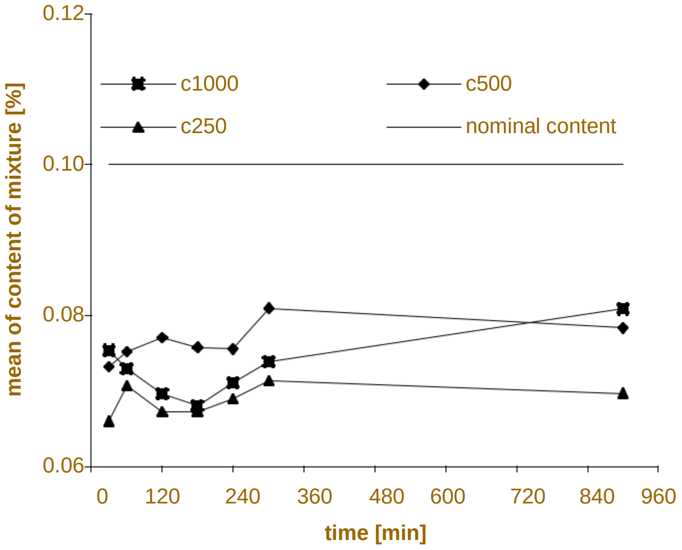
gp250; mixing 300 minutes
magnification: 5000x

gp250; mixing 900 minutes
magnification: 200x

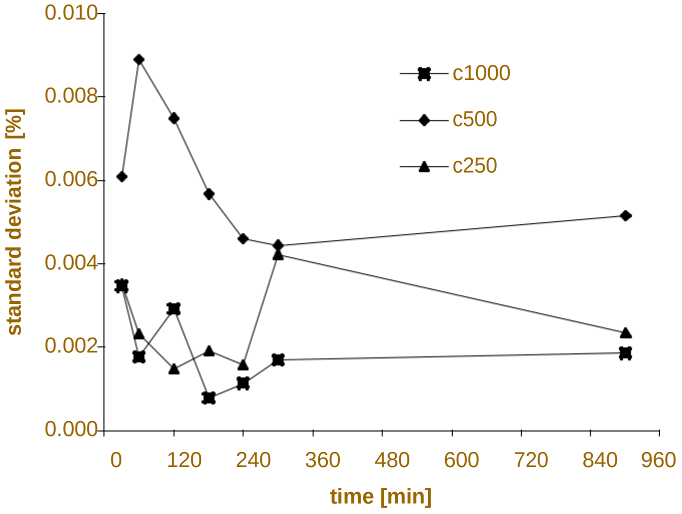
Figure 46: Examples of SEM photographs of different stages during the dry coating mixing process of gp1000, gp500 and gp250 with Meythlene blue. By scratching on the surface of a gp1000 dry coated particle, the original glass surface appears as shown in the photograph in the upper right corner.

5.2.2.2 Process Investigations of Mixtures with Cellets® Carriers

The process descriptions and monitoring of mixing c1000, c500 and c250 as carriers with Methylene blue as guest particles are depicted in figure 47 following the same analysis as described in the previous chapter.



(a)



(b)

Figure 47: Dry coating process description and monitoring of binary mixtures of c1000, c500 and c250 with Methylene blue as guest particles. (a) depicts the mean of the contents of mixtures and (b) the corresponding standard deviations (n = 3).

The Cellets® carrier particles applied in the estimation of the mixing processes demonstrate slight increasing contents with proceeding mixing times. Thereby, the c1000 show values from 0.0754% (w/w) to 0.0808% (w/w) with increasing mixing times, whereas c500 mixtures show values of 0.0732% (w/w) to 0.0810% (w/w).

Lowest values can be found using the c250 as mixture components from 0.0660% (w/w) to 0.0714% (w/w), respectively. The standard deviations of the c1000 mixtures show generally lowest values of around 0.0019% (w/w) compared to the mixtures with smaller carrier particles indicating a reliable mixing process. The values of the mixtures prepared with the c250 show similar values of approximately 0.0025% (w/w) whereas the c500 mixtures stand out with higher values of 0.0061% (w/w). Still, the difference between the standard deviations compared to the content values is not high with values of coefficient of variations around 2.7%, 7.9% to 3.6% resulting in good reproducibility of the three mixing processes.

The weight balance of the Cellets® applied as mixture carrier particles is depicted in figure 48 affirming the order of highest content values for the c500 with 76.6% of initial Methylene blue, followed by the c1000 73.6% and the value of 68.7% for the c250, respectively.

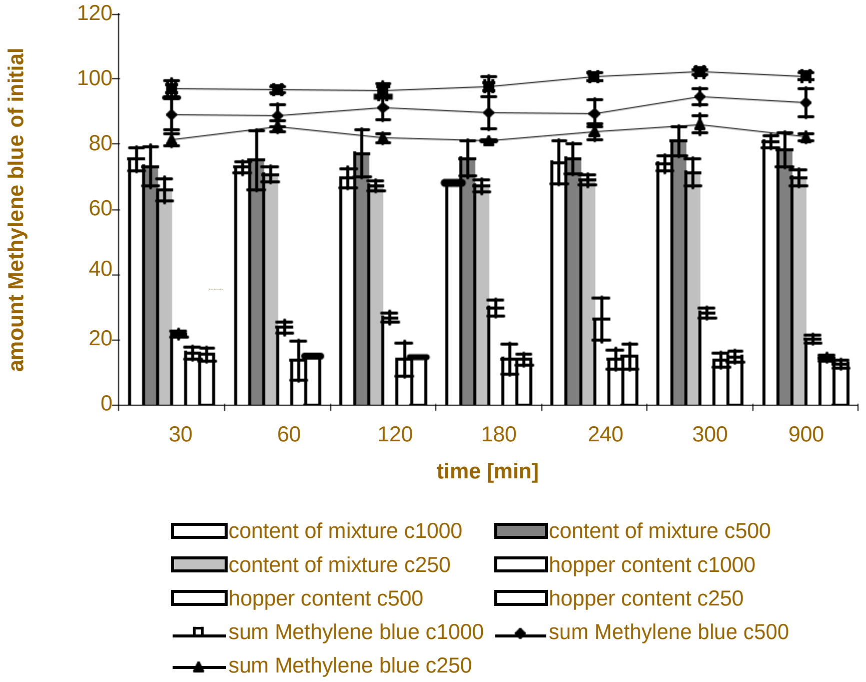


Figure 48: Mass balance of applied Cellets® 1000, 500 and 250 as carrier particles in dry coating mixtures with Meythlene blue.

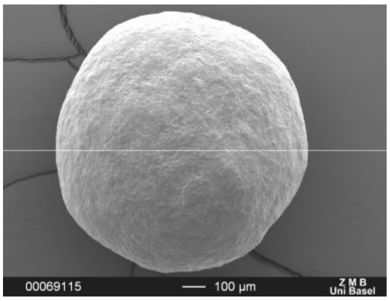
The values of the hopper contents correspond to the order of the values of the contents of mixtures of the initial weight of Methylene blue of 25.2% for the c1000, 14.2% for the c500 and 14.5% for the c250, respectively. The recovery of Methylene blue displayed by the curves of the sum of contents of mixtures added with the hopper contents decrease with decreasing particle sizes from 98.8% of the c1000, 90.8% for the c500 to 83.2% of the c250. Therefore, the distribution of Methylene blue on the surfaces of the carriers as well as the mixing equipment increases with increasing particle size resulting in a loss of Methylene blue of approximately 1.2% for the c1000, 9.2% for the c500 and 16.8% for the c250. The difference of the sum of recovered Methylene blue to initial 100% can be found on the sampling train, inside the sampling vessels and in the mixture as single or agglomerated fines. As described above, the decreasing particle sizes lead to an increase of the total surface area of the particles and the assumption of a better distribution as shown in table 12.

Table 12: Calculation of total surface area per mixture.

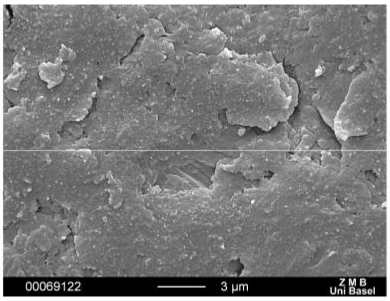
carriers	total mixture weight [g]	weight of 1 particle* [g]	total number of particles -	surface area of 1 carrier [cm^2]	total surface area of carriers [cm^2]
c1000	15	$1.42 \cdot 10^{-3}$	10570	0.0496	524.2
c500	15	$6.49 \cdot 10^{-5}$	230723	0.0062	1420.9
c250	15	$1.72 \cdot 10^{-5}$	873244	0.0025	2197.3

* calculated according to equation (5)

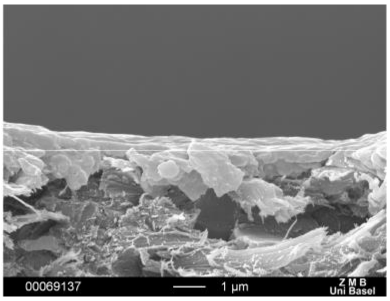
In contrary, with decreasing particle sizes, the loss of Methylene blue is increasing affirming the importance of the power of a single particle to roll the active on the surfaces of itself and the mixing equipment. Due to the rolling mixing mechanism of the particles in the mixing equipment inside the Turbula®, the original structure of Methylene blue disappears which is exemplarily depicted in figure 49 showing particles in different stages of the mixing processes with Methylene blue on the surface. The original structure of the Cellets® carrier particles is not visible any more.



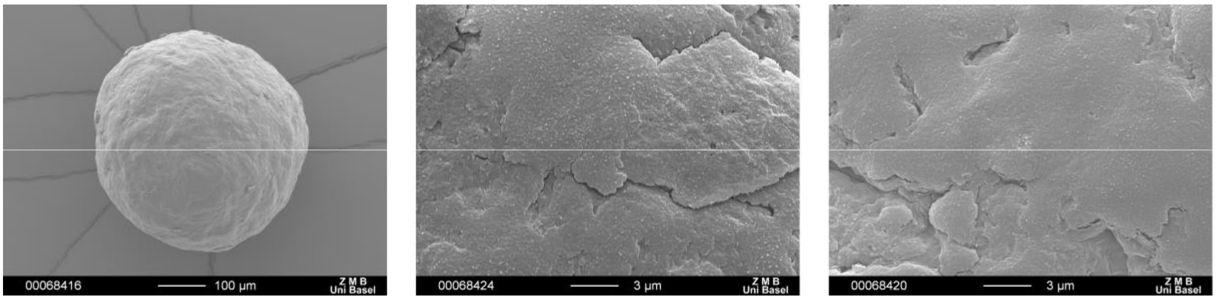
c1000; mixing 60 minutes
magnification: 70x



c1000; mixing 120 minutes
magnification: 5000x



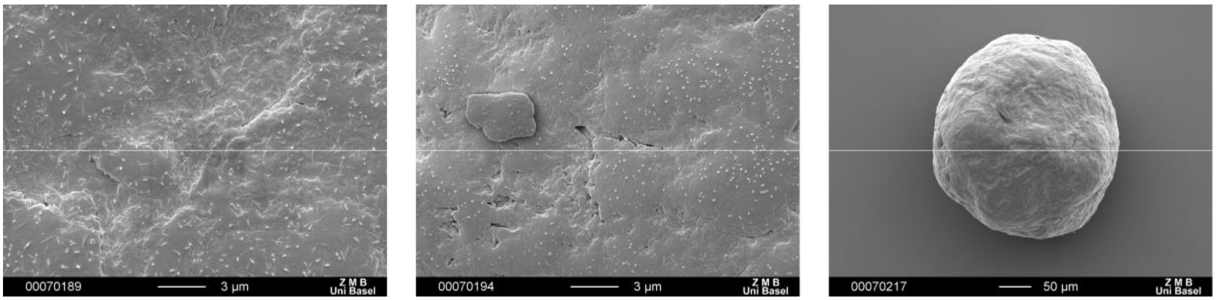
c1000; mixing 240 minutes
Magnification: 10000x (crosscut)



c500; mixing 30 minutes
magnification: 150x

c500; mixing 300 minutes
magnification: 5000x

c500; mixing 900 minutes
magnification: 5000x



c250; mixing 180 minutes
magnification: 5000x

c250; mixing 300 minutes
magnification: 5000x

c250; mixing 900 minutes
magnification: 200x

Figure 49: Examples of SEM photographs of different stages during the dry coating mixing process of c1000, c500 and c250 with Meythlene blue. In the upper right corner, a cross- section through a c1000 dry coated particle shows the thin layer of Methylene blue on the carrier.

Again, the process investigations indicate no explicit estimation of the ideal mixing times for the Cellets® carrier particles as mixture components. High contents of the guest particles can be achieved with good recovery of the active considering the mixing processes as stable and reliable. With slight displacement of the contents between the particle sizes leading to the sum of applied Methylene blue, decrease of particle sizes results in an increased loss of the active. As shown by the SEM photographs, the produced particles must be considered as coated by rolling the guest particles on the carrier surfaces confirming the findings with the applied Glass pellet carrier particles from above with a shear mixing mechanism based on the coarse carrier particles.

5.2.2.3 Comparison of Dry Coated Particle Mixture Qualities

Investigations of the mixing processes comparing Glass pellets and Cellets® as carriers with Meythlene blue as guest particles demonstrate only small differences. The contents of the mixtures after the various mixing times show slightly higher and constant values for the mixtures produced with the Glass pellets compared to the Cellets® mixtures indicating slightly increasing contents with longer mixing times but with values for the standard deviations and corresponding coefficients of variation in approximately the same range. Comparison of the weight balances supports these findings by demonstrating higher contents of mixtures in conjunction to the initial applied Methylene blue of Glass pellets mixtures. The mixing processes using the Cellets® carriers show higher hopper contents whereas the loss of both carrier materials are located approximately in the same range indicating a displacement of the Methylene blue distribution from the Cellets® towards the mixing equipment. Additionally, both carrier materials demonstrate increasing loss of Methylene blue with decreasing particle sizes. The SEM photographs show distinctively the thin layer of Methylene blue on the surface of the carriers without keeping the initial size and shape indicating a rolling mixing mechanism due to shear forces caused by the carrier particles. Despite carrier particles possess different densities, the mechanical treatment can be considered sufficient and equal to receive a dry coated layer. The higher contents of mixtures achieved with the Glass pellet carrier particles can be explained by the higher density of glass. Nevertheless, the difference can be considered small due to the rough surface texture of the Cellets® indicating strong influence on the processes with total surface areas of approximately the same ranges of all particle sizes. High density, which would actually support the shear mixing mechanism inside the Turbula®, can be compensated by rough surface textures. Furthermore, the process investigations indicate the importance of the strength of a single particle by the properties of size and weight (density of the single particle) shown by the decreasing values for decreasing particle sizes throughout the analysis. Nevertheless, the process investigations of mixing by dry coating display stable and reliable processes for different carrier particles and sizes whereas an estimation of the ideal mixing times has not yet been determined.

By displaying the mixing processes as mixing kinetics, the qualities of mixtures for each mixing time can be summarized by the means of the coefficients of variation of the mixtures according to equation (10) with the corresponding standard deviations calculated with equation (11) whereas an estimation of the ideal mixing times becomes possible. Figure 50 depicts the mixing kinetics for the Glass pellet carrier mixtures with Meythlene blue guest particles.

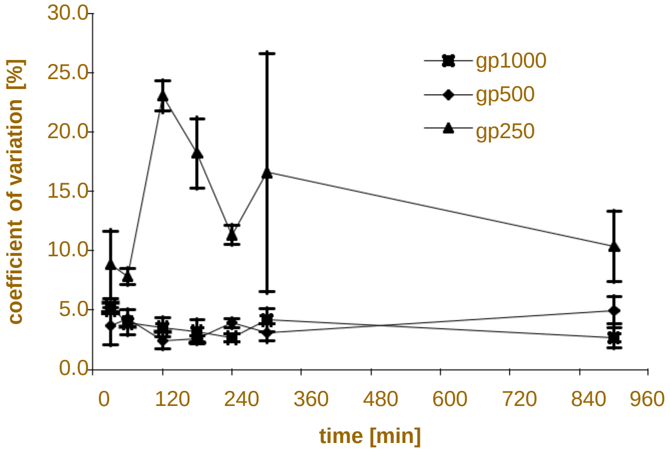


Figure 50: Mixing kinetic of Glass pellet carrier particles with 0.1% (w/w) Methylene blue displaying the qualities of mixtures as a function of time.

