

Master Thesis for the degree Master of Pharmacy

**USE OF ORDERED MIXTURES TO OBTAIN
HIGH DOSE HOMOGENEITY IN MINI-TABLETS
STUDIES OF ORALLY DISINTEGRATING SYSTEMS FOR
CHILDREN**

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ABSTRACT

Studies have shown that homogeneity is higher in ordered mixtures compared to random mixtures. Based on this ordered mixtures should be particularly suitable for the preparation of mini-tablets. The overall aim of the study was to compare the homogeneity of ordered mixtures prepared using different particle size of carrier particles, and test their suitability for preparation of mini-tablets. The mini-tablets are intended for use as orally disintegrating systems (ODT) for children.

Granulated, spray dried and co-processed mannitol samples were used as carrier particles and sodium salicylate and ibuprofen were studied as fine particulate drug for preparation of ordered mixtures. For compression of mini-tablets, ordered mixtures were prepared using mannitol samples, Pearlitol 200SD,300DC,400DC and 500DC (Pearlitol, France) in combination with sodium salicylate (Sigma Aldrich, Germany). The drug substances were grinded manually in mortar with pestle and screened through a sieve of 45 μm in mesh size. Also the carrier materials were sieved in order to collect the following fractions; 180-250 μm (Paratek ODT, Pearlitol (Flash, 200SD and 300DC)), 250-355 μm (Pearlitol 400DC) and 355-500 μm Pearlitol 500DC. The raw materials were characterised using microscopic methods, Helium pycnometry, steady state and Blaine permeametry, particle size analysis (laser diffraction and sieving analysis), bulk and tapped density. Micronized sodium salicylate was mixed with selected carrier (1% w/w) in a Turbula mixer for 24 and 48 hours (n=2). The homogeneity of the ordered mixtures were examined by withdrawing 30 random sample units from the powder mixtures using a micro-thief ($20 \pm 2\text{mg}$). The sample units were quantified by direct UV-assay. The amount of drug in each sample was normalised by dividing the experimentally determined content by the theoretically calculated content. The homogeneity of the mixtures was expressed as the relative standard deviation of the normalised values. A conventional mixture (drug particles screened through 500 μm mesh size, mixed with mannitol sample in Turbula mixer for 10 min), was made for a comparison of the relative standard deviation with the relative standard deviations of the ordered mixtures.

All the ordered mixtures resulted in high dose homogeneity after 48 hours of mixing. The lowest particle size fraction resulted in ordered mixture after 24 hours and the larger particle size fractions needed 48 hours. The high dose homogeneity was proven also in the mini-tablets. The conventional mixture showed poor homogeneity, but resulted in better homogeneity when sample size increased. This proved ordered mixtures ideal solutions for mini-tablets, as the production is dependant on homogenous powder mixtures. All mini-tablets complied with the requirements for uniformity of mass and content for single dose

preparations. The mini-tablets demonstrated low friability's, high crushing strengths and suitable simulated wetting times with respect to European Pharmacopoeia requirements, which made them possible to use as ODTs.

1. INTRODUCTION

1.1 Powder mixtures

Powder mixing is a fundamental process in pharmaceutical industry. The first step in preparation of solid dosage forms usually consists of preparation of a powder mixture. The powder mixtures should be made with high quality, this means high content uniformity, to ensure a high content uniformity of the end product. This again is crucial in order for the patients to receive accurate amounts of active ingredient.

The mixing process can be challenging, especially difficult for high potent drugs that are given in low doses. This is because variation of drug content increases with decreasing amount of drug. In these cases, particle size reduction is a keyword in order to achieve homogeneity throughout an entire powder mixture. Particle size reduction can be accomplished by grinding, for examples using mortar and pestle in small scale or by milling on larger scales. The grinding process often results in electrostatic charging of the small particles. The electrostatic forces can be taken advantage of by mixing with coarse particles for preparation of ordered mixtures. Some advantages associated with ordered mixtures are high dose homogeneity, improved dissolution rate and bioavailability, as well as prevention of segregation.

1.1.1 Definitions

Random mixture:

Particles are mixed by movements which split and recombine the clusters of particles until there is a possibility of an equal chance of the particles to appear at any place in any time (figure 1a). The random mixing process results in groups of equal particles next to each other. The requirements for making a random mixture are particles of equal size and weight, with no surface area effects. Random mixtures have a standard deviation which decreases with increasing sample size, when sampling.

Perfect random mixtures:

The concept is the same as for random mixture, however, the mixture is obtained when each particle has a particle of another component in a close range. This is the point where there is equal chance of finding a particle of a component throughout entire powder blend (figure 1b).

Ordered (interactive) mixtures:

An ordered mixture is considered to be completely different from a random mixture. The mixing process relies on surface effects. An ordered mixture consists of micronized drug particles adhering to coarser particles of another component. Ordered mixtures have been made with almost zero variation, and they feature a higher degree of homogeneity than random mixtures, when sampling (Yip and Hersey, 1977a, Egermann, 1980).

Perfect ordered mixture

A perfect ordered situation for a powder mixture is obtained when each particle of a component is next to a particle of another component (Poux et al., 1991). The situation could easily be thought of as a chessboard like pattern (figure 1c). The concept is the same as for ordered mixture, but the standard deviation of the finer drug particles in a sample of any size greater than one single ordered unit is zero. This is the perfect ordered mixture, and the ultimate goal for preparation of ordered mixtures.

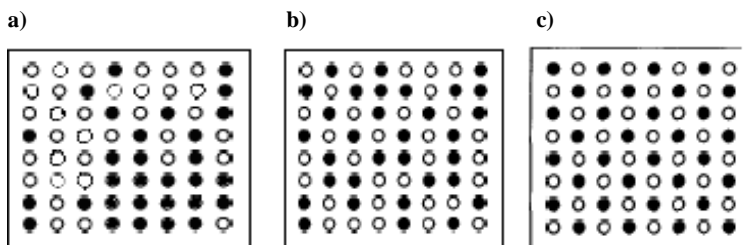


Figure 1. Illustrations of different powder mixtures: a) random mixture, b) perfect random mixture, c) perfect ordered mixture. Figure b and c comes from (Lelan, 1989) but found in (Poux et al., 1991).

1.1.2 Sampling

To ensure homogeneity of a powder mixture, determination is required. Since it is not possible to test the whole powder mixture, one has to rely on taking a sufficient number of random samples to ensure that it is representative for the whole powder mixture. This can be realized using a powder thief (Muzzio et al., 2003). A powder thief is an equipment especially designed for taking out defined amounts of sample units from a powder batch. A powder thief has one or more cavities stamped in a hollow cylinder. These cavities can be opened and closed in a controlled manner by an outer rotation or pulled down sleeve (Muzzio et al., 1997). The powder thief is inserted into the powder with closed cavities. When insertion is complete, the cavities are opened and powder flows into the cavities, which can be closed and

the powder thief is withdrawn from powder bed. By randomly sampling using a powder thief the idea is that every particle in the powder mixtures should have an equal chance of being chosen for homogeneity testing.

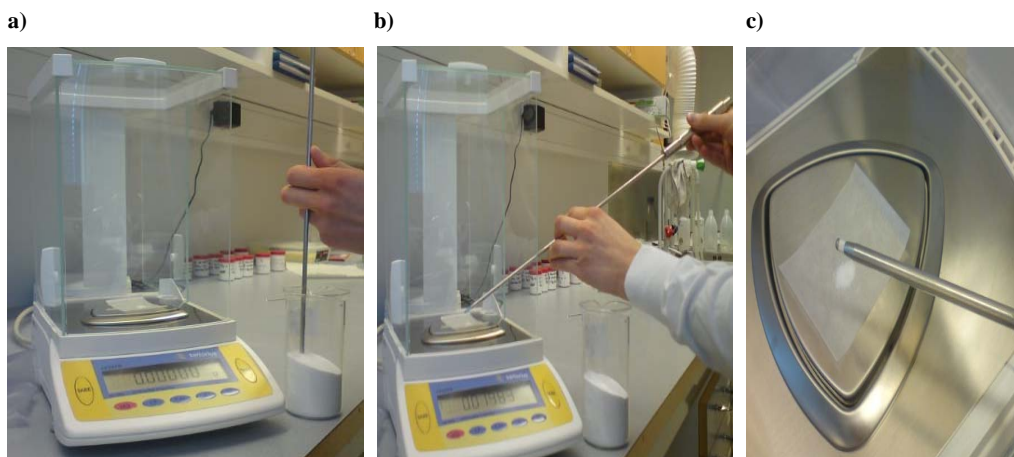


Figure 2. Example of experimental use of a powder micro-thief. A sample is withdrawn for homogeneity determination. a) Insertion-with following opening and closing of cavity, b) sample unit withdrawn, c) sample unit is released from the cavity and weighed to check the mass

1.1.3 Homogeneity

A homogenous powder mixture is described by Blumberg and Maritz as a complete mixture, where the chance of picking a red particle is equal throughout the whole mixture made of different colours (Blumberg and Maritz, 1953). In this respect an ordered mixture will have zero standard deviation of the sample concentration at all sample sizes provided that the sample size is greater than the size of a single ordered unit described by Yip and Hersey (Yip and Hersey, 1977a). The European Pharmacopoeia 7.2. describes the test of “uniformity of dosage unit” (chapter 2.9.40) to ensure the consistency in dosage units. The same test may be applied on sample units taken by random sampling from a powder mixture. The European Pharmacopoeia recommends testing of 30 items, for a bulk powder this implies 30 sample units. The relative standard deviation of the content of active ingredient, in the randomly picked samples from a mixture, seems to be a common parameter used to reflect the homogeneity in a powder mixture in literature (Mihrianyan et al., 2008).

1.2 Powder mixing

1.2.1 Mixing mechanisms

Powder particles have to move relative to each other in order to make a powder mixture. The mixing process of particles can be done by three different types of mechanisms known as mixing by convection, diffusion and shear.

Mixing by convection consist of movement of groups of particles from one part to another within a powder mixture. The particles within a group in movement do not become mixed together.

Mixing by diffusion is characterized by motion of individual units in a powder mixture. The mixing process can ensure mixing on a fine scale. Powder beds that are forced to move will become less tightly packed, which increases the chance of individual particles to fall into the voids that will be created during the powder movement.

Shear mixing is considered to be a combination of the two other mixing mechanisms. The mixing process could be described as the movement of a layer of material over another layer. The mixing occurs by removal of mass by convective mixing, which again causes an unstable shear plane that result in a collapse of the powder mixture.

All mixers (mixing equipments) use one of these mechanisms as a predominant mode of action, but all the mechanisms occur together to a greater or lesser extent (Aulton, 2007, Poux et al., 1991). Despite of that, Venables and Wells claims that the ideal particle movements should be obtained by moving particles three dimensional and randomly. Particles are supposed to move both individually and in groups, with no particles being in a region with no movements (Venables and Wells, 2001).

1.2.2 Mixing equipments

Tumbling and convective mixers are most commonly used for mixing of pharmaceutical powders. The mixers rely on different operating principles. The tumbling mixers are used by means of filling powder into a vessel that is attached to a rotational shaft, which gives overall rotational motion to the entire vessel. In contrast, convective mixers use a stationary vessel and a rotating paddle. The main mechanism of the mixers in this group relies on the

convective mixing done by the paddle. Many names have been used for the commercially available tumbling and convective mixer. However, there is one that has been extensively used in research articles to achieve best possible homogenous powder mixing. That is a Turbula mixer. A Turbula mixer is a tumbling mixer and uses three dimensional movements, which makes the powder particles always change rhythmically pulsing motion. The results will in a minimum of time to fulfil the highest homogeneity standards required for powders in research or pharmaceutical industry (Willy A. Bachofen AG Maschinenfabrik) .



Figure 3. Example of a Turbula mixer (Willy A. Bachofen AG Maschinenfabrik)

1.3 Powder segregation

Segregation is the opposite of mixing, also described as reverse mixing or de-mixing. Segregation refers to the situation where large particles and small particles separate, and takes place because particles in a powder mixture have different sizes, shapes and/or densities. The differences in particle properties play an important role in deciding the behaviour of the particles when forced to move, and consequently also in their tendency to separate. There are three main mechanisms of segregation taking place in a segregating mixture: percolation segregation, trajectory segregation and dusting out (Aulton, 2007).

In powder mixtures where segregation has taken place, particles exhibiting similar properties will appear as clusters in different regions of the powder bed (Aulton, 2007, Venables and Wells, 2001). For powder mixtures that are prone to segregation, there is often an optimum mixing time. This is because the segregating factors need time to occur. At first the mixing effect will be larger than the segregating effect, but after a certain time, the opposite will be the case. In contrast to segregating mixtures, non-segregating mixtures will be improved by continued increase in mixing time. To achieve that kind of mixture, many factors, such as an appropriate choice of particles, particle size, shape and density have to be controlled.

1.4 Particle characteristics

1.4.1 Particle size

The particle size is one of the basic characteristics of powder particles. The particle size is often referred to as an average of all particles in a distribution. The characteristics of the particle size distribution are therefore nearly as important as the size of the single particle. A wide distribution contains particles of various sizes (figure 4, a), whereas a narrow distribution contains particles of nearly the same particle size (figure 4, b).

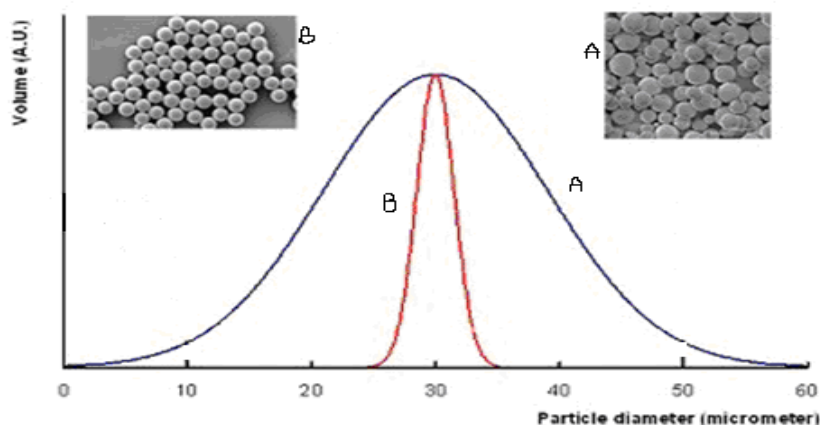


Figure 4. Illustration of wide and narrow particle size distribution. a) wide particle size distribution, b) narrow particle size distribution (Nanomi monosphere for drug delivery)

When particle size is determined it is often easily approximated to a sphere with a diameter that is equivalent diameter of the particle. However, all particles are not perfect spherical in shape. In fact, the particle size could be quite different for a particle considering the orientation and shape of particle. Two diameters that are widely used to describe particles are the Feret's and Martin's diameter (figure 5). Martin's diameter is considered to be the boundary separating a particle in equal particle sizes. The distance between two tangents on opposite sides is referred to as Feret's diameter.

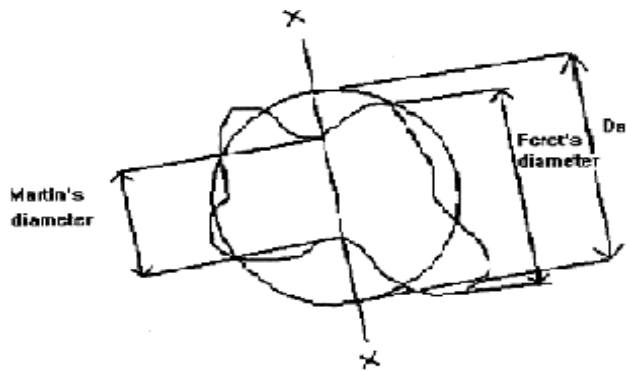


Figure 5. Illustration of different estimation of particle size dependent on orientation and shape of the particle (Aulton, 2007).

Two of the most frequently used methods for classifying particles are analytical sieving and the use of particle size analysers. Sieving is the easiest, oldest and cheapest method for classifying particles and is also described in the European Pharmacopoeia. The classification can also be done using laser diffraction equipments known as particle size analysers. A laser beam passes through particles in a suspension. The angle of diffracted light is related to the particle size. The angle increases as the particle size is reduced.

Particle sizes should always be considered in order to make a powder mixture that is less prone to segregation. In general, segregation is increased when particle size distribution is increased (Sommier et al., 2001). A wide particle size distribution makes percolation segregation of finer particles falling into the gaps between the coarser particles and moving to the bottom of the mixer very likely to happen. This is expected to happen to a certain extent whenever a powder mixture of different particle sizes is in movement. Also trajectory segregation may occur in powders of wide particle size distribution. Larger particles have a larger kinetic energy caused by the larger mass, and for that reason they move greater distances than small particles. When the difference in particle size reaches three times or more in mean diameter of two or more components, significant segregation may take place (Johanson, 1996). It is then reasonable to assume that by keeping particle size in a narrow range, it will be possible to reduce segregation, but segregation could also be caused by other factors, such as differences in density and shape.

In spite of the fact that a broad particle size distribution favours segregation, the most homogenous powder mixtures, the interactive mixtures, consist of very small particles mixed

with larger particles. Harnby explains this by electrostatic forces: when the particle size is reduced below a certain level electrostatic forces will appear (Harnby, 2000). These forces will be dominating over the gravitational forces, and more or less be hindering the segregation. It is known that at some point when particle sizes reach below 40 μm an ordered mixture can be formed (Venables and Wells, 2001). This is due to the increased surface area of the small particles, which leads to weak inter-particulate forces known as van der Waals forces. It results in micronized particles forming aggregates. Therefore, hindering of segregation can be obtained by mixing particles of a narrow size distribution with micronized particles (usually drug) that will attach to the surface of the coarser particles.

1.4.2 Particle shape

Particles may have many different shapes. The shapes can be all from spherical to very irregular and something totally opposite of spherical, needle like (figure 6). Segregation is more likely to happen in a powder mixture with particles of different shapes rather than powder mixtures with similar shapes provided that non of the components are cohesive (Swaminathan and Kildsig, 2002). The shape of the mixed components need to be of significant difference from each other, for example smooth spheres and needles, for making segregation able to happen (Lawrence and Beddow, 1969).

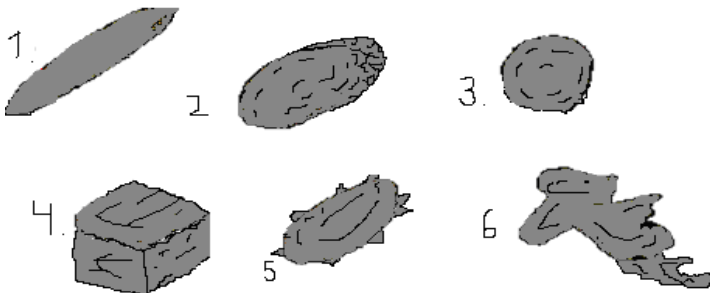


Figure 6. Examples of different particle shapes. 1) needle, 2) oblong, 3) spherical 4) cube, 5) flake, 6) irregular

Spherical particles show better flowability compared to all other shapes of particles, which also makes them easier to mix. The improved flowability is caused by the smaller surface area to weight ratio, which results in less contact points to other surface areas. By using spherical particles it is possible to reduce time of mixing compared to mixtures of flat (flake) particles (Aulton, 2007).

1.4.3 Particle density

Components of different densities might affect the mixing. An individual particle has three different types of densities. The reason for having three different types is caused by the consideration of pores. The pores are divided in closed pores, which are not connected to surface, and open pores which are connected to the surface of the particle (figure 7). True density is the mass divided by the volume of particle, excluding both open and closed pores of the measured particle. Apparent density is the mass divided by the volume, including closed pores but excluding the open pores. Effective density is mass divided by the volume, including all pores (Venables and Wells, 2001).



Figure 7. A cross section through a particle is made for an illustration of both open pores and closed pores. The closed pores inside particle does not reach surface as illustrated by light grey color. Open pores are seen reaching surface.

Segregation could happen with large difference in particle density (Lloyd et al., 1970). The more dense particles are more prone to segregate to the bottom of the mixer than less dense particles, even though the particles have the same size. Denser particles can also move a greater distance than particles of less density but the same size, causing segregation. It is widely agreed that density plays a minor role in segregation compared to for example size differences. This is because of the smaller range of densities in particle systems compared to the size range of particle systems. A 5:1 range in density differences is large for particles, but still minor compared to the difference in size range of 1000:1, which is quite common (Hogg, 2009). Powder particles used in pharmaceutical industry often have very similar densities, and therefore this factor may not be that important (Aulton, 2007). The contribution of density will be neglect able when mixing micronized and coarse particles to obtain ordered mixtures.

1.4.4 Particle external surface area

Powders can be characterised, with respect to their external surface area, by the widely used method permeametry (Alderborn et al., 1985). A fluid that moves through a powder plug will be met by a resistance that is regulated by the pore structure of the plug. Permeameters can very accurately measure the flow rates of a fluid (air) and the following pressure head across the powder bed as the measurements proceed. By utilizing permeameters it will be possible to estimate external surface area of powders with derived empirical equations such as those proposed by Alderborn et al and Eriksson et al (Alderborn et al., 1985)(Eriksson et al., 1993).