The means of the coefficients of variation of mixtures prepared with gp1000 carrier particles display values between 2.66% and 5.21% with a minimum after 120 minutes of mixing of 3.54% ± 0.81%. The corresponding standard deviations are located in the range of 0.54 to 1.04%. Similar values can be achieved using the gp500 as carrier particles with values between 2.43% and 4.97% and standard deviations of 0.24% and 1.56%, respectively. The lowest value can be found after 120 minutes of 2.43% ± 0.70%. With excessive higher values and an irregular progression, the mixing process using gp250 exhibits values of the means between 7.83% and 23.04% with corresponding standard deviations of 0.67% to 10.05%. After mixing 60 minutes, an ideal mixing time can be determined with values of 7.83% ± 0.67% comparable to the ones received with mixtures of the larger particles sizes. Therefore, similar qualities of mixtures can be achieved by mixing the gp1000 and gp500 as carriers whereas mixtures with gp250 deliver distinctive lower quality of mixtures. The reason can be given including the results of the process investigations where an increasing loss of Methylene blue was found with decreasing particle sizes. Even though possessing a high density supporting the process, the size, weight and surface texture of the single gp250 carrier particles are insufficient to retain the guest particles causing lower contents and higher standard deviations, which results in higher and irregular coefficients of variation. The qualities of mixtures of applied gp1000 and gp500 are delivering constant contents with small standard deviations and therefore higher qualities of mixtures compared to the mixtures received by the gp250 indicating less impact of the texture of the particles due to the size and weight of the single particles.

Figure 51 shows mixing kinetics of mixtures prepared with Cellets® carrier particles.

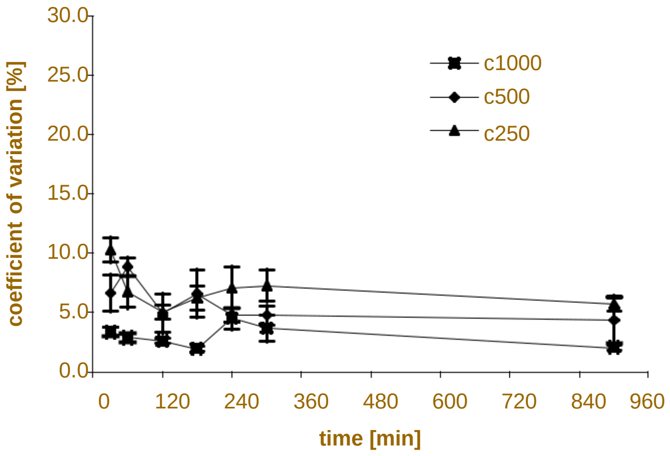


Figure 51: Mixing kinetic of Cellets® carrier particles with 0.1% (w/w)

With the minimum of 1.94% ± 0.22% after mixing 180 minutes, the means of the coefficients of variation of the c1000 mixtures display values between 1.94% and

4.51% with corresponding standard deviations from 0.21% to 1.08%. Slightly higher values can be found for the mixtures prepared with the c500 carrier particles between 4.34% and 8.88% and corresponding standard deviations of 0.63% and 1.97%, respectively. After 240 minutes, the highest mixture quality of 4.82% ± 0.63% can be found. The qualities of mixtures using the c250 carrier particles display means between 5.04% and 10.26% with corresponding standard deviations of 0.56 and 1.78%. The ideal mixing time can be estimated after 120 minutes of mixing with 5.04% ± 0.56%. The decrease of particle sizes indicates a slight degradation of the mixture qualities but with only a small impact. The surface texture and the non-spherical shape of the Cellets® carrier particles apparently support the dry coating mixing process as shown by the rather high contents of the process investigations and the high qualities of achieved mixtures shown by the mixing kinetics.

As seen in the process investigations, differences between the mixtures of Glass pellets and Cellets® carrier particles are small and can be confirmed by the investigations of the qualities of mixtures. High density supports the Glass pellet carriers to achieve high quality mixtures but with decreasing particle size, the spherical and especially smooth surface of the particles become disadvantageous with a limiting particle size between 500 and 250 m and a particle size ratio between 1:14 and 1:7 to the active. Non- spherical shape and especially a rough surface texture convey the dry coating mixing process as shown by the previous investigations with the Cellets® carrier particles irrespective of the particle size but with longer necessary processing times. It can be assumed that a possible limiting particle size for the Cellets® is located below 250 m and a particle size ratio of 1:7 in the applied dilution of Methylene blue. Still, the estimations of the ideal mixing times summarized in table 13 indicate only a small difference. As seen in the investigations of non- interactive particle mixtures, dry coating processes follow the same assumption of balanced mixing and demixing of mixture qualities with proceeding of the process. The assumption of offering more total surface area to the guest particles could prolong mixing times and improve mixture qualities must be denied for the examined materials. Therefore, dry coating mixing processes must be optimized and investigated separately for all mixture compositions and mixing equipments as well as for all other mixing processes.

Table 13: Summary of the estimation of the ideal mixing times by the mixing kinetics.

carrier particles	ideal mixing time [min]
gp1000	120
gp500	120
gp250	60
c1000	180
c500	240
c250	120

5.2.2.4 Mechanical Stability of Dry Coated Particles

The mechanical stability of dry coated particles is of interest, when the produced particles are stored, transported or used for further processes such as tableting or encapsulation. By comparing the produced materials to regularly coated particles, the stability in terms of the mechanical strength of the interaction between carrier particles and the active layer can be investigated. A sieve tower agitating the particles for 1 hour at a frequency of 50Hz at different amplitudes of 1, 2 or 3mm whereas 1mm can be considered as a week and 3mm as a strong treatment can simulate the mechanical exposure. Applied dry coated particles were produced using all sizes of Glass pellets and Cellets® as carriers with Methylene blue as the active by mixing for the ideal mixing times determined in the previous chapter. 2g of each produced particle material were tested at the three amplitudes for three times including blue- coated glass pellets 1mm as a standard for comparison. The abrasion was calculated based on the contents of each material and analysed using the UV/Vis spectrometer of residual Methylene blue on the applied sieves by rinsing with water.

Without the use of a plasticizer inside the coat, the blue coated glass pellets 1mm should loose their layer already after small inputs of mechanical energy. As displayed in figure 52, this assumption for the standard particles can be confirmed with values of 42.21% ± 29.84% at amplitude 1mm, 85.75% ± 13.69% at 2mm and 97.28% ± 2.44% at 3mm, respectively.

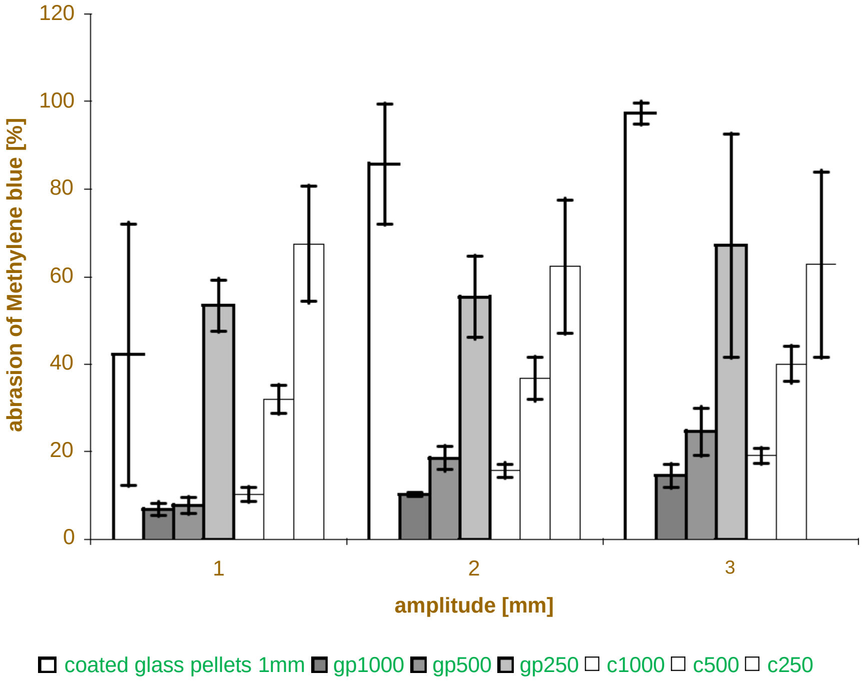
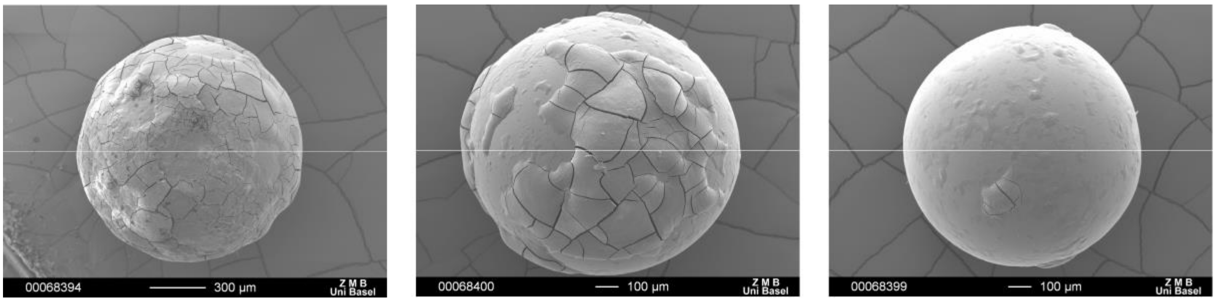


Figure 52: Estimation of the stability of dry coated particles in different sizes and different carrier particle materials compared to regularly coated particles.

The dry coated carriers gp1000 display a small increase of the abrasion from 6.85% ± 1.37%, 10.16% ± 0.42% to 14.47% ± 2.62% with increasing mechanical treatment. Similar slightly higher values are shown by the gp500 dry coated particles from 7.71% ± 1.75%, 18.53% ± 2.73% to 24.57% ± 5.39%, respectively. The dry coated particles gp250 exhibit distinctively higher values from 53.41% ± 5.84%, 55.30% ± 9.24% to 67.13% ± 25.52% indicating a much smaller interaction of the Methylene blue layer with the surface confirming the findings of reduced mixture qualities due to the size, weight of the single particles and the surface texture. The increase of mechanical intensity regarding the dry coated Cellets$^{\circledR}$ carrier particles results in a slight increase of the abrasion for all particle sizes keeping the ratio between the particle sizes at approximately the same level. Values for the dry coated c1000 carriers increase slightly from 10.22% ± 1.52%, 15.70% ± 1.46% to 19.01% ± 1.69%, for the c500 from 32.02% ± 3.15%, 36.65% ± 4.78% to 39.95% ± 4.03% and for the c250 from 67.49% ± 13.22%, 62.35% ± 15.22% to 62.83% ± 21.17%, respectively.

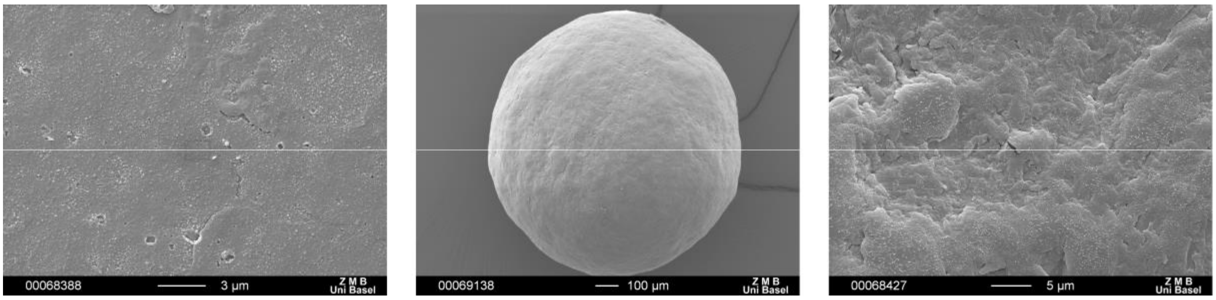
Comparing the exposure of the dry coated carrier particles to mechanical treatment, the results indicate that with increasing mechanical treatment, the interaction of the layers with the surfaces of the respective carriers is decreasing. With increasing mechanical exposure of the particles, a loss of active can be determined. Nevertheless, no dry coated particle material reaches levels achieved with the standard coated particles where it can be assumed that a stronger interaction and more stable particles are produced with dry coating. Figure 53 confirms this assumption where particles at different intensities are depicted by SEM photographs.



coated glass pellets 1mm
magnification: 150x

after amplitude 1mm
magnification: 70x

after amplitude 3mm
magnification: 70x



gp500; amplitude 3mm
magnification: 5000x

c1000; amplitude 3mm
magnification: 70x

c500; amplitude 3mm
magnification: 2500x

Figure 53: Examples of SEM photographs displaying the coated glass pellets 1mm and dry coated carrier particles after mechanical treatment of different intensities. The disruptions of the coating of the coated glass pellets 1mm are due to the residual water content of the coat heated up by the SEM.

The conventionally coated glass pellets 1mm blue loose their coating by parts breaking off the surface whereas the dry coated particles still show their layer regularly distributed on the total surface. By decreasing particle sizes, the interaction is decreasing as well which confirms the findings from the previous results about the shape, surface texture and density influences. Dry coated particles can be considered at least as resistant to mechanical exposure such as storage, transportation or by appliance in further production processes as coated particles produced with regular coating processes.

5.2.3 Application of the Percolation Theory to Dry Coating

Powders can be regarded as disperse systems of solid particles distributed in air as the continuous phase [13]. Therefore, these systems consist of particles in a highest and random packing arrangement with void spaces in between where a respective porosity can be defined. By applying the percolation theory though, the system can be regarded as a random three dimensional network of pores within a solid continuum with air percolating through the interparticle void spaces continuously
[71]. As an example of the percolating pore structure in solids, tablets featuring lower porosities due to the applied compression still offering air a percolating pore structure for transportation up to a certain degree [71]. The interparticle void space exhibits an internal surface. The internal surface can be considered as equal to the sum of all particle surfaces, whereas with decreasing particle sizes, the value of the surface is increasing. Figure 54 depicts the random packing arrangement of solid particles with the random network of pores of carrier particles for the dry coating process.

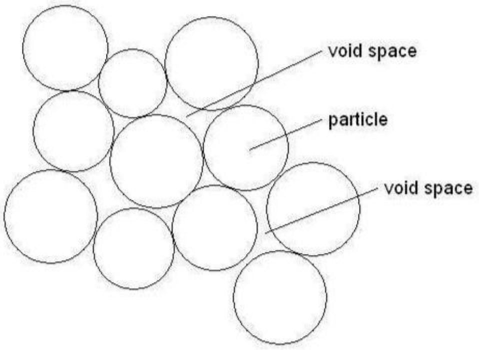


Figure 54: Illustration of the random packing arrangements of carrier particles and the random network of pores displayed as a two dimensional cross- section.

By adopting the percolation theory to dry coating processes, the qualities of mixtures may be considered as dependent on the concentration of interactive fines applied with the coarse carrier particles during mixing. Preparing a dry coating mixture with a small concentration of fines, all guest particles are fixed to the surfaces of the carriers due to the rolling shear mixing mechanism including desagglomeration of initial agglomerated guest particles. The fines cover the total surface of the carriers only to a small but regular degree without or at least with only a small amount of free fine particles located in the interparticle void space resulting in high mixture qualities. Thereby, the fine particle concentration stays clearly below the saturation concentration of the carrier surfaces. With increasing concentrations of applied fines, the qualities of mixtures remain at high levels including an increase of free fines without large influences. The dry coat is gaining size until the saturation of the carrier surfaces with increasing fine particle concentration is reached, which can be defined as the saturation concentration of the carrier particles or in other words the critical fine particle concentration CFPC. Increasing the fine particle concentration over the CFPC results in an oversaturation of the carrier particles, whereas the initial void spaces between the dry coated particles are filled with fines and fine particle clusters resulting in decreasing mixture qualities. By further increase of the concentration of the fines, all void spaces are filled with guest particles forming a second infinite cluster. The fines percolate the binary system as a result of the supersaturation of the carrier particles. A further increase of the concentration of fines would result in large clusters besides filling the void spaces where the mixing and demixing equilibrium would tend towards demixing.

The theoretical implementation of the percolation theory on dry coating processes just described was studied by applying the carrier particles Glass pellets and Cellets® described above with increasing concentrations of Methylene blue at total mixture weights specified in table 5. The contents of mixtures were determined according to equation (10) after mixing in the Turbula® at 21 rpm for the estimated ideal mixing times summarized in table 13 with the mixing metal element charged in the preferred wb sequence to study the saturation process. Sampling was carried out including the required details for sampling and sample analysis for at least 25 samples. Certain mixtures were sieved prior to sampling for 1 minute at the minimum amplitude of 1mm with the sieve tower to separate fines from the produced dry coated particles without massively affecting the structure. The sieves used to remove the fines were also rinsed and measured whereas the received value is defined as the sieve content. Additionally, weight balances were calculated by adding the amounts of the contents of mixture, hopper contents and if present, the sieve contents of Methylene blue at the corresponding fine particle concentrations for the sieved and unsieved mixtures.

5.2.3.1 Saturation Process of Mixtures with Glass Pellets Carriers

An exact determination of the free fine particle concentration in the void spaces between the carrier particles is not possible. By determining the contents of mixtures with increasing fine particle concentrations, a possible existing saturation of carrier surfaces may be quantified whereas a CFPC becomes assessable.

Figure 55 shows the contents of mixtures as a function of the fine particle concentration of initially applied Methylene blue. By sieving the mixtures prior to sampling and sample analysis, free fine particles and fine particle clusters can be removed, which simply adhere to the dry coated particles not as a part of the uniform dry coat.

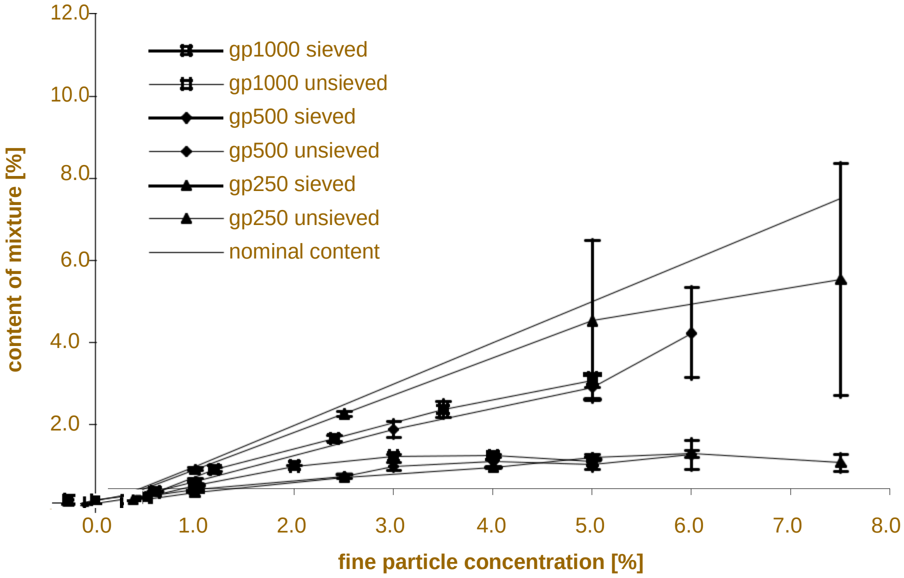
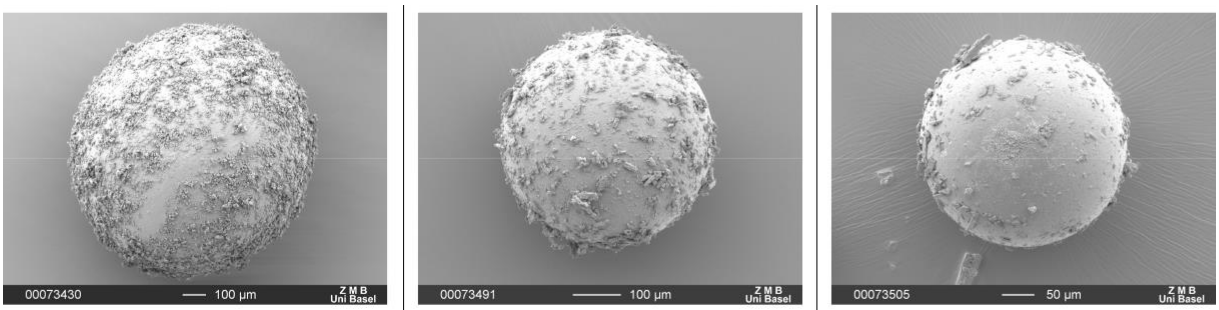


Figure 55: Contents of mixtures of gp1000, gp500 and gp250 carrier particles with Methylene blue as a function of the fine particle concentration compared to the nominal content.

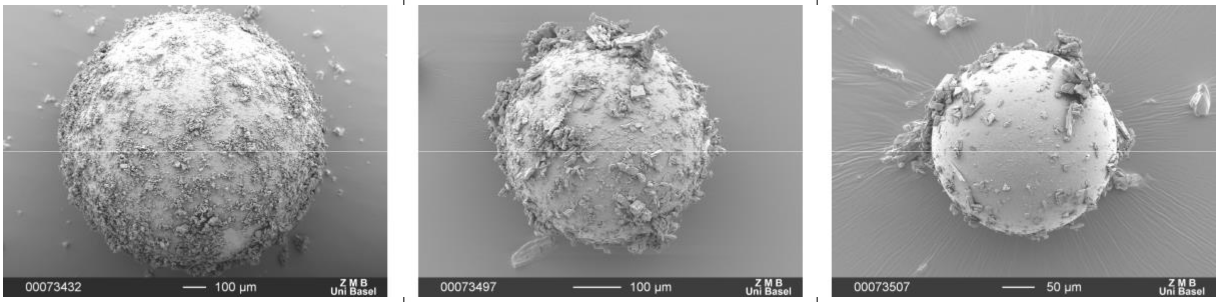
The results obtained with the Glass pellets carrier particles sieved prior to sampling show distinctively constant levels of contents of mixtures with increasing fine particle concentration. With flattening curves of the contents of mixtures with increasing fine particle concentration for all particle sizes, highest values of the contents of mixtures are 1.2560% ± 0.0293% (w/w) for the gp1000 carrier particles at an applied fine particle concentration of 4.0% (w/w), 1.0982% ± 0.1104% (w/w) for the gp500 at 4.0% (w/w) and 1.3001% ± 0.0838% (w/w) for the gp250 at 6.0% (w/w) of initially applied Methylene blue in the mixture, respectively. The highest values obtained by the measurements of the contents of mixtures can be regarded as the saturation concentration of the carrier particles. Even though the values of the contents are located approximately in the same range, the initially applied fine particle concentration has to be increased for the gp250 carrier particles to reach the saturation level. The standard deviations of the contents of mixtures are all located in the same range from 0.0025% to 0.0303% (w/w) for the gp1000, 0.0019% to 0.3578% (w/w) for the gp500, and from 0.0012% to 0.2048 % (w/w) for the gp250 indicating increasing values for increasing fine particle concentrations. The contents of mixtures received without sieving prior to sampling do not aspire to a certain limit, but increase continuously with increasing fine particle concentrations. By following the nominal content, higher levels of contents of mixtures can be reached with highest values for the gp1000 of 3.0848% ± 0.1739% (w/w) at the initially applied fine particle concentration of 5% (w/w), 4.2398% ± 1.0947% (w/w) for the gp500 at 6% (w/w) and 5.5369% ± 2.8269& (w/w) at 7.5% (w/w) for the gp250, respectively. Thereby, the results indicate only a small difference between mixtures prepared with the gp1000 and gp500 carrier particles with similar progress of the content curves compared to the mixtures prepared with the gp250, which show values closer to the nominal content. With increasing fine particle concentration, the standard deviations increase constantly from 0.0035% to 0.1739% (w/w) for the gp1000 mixtures, 0.0018% to 1.0947% (w/w) for the gp500 and from 0.0058% to 2.869% (w/w) for the gp250 mixtures. The received results of sieved and unsieved dry coated mixtures at increasing fine particle concentrations display distinctively the influence of the fines on mixture qualities. While the sieved mixtures derive high mixture qualities even after the saturation of the carrier surfaces due to the removal of the free fines and fine particle clusters, the unsieved mixtures indicate decreasing mixture qualities with increasing fine particle concentrations. Figure 56 displays examples of SEM photographs of dry coated particles before and after sieving, which confirm the aforementioned results.



gp1000; sieved, 2%
magnification: 70x

gp500; sieved, 5%
magnification: 150x

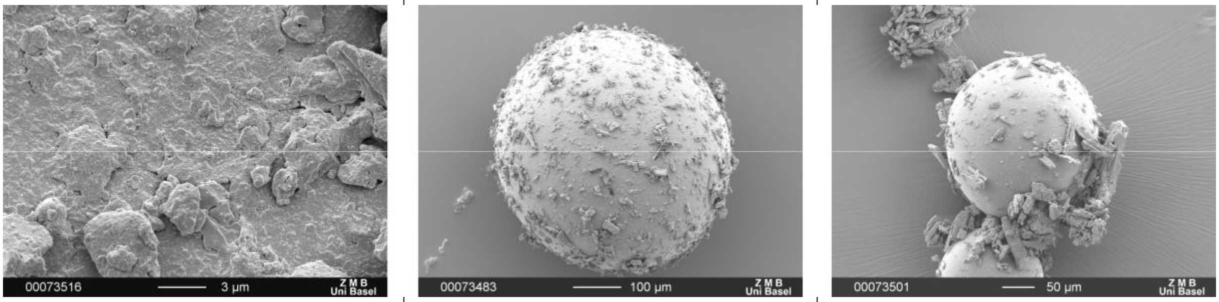
gp250; sieved, 5%
magnification: 200x



gp1000; unsieved, 2%
magnification: 70x

gp500; unsieved, 5%
magnification: 150x

gp250; unsieved, 5%
magnification: 200x



gp1000; sieved, 2%
magnification: 5000x

gp500; unsieved, 3%
magnification: 150x

gp250; unsieved, 4%
magnification: 200x

Figure 56: Examples of SEM photographs showing dry coated particles with the carrier particles gp1000, gp500 and gp250 before and after sieving at different fine particle concentrations. The specified concentration levels are values of initial applied Methylene blue.

All particles feature the dry coated layer and additional Methylene blue particles adhering on the surface of the carriers. Even though in being below the saturation concentration, the gp1000 dry coated particles show additional but small and converted Methylene blue particles on the surfaces of the sieved and unsieved particles. By sieving prior to sampling, the slightly larger but still converted Methylene blue particles and particle clusters on the surfaces of the gp500 below the saturation concentration can be removed. The largest Methylene blue particle clusters can be found on the unsieved dry coated gp250 particles (below saturation concentration), which exhibit their initial shape and size.

Figure 57 displays the weight balance of the sieved and unsieved mixtures for monitoring of the Methylene blue distribution of the saturation process prepared with gp1000 carrier particles displaying the converted amounts of the contents of mixtures, hopper contents and sieve contents compared to the initial amount of Methylene blue applied in the compositions of the mixtures.

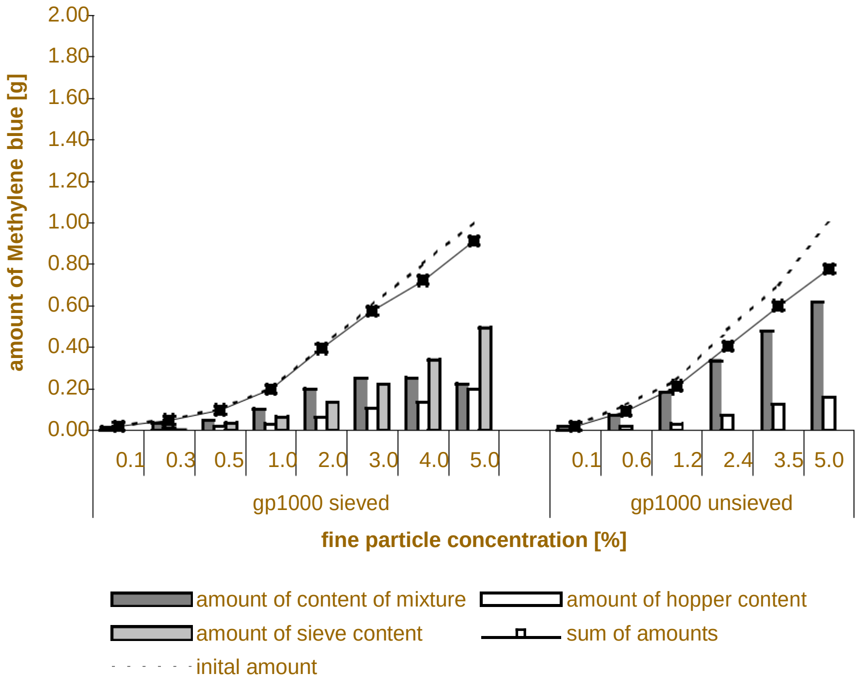


Figure 57: Weight balance of sieved and unsieved mixtures using gp1000 as carrier particles comparing the different amounts of Methylene blue received by measuring the contents of mixtures, the hopper and the sieve contents to the initially applied active.

The amounts of Methylene blue of the hopper contents are located in the same range for both sieved and unsieved mixtures with increasing values for the increasing fine particle concentrations. The increasing amounts of the sieve contents received by the analysis of the sieved mixtures are causing the increasing contents. Only a small difference between the sum and initial amount of Methylene blue can be seen, whereas the amount of the difference can be recovered on the sampling track and inside the sampling vessels, which are not analyzed. Figure 58 displays the weight balances of the sieved and unsieved mixtures prepared with the gp500 carrier particles.

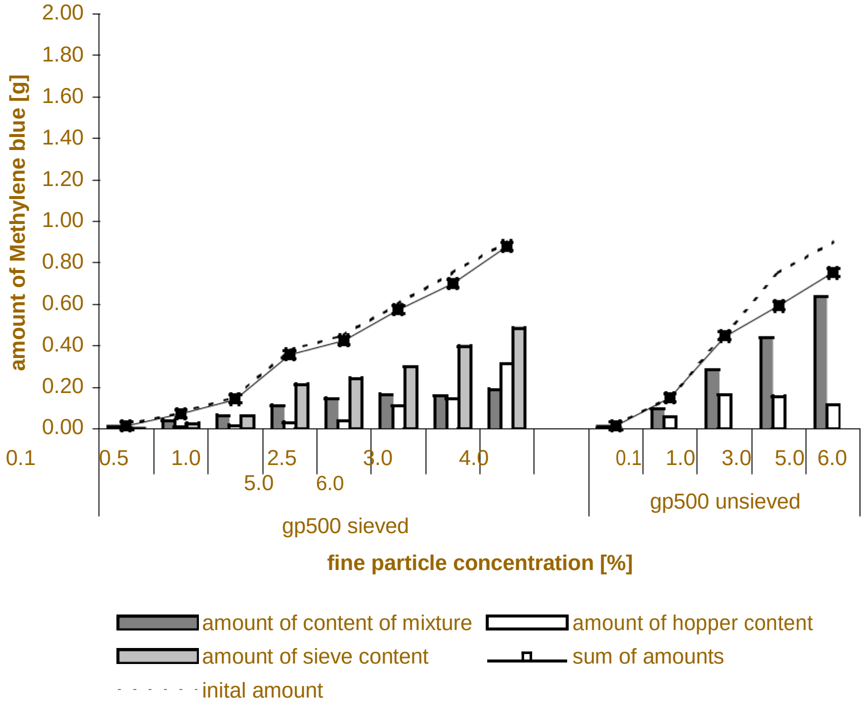


Figure 58: Weight balance of sieved and unsieved mixtures using gp500 as carrier particles comparing the different amounts of Methylene blue received by measuring the contents of mixtures, the hopper and the sieve contents to the initially applied active.

As seen by the weight balances of the gp1000 carrier mixtures, the amounts of the hopper contents obtained by the gp500 sieved and unsieved mixtures are located in approximately the same range with increasing values for increasing fine particle concentrations. The amounts of the sieve contents increases as well with the same values obtained by the gp1000 mixtures resulting in increasing contents of mixtures shown by the unsieved mixtures. Again, only a small difference between the sum and the initial amount of Methylene blue can be found. By using the gp1000 and gp500 as carriers in mixtures with Methylene blue as guest particles, no differences can be found on contents of mixtures as well as on the weight balances. As stated by the estimations of the ideal mixing times, the only difference can be found by the particle sizes with a reduction from approximately 1000 to 500 m with particle size ratios of 1:32 and 1:14 compared to Methylene blue and are not influencing the mixture qualities of the spherical and smooth carrier particles. Figure 59 shows the weight balances of sieved and unsieved gp250 carriers mixed with Methylene blue.