1.5 Ordered mixtures

1.5.1 General

Ordered mixtures consist of small particles $\leq 10 \mu\text{m}$ in diameter, adhering to larger carrier particles of about $200 \mu\text{m}$ in diameter (Sundell-Bredenberg and Nystrom, 2001, Yip and Hersey, 1977b). When mixing two components with so different particle sizes, the micronized particles can adhere to the larger particles creating an ordered mixture due to electrostatic forces. Ordered mixtures are also called interactive mixtures. Hersey was the first to present the concept of ordered mixtures; the fact that mixtures of high degree of homogeneity could be made by adhesion of micronized particles onto larger carrier particles (Hersey, 1975, Yip and Hersey, 1977a). However, the essence of creating an ordered mixture was first discovered by Travers and White in 1971, when they mixed micronized sodium bicarbonate with sucrose crystals and the powder mixture exhibited minimal segregation (Travers and White, 1971). The particles were no longer independent of each other. The removal of a carrier particle would automatically lead to removal of the adsorbed micronized particles. Later, other studies have confirmed that it is possible to get a high degree of homogeneity in an ordered mixture (Hersey, 1975, Bredenberg et al., 2003). Sundell- Bredenberg and Nyström found almost zero variations between powder samples, in a study of homogeneity of ordered mixtures, with fine model drug fraction $<10 \mu\text{m}$ (Sundell-Bredenberg and Nystrom, 2001). The authors found that high dose homogeneity can be created by dry mixing of micronized drugs in proportions as low as 0.015 % (w/w). According to Yip and Hersey an absolute homogenous system (perfect ordered mixture) have zero standard deviation of sample concentration at all sample sizes provided that the sample size is greater than the size of a single ordered unit (Yip and Hersey, 1977a).

1.5.2 Estimation of surface coverage

Every system has a definite number of micronized particles that maximally can adhere to a single large particle. The definite number tells when every adherence site on the carrier particle is occupied (Hersey, 1975). Estimation of external surface area of both types of particles is necessary in order to calculate the amount of micronized particles required to (approximately) form a monolayer on the surface of the carrier particles, prior to making an interactive mixture. These calculations can be done as described by Nyström et al. (Olsson et al., 1998, Nyström et al., 1982). Shortly described:

The amount of micronized particles ($m(\text{micronized particles})$) added to a certain amount of carrier particles ($m(\text{carrier particles})$) to form an ordered mixture corresponds to the amount required to approximately form a thin film (monolayer) of particles on the surface of the carrier particles. It has to be assumed that the covering capacity of one of the micronized particle corresponds to its projected surface area, i.e. one quarter of the external surface area of the micronized particle:

$$\text{Equation 1(Eqn1): } m(\text{micronized particles}) = \frac{R * (m(\text{carrier particles}) * SW(\text{carrier particles}))}{SW(\text{micronized particles})/4}$$

Where $SW(\text{carrier particles})$ and $SW(\text{micronized particles})$ of equation 1 refer to the weight specific surface area of the carrier particles and the micronized particles (Olsson et al., 1998). By using a lower constant amount, it might be discovered that some large particles might have a relative large number of small particles connected with them than others (Hersey, 1975).

1.5.3 Examples of use of ordered mixtures

Ordered mixtures can be utilized for improvement of dissolution rate of drugs (Nilsson et al., 1988). Westerberg and Nyström show that dissolution rate of interactive mixtures can be very fast, almost as fast as a well-dispersed suspension, if the surface area coverage of the carrier particles is kept low (Nystrom and Westerberg, 1986). The dissolution properties of the small adhering particles are improved since the larger carrier particles are soluble and dissolve rapidly, thereby releasing the smaller (usually drug) particles into the dissolution media. The use of ordered mixtures enhances the dissolution rate, which can lead to a rapid absorption of drug, thereby improving the effect of the drug.

Mattsson and Nyström have shown that tablet strength of ordered mixtures in some cases is significantly higher than the strength of tablets compacted of individual materials. They explain the adhering material as a direct reason for an increased number of bonds that need to be broken during tablet strength measurements (Mattsson and Nyström, 2001).

1.6 Mini-tablets

Mini-tablets are tablets with a low diameter. Lennartz and Mielck use 2-3mm in diameter or smaller when they define mini-tablets (Lennartz and Mielck, 1998). Flemming and Mielck use equal to or less than 2 mm in diameter (Flemming and Mielck, 1995). Mini-tablets can be used as single tablets or they can be used to create multiple unit dose systems (MUDS) (De et al., 2000). MUDS can be obtained when mini-tablets are compacted using a tablet machine or filled into hard gelatine capsules. In the latest years, there has been an increasing interest of developing MUDS by incorporating pellets or mini-tablets into tablets instead of hard gelatine capsules because of the higher production costs of capsule-filling (Lopes et al., 2006).

Mini-tablets are an attractive alternative to pellets for creating MUDS. Compared to pellets mini-tablets are more robust, in addition to have a smoother surface and a more uniform size, this makes them more suitable for coating processes compared to pellets. They also need less coating material, which makes the coating process less expensive (Lennartz and Mielck, 1998, Munday, 1994). Lennartz and Mielck have shown higher mechanical strength of mini-tablets compared to conventional tablets by producing mini-tablets and tablets at similar high pressure. They demonstrate better mechanical strength and reduced capping for the mini-tablets. They explain the difference observed by the ratio between outer surface and volume of the tablet. The smaller the tablets are in diameter the more this ratio increases. The result makes mini-tablets more attractive especially for drug that are known to be problematic in manufacturing. They also claim that there is an advantage that higher contents of active ingredient possibly could be manufactured in mini-tablets compared to tablets (Lennartz and Mielck, 1998).

The small size of the mini-tablets makes them very easy to swallow compared to conventional tablets. Mini-tablets could for that reason offer an alternative to conventional tablets. They can also enable easy administration and flexible dosing, which is especially appropriate for growing children by means of weight based dosing (Stoltenberg and Breikreutz, 2011).

1.7 Orally disintegrating tablets

Orally disintegrating tablets (ODTs) are defined as solid dosage forms containing an active ingredient that will rapidly be dissolved, within seconds, when placed inside the oral cavity according to The US Food and Drug Administration Centre for Drug Evaluation and Research (Hirani et al., 2009). The European Pharmacopoeia describes orally disintegrating tablets as uncoated tablets meant to be placed in mouth where they disperse rapidly before being swallowed. The tablets should be disintegrated in less than 3 minutes. Krause and Breitzkreutz go further in categorising the orally disintegrating tablets as fast dissolving with a disintegration time of less than 60 seconds (Krause and Breitzkreutz, 2008). ODTs are also known as orodispersible tablets (Ph.Eur), quick disintegrating tablets, porous tablets, rapimelts, etc (Bharawaj et al., 2010). They are meant to disintegrate rapidly in saliva, without the need of drinking extra water (Hirani et al., 2009).

In general ODTs make it easier for people that have problems swallowing, by means of having need for dividing or chewing the tablets and drink a lot of water. Having the possibility to take an ODT without the need of water can be advantages when travelling to or living in a country where water quality is low. The ODTs offers an ability of ease of administration to patients who cannot or refuse to swallow a tablet or capsule. This includes stroke victims, paediatric, geriatric, psychiatric patients, etc (Bharawaj et al., 2010). ODTs are made for rapid dissolution and absorption of drug from the mouth, which may cause faster onset of pharmacological effect in the patient (Bharawaj et al., 2010). The rapid onset of action makes ODTs useful for people who suffer from acute disorders like for example migraine. The onset of action for conventional tablets is influenced by several parameters such as for example gastric emptying, which means that from the time of administration to time of pharmacological effect might take hours. This is generally not acceptable in acute disorders (Bredenberg et al., 2003). ODT products have shown to improve patient compliance compared to conventional tablets or capsules and this is the reason why ODTs have attracted a lot of attention over the last few decades (Hirani et al., 2009). ODTs can be valuable to patients with mental illness, where patient compliance is important for treating chronic indications such as for example depression.

1.8 Suitable formulations for paediatric patients

Children represent a very heterogeneous patient group. From newborn to adolescent they go through large physical developmental differences with respect to dose, absorption, pharmacokinetics, sensitivities and compliance. Metabolic changes, body water to fat ratio and protein binding may also go through enormously changes with age (Krause and Breitzkreutz, 2008). There is a lack of suitable and safe drug formulations for children, perhaps especially for the very young children. Studies show that from the age of 6 most children receive solid dosage forms for peroral drug administration, whereas children below that age receive liquid formulations (Schirm et al., 2003). Recently, the new European regulations on paediatric medicines induced an increased need for child appropriate dosage form. The WHO guidelines recommends the use of solid dosage forms over liquid forms due to compactness and stability (Stoltenberg et al., 2010). This is especially important when it comes to paediatric patients in the developing countries. Orally disintegrating mini-tablets could be an appropriate dosage form for children.

A study of acceptability of placebo mini-tablets in 100 pre-school children has been published by Thomson and co-workers (Thomson et al., 2009). The study showed that 46 % of the children of 2 years of age swallowed the mini-tablet, compared to 85 % of children of 5 years of age. However, mini-tablets were chewed or swallowed by children of 2 to 4 years of age, and widely accepted for children ≥ 4 years of age. Throughout the study no one choked or aspirated the mini-tablet (Thomson et al., 2009). This suggests that mini-tablets could offer a safe alternative as a child-appropriate dosage form.

Also ODTs, which melt in mouth, are mentioned as a child-appropriate dosage form.

One of the advantages that they could offer is to overcome the swallowing difficulties with tablets that are experienced in children. In the paper Formulation of Choice for the Paediatric Population they describe ODTs as easy to administer and difficult to spit out provided rapid dispersion (Medicinal, 2005). They could also provide flexible dosing which is appropriate for children when there is need for weight based dosing (Stoltenberg and Breitzkreutz, 2011).

Nevertheless, designing paediatric dosage forms would require through selection of potential excipients in order to avoid adverse effects that can occur in children. A limited use of excipients is recommended, since children are a very heterogeneous group (Cram et al., 2009).

2. Aim of the study

The overall aim of the study was to prepare ordered mixtures using carriers of different particle size and manufacturing method, and test their suitability for preparation of mini-tablets with high dose uniformity. The mini-tablets were intended for use as orally disintegrating systems (ODT) for children.

The specific objectives were:

- To study the influence of particle size of the carrier on the mixing time required to obtain homogenous powder mixtures
- To study the effect of particle size and external surface area of carrier particles on the homogeneity of powder mixtures
- To study the homogeneity of mini-tablets prepared from ordered mixtures in terms of mass and dose-variation
- To study the suitability of the mini-tablets as orally disintegrating systems with respect to tablet hardness and disintegration features assessed by crushing strength, friability and simulated wetting time, respectively.

3. Materials and methods

3.1 Materials

Sodium salicylate (Sigma Aldrich, Germany) and Ibuprofen 50 (BASF, Germany) were used as micronized particles, and mannitol of different grades were used as carrier particles in preparation of ordered mixtures. Mannitol samples were from the Pearlitol series (Roquette Pharma, France) and Parteck ODT (Merck, Germany). Information on particles size of the tested qualities is given in the table below.

Table 1. Information on mean particle size and particle size distribution for the mannitol samples used. Data is provided by the producer.

Sample	Information provided by producer							
	Web page	% residue on sieve (Certificate of analysis)						
	Mean particle size [μm]	% >75 μm	% >100 μm	% >150 μm	% >200 μm	% > 315 μm	% > 500 μm	% >800 μm
Parteck ODT *	70-120							
Pearlitol flash	200		87			6		
Pearlitol 200SD	180	93		56		1.5		
Pearlitol 300DC	250				96	49	0.1	
Pearlitol 400DC	360		100				15	
Pearlitol 500DC	520			96				0

*No Certificate of analysis received from producer

Pearlitol 300DC, 400DC and 500DC are all granule qualities of mannitol specially prepared for direct compression. The numbers indicate the mean particle size of the product. The letters DC indicate that the product is intended for direct compression. The SD product is prepared by spray drying and show different particle characteristics. The SD product is also suitable for direct compaction. Parteck ODT and Pearlitol Flash are specialized materials for preparation of orally disintegrating tablets and contain mannitol co-processed with a disintegrant. Parteck ODT contains crosscarmellose sodium, whereas Pearlitol Flash contains low proportion of starch.