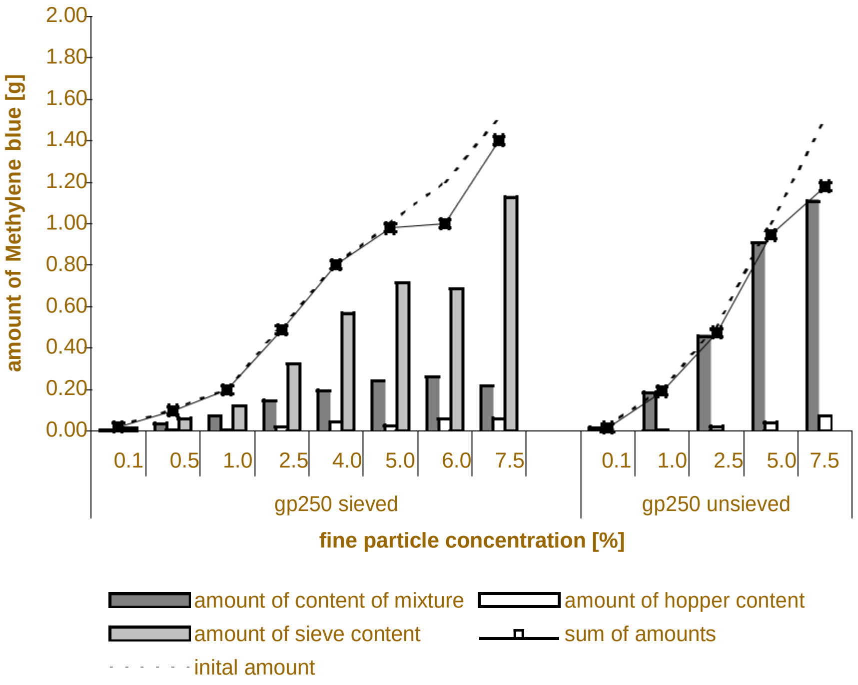


Figure 59: Weight balance of sieved and unsieved mixtures using gp250 as carrier particles comparing the different amounts of Methylene blue received by measuring the contents of mixtures, the hopper and the sieve contents to the initially applied active.

The sieved and unsieved mixtures of the gp250 carriers with Methylene blue show the same amounts of hopper contents with increasing fine particle concentrations with distinctively lower values compared to the results obtained by the gp1000 and gp500 mixtures. A fast increase of the amounts of the sieve contents can be seen without loosing initially applied Methylene blue. The reduction of the amount of Methylene blue on the mixing and sampling equipment compared to the results obtained with the gp1000 and gp500 mixtures can be explained again by the reduced particle size of approximately 250 m with a ratio of 1:7 compared to the active whereas the size, weight and surface texture of the single gp250 particle shows inferior properties for the dry coating process. The previous findings of the study of the saturation process by regarding the contents of mixtures and the weight balances can be confirmed by the SEM photographs whereas initial Methylene blue particles and particle clusters can only be seen on the surfaces of the unsieved and sieved gp250 dry coated carrier particles. Nevertheless, a saturation concentration of the surfaces of the Glass pellets carriers with Methylene blue exists distinctively between 4 to 6% (w/w) of initially applied active whereas most effective saturation can be obtained by applying the gp1000 followed by the gp500 and gp250 carriers.

5.2.3.2 Saturation Process of Mixtures with Cellets® Carriers

The contents of mixtures with sieved and unsieved Cellets® carrier particles as a function of the fine particle concentration of initially applied Methylene blue in the mixtures is depicted in figure 60.

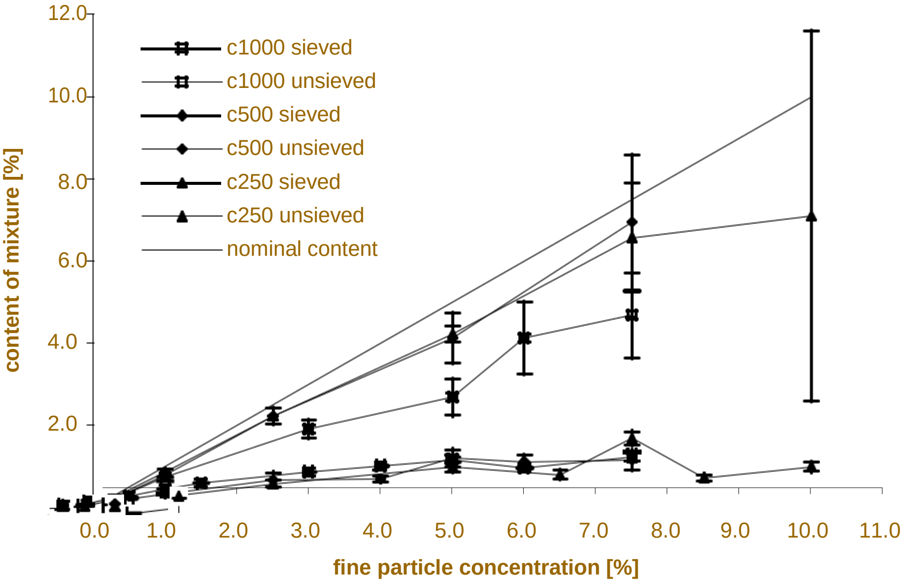
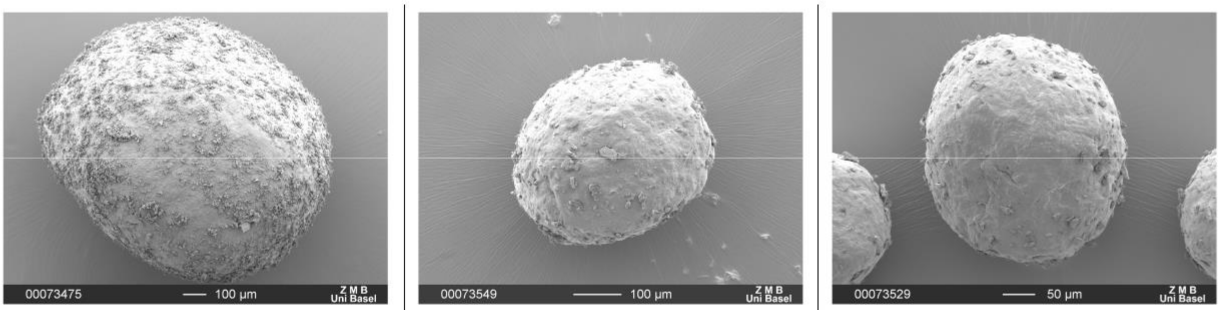


Figure 60: Contents of mixtures of c1000, c500 and c250 carrier particles with Methylene blue as a function of the fine particle concentration compared to the nominal content.

The distinctive flattening of the curves of the contents of mixtures after sieving indicates the saturation of the carrier surfaces of the c1000, c500 and c250 particles. With increasing fine particle concentrations, highest values of the contents of mixtures can be found at an applied fine particle concentration of 5.0% (w/w) of 1.1693% ± 0.0535% (w/w) for the c1000, at 5.0% (w/w) of 1.2034% ± 0.2029% (w/w) for the c500 and at 7.5% (w/w) of 1.6851% ± 0.1633% (w/w) for the c250 mixtures, respectively. The initially applied fine particle concentration has to be increased in order to reach the saturation level for the c250 carriers whereas the c1000 and c500 can be considered as identical. The standard deviations of the contents of mixtures show values from 0.0015% to 0.0932% (w/w) for the c1000, 0.0041% to 0.2340% (w/w) for the c500, and from 0.0023% to 0.1693% (w/w) for the gp250 indicating increasing values for increasing fine particle concentrations. Without sieving, the measurements of the contents of mixtures increase continuously with increasing fine particle concentrations following the nominal content with values of 4.6781% ± 1.0251% (w/w) at the initially applied fine particle concentration of 7.5% (w/w) for the c1000 mixtures, 6.9426% ± 1.6301% (w/w) at 7.5% (w/w) for the c500 and of 7.0958% ± 4.4967% (w/w) at 10.0% (w/w) for the c250, respectively.

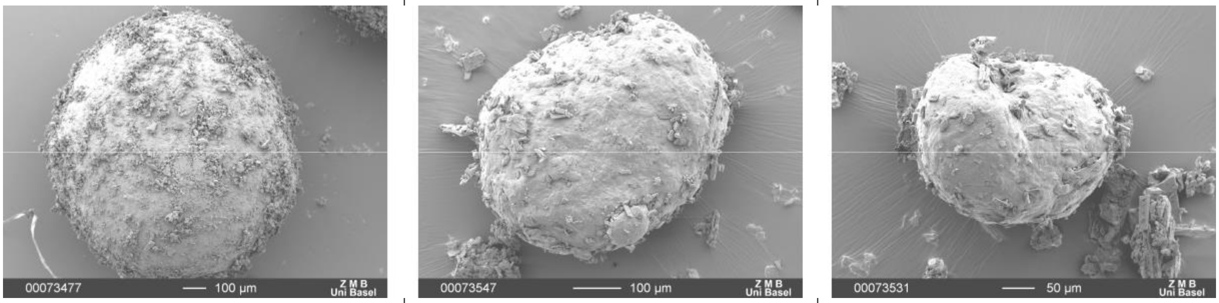
Thereby, the results indicate a small difference between the c500 and c250 mixtures with values closer to the nominal content compared to the values obtained by the c1000 mixtures. With increasing fine particle concentrations, the standard deviations increase constantly from 0.0012% to 1.0251% (w/w) for the c1000 mixtures, 0.0041% to 1.6301% (w/w) for the c500 and from 0.0030% to 4.4967% (w/w) for the c250 mixtures. As seen with the Glass pellets carrier particles, the received results of sieved and unsieved dry coated mixtures at increasing fine particle concentrations show distinctively the influence of fines on the mixture contents deriving higher values by not sieving the mixtures. After the saturation of the carrier surfaces, the unsieved mixtures indicate decreasing mixture qualities with increasing fine particle concentrations due to the fraction of fines and fine particle clusters not removed from the mixtures. SEM photographs in figure 61 show examples of the dry coated particles before and after sieving.



c1000; sieved, 6%
magnification: 70x

c500; sieved, 5%
magnification: 150x

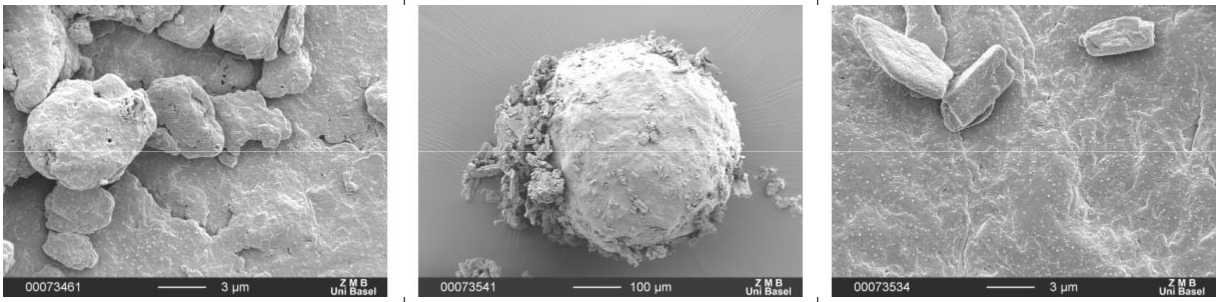
c250; sieved, 7.5%
magnification: 200x



c1000; unsieved, 6%
magnification: 70x

c500; unsieved, 5%
magnification: 150x

c250; unsieved, 7.5%
magnification: 200x



c1000; unsieved, 5%
magnification: 5000x

c500; unsieved, 7.5%
magnification: 150x

c250; unsieved, 8.5%
magnification: 5000x

Figure 61: Examples of SEM photographs showing dry coated particles with the carrier particles c1000, c500 and c250 before and after sieving at different fine particle concentrations. The specified concentration levels are values of initial applied Methylene blue.

All particles feature the dry coated layer and Methylene blue particles, which adhere additionally on the surface. In being above the saturation concentration, the c1000 particles show a light difference between unsieved and sieved particles with smaller and converted Methylene blue. The c500 and c250 particles displayed feature an increased amount of active on the surface of the unsieved mixture particles at the saturation concentrations. The sieved particles though exhibit no additional guest particles at the saturation concentrations.

Figure 62 displays the weight balances of c1000 mixtures for monitoring of the saturation process.

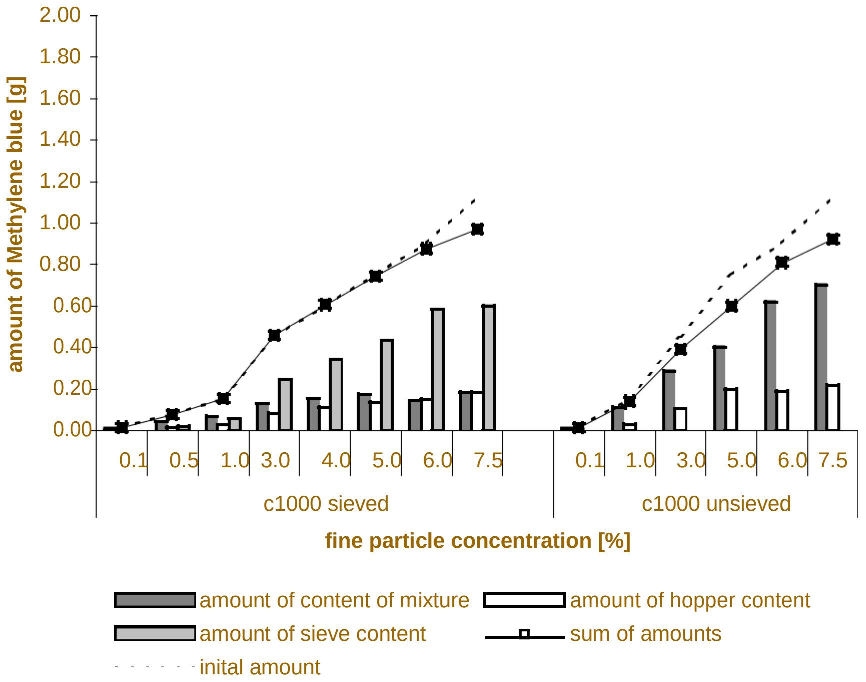


Figure 62: Weight balance of sieved and unsieved mixtures using c1000 as carrier particles comparing the different amounts of Methylene blue received by measuring the contents of mixtures, the hopper and the sieve contents to the initially applied active.

The amount of Methylene blue on the mixing and sampling equipment is located in the same range for both sieved and unsieved mixtures with slightly increasing values of applied increasing fine particle concentrations. Also, the amounts of the sieve contents as an estimation of the free fines in the mixtures are increasing. The recovery of Methylene blue indicates small losses of the mixtures not sieved prior to sampling whereas the fines adhere to the sampling train and the sampling vessels. Figure 63 displays the weight balances of sieved and unsieved mixtures prepared with the c500 carrier particles.

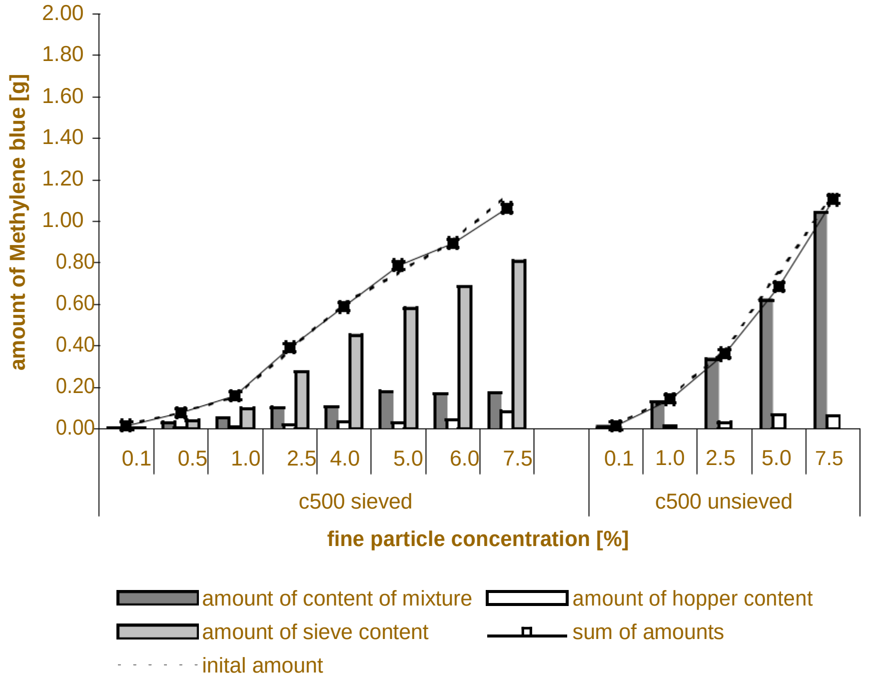


Figure 63: Weight balance of sieved and unsieved mixtures using c500 as carrier particles comparing the different amounts of Methylene blue received by measuring the contents of mixtures, the hopper and the sieve contents to the initially applied active.