3.2 Particle characterisation of raw materials

3.2.1 Sieving analysis

The mannitol samples were subjected to sieving analysis as described in European Pharmacopoeia using Retsch (AS-200 Basic, Germany) particle size distribution equipment. The recommended weight of powder (100g) was weighed and put onto the sieves before agitation started. The sieves were weighed every 5 minute and the analysis was stopped when less than 0.2 % of the tested material passed through the sieve. Parateck ODT, Pearlitol flash, Pearlitol 200SD and Pearlitol 300DC were analysed using sieves of mesh sizes ranging from 45 -500 μm in diameter. As larger particles were expected in the bulks of Pearlitol 400DC and Pearlitol 500DC, the mesh size of the sieves were selected accordingly; sieves ranging from 63-710 μm in diameter.

3.2.2 Fractionation of powder samples

Since the particle size distribution was broad for all mannitol samples, selected fractions were collected. The following fractions were collected:

- 180-250 μm : Parateck ODT, Pearlitol flash, Pearlitol 200SD and Pearlitol 300DC
- 250-355 μm : Pearlitol 400DC
- 355-500 μm : Pearlitol 500DC

The actives, sodium salicylate and ibuprofen, were grinded manually using mortar and pestle and sieved in order to obtain particles as small as possible. The fraction below 45 μm in diameter was collected and used in further analysis.

3.2.2 Particle size analysis by laser diffraction

The particle sizes of sodium salicylate and ibuprofen were estimated using Beckman Coulter laser diffraction particle size analyzer (LS230, USA). Both micronized actives were checked for solubility in literature. Different suspensions were made, based on their solubilities. Sodium salicylate was suspended in ethanol, whereas ibuprofen was suspended in water. The suspensions were fed into the cavity of the laser diffraction particle size analyser. A particle size distribution (volume % program) was recorded and particle size determined.

3.2.3 Microscopy

The powder samples were examined using a Motic stereo zoom microscope (SMZ-168, UK) to look at the shape of the particles and get a rough estimate of particle size and size distribution.

3.2.4 Scanning electron microscopy

Scanning electron microscopy micrographs were taken of micronized actives and carrier particles. This was done to confirm the shape, the size of the particles and the size of distribution. All powder sample were spread onto sticky carbon tabs mounted on aluminium stubs, the excess powder particles were carefully removed (tapped and blown away by hand balloon) before sputter-coating with gold/palladium using a Polaron Sputter-Coater (SC7640, USA). The materials were examined using a Jeol Scanning Electron Microscope (JSM-6300, Japan).

3.2.5 Apparent particle density

The apparent particle densities of all powders were measured using a helium pycnometer from Micromeritics (AccuPyc 1330, USA). Two different samples were tested, and each was measured 10 times. The average was found by taking the average of the two averages from both of the separate series of samples.

3.2.6 External surface area

The external surface areas of the carrier particles (different mannitol samples) and micronized particles of sodium salicylate and ibuprofen were determined by different permeametric methods (Eriksson et al., 1993, Alderborn et al., 1985).

Steady state permeametry

Steady state air permeametry was used to determine the external surface area of the carrier materials (mannitol samples). The external surface area was found by measurement of the resistance met by the air when moving through a powder plug. The resistance was regulated based on the porosity of the powder plug.

Dry powder was filled to 2/3 of the test cylinder volume (figure 8). The mass of the powder and the height in the cylinder were recorded (figure 8 b and 8c, respectively). The sample was mounted in the setup as shown in figure 9.

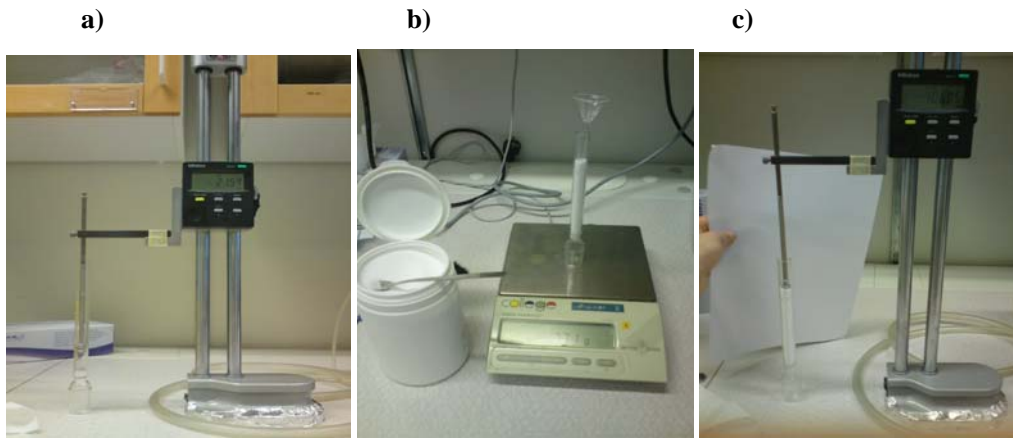


Figure 8. Test cylinder used for measurements of specific surface area by steady state permeametry: a) calibration of height, b) samples weight, c) measurement of height

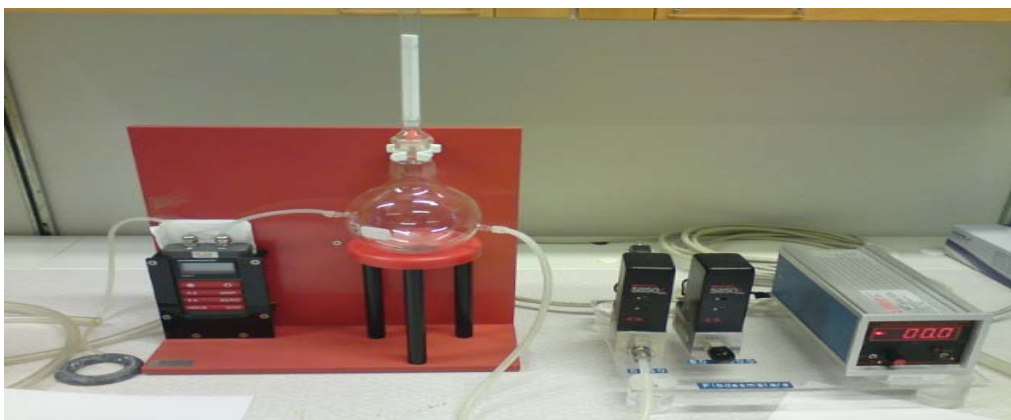


Figure 9. Experimental set-up: From left the manometer, sample, and to the right a flow meter (0-50 ml/min) and on the outer right hand side the system for adjustment of flow connected to a vacuum pump (not shown).

The flow of air through the system was adjusted (right side) and the pressure throughout six adjustments was recorded using the manometer. Permeability plots were made by plotting the air velocity as a function of the pressure difference per unit length of the bed of sample. The slope of the line gave the used permeability coefficient. The measurement was performed in three replicate for every material. Each parallel was performed with a fresh sample. An average of three samples was used for calculations of the external surface area of a sample.

The estimation was done using following main equations:

Eqn. 2:
$$Pc = u / (\Delta P/L)$$

where u = air velocity (m/s), Pc = permeability coefficient ($m^4 N^{-1} s^{-1}$), ΔP = difference in pressure across the bed of particles (Nm^{-2}) and L = length of bed of particles (m)

Eqn 3:
$$Sv^2 = (e^3 / (1-e)^2) * 1 / (k * \eta * Pc)$$

where Sv = specific surface area (m^2/m^3), e = porosity of bed of particles(-), k = aspect factor (a constant), η = viscosity of air ($1.81 * 10^{-5} Nsm^{-2}$) and Pc = permeability coefficient ($m^4 N^{-1} s^{-1}$)

The apparent density of the material was required for the calculations of the external surface area and was determined by helium pycnometry. The porosity of the powder bed was given by the expressed sample weight, density and height together with the given constant for diameter of cylinder. For further details on the method of steady state permeametry, please refer to Eriksson et al. (Eriksson et al., 1993).

Blaine air permeametry

Blaine air permeametry was used to determine the external surface area of micronized materials (e.g. sodium salicylate and ibuprofen). Blaine air permeameter is used for measurement of the time for a constant volume of air to flow through a sample. The flow rate and the pressure head across the powder sample changes as Blaine permeametry measurement proceeds. The method is valid for particles up to approximately $50 \geq \mu m$ in diameter. First, the apparent density was determined by helium pycnometry. A given sample was used to get an appropriate time. The times should be above 4 seconds. Then the porosity of the powder plug was estimated by the weight of sample, density, together with given constants as the diameter and height of cylinder. The appropriate mass of powder was filled into the steel cylinder of the sample holder (figure 10).

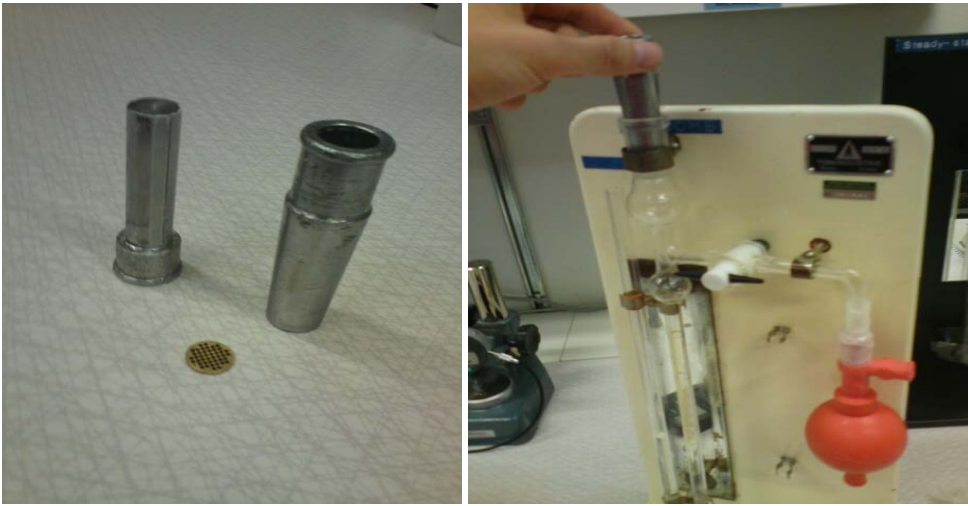


Figure 10. Left: Steel cylinder of the sample holder and plug, right: positioning of the sample holder in the test set-up.

The powder bed inside the steel cylinder of the sample holder was compressed using the plug. The plug was removed, and the sample holder was placed into position for measurements (figure 10).

The level of liquid in the tube of the Blaine permeameter was checked before start (figure 11). The liquid was sucked to the right side of the manometer using a pelleus balloon. The valve was closed (vertical position) and the time it takes for the liquid to flow from one given point to another was measured (figure 11). The required time should, as mentioned, be more than 4 seconds. The available height differences to choose between were 11 to 1.5 cm and 7 to 1.5 cm. The time needed reflects the particle size and the porosity of the powder plug as well as the weight of sample had to be adjusted for each material. The measurement was performed in three replicate for every material. Each parallel was performed with a fresh sample.



Figure 11. The Blaine apparatus

Following empirical equations have been used to estimate the external weight specific surface area from measured resistance.

Eqn 4:
$$Sk^2 = \frac{2 * g \xi t}{(5L\eta \ln(\frac{h_2}{h_1}))} * (d_t/d_m)^2 * E^3 / (1-E)^2$$

where g =gravitational constant (9.81 ms^{-1}), ξ = density of manometer liquid(1 g/cm^3),
 t = time for measurements (s), L = height of powder plug (constant 1.47 cm), η = viscosity of air
($1.81 * 10^{-5} \text{ Nsm}^{-2}$), h_2 =height of start point manometer (cm), h_1 = height of stop point
manometer (cm), d_t = diameter powder plug (constant 1.27 cm), d_m =diameter manometer arm
(constant 0.697 cm), E = porosity of powder bed

Correction for slip flow has to be performed since fine powders, of sodium salicylate and ibuprofen, is investigated and not compacts, which Blaine permeametry is most commonly applied for:

Eqn 5:
$$S_m = \frac{2 * g \xi t}{(PL \ln(\frac{h_2}{h_1}))} * (d_t/d_m)^2 * (E^2 / (1-E)) * 0.96 \sqrt{(R * T / M)}$$

where P =atmospheric pressure ($1.013 * 10^{-5}$), R =universal gas constant ($8.315 \text{ J K}^{-1} \text{ mol}^{-1}$),
 T = absolute temperature (293 K), M = molecular mass of air (29 g mol^{-1})

The total surface (volume specific surface) area can be calculated by combining eqns. 4 and 5.

Eqn 6:
$$S_v = S_m/2 + \sqrt{(S_m^2/4) + S_k^2}$$

The weight specific surface area can be found by dividing Eqn. 6 with the apparent density of tested powder sample. For further details on the method for measuring the external surface area using Blaine air permeameter please refer to literature (Alderborn et al., 1985).

3.2.7 Estimation of diameter on micronized particles from external surface area

The particle diameter of the micronized drug substances were estimated from their volume specific surface areas using the Heywoods shape factor. A shape factor of 10 was chosen for both sodium salicylate and ibuprofen. The shape factor 6 is a perfect sphere (Eriksson et al., 1993, Mihranyan et al., 2008). The diameter was calculated from equation 7:

Eqn. 7
$$\text{Diameter } (\mu\text{m}) = \text{Heywood shape factor}/\text{external surface area} * 10000$$

where Heywood shape factor =10 and external surface area determined by Blaine permeametry (section 3.2.6)

3.2.8 Bulk and tapped density

The bulk and the tapped density of the carrier particles were examined. The results were expressed using Hausner ratio and Carr Index, related to 50.00 gram of sample. Different graduated cylinders were used due to different porosities; the cylinders used were 100ml and 250ml. The 250 millilitre cylinders were used for the carrier particles of Parateck ODT, Pearlitol Flash, and Pearlitol 200SD. The carrier particles of Pearlitol 300DC, 400DC and 500DC were tested in a 100 ml graduated cylinder. The different powder samples of mannitol were carefully poured into the cylinders without compacting. The untapped volumes were read to the nearest graduate unit. The cylinders were secured in the support and tapped using Erweka (SVM, Germany) according to the European Pharmacopoeia: 10, 500 and 1250 taps were carried out on the same powder sample, and the corresponding volumes were read to the nearest graduate unit. The examination was stopped when the difference in height was less than 2 ml, this happened at 1250 taps for all the mannitol samples.

From the bulk and tapped density the Hausner ratio and Carr Index were calculated to give an approximation of the powder flowability.

Eqn 8: Hausner ratio: V_0 / V_f

Eqn 9: Carr Index: $100 * (V_0 - V_f) / V_0$

where V_0 is the unsettled apparent volume. V_f is the final tapped volume, when no further changes in volume of the material occurs.

3.2.9 Powder Flow rate and Angle of repose

The powder flow rate of the mannitol samples were tested using the method described by the European Pharmacopeia. A dry funnel was held steady by pegs, in a suitable device. The height from the funnel to the plate was adjusted, in order for the free flowing powder particles to form a pyramid on the plate. The height from the tip of the funnel to the plate was approximately 3 cm. The powder samples were weighed and poured into the closed funnel. The times for the powder particles to flow through the funnel, when unblocked, forming a pyramid was measured. The average flow rate was expressed in seconds and tenths of seconds, associated to the movement of 50.00 gram powder sample. The heights and the diameters of the pyramids were measured and the angle of repose was calculated. Three parallels of the same powder were carried out.

Eqn 10: Angle of repose: $\tan \alpha = \text{height} / \text{radius}$

3.3 Preparation of powder mixtures

3.3.1 Conventional mixture

Mannitol and sodium salicylate were mixed in a Turbula mixer (W.A. Bachofen AG; Switzerland) at 96 rpm for 10 minutes. The mixture containing 1 % active ingredient was produced by mixing 1.0 gram of sodium salicylate and 99.0 gram Pearlitol 300DC. The active was screened through a sieve of 500 μm in mesh size to make sure that there were no larger particles. Mannitol was sieved to obtain the desired fraction for that particular sample (e.g. 180-250 μm). The conventional mixture was made in order to have a comparison of the relative standard deviation of a conventional mixture with the relative standard deviations of the ordered mixtures.

3.3.2 Ordered mixture

Mixtures containing 1 % active were obtained by adding 1.0 g gram micronized sodium salicylate and 99.0 gram selected carrier. The appropriate fraction of the selected carrier and micronized active were mixed in Turbula mixer (W.A. Bachofen AG; Switzerland) at 96 rpm for 24 h and 48 h. The filling load of the glass jar in the container was optimised. Ordered mixtures were prepared with the carriers Pearlitol 200SD (180-150 μm), 300DC (180-250 μm), 400DC (250-355 μm) and 500DC (355-500 μm). All ordered mixtures were prepared in duplicates, the exception was 200SD due to lack of material.

3.4 Powder mixture characterization

The four ordered mixtures (section 3.3.2) were characterised according to the methods described above for bulk and tapped density (section 3.2.8), powder flow rate and angle of repose (section 3.2.9).

3.4.1 Homogeneity

The homogeneity of the mixed powders was determined according to the method described by European Pharmacopoeia. Thirty sample units were withdrawn from each of the powder mixtures by random sampling using a powder micro-thief (Sampling Systems, UK). The sample unit mass was 20 ± 2 mg. Each sample unit was dissolved in phosphate saline buffer pH 6.8 in 10.0 ml volumetric flasks. pH of the phosphate saline buffer was chosen to simulate the pH of saliva (European Pharmacopoeia 6.7). A calibration curve was made by dilution of a stock solution of 0.1mg/ml sodium salicylate into the following concentrations: 0.01mg/ml, 0.015mg/ml, 0.020 mg/ml, 0.025mg/ml and 0.030 mg/ml. The quantification was done by direct UV-assay at 295 nm.

The theoretical amount of sodium salicylate in the sample units was calculated (1% of mass sampled by the powder-thief) and compared with the experimentally determined amount. The drug content of the sample was normalised by dividing the experimentally determined value by the theoretically calculated value. Homogeneity of the mixtures was expressed as the relative standard deviation of the normalised average of 30 samples.

3.4.2 Surface coverage of micronized particles on the carrier

The coverage of micronized particles on the surface of the carrier particles was calculated for the four ordered mixtures using the external specific surface areas of the carrier and micronized particles as determined by steady-state air permeametry and Blaine air permeametry (section 3.2.6) (Eriksson et al., 1993, Alderborn et al., 1985).

$$\text{Eqn 11 : } m(\text{micronized particles}) = \frac{R * (m(\text{carrier particles}) * SW(\text{carrier particles}))}{SW(\text{micronized particles})/4}$$

(same as eqn 1)

3.4.3 Scanning electron microscopy

Scanning electron microscopy micrographs were made of the four ordered mixtures (section 3.3.2). This was done according to the method described in section 3.2.4. The micrographs were compared to those of the raw materials in order to look for physical evidence of ordered mixtures. It was tried to discover the attachment of micronized sodium salicylate particles on the surface of the carrier particles.

3.5 The compaction of mini-tablets

3.5.1 Addition of lubricant

Magnesium stearate (1 % w/w) was added to the mixture of sodium salicylate and mannitol by volumetrically blending using a card in the mortar. The four ordered powder mixtures were compressed into four batches of mini-tablets (200SD, 300DC, 400DC, and 500DC mini-tablets).

During compression punches and dies were lubricated with a 5 % suspension of magnesium stearate in acetone, in order to avoid sticking of the material to the die.

3.5.2 Manual filling of dies

An appropriate amount of powder to make mini-tablets (120 mg) was weighed in from the powder mixtures and manually filled into the dies of the mini-tablet multi tooling. The mini-tablet multi tool produces 15 mini-tablets per stroke. The punches are concave and 2 mm in diameter, and located in 2 lines; 7 in front and 8 in the back. The production of homogenous mini-tablets is depending on reproducible filling of the dies. Thus a standardized method was required. This was done by forming two lines of the powder; one in the front of the seven holes and one behind the eight as illustrated in figure 12. The powder lines were then pushed towards each other. The remainder of powder particles were then pushed towards the left and the right side, filling more of the possible gaps of the corners. Step three made it possible to optimise corner filling. It was done by pushing the powder particles first to the sides, then a few times from side to side. A few times forward and back were also done to make every particle disappear into the dies. The filling method was validated by checking the mass of the mini-tablet produced from each of the positions in 12 of the 24 strokes, (including all batches).

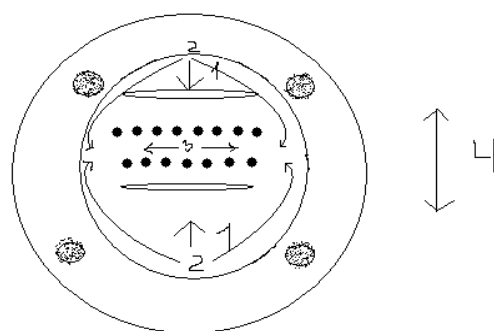


Figure 12. The drawn picture of the minitab-let multi tooling, seen from above, is made to get insight in the challenges of making mintablets with equal amount.

3.5.3 Compaction of mini-tablets

Mini-tablets were compacted with a costume made compaction simulation consisting of a Schmidt Servopress 450 (Schmidt Technology GmbH, Germany) equipped with a powder compression device (IBR Reichenbach, Germany). Maximum 5 % variation in mini-tablet mass was accepted during tableting (8 ± 0.4 mg). All mini-tablets were compressed with a velocity of the upper punch of 10mm/sec, and a pressure of 170 MPa. The pressure was regulated through the length of distance the upper punch went, measured by 2 sensors (LS 487, Germany). The pressure was calculated as an average of 2 forces; max force upper and max force bottom measured by Kistler Instumente AG force sensor (9363, Switzerland). The compression force was kept at 8 ± 0.24 kN, thus the calculated pressure.