Comparison of the amounts of the hopper contents of Methylene blue for both mixture types displays again no differences whereas a reduction of the values in comparison to the values obtained by the c1000 mixtures can be seen. As indicated before, with increasing fine particle concentrations, an increase of the amounts of the sieve contents can be determined whereas higher values compared to the c1000 values are observed. Again, the initially applied Methylene blue can be recovered in both types of mixtures with small losses at high concentrations of Methylene blue. The amounts of the contents of the c250 mixtures are depicted in figure 64.

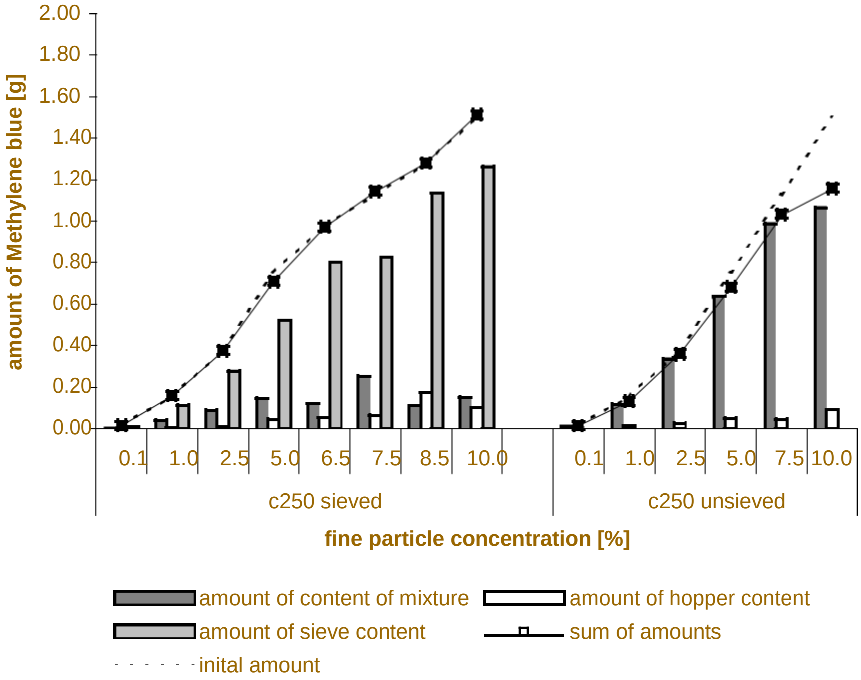


Figure 64: Weight balance of sieved and unsieved mixtures using c250 as carrier particles comparing the different amounts of Methylene blue received by measuring the contents of mixtures, the hopper and the sieve contents to the initially applied active.

The values obtained by analyzing the c250 mixtures are all located in the same range as the values received by analyzing the c500 mixtures with increasing levels of the amounts of the sieve contents with increasing fine particle concentrations.

The mixtures analyzed after sieving indicate increasing mixture content levels with decreasing particle sizes with a necessary increase of the initially applied fine particle concentration to saturate the carrier surfaces. The influence of the fines is once more shown by the increasing contents of unsieved mixtures. The results can be confirmed by regarding the weight balances, whereas only a small difference can be found between the c1000 and the smaller carriers. During the mixing of the particles, the Methylene blue is less distributed on the mixing and sampling equipment with decreasing particle sizes indicated by the differences of the higher mixture contents of the unsieved mixtures and the difference of the sieve and hopper contents. Nevertheless, the non- spherical shape and especially the surface texture helps the carrier particles to overcome the equal density to Methylene blue whereas the density difference would support the rolling mixing mechanism inside the

Turbula® with the SEM photographs confirming the just mentioned results. Therefore, the results prove the existence of a saturation concentration for the Cellets® between 5 to 7.5% of initially applied active as well, whereas the c1000 show most effective saturation indicated by the lowest initially applied fine particle concentrations and lowest sieve contents followed by the c500 and c250.

5.2.3.3 Influencing Properties on the Saturation Process

As shown by the previous investigations of the estimation of the saturation concentrations of the Glass pellets and Cellets® carrier particles, a saturation of the dry coated particles with Methylene blue as guest particles is demonstrated for all particle sizes. The received saturation concentrations of the mixtures are located in approximately the same range for both carrier materials with values between 1.0982% ± 0.1104% (w/w) and 1.6851% ± 0.1633% (w/w) whereas higher amounts of the guest particles must be applied to reach the saturation levels with mixtures composed of the Cellets® carrier particles. This can be explained by the difference of the density ratios of the Glass pellets and the Cellets® compared to the active of 1:2 for the Glass pellets and equal values for the Cellets® carriers, respectively. Therefore, by increasing density differences of the carriers compared to the guest particles, a lower amount of active is necessary to reach the saturation of the surfaces of 4 to 6% (w/w) of initially applied active for the Glass pellets and 5 to 7.5% (w/w) for the Cellets® carrier particles, respectively.

The influence of the particle size and therefore the surface area can be regarded by calculating the total surface area of the carriers in the mixtures. Table 14 displays the reduction of the surface areas at each particle size due to the constant total mixture weights, which had to be applied to accomplish the mixing and sampling procedure and the increasing amount of Methylene blue in the mixtures by increasing fine particle concentrations. The nominal contents shown in the table are the lowest and highest values of Methylene blue applied to study the saturation process.

Table 14: Reduction of the amount of carriers per mixture with increasing fine particle concentration.

carriers	nominal content* [%]	weight of applied carrier particles [g]	number of carriers** -	total surface area [cm^2]
gp1000	0.1	19.98	8743	398.4
	5.0	19.00	8315	378.8
gp500	0.1	14.99	86876	711.6
	6.0	14.10	81745	669.5
gp250	0.1	19.98	743128	1765.5
	7.5	18.50	688082	1634.7
c1000	0.1	14.99	10570	524.2
	7.5	13.88	9787	485.4
c500	0.1	14.99	230723	1420.9
	7.5	13.88	213632	1315.7
c250	0.1	14.99	873244	2197.3
	10.0	13.5	786707	1979.5

* lowest and highest applied concentrations of Methylene blue

** calculated by using equation (5) to calculate the weight of a single particle

The increasing total surface areas of decreasing particle sizes for both materials can be used to convert the contents of mixtures received by the investigations of the saturation processes to contents of Methylene blue per surface area. Theoretically, the smaller the particle size followed by the increase of the total surface area, the carriers should gather the more active. Figure 65 depicts the summary of the Glass pellets mixtures compared to the summary of the Cellets® dry coated carriers whereas the surface dependent contents are displayed as a function of the fine particle concentration.

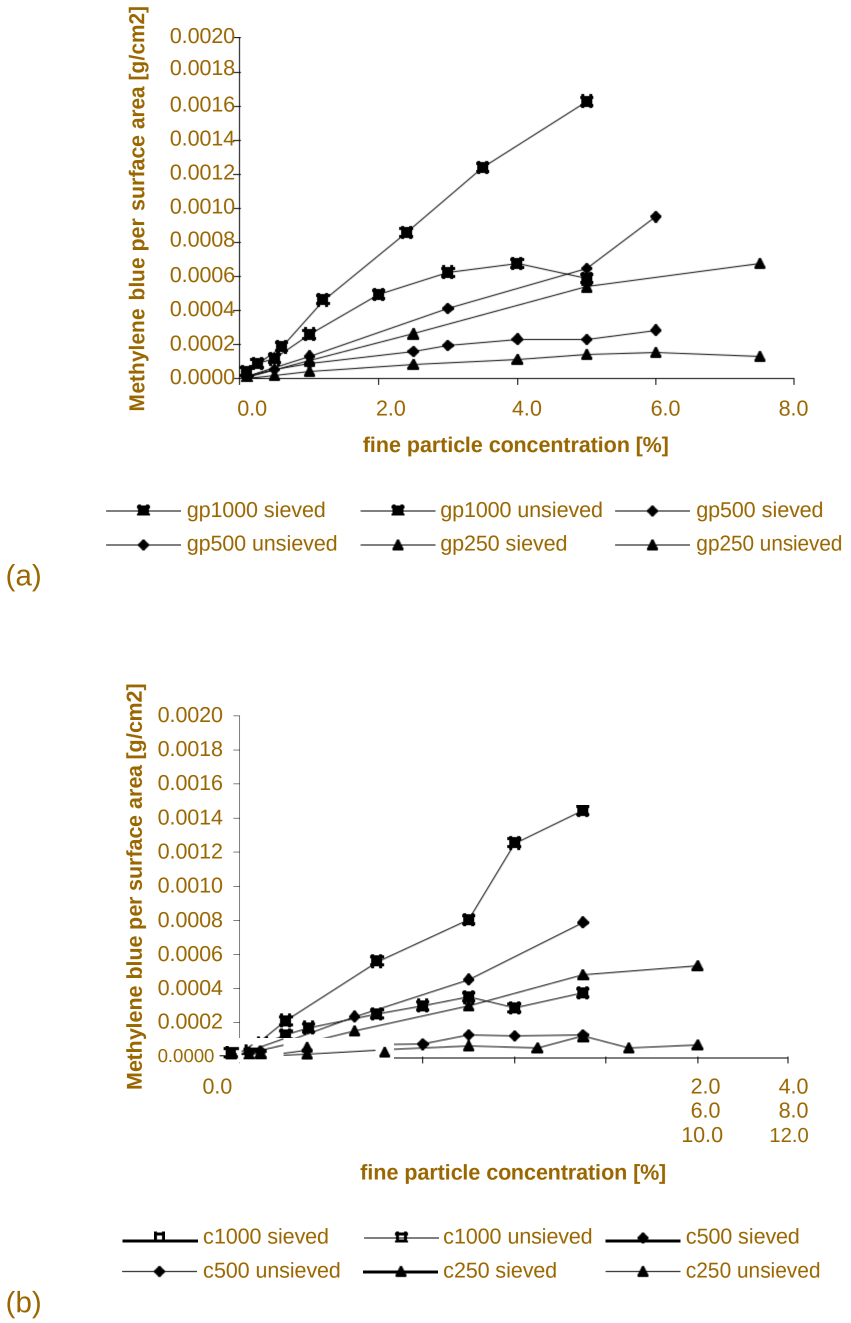


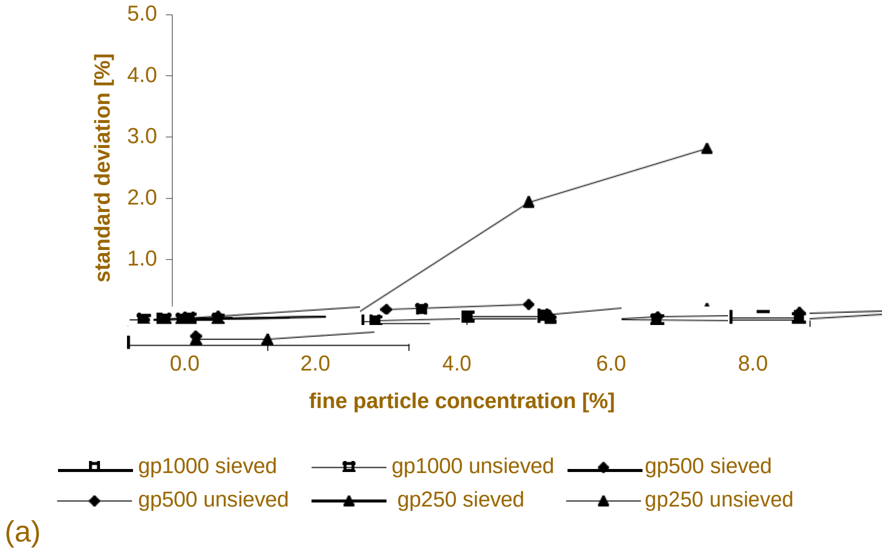
Figure 65:Comparison of the contents of mixtures converted to the contents of Methylene blue per surface area of (a) the Glass pellets and (b) the Cellets® carrier particles.

The calculation of the contents of Methylene blue per surface area of the unsieved mixtures generates highest concentrations for the gp1000 of 1.6mg/cm^2 at 5% (w/w) of initially applied Methylene blue, for the gp500 of 0.95mg/cm^2 at 6% (w/w), for the gp250 of $0.68mg/cm^2$ at 7.5% (w/w), for the c1000 of $1.45mg/cm^2$ at 7.5% (w/w), for the c500 of $0.79mg/cm^2$ at 7.5% (w/w) and for the c250 of $0.54mg/cm^2$ at 10% (w/w), respectively. Even though the values are located in the same range, the initially applied amount of Methylene blue has to be increased. The values of the converted contents per surface area of the sieved mixtures are located at $0.68mg/cm^2$ at 4% (w/w) for the gp1000, at $0.23mg/cm^2$ at 4% (w/w) for the gp500, at $0.16mg/cm^2$ at 6% (w/w) for the gp250, at $0.35mg/cm^2$ at 5% (w/w) for the c1000, at $0.13mg/cm^2$ at 5% (w/w) for the c500 and at $0.12mg/cm^2$ at 7.5% (w/w) for the c250 carriers, respectively.

The results obtained by the comparison of the contents of mixtures per surface area demonstrate distinctively the reduction of the saturation concentrations by decreasing particle sizes of both carrier particle systems in contrary to the theoretical predictions. The impact of density is displayed by higher levels of the saturation concentrations per surface area for the Glass pellets as well. The findings confirm the previous results obtained by the investigations of the saturation process where increasing density differences between carrier and guest particles advance the saturation process. Surface texture seems to be less important compared to the density and the particle size differences as shown by the lower values of the contents per surface areas. To summarize, the important particle properties for the saturation of carrier particles in dry coating are the density and particle size differences between the carrier and guest particles. Additionally, a dynamic equilibrium of mixing and demixing of the saturation process can be seen by regarding the irregular course of the saturation curves of all carrier systems after the saturation concentration.

5.2.3.4 Estimation of the Critical Fine Particle Concentration

So far, a saturation concentration with corresponding important particle properties has been identified for the saturation process of dry coated particles. By regarding the standard deviations of the contents of mixtures calculated according to equation (11), a possible CFPC can be estimated and compared to the saturation concentrations received from above. At the beginning of the saturation process, no differences between the sieved and unsieved mixtures in terms of the standard deviations should be seen. As soon as the surfaces of the carriers are saturated, an increase of the standard deviations of the unsieved particle mixtures should indicate the CFPC whereas the standard deviations of the sieved mixtures should remain at constant low levels. Figure 66 depicts the standard deviations of the Glass pellets and Cellets® carrier particle mixtures as a function of the fine particle concentration.



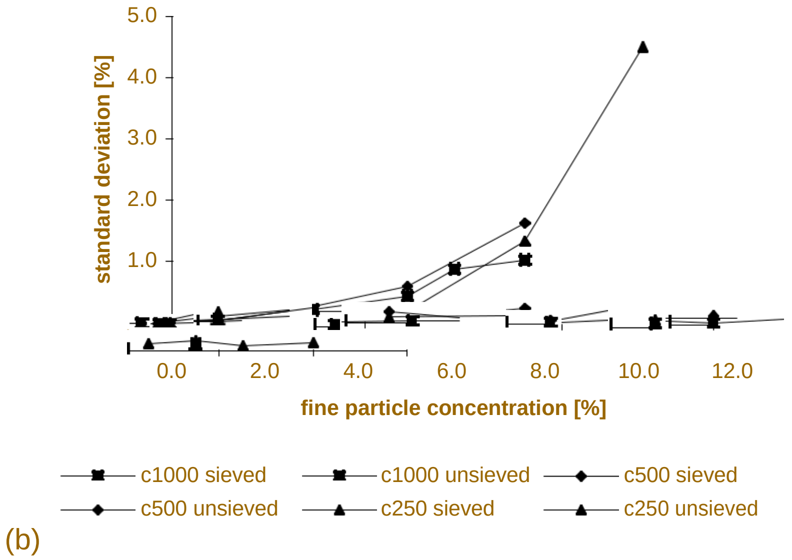


Figure 66: Comparison of the standard deviations of mixtures of Methylene blue with (a) the Glass pellets and (b) the Cellets® carrier particles as a function of the fine particle concentration. The increasing standard deviations indicate the CFPC.