Eqn 11: $P = F / A$

In the case of compaction of mini-tablets (no 15) area is given by $\pi \cdot r^2 \cdot 15$

Table 2. Summary of applied conditions during preparation of mini-tablets

Amount equivalent to 15 mini-tablets (mg)	compression force (kN)	amount equivalent to 1 mini-tablet (mg)	Magnesium stearat (mg per tablet)	Ordered powder mixtures. 1 mini-tablet contains (mg)				active ingredient per mini-tablet (mg)
				200SD	300DC	400DC	500DC	
120,00	8	8	0,08	7,92	7,92	7,92	7,92	0,0792

The temperature and the humidity of the laboratory were recorded during tablet compression using ebro humidity/ thermometer (EBI-20, Germany).

3.6 Characterisation of mini-tablets

3.6.1 Mass variation

20 randomly sampled mini-tablets from each of the batches were individually weighed (European Pharmacopeia 7.0, chapter 2.9.5). The average mass was made by calculation. The individual mass deviations from the average mass of the mini-tablets were examined and compared to the acceptance criteria of the European Pharmacopeia.

3.6.2 Friability testing

The friability of the mini-tablets was tested by using standard friability apparatus from Erweka (Tar-20, Germany). The measurements were performed according to the European Pharmacopoeia. This means a drum rotating speed of 25 rpm for 4 min. 20 randomly selected mini-tablets from each batch were weighed before and after friability testing. The percentage weight loss was calculated.

3.6.3 Crushing strength

The crushing strength of the mini-tablets was determined using a Stable Micro System texture analyser (TA.XT.plus, UK). Mini-tablets were examined using a probe 4 mm in diameter. Twenty mini-tablets from each batch were placed separately on the plate and crushed. The radial tensile strength was measured. The probe had a pre-test rate of 2 mm/sec until contact with the mini-tablets (trigger force 5 g), and then the test rate was changed to 0.03 mm/sec. A force-distance diagram was recorded and the maximal force was determined for each of the mini-tablets. The crushing strength was detected in Newton. The tablet hardness was expressed as the relative standard deviation force needed to crush the 20 mini-tablets.

3.6.4 Simulated wetting test

The simulated wetting test was performed as described by Park and co-workers (Park et al., 2008). The test was developed for orally disintegrating tablets. Shortly described: One filter paper disc (5 mm in diameter) was placed in each well of a 96 well-plate. 20 µl of a 0.1 % (w/w) Brilliant blue 85E dye solution (Sigma, Germany) was added. One mini-tablet was carefully placed, with the compacted sides in the horizontal direction, on the surface of the filter paper using forceps. The time required for the mini-tablet to be completely coloured blue by the brilliant Blue 85E dye solution was measured as the wetting time.

3.6.5 Quantification of active and dose variation in mini-tablets

Ten mini-tablets, randomly sampled from each batch, were dissolved separately in phosphate saline buffer pH 6.8 in 5.0 ml volumetric flasks. The concentration of the active ingredient in each of the mini-tablets was determined using the direct UV-assay described above (section 3.4.1). Due to the magnesium stearate in the mini-tablets, samples were filtered using a 0.22 µm syringe filter Pall Life Science (Acrodisc, USA) prior to quantification. Also the standard solutions were filtered to ensure that they were treated equally. The theoretical amount of sodium salicylate in the mini-tablet was found by first subtracting 1 % of the weight of the mini-tablet (e.g. contribution of magnesium stearate) and then another 1 % of this new amount represented the amount of sodium salicylate. The amount of drug was normalised by dividing the experimentally determined amount by the theoretically calculated one. The homogeneity was expressed as the relative standard deviation of the normalised values. The homogeneity of the mini-tablets was compared to the homogeneity of the corresponding ordered mixture.

The drug content determined in separate mini-tablets was also used for testing of uniformity of content of single dose preparations according to the European Pharmacopoeia. The dose variation in each batch was compared to the acceptance criteria of the Pharmacopoeia.

4. Results and discussion

4.1 Particle characterisation of raw materials

4.1.1 Particle size of carrier materials

The sieving analysis performed for the mannitol samples gives more detailed information on particle size and particle size distribution of the batches used in the current study than the general product information. The results of the sieving analysis are presented in table 3 and figure 13 and showed that all the mannitol samples had a wide particle size distribution. The sieving analysis was important to do in order to achieve carrier particles with a narrow particle size distribution. This is a recommended when making ordered mixtures. From the results presented in table 3 and figure 13, it can be seen that Parreck ODT had the broadest particle size distribution of all samples tested. The six mannitol samples were roughly divided in two groups with respect to their particle size distribution; one group containing Parreck ODT, Pearlitol Flash and Pearlitol 200SD showed a lot of fine particles, and the other group containing the remaining Pearlitol qualities (300DC, 400DC and 500DC) showed coarser particle sizes.

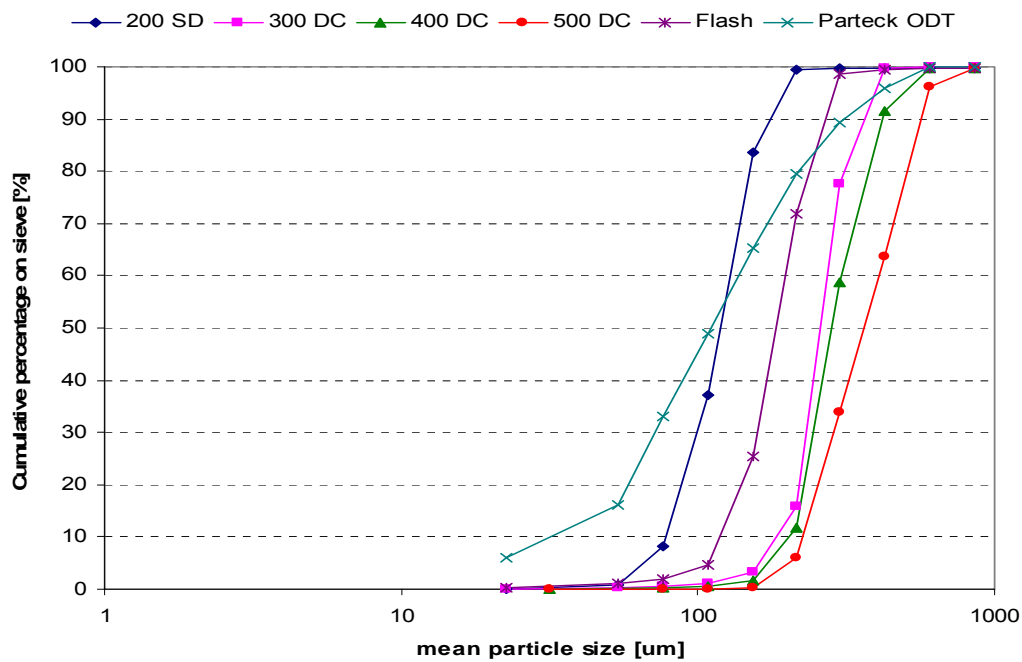


Figure 13. Particle size distribution of the different mannitol samples

Table 3. Results from the sieving analysis of the different mannitol samples. Particle size fractions that were selected for further studies in the master project are shown in bold.

Sample	Fractions selected [µm]	Classification observed through particle size analyses									
		% residue on sieve									
		<63		63-90	90-125	125-180	180-250	250-355	355-500	500-710	>710
		µm	µm	µm	µm	µm	µm	µm	µm	µm	
Parateck ODT	180-250	5.89	10.25	16.8	15.99	16.38	14.07	9.88	6.55	4.07	
Pearlitol Flash	180-250	0.36	0.6	0.83	2.87	20.65	46.46	26.93	0.89	0.04	
Pearlitol 200SD	180-250	0.02	0.88	7.34	28.85	46.54	15.87	0.25	0.04	0.00	
Pearlitol 300DC	180-250	0.01	0.13	0.32	0.6	2.11	12.72	61.59	22.37	0.02	
Pearlitol 400DC	250-355	0.09		0.17	0.34	1.05	10.23	46.85	32.67	8.41	0.03
Pearlitol 500DC	355-500	0.01		0.01	0.02	0.17	5.73	27.99	29.86	32.37	3.7

For further studies one series of different mannitol samples were selected among those containing most fine particles. This series contain two samples of co-processed mannitol specially developed for ODTs (Parateck ODT and Pearlitol Flash) and one pure mannitol sample (Pearlitol 200SD). From these samples the fraction 180-250 µm was collected, since the carrier particles of ordered mixtures are recommended to be around 200 µm (Sundell-Bredenberg and Nystrom, 2001, Yip and Hersey, 1977b). The different mannitol samples contained different amounts of this fraction. Most fitting to the selected fraction was Pearlitol Flash with 46.5% of particles in this size range. Both Parateck ODT and Pearlitol 200SD contained less than 16% particles in the selected size range.

A series of samples was selected for further studies from the mannitol grades that were manufactured by the same method, named the DC quality. This series was select for studies of the effect of particle size of the carrier; the selected particle size fractions were 180-250 µm (Pearlitol 300DC), 250-355 µm (Pearlitol 400DC) and 355-500 µm (Pearlitol 500DC). Consequently, also a third comparison is possible; the influence of manufacturing method for the carrier particles 180 - 250 µm (SD quality versus DC quality).

4.1.1 Particle size analysis of drug substances

The particle size analysis of grinded sodium salicylate, measured by laser diffraction, showed a mean particle size of 5.019 micrometer in diameter and a standard deviation about 3.179 (Table 4). The particle size median was calculated to 4.867 micrometer in diameter. The laser diffraction analysis showed that the particle size distribution is extremely broad for the micronized powder, ranging from 0.4 micrometer to about 130 micrometer in diameter. Only 10 % of the particles were found to be above 24.11 micrometer.

Particle size analysis of ibuprofen showed larger particles with a mean size of 78.18 micrometer in diameter, and the median was close to 100 micrometer. The volume percentage gave also an indication of larger particles. Both of the drugs had been sieved screened through 45 micrometer sieves, thus the diameter were expected to be less than this. The big particles identified for ibuprofen are expected to be aggregates. This substance was found to be extremely electrostatic.

Table 4: Particle size analysis of drug substances by laser diffraction

Sample	Particle size		Particle size				
	[μm]		D10	D25	D50	D75	D90
Sodium salicylate	5.019	3.179	24.11 μm	11.05 μm	4.867 μm	2.182 μm	1.076 μm
Ibuprofen 50	78.18	2.547	139.9 μm	120.4 μm	98.51 μm	74.86 μm	48.12 μm

4.1.1 Particle shape and morphology

Scanning electron microscopy (SEM) micrographs of the two drug substances can be seen in Figure 14 and 15. The drugs were found to be quite different in shape and morphology. Figure 14 shows sodium salicylate particles as micronized flakes of many different shapes. The micrograph indicates particles with sharp edges and broad size distribution. In contrast, the SEM micrograph of ibuprofen in Figure 15 shows particles with a smooth surface and a very rounded but elongated shape. Ibuprofen has no sharp edges, which could give an indication of the breaking of particles due to the micronized process. The different particle shapes and morphology of the drugs are expected to be the main reason for the difference in electrostatic behaviour.

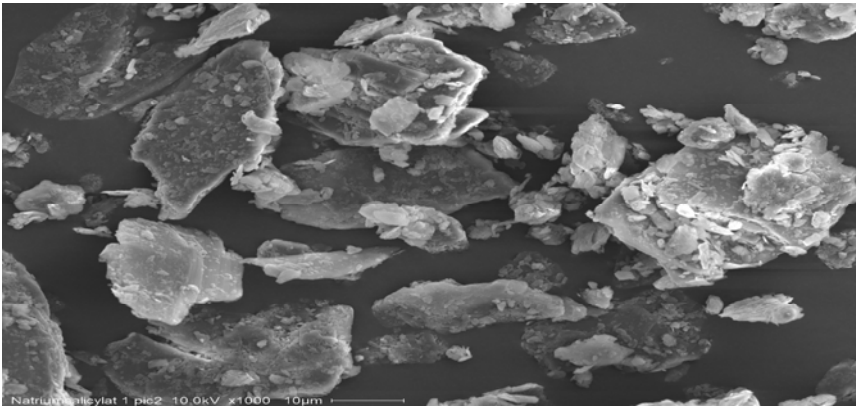


Figure 14. SEM micrograph of sodium salicylate particles; fraction <45 micrometer in diameter

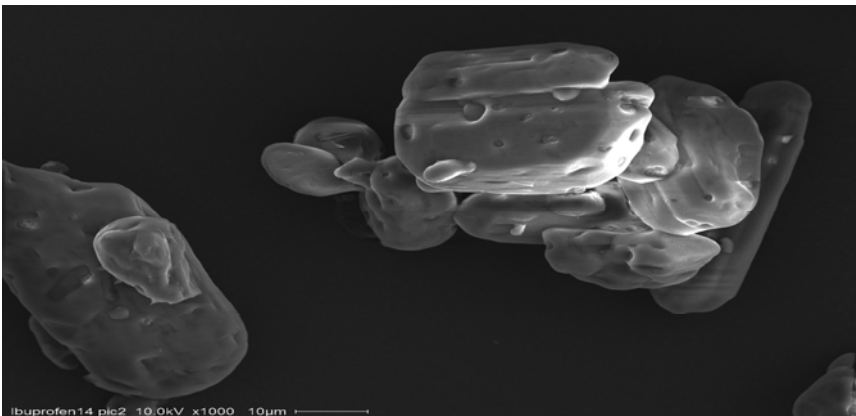


Figure 15. SEM micrograph of Ibuprofen; fraction < 45 micrometer in diameter

Figure 16-21 show microscopy images of the different mannitol samples in the selected size fraction. The images indicate two different types of particles: Parateck ODT (figure 16) and Pearlitol 200SD (figure 17) showed particles with irregular and pore like structure, which is typical for spray dried products; whereas Pearlitol Flash (figure 18) seemed to have a more crystalline surface. Figure 19-21 which are depicting the DC grades of increasing particle sizes showed more compact and rounded particles, which reflects the manufacturing procedure of the material.

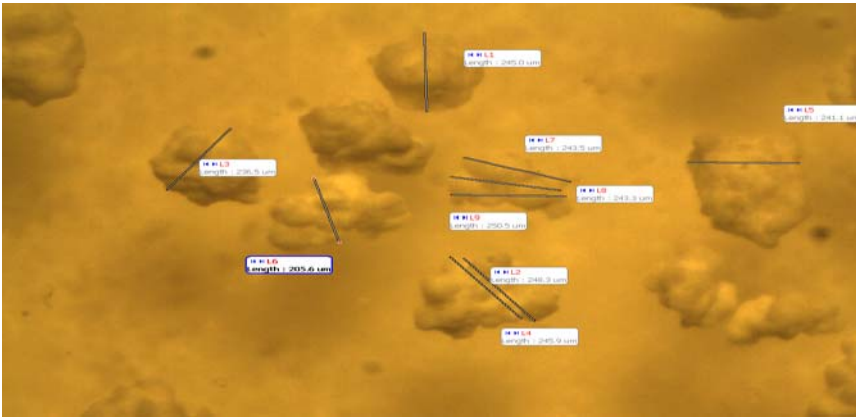


Figure 16. Microscopy image of Parateck ODT; fraction 180-250 micrometer in diameter

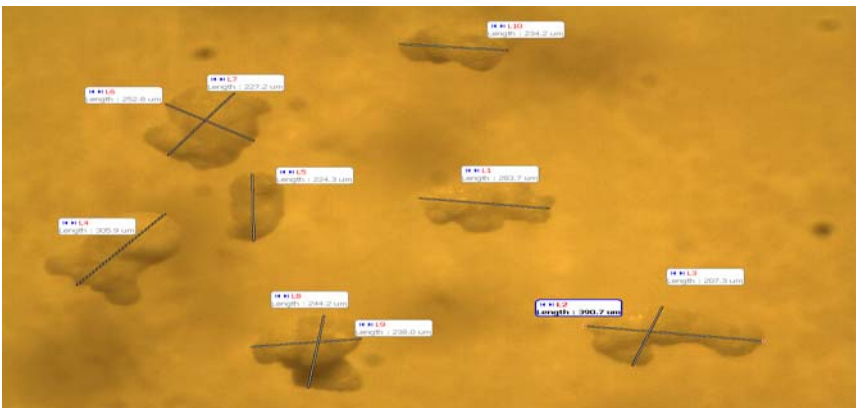


Figure 17. Microscopy image Pearlitol 200SD; fraction 180-250 micrometer in diameter

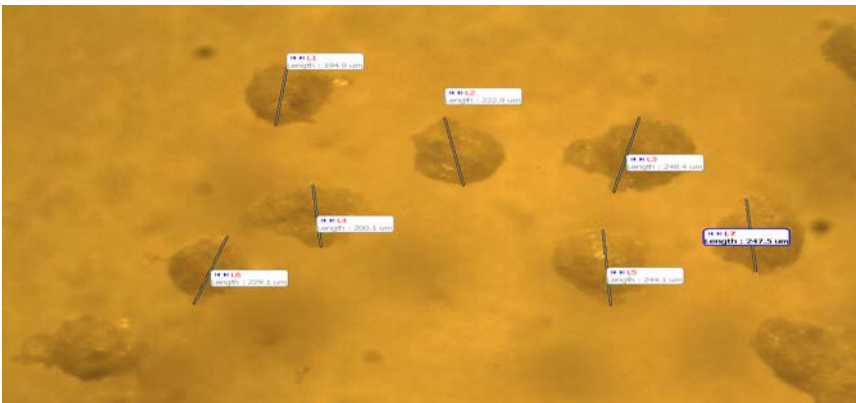


Figure 18. Microscopy image Pearlitol Flash; fraction 180-250 micrometer in diameter.

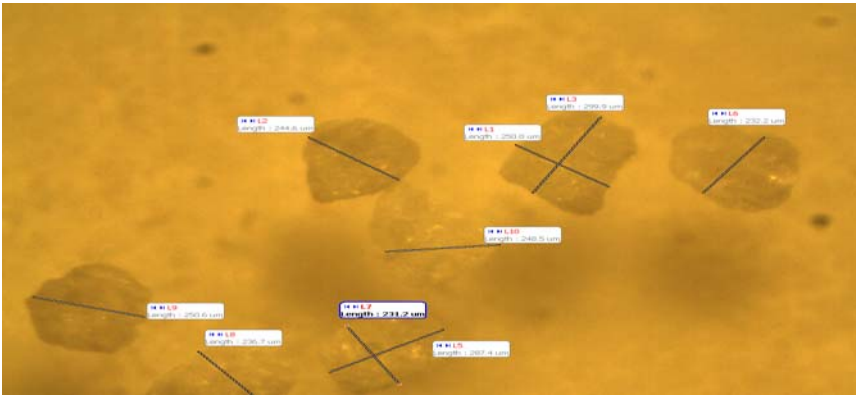


Figure 19. Microscopy image Pearlitol 300DC; fraction 180-250 micrometer in diameter

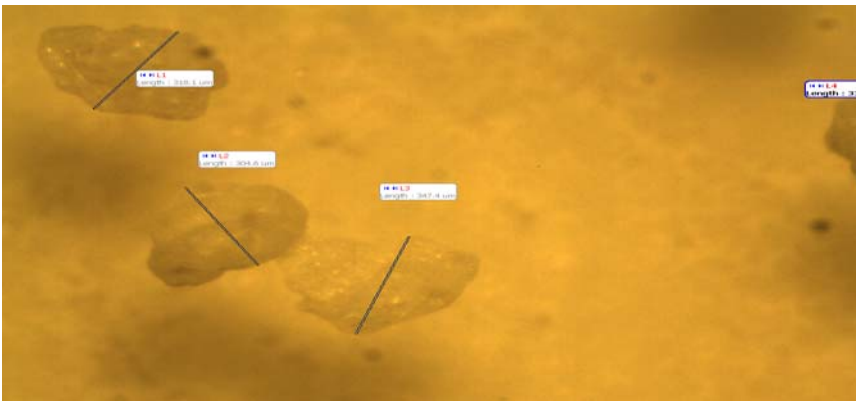


Figure 20. Microscopy image Pearlitol 400DC; fraction 250-355 micrometer in diameter

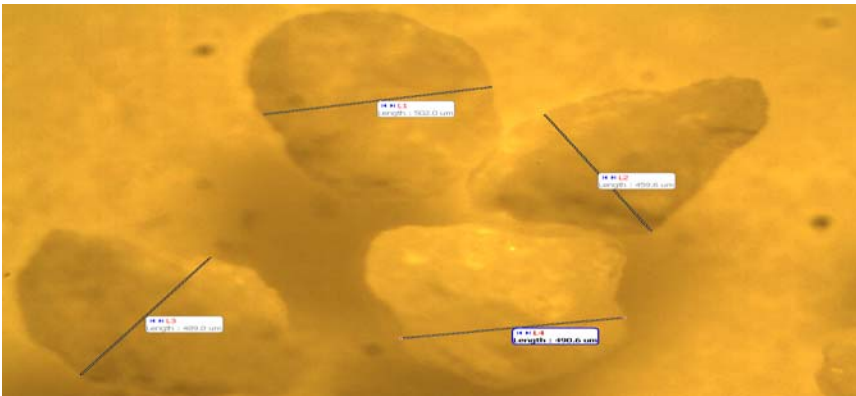


Figure 21. Microscopy image Pearlitol 500DC; fraction 355-500 micrometer in diameter

4.1.2 Apparent particle density and external surface area

Table 5 shows that the two drug substances are very different both with respect to particle density and external surface area. The external surface area of sodium salicylate is approximately 7 times higher than that of ibuprofen. This suggests that the particles of sodium salicylate are much smaller than those of ibuprofen, since the external surface area increases as the particle size is reduced. This is in agreement with the SEM micrographs which show a high number of small particles or fragments for sodium salicylate. The particle size estimated from the surface area show a mean size of value 3.29 which is close related to the 5.019 ± 3.179 micrometers for sodium salicylate found by laser diffraction. The mean particle size of ibuprofen is much smaller when estimated from the external surface area compared to the laser diffraction method. This confirms the hypothesis that agglomerates were measured by laser diffraction. As mentioned earlier, ibuprofen was very difficult to handle due to electrostatic forces and severe agglomeration.