At the beginning of the saturation process, the sieved and unsieved Glass pellet carrier mixtures show low values before the saturation concentrations of the carriers is reached. The values of the gp1000 and gp500 unsieved carrier mixtures stay clearly at low levels comparable to the corresponding sieved mixture values even after trespassing the saturation concentrations of between 4 to 6% (w/w) of applied Methylene blue. The saturation of the surface areas of the gp1000 and gp500 can be reached but a CFPC cannot be determined. The rolling mixing mechanism of these carrier particles inside the Turbula® is too strong whereas the initial Methylene blue particles are not only desagglomerated but downsized as well. The values of the standard deviations stay at low levels due to the particle size reduction and regular distribution of the active in the mixtures. By applying the gp250 carriers with Methylene blue as guests, the standard deviations of the unsieved mixtures increase beginning at 2.5% (w/w) of the initial active indicating the CFPC. With increasing fine particle concentrations, an increase of the difference between the sieved and unsieved mixture values can be seen whereas the beginning of the increasing standard deviations correspond to the beginning of the flattening of the saturation concentration curve for the gp250 carrier mixtures. The Cellets® carriers show as well low values for both sieved and unsieved mixtures standard deviations before the saturation of the carrier surfaces is reached. As soon as the saturation process reaches the saturation concentrations of the carriers of between 5 to 7.5% (w/w) of initial active, the standard deviations of the unsieved mixtures increase distinctively beginning at 3% (w/w) of initially applied Methylene blue for the c1000, at 2.5% (w/w) for the c500 and at 2.5% (w/w) for the c250 mixtures, respectively. It is obvious that the desagglomeration properties of the carriers are not developed to the same level as the Glass pellets carrier particles due to the lower density difference between the carriers and the active. With decreasing particle sizes, the decrease of the CFPC can be found.

The results obtained with the gp1000 and gp500 mixtures indicate no existence of a CFPC in the applied fine particle concentrations even though a saturation concentration can be determined. Due to the high density difference between the carriers and the active, the mixing mechanism of rolling reduces the particle size of the active and the shape additionally causing better mixture qualities. A possible increase of the standard deviations can be assumed though with further increase of the fine particle concentrations by filling the void spaces. The gp250 mixtures indicate clearly that the saturation concentration of the carrier surfaces is comparable to the increase of the standard deviations with a beginning of filling the void spaces with Methylene blue without further desagglomeration of the active. The saturation concentrations of the Cellets® carrier particles are corresponding to the estimation of the CFPC as well. With a slight earlier appearance as indicated by the saturation process investigations due to the smaller density difference between the carriers and guests, the desagglomeration and downsizing of the active is not comparable to the same degree as for the Glass pellets carriers.

The obtained results demonstrate the existence of a saturation concentration for all carrier particles produced with the dry coating process. In a first approximation, the CFPC can be equated to the saturation concentrations. Even though the results obtained with the gp1000 and gp500 carriers show no increase of the standard deviations and therefore no existing CFPC at the applied fine particle concentrations, the gp250, c1000, c500 and c250 demonstrate clearly an increase of the standard deviations and therefore a reduction of the mixture qualities. As summarized in table 15, the values of the CFPC at the applied fine particle concentrations slightly differ compared to the values obtained by the investigations of the saturation processes of the carrier particles.

Table 15: Comparison of the saturation concentrations and the estimated CFPC.

	saturation concentration		CFPC (estimate)
	initial fine particle concentration	fraction absorbed on particle surface*	
carriers	[%]	[%]	[%]
gp1000	4	1.2560 ± 0.0293	not available
gp500	4	1.0982 ± 0.1104	not available
gp250	6	1.3001 ± 0.0838	2.5
c1000	5	1.1693 ± 0.0535	3
c500	5	1.2043 ± 0.2029	2.5
c250	7.5	1.6851 ± 0.1633	2.5

* equivalent to the contents of unsieved dry coated mixtures

An explanation therefore can be given by the applied method of detecting the saturation concentration by sieving followed by the estimation of the CFPC, which influences the experimental results to a certain degree as shown by the SEM photographs of small adhering additional active particles to the carrier surfaces without being part of the thin layer. Nevertheless, it can be concluded that a saturation concentration and a CFPC exists whereas an exact determination remains difficult. The absorbed fractions (equals the contents of sieved mixtures) on the particle surfaces show values below the CFPC indicating that the qualities of mixtures change after the saturation process is completed. Therefore, the proposed picture of the saturation process based on the percolation theory can be regarded as a useful tool to describe the dry coating saturation process as indicated by the evidence of the saturation process results and the existence of the CFPC where a change of the binary mixture system is indicated by altering of the mixture qualities.

6. Conclusions and Outlook

Development of a New Sampling Apparatus

The development and construction of the mixing and sampling equipment followed the «Golden Rules of Sampling» based on the known sampling theory aiming towards a simple, short and reliable procedure disallowing structural disturbances of the mixtures and without affection of the received results. To evaluate the equipment, separate parts of the mixing and sampling procedure were investigated to identify possible impacts on the sequential system and the emerging results. Furthermore, non- interactive binary powder mixtures were prepared in order to compare received mixing results to calculations based on the common mixing theory.

Following equation (13), the accuracy of the sample analysis was estimated independently. The resulting value for s_a^2 can be considered negligible whereas measurements of samples will not be affected by the UV/Vis spectrometer. The qualitative estimation of the impact of sampling upon mixture qualities shows no differences between the sampling glass and metal elements compared to the standard pharmacopoeia hopper tending to core flow with white followed by blue particles as the preferable sampling sequence of charging. A quantitative estimation of the sampling error s_s^2 according to equation (13) remains difficult and must be neglected. By neglecting s_a^2 and s_s^2 of equation (13), s_m^2 can be regarded almost as identical to s^2 demonstrating sample analysis and sampling as parts of the mixing and sampling procedure without affects upon mixing results.

Handling of non- interactive powder mixtures must already be considered as a mixing step due to one convective motion before the sampling procedure. The sequence of charging mixture components before mixing must therefore be white followed by blue particles. The impact of handling on mixture qualities demonstrates furthermore no differences between the applied equipments. Nevertheless, using the developed mixing and sampling equipment can achieve the requested simple, fast and reproducible handling operations.

Results obtained with the total sequential mixing and sampling procedure of non-interactive particle mixtures including mixing show good agreement to predictions of theoretical qualities of mixtures based on the common mixing theory by applying the common equation (3) of Stange- Poole. Thereby, the Turbula® mixer delivers fast processing times and reliable results without altering the particle properties due to its diffusive mixing mechanism.

To conclude, the requested properties of the sequential mixing and sampling procedure are shown to be fulfilled with the developed and constructed mixing and sampling equipment including the Turbula® mixer. The obtained samples reflect linearly the content distributions of vertical flowing binary mixtures. The developed sequential system of mixing and sampling can be applied for further investigations of mixture qualities and investigations of mixing processes of all kinds for example by applying other mixer types. Mixing and sampling with the introduced procedure is very extensive, especially the sample analysis with the UV/Vis spectrometer. In order to reduce the dedicated time for sample analysis, other methods should be examined to determine the contents of mixtures right after sampling as for example by the aspiring near infrared spectroscopy.

The Dry Coating Mixing Process

Originating from the old concept of ordered mixing, dry coating has gained more interests as an application in dry solids mixing in pharmaceutical technology where particles with attractive properties can be generated by simple mixing. The dry coating process was investigated by applying the diffusive Turbula® mixer. With different non- interactive carrier particles for interactive fines, the mixing mechanism was analyzed based on the properties of the applied mixture components and the resulting particles to identify the important process parameters with the developed and constructed mixing and sampling equipment.

For the investigation of the dry coating mixing process, the properties of the chosen mixture components were determined. Methylene blue was employed as guest particles with interactive properties shown by a small size and broad particle size distribution, a rather high Hausner ratio indicating insufficient flowability confirmed by the flowability measurements. Additionally, the determination of the residual moisture content resulted in a rather high value which can be regarded as a supporting aid for the dry coating process with increasing the interaction forces. The requested non- interactive properties of the chosen carrier particles Glass pellets and Cellets® were shown by the determinations of the particle sizes with corresponding narrow particle size distributions, low values of Hausner ratios as well as the differences of the densities and the surface texture. As indicated by the flowability measurements performed with the developed and constructed sampling glass and metal equipments though, the mixing and sampling glass elements featured irregular flow patterns. By investigating the possible influences upon the qualities of mixtures, the mixing and sampling metal equipments showed superior properties due to the reduction of the electrostatic charging of the produced particles. It can be concluded that the mixing and sampling metal equipment must be used for further investigations of the dry coating processes with the developed and constructed mixing and sampling equipment. In order to analyse the applied materials for the investigation of the dry coating mixing process, dissolution of Methylene blue was examined to approve the operating of the sample analysis measurements. By using aqueous solutions of acetic acid as solvent for the dry coated Cellets®, the primary problem of swelling of the carriers followed by diffusion of the active inside the carriers was solved.

Therefore, investigations with Cellets® of all kinds involving content measurements must incorporate these properties. By introducing another method of sample analysis though as for example high pressure liquid chromatography, the analysis would be more expensive, but this circumstance could be avoided.

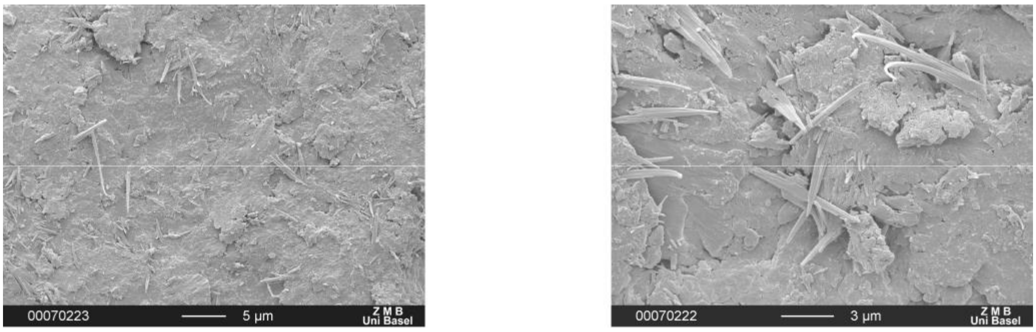
The dry coating mixing process was investigated with different carrier particles regarding the produced dry coated particles and the resulting mixture qualities. The process investigations demonstrated small differences between the received contents of mixtures with high reproducible values. The investigation of the mixing process using the Glass pellets carrier particles displayed rather constant contents whereas the Cellets® showed slightly increasing contents with longer processing times. The reduction of the particle sizes displayed decreasing contents in the same range for both carrier materials whereas the surface texture of the Cellets® overcame the reduced density differences. Regarding the mixture qualities, the differences between the carrier systems was shown to be small as indicated by the process investigations. With decreasing particle sizes though, the Glass pellets demonstrated a decrease of the mixture qualities between the particle sizes of 500 and 250 m with size ratios compared to Methylene blue of 1:14 to 1:7. The Cellets® demonstrated equal qualities of mixtures tending to lower qualities for decreasing particle sizes whereas the possible border must be located below 250 m with a size ratio of below 1:7 compared to the active. The estimated mixing times showed the density difference dependency of the process whereas prolonged mixing times must be accepted with lower densities of the carriers compared to the active. The dry coating process proceeded comparable to non- interactive mixing processes where a dynamic equilibrium between mixing and demixing is common.

The important particle properties were identified as the density, the particle size and the surface texture of the carrier particles. The density difference between the carriers and the interactive guest particles can be regarded as most important whereas an increased density difference results in faster processes and increased rate of yield. The particle size is determined to support the dry coating process by increasing particle sizes even though with smaller sizes, more potential total surface area is available. Rougher surface textures support the process to overcome the disadvantageous reduced density difference. Nevertheless, density and particle size are considered to influence the dry coating process more.

The mixer properties, especially the mixing mechanism, is demonstrated to change from a diffusive to a rolling shear mixing mechanism of the Turbula® due to the carrier particles and supported by the three dimensional movement of the mixer. The produced particles displayed distinctively a thin layer with a change of the initial particle size and shape of the active. The desagglomeration of the active is supported by the process as a part of the commonly necessary operating conditions due to the mixing mechanism and can be considered as sufficient. Furthermore, the filling volume depends on the applied developed and constructed mixing equipment and is comparable to the known values of 50 to 70% for the Turbula®. Mixing times in dry coating show distinctively prolonged processing times. As the only identified variable process parameter, the results of the estimated mixing times demonstrate clearly the necessary optimization of mixing processes and supports the general opinion to separately study mixing processes for all mixture types, mixers and mixture compositions.

By investigating the produced particles on resistance to mechanical exposure, the dry coated particles demonstrated increased resistance compared to regularly coated particles with decreasing stability of decreasing particle sizes even at highest levels of the simulated mechanical treatment. Therefore, the produced dry coated particles can be stored, transferred and even applied in further pharmaceutical production processes such as tableting or encapsulation. Furthermore, a quantitative determination of the interaction forces would be of interest.

By regarding the carrier particles, future investigations could include other particles with different sizes, size distributions, shapes and surface textures as for example granules, to find more suitable particles. Additional characterization of the important and necessary properties of possible guest particles must be pursued such as for example the deformation capacity. So far, the residual moisture content of Methylene blue has not been taken into account, which has definitely a large influence on the outcome of the results in this study. Therefore, the emphasis of residual moisture contents in dry coating must be studied in order to understand the process where the residual water content must have a large influence on the formation of the layer. Functional coatings, such as enteric- coatings, might be applied as a second layer. For demonstration, figure 67 depicts Sudan red particles (Sigma Aldrich GmbH, Buchs, Switzerland) on a dry coated Cellets® 1000 with 0.1% (w/w) Methylene blue.



c1000 dry coated with Methylene blue and Sudan red as second layer magnification: 2500x

c1000 dry coated with Methylene blue and Sudan red as second layer magnification: 5000x

Figure 67: Dry coated Sudan red particles on a dry coated Cellets® 1000 particles with 0.1% (w/w) Methylene blue.

Further investigations could also include production of larger amounts of dry coated particles and the identification of scale- up problems as found in tableting or granulation [13]. Compared to the processing times of mixing non- interactive particles, dry coating requires apparently longer process times in the Turbula®. Possibilities of reducing the mixing times could be investigated in further studies by introducing more energy in the mixing system, like for example increasing mixer velocities or input of temperature to the mixing vessel. Possible substances might be identified which convey the dry coating process such as plasticizers in coatings or glidants with influencing the stability of the produced particles also. To conclude, the presented prospects display distinctively the need of further investigations as well as the countless possibilities of the dry coating mixing process as a new and potential production process in pharmaceutical technology.

Application of the Percolation Theory in Dry Coating

Percolation theory can be applied in pharmaceutical technology to explain various important topics during the development of solid dosage forms as for example the compression of powder systems [85]. By proposing a critical fine particle concentration, the percolation theory was applied on the dry coating process to identify the impact on mixture qualities and description of the saturation process of the particles. Furthermore, the obtained results were used to propose the implementation of the theory to the dry coating process with a qualitative comparison of the critical fine particle concentration to the percolation threshold.

By investigating a possible existence of a saturation concentration, an estimation of a possible CFPC becomes feasible. The results display distinctively the existence of a saturation concentration. By comparing sieved and unsieved dry coated mixtures of the applied carrier particles, investigations of the saturation concentrations, SEM photographs and the calculations of the weight balances indicated saturation concentrations in approximately the same range for both applied carrier particle systems. The influencing particle properties determined by the investigations of the dry coating process to determine the ideal mixing times were confirmed as the density, the particle size and the surface texture. Density supported the saturation concentration process displayed by the initially applied Methylene blue concentrations of 4 to 6% (w/w) received by the sieved mixtures compared to the values for the Cellets® of 5 to 7.5% (w/w). The reduction of the particle sizes resulted in a reduction of the contents of mixtures shown by the calculation of the contents per surface areas of sieved and unsieved mixtures in contrary to the assumed prediction, whereas increasing available total surface areas would increase the saturation concentrations. Again, the surface texture had to be determined as less important during the saturation process. Nevertheless, a saturation concentration was shown to exist whereas a possible estimation of the CFPC became possible. By regarding the standard deviations of the mixtures as a function of the fine particle concentration, the gp1000 and gp500 indicated no existing change of the mixture qualities by comparing the sieved with the unsieved mixtures. Due to the density as well as the particle size difference compared to the active, the mixtures featured no CFPC in the studied concentration levels and it must be assumed that a CFPC of the two carriers is located above the investigated fine particle concentrations. The gp250 and the Cellets® carrier mixtures though displayed an increase of the standard deviations of the unsieved compared to the sieved mixtures with a slight dislocation of the initially applied Methylene blue concentration compared to the findings of the saturation concentrations. Therefore, it must be concluded that the determination of the CFPC still remains difficult whereas the used method must be optimized in further investigations. Additionally, the mixing times must be optimized at the saturation concentrations as stated by the investigations of the dry coating mixing process to determine more precisely the saturation concentration and the CFPC.

As shown by the previous results, the proposed CFPC exists in practice shown for several particle types. Therefore, the implementation of the percolation theory to the dry coating process of binary mixtures is legitimated qualitatively. By a saturation of the carrier surfaces at the CFPC, the system changes as proposed in terms of a decrease of the mixture qualities whereas the determined CFPC and saturation concentrations can be regarded as equal or at least in the neighborhood of the percolation threshold. By optimizing the method of detecting the saturation concentration and therefore the CFPC, an advanced elaboration of the quantitative estimation of the CFPC and therefore a determination of the percolation threshold becomes possible. The course of the saturation curves of the investigated saturation processes fluctuated after the saturation concentration was reached indicating a dynamic equilibrium of mixing and demixing which allows the proposed comparison to the micelle formation process of surfactant- water systems with the existing critical micelle concentration. Regarding the possible application of the percolation theory in dry coating, an exact determination of the CFPC would aid the development of robust dosage forms, their design and as a consequence reduce time to market, economic losses and most important risks to patient’s health.

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Appendix

Appendix A: Specifications of the mixing and sampling equipment

Plexiglass hopper specifications

properties	
total length	33.0cm
diameter (inner)	
- top	19.5cm
- bottom	1.3cm
wall thickness	0.5cm
half centered angle	17°

developed and constructed mixing and sampling glass and metal parts

properties	glass	metal
body part		
- total length	6.0cm	6.0cm
- length of thread	1.5cm	1.5cm
- length of even part	3.5cm	3.0cm
- length of connecting part	1.0cm	1.5cm
- inner diameter	2.5cm	2.5cm
- wall thickness	0.1cm	0.1cm
- inner diameter of connecting part	3.5cm	3.5cm
hopper insert		
- total length	7.0cm	7.0cm
- length of connecting part	1.8cm	2.0cm
- length of even part	4.0cm	3.5cm
- length of hopper part	1.2cm	1.5cm
- inner diameter	2.5cm	2.5cm
- wall thickness	0.1cm	0.1cm
- half centered angle of hopper part	30°	30°
mixing insert		
- total length	7.3cm	7.3cm
- length of connecting part	2.0cm	2.0cm
- length of even part	5.3cm	5.2cm
- inner diameter	2.5cm	2.5cm
- wall thickness	0.1cm	0.1cm

carriers

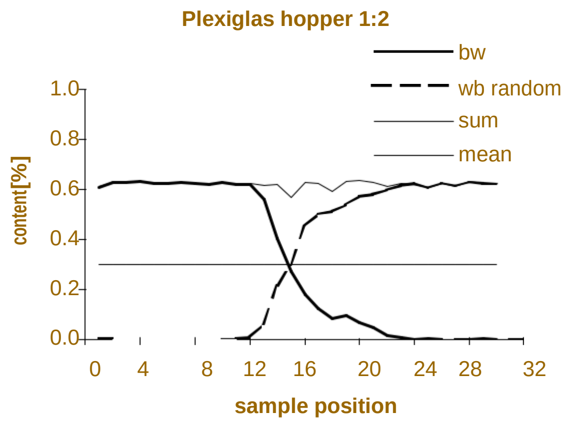
properties	body part carrier	mixing insert carrier	sampling insert carrier
length	3.5cm (without screws)	3.5cm	3.5cm (without flexible sealing arm)
outer diameter	6.0cm	6.0cm	6.0cm
inner diameter	3.2cm	3.0cm	3.0cm
inner diameter for connecting part	3.7cm (depth 0.8 cm)	3.3cm (depth 1.0 cm)	3.3cm (depth 1.0 cm)
connecting screws	4.5cm	-	-
length flexible sealing arm	-	-	9.0cm

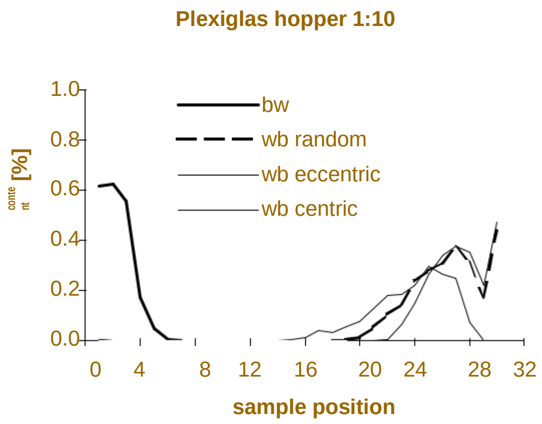
sampling train and sampling track

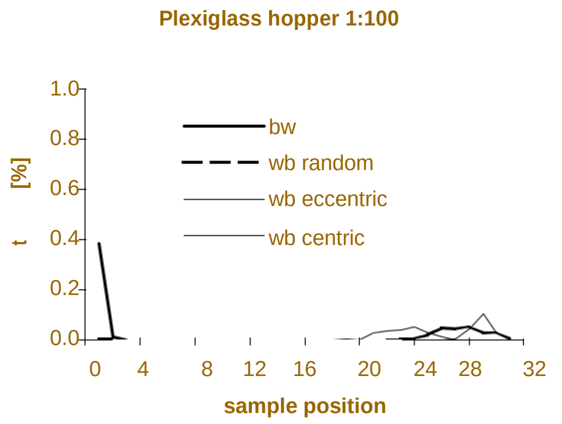
sampling train	
- length	110.0cm
- height	6.8cm
- depth	5.0cm
- thickness of funnel compartment	2.0cm
-number of compartments	32
- distance from funnel compartment to funnel compartment (center)	3.5cm
- diameter upper edge funnel hopper	4.5cm
- diameter lower edge funnel hopper	1.8cm
- number of wheels	8 (4 on each side)
sampling bracket	
- heigth	15cm
- carrier holder	5cm
sampling track	
- length	250.0cm
- width	7.0cm
- channel depth	0.2cm

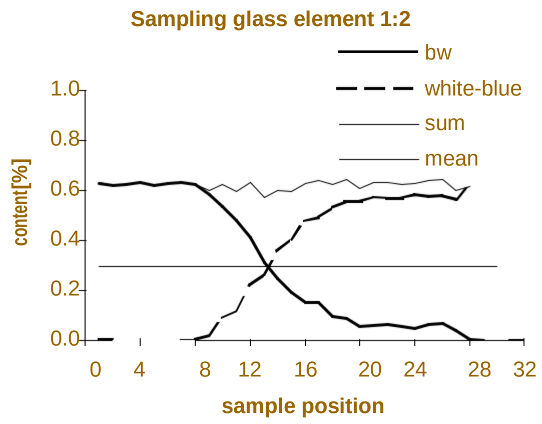
Appendix B: Impact of Sampling on the Quality of Mixture: Flowability profiles

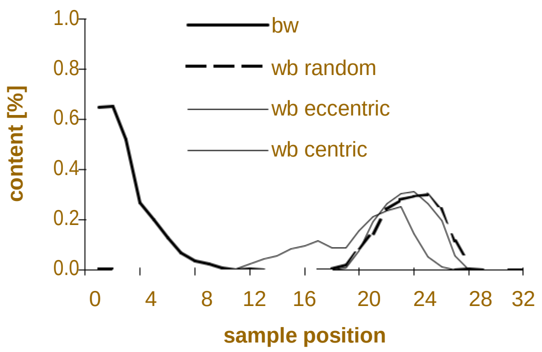
Flowability profiles of discharged diluted coated glass pellets 1mm mixtures; labeled are the respective sampling equipment and the dilution rate


Plexiglas hopper 1:2

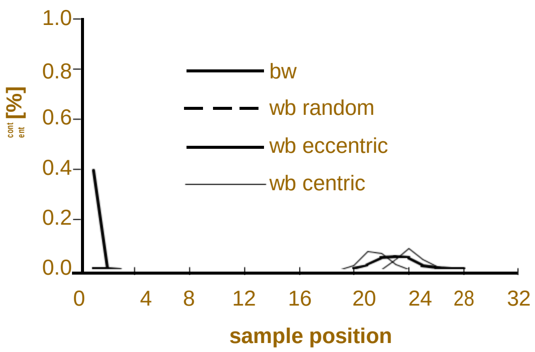

Plexiglas hopper 1:10


Plexiglass hopper 1:100

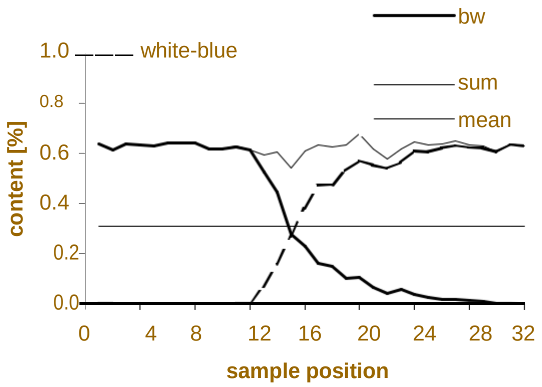

Sampling glass element 1:2



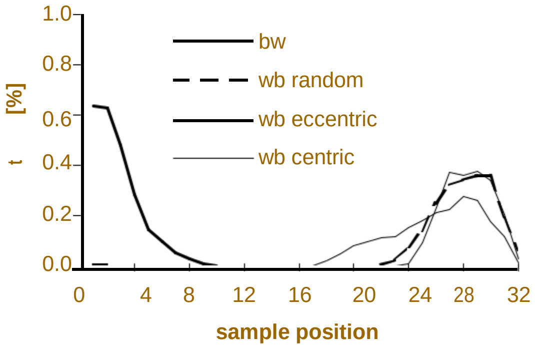
Sampling glass element 1:10



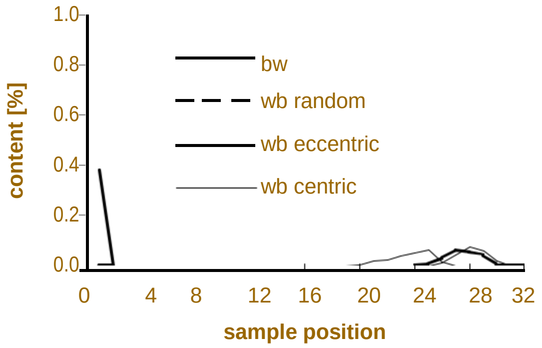
Sampling glass element 1:100



Sampling metal element 1:2



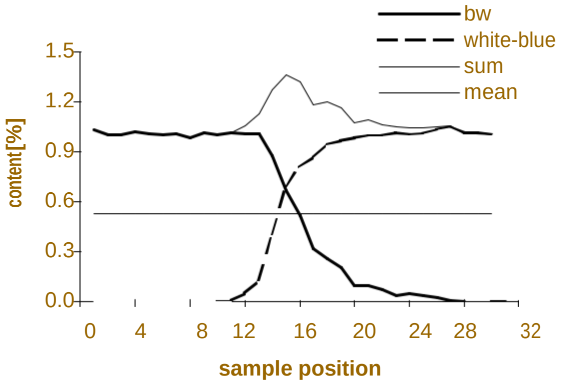
Sampling metal element 1:10



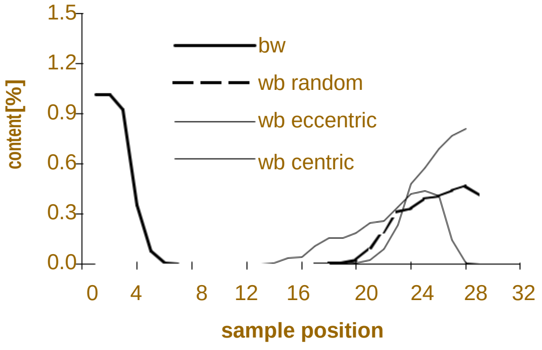
Sampling metal element 1:100

Flowability profiles of discharged lactose particles 1mm mixtures; labeled are the respective sampling equipment and the dilution rate

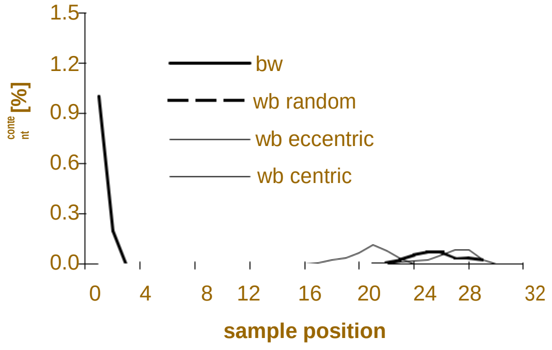
Plexiglas hopper 1:2



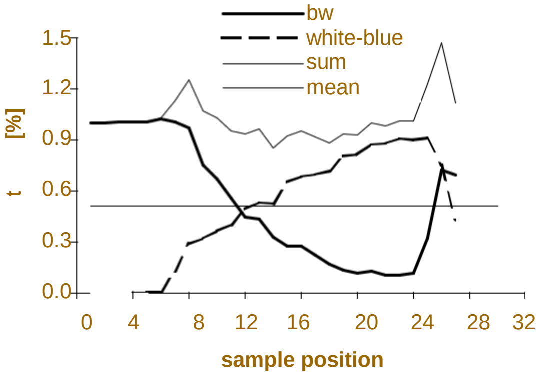
Plexiglas hopper 1:10



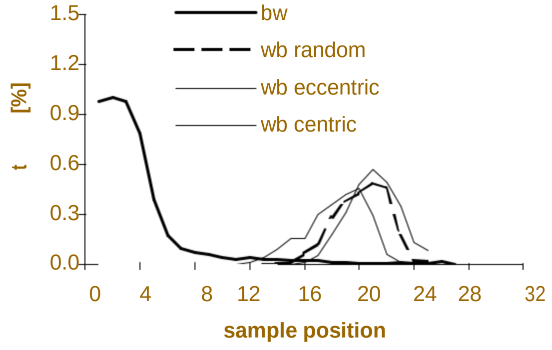
Plexiglas hopper 1:100



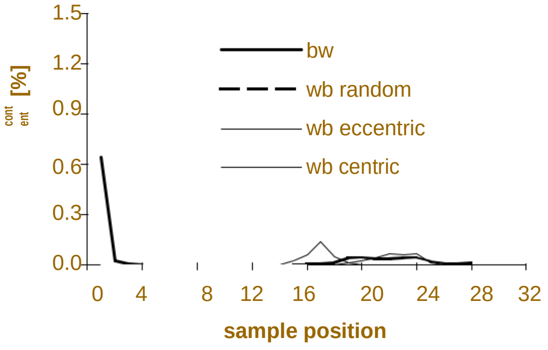
Sampling glass element 1:2

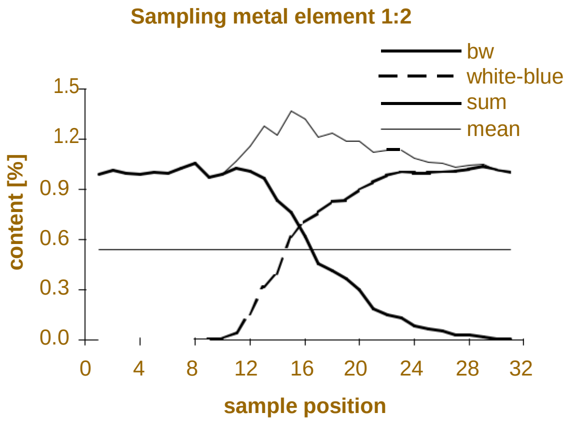


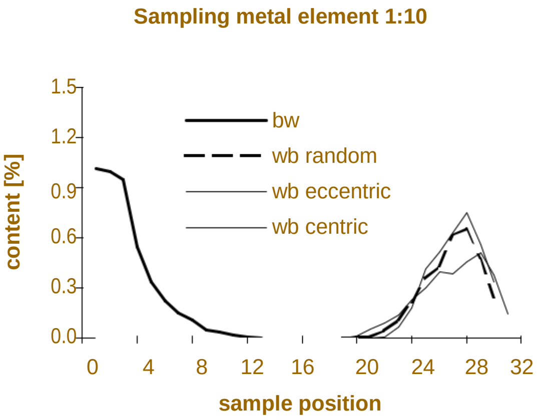
Sampling glass element 1:10

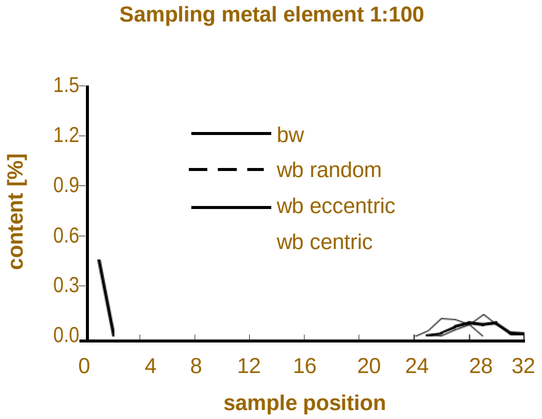


Sampling glass element 1:100




Sampling metal element 1:2
bw
white-blue
sum
mean
content [%]
1.5
1.2
0.9
0.6
0.3
0.0
0
4
8
12
16
20
24
28
32
sample position

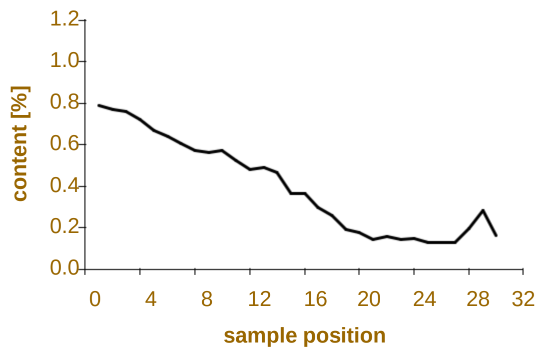

Sampling metal element 1:10
bw
wb random
wb eccentric
wb centric
content [%]
1.5
1.2
0.9
0.6
0.3
0.0
0
4
8
12
16
20
24
28
32
sample position


Sampling metal element 1:100
bw
wb random
wb eccentric
wb centric
content [%]
1.5
1.2
0.9
0.6
0.3
0.0
0
4
8
12
16
20
24
28
32
sample position

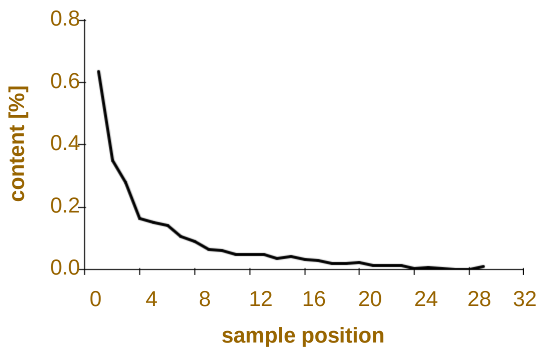
Appendix C: Impact of Handling on Quality of Mixtures: Flowability Profiles

Flowability profiles of discharged coated glass pellets 1mm mixtures after handling; labeled are the respective sampling equipment and the dilution rate

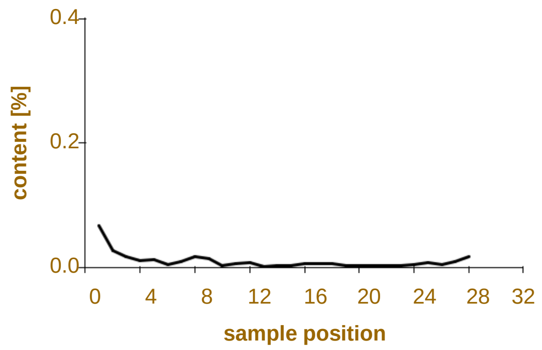
Plexiglas hopper 1:2



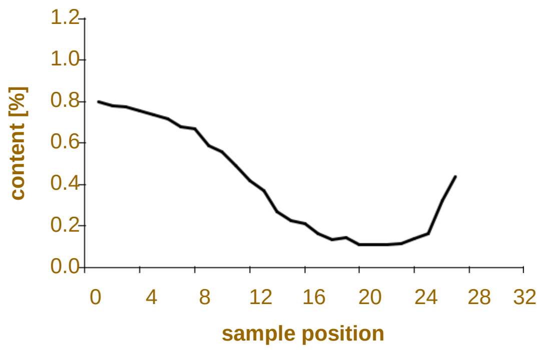
Plexiglas hopper 1:10



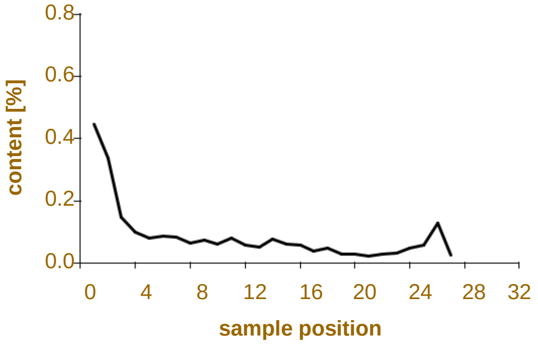
Plexiglas hopper 1:100



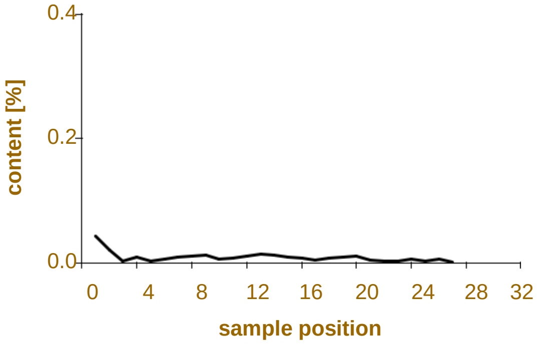
Sampling glass element 1:2



Sampling glass element 1:10

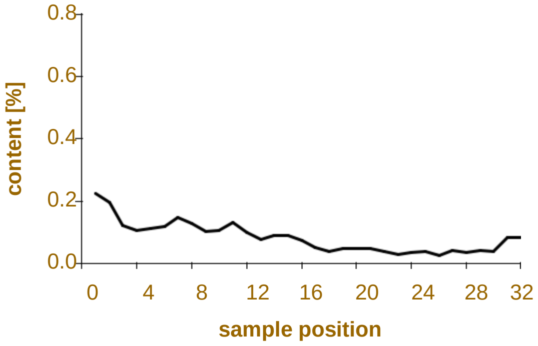


Sampling glass elemet 1:100

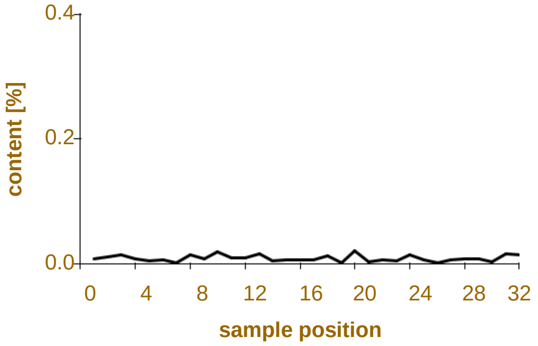


Sampling metal element 1:2

Sampling metal element 1:10

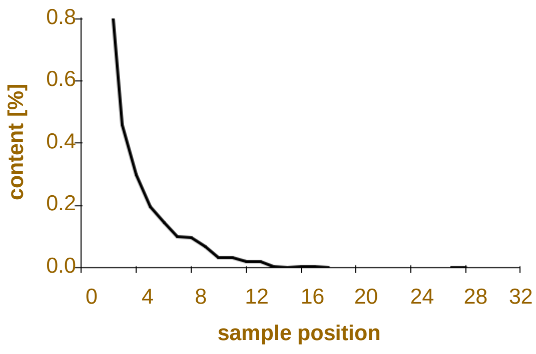


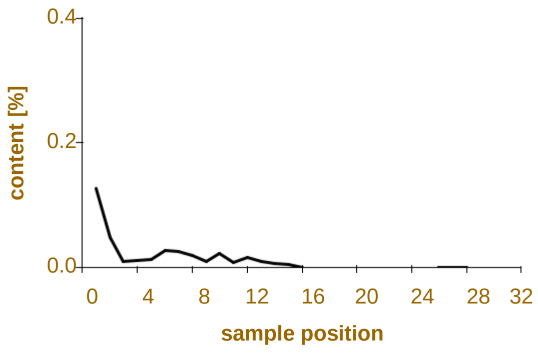
Sampling metal element 1:100



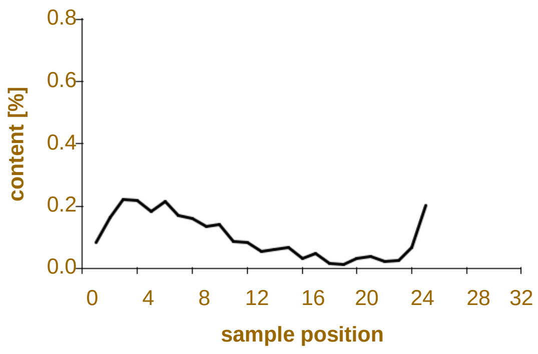
Flowability profiles of discharged lactose particles 1mm mixtures after handling; labeled are the respective sampling equipment and dilution rate

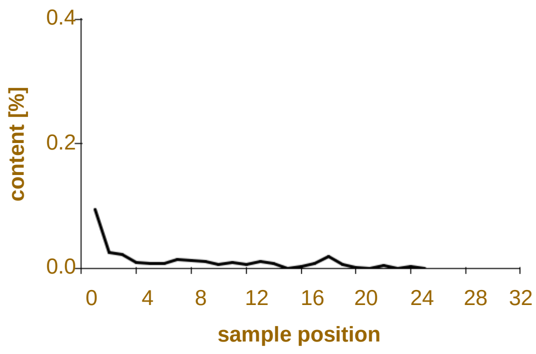

Plexiglas hopper 1:2

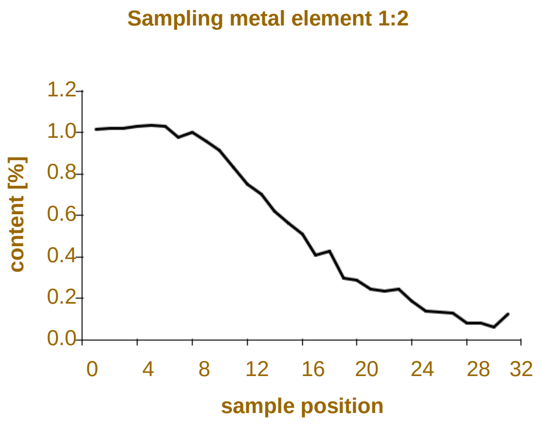

Plexiglas hopper 1:10

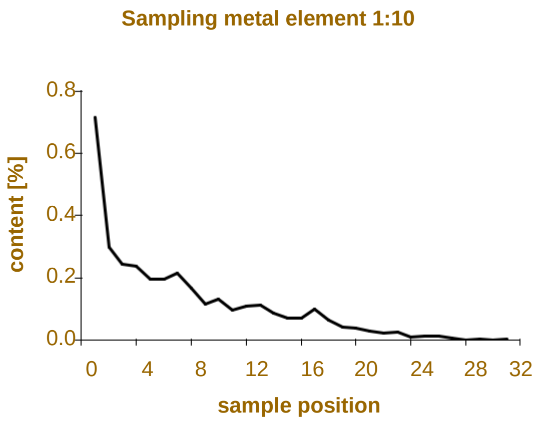

Plexiglas hopper 1:100

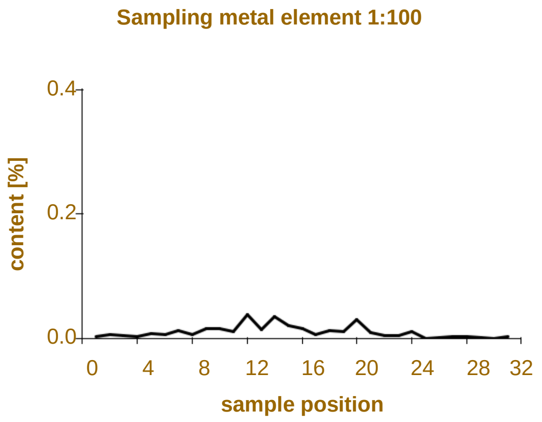

Sampling glass element 1:2


Sampling glass element 1:10


Sampling glass element 1:100

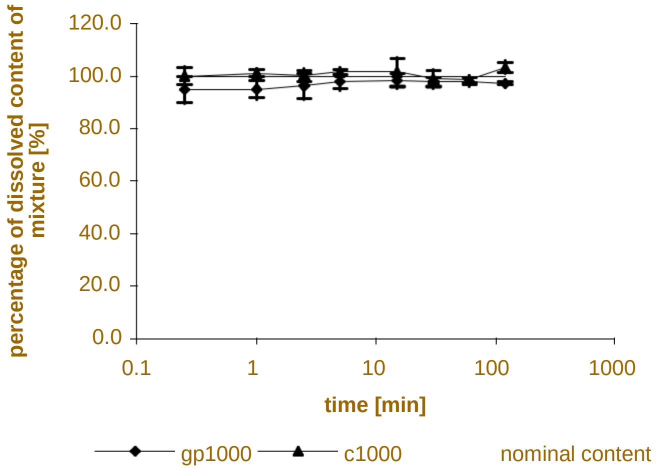

Sampling metal element 1:2

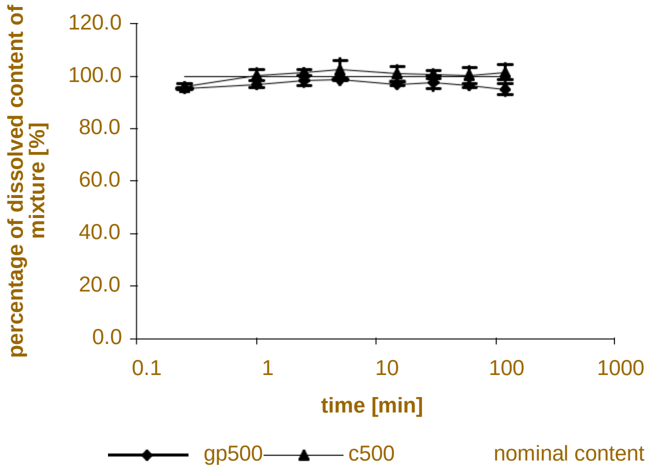

Sampling metal element 1:10

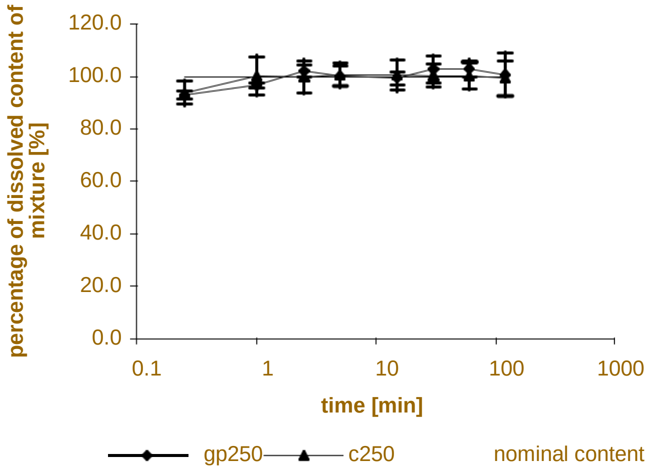

Sampling metal element 1:100

Appendix D: Dissolution

Dissolution profiles of dry coated Glass pellets and Cellets® carrier particles in 0.1% (w/w) mixtures of Methylene blue; particles are mixed for 120minutes in with the mixing metal element; Glass pellets are measured in water, Cellets® in acetic acid


percentage of dissolved content of mixture [%]
120.0
100.0
80.0
60.0
40.0
20.0
0.0
0.1
1
10
100
1000
time [min]
gp1000
c1000
nominal content


percentage of dissolved content of mixture [%]
120.0
100.0
80.0
60.0
40.0
20.0
0.0
0.1
1
10
100
1000
time [min]
gp500
c500
nominal content


percentage of dissolved content of mixture [%]
120.0
100.0
80.0
60.0
40.0
20.0
0.0
0.1
1
10
100
1000
time [min]
gp250
c250
nominal content

Curriculum Vitae

Personal details

Name	Thomas Alexander Meyer
Date of birth	6. March 1977
Place of origin	Willisau- Land, LU

Education

1984 - 1989	Primary school Pfeffingen
1989 - 1991	Secondary school Aesch
1991 - 1993	Progymnasium Aesch
1993 - 1994	Gymnasium, Typus C, Muenchenstein
1994 - 1995	Bullitt East High School, Mt. Washington, Kentucky Diploma
1995 - 1997	Gymnasium, Typus C, Muenchenstein
1999 - 2004	Academic studies in Pharmacy, federal diploma University of Basel
2005 - presence	Dissertation at the Institute of Pharmaceutical Technology University of Basel

Professional activities

2002 - 2004	as cand. pharm. at the Barfuesser Apotheke, Basel
2004 - 2005	as pharmacist at the Barfuesser Apotheke, Basel
2005 - 2008	as a Ph. D. student at the Institute of Pharmaceutical Technology, University Basel; practical training of pharmacy students and supervision of diploma thesis