Table 5: Apparent particle density (helium pycnometry), external surface area (Blaine permeametry) and mean particle size estimated from the surface area for the drug substances, mean and standard deviation

Sample	Apparent particle density [g/cm ³]	External specific surface area [cm ² /g]	Estimated mean particle size [μm] *
Sodium-salicylate	1.5682 ± 0.00683	19 405 ± 1038.878	3.29
Ibuprofen	1.1148 ± 0.000172	2 877 ± 19.976	31.18

* Estimated diameter assuming Heywood shape factor of 10

The results of mannitol samples in table 6 (page 46) indicate major differences among the samples. Firstly, the co-processed samples (Parateck ODT and Pearlitol Flash) shows slightly higher apparent particle density compared to the other samples, which could be related to the fact that they contain small fractions of an additional component probably of high density. These samples have particles of high external surface area. Secondly, the apparent particle density of the Pearlitol DC qualities is very similar and is not affected by the particle size, which is as expected. The external surface area of these samples is highest for the smallest size fraction and decreases with increasing size fraction, which also agrees well with the theory. Finally, the Pearlitol 200SD has the lowest particle density which probably is the result of the manufacturing method resulting in much less dense packing of material. The less dense packing is in an agreement with the microscopy image showing a fluffy particle, known to contain only mannitol. As a result of the more fluffy structure the particles also have a high

external surface area. The values are in the same size range as for the co-processed types. These results confirm that it will be interesting to compare Pearlitol 200SD and 300DC for preparation of ordered mixtures; the particles are of very different character even though the particle size fraction is the same.

Table 6. Apparent particle density (helium pycnometry) and external specific surface area (steady state permeametry) of the mannitol samples, mean and standard deviation

Sample	Investigated particle size fraction [μm]	Apparent particle density [g/cm ³]	External specific surface area [cm ² /g]
Parteck ODT	180-250	1.4998± 0.00123	997± 29.577
Pearlitol Flash	180-250	1.4978± 0.000352	874± 10.546
Pearlitol 200SD	180-250	1.4679± 0.000454	870± 5.261
Pearlitol 300DC	180-250	1.4815± 0.000304	432± 2.229
Pearlitol 400DC	250-355	1.4816± 0.000364	332± 2.159
Pearlitol 500DC	355-500	1.4804± 0.000514	246± 2.801

Table 7. Amount of drug (g) required to form a monoparticulate layer on one hundred gram of carrier particles calculated from external surface area of drug and mannitol samples

Sample	Investigated particle size fraction [μm]	Amount of drug required to form a monoparticulate layer on carrier particles	
		Sodium-salicylate [g]	Ibuprofen [g]
Parteck ODT	180-250	21	139
Pearlitol Flash	180-250	18	121
Pearlitol 200SD	180-250	18	121
Pearlitol 300DC	180-250	9	60
Pearlitol 400DC	250-355	7	46
Pearlitol 500DC	355-500	5	34

The measurements of external surface area can be used to calculate the appropriate amount of drug that should be mixed with each of the carriers to form an ordered mixture. Table 7 shows the amount of drug necessary to form a monoparticulate layer around 100 g of the different carrier particles. The amounts are calculated based on the external surface area of the drug particles (Table 5) (page 45) and the different types of mannitol samples (table 6). The mannitol samples of high external surface area (Parteck ODT, Pearlitol Flash and 200SD) required significantly higher amount of drug than the DC samples of low external surface area. For the DC samples there are also an effect of particle size, since the particles size is affecting the external area. Sodium salicylate is much better suited for preparation of ordered

mixtures than ibuprofen, since the particle size is much smaller and the surface area is correspondingly higher. The amount of drug required to form a monoparticulate layer is more reasonable for sodium salicylate. The results of ibuprofen should be used with big caution since the material is associated with high degree of agglomeration due to electrostatic forces.

4.1.3 Powder flow properties

Bulk and tapped density

It is necessary for carriers that are supposed to be used for direct compaction to possess good flow and compression properties. The packing characteristics of the mannitol samples are calculated as the Hausner ratio and Carr Index. These parameters also give an indication of the flowability of the particles, in this case the carrier particles. From the results presented in table 8 (page 48), five of the six mannitol samples achieved flow character good based on the Hausner ratio, which is characterised by a HR-value between 1.12 and 1.18. The last sample Pearlitol 500DC showed excellent flow character (1.00-1.11). The results from calculation of Carr Index confirmed these findings. Both Hausner ratio and Carr Index characterises all the carrier particles as well suitable for direct compaction.

Powder flow rate and angle of repose

The characteristic related to angle of repose is given by the friction between particles, known as the resistance to movement between particles. Very well flowing materials have a low possible angle of repose. From the results shown in table 8 (page 48) all angle of repose degrees for the mannitol samples showed flow character excellent, i.e. an angle in the range 25-30. The results given by the angle of repose showed a rank order from the poorest to the best as followed; Pearlitol 200SD, 500DC, 400DC, Flash, 300DC and Parateck ODT. Looking at the group of the Pearlitol DC samples of different size fractions a small increase in flowability with decreasing particle size could be identified from 500DC→400DC→300DC. This suggests that there is less friction between the particles and can be a result of more spherical particle shape. Among the samples of particle size fraction 180-250 micrometer in diameter (Parateck ODT, Pearlitol 200SD, Pearlitol Flash and Pearlitol 300DC) only small differences in angle of repose was found. Pearlitol 300 DC had a very similar angle of repose value as Flash, better than 200SD but poorer than Parateck ODT. Surprisingly, the flow rate of the carriers showed quite different results: 500DC showed the highest flow rate with 20.22 gram per second, which is long compared to the 200SD with only 6.32 gram per second. They

were ranked from low to high flow rate as followed; 200SD, 400DC, 300DC, Flash, Parateck ODT and 500DC. This might be explained by the particle size; at constant mass a powder of small particles sizes contains a higher number than a powder of high particle size. The flow rate measure the amount of powder per seconds and will therefore favours the powder of small particle size. Most of the samples showed some degree of electrostatic tendency, observed as sticking to the glass tract, only Parateck ODT and Pearlitol 500 DC did not show this behaviour. It can be concluded that all powder materials suggested as carriers for preparation of ordered mixtures were found to have satisfying flow, which is important in the current study both for the ordered mixtures and for the filling of the dies in mini-tablett production.

Table 8. Results from both bulk and tapped density, and powder flow rate and angle of repose for the mannitol carriers

Material [g]	50					
Graduated cylinder [ml]	250			100		
Carriers	Flash	Parateck ODT	200SD*	300DC×	400DC	500DC
Particle size fraction [µm]	180-250	180-250	180-250	180-250	205-355	355-500
untapped volume	106	106	104	79	78	79
10 taps	100	100	98	76	76	76
500 taps	94	92	92	70	69	71
1250 taps	92	92	92	69	68	71
Hausner ratio	1.15	1.15	1.13	1.14	1.15	1.11
Flow character based on Hausner ratio	Good	Good	Good	Good	Good	Excellent
Carr Index	13.21	13.21	11.54	12.66	12.82	10.13
Flow character based on Carr Index	Good	Good	Good	Good	Good	Excellent/Good
Flow rate [g/sec] ⁻¹	10.21	19.31	6.32	9.81	9.06	20.22
Angle of repose	27.35	26.92	29.54	27.32	28.34	29.05
Flow character based on angle of repose	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent

*200SD comes from a different batch compared to the reset of the project

× Particle size fraction 180-250 µm in diameter is collected from 400DC instead of 300DC

4.2 Powder mixture characterisation

For preparation of ordered mixtures, the co-processed mannitol types were excluded. This was because of limited time. The two series that will be followed in further evaluations are the different particles sizes of the DC materials and the two manufacturing processes (DC and SD for the size fraction 180-250 μm).

4.2.1 Calculated degree of surface coverage for ordered mixtures

Based on the calculation of required amounts of drug to cover the surface of carrier particles with a monolayer of micronized drug (see table 7, section 4.1.2) very different amounts of drug should be used for the selected mannitol carriers. Therefore, it was decided to add a constant amount of 1 % w/w of drug for preparation of ordered mixture. The calculated surface coverage from addition of 1 % sodium salicylate to the different carrier types is shown in table 9. The surface area unit ratio for the ordered mixtures was found to increase from the lowest particle size fraction to the largest. For the DC products the calculated surface area unit ratio increased roughly by almost 50 % for every 100 μm in diameter. The increased surface coverage is in good agreement with the increased external surface area determined for the samples. When it comes to the two samples of different manufacturing process (DC and SD, 180-250 μm in diameter), the Pearlitol 200SD with the highest external surface area shows the lowest surface coverage, as expected. The surface area unit ratio of Pearlitol 300DC was found to be twice that of 200SD, which agrees well with the size of the estimated external surface area, which also differed by a factor 2.

Table 9; Calculations of the degree of surface coverage by 1 % (w/w) micronized sodium-salicylate particles (mean particle size 3.29 μm) on the surface of mannitol carrier particles of different size fractions based on external surface area of drug and mannitol samples

Sample	Investigated size fraction [μm]	Calculated surface area unit ratio
Pearlitol 200SD	180-250	0.056318231
Pearlitol 300DC	180-250	0.113495204
Pearlitol 400DC	250-355	0.147721920
Pearlitol 500DC	355-500	0.199281622

4.2.2 Powder flow properties

Bulk and tapped density

Table 10 summarises (page 51) all powder flow results obtained for the ordered mixtures. The packing characteristic of the powder mixtures given by Hausner ratio and Carr Index expressed flow character good for all (HR 1.12-1.18 and CI 11-15). Hausner ratio was actually found to be identical for all the ordered mixtures. Carr Index showed very small differences in values. Most ordered mixtures had the same packing characteristic (good) as the used carriers (see section 4.1.3.), only 500DC was moved within the interval of good flow instead of being borderline excellent – good, as for the carrier.

Powder flow rate and angle of repose

The flow character of the ordered mixtures expressed by angle of repose indicated excellent flow for all the ordered mixtures. All ordered mixtures showed the same flow characteristic as the raw material, based on angle of repose, even though values were slightly lower.

In contrast to the flow rates of the carriers, where only 1 showed a flow rate above 20 g/sec, all ordered mixtures showed flow rates above 20 g per seconds, which represents excellent flow. None of the ordered mixtures were sticking to the glass tract. The decreased degree of electrostatic tendency and the improved flow rate for most of the ordered mixtures could be explained by the use of magnesium stearate prior to the compaction of mini-tablets. Jones suggested that glidants were able to improve flowability by minimizing electrostatic charge (Jones, 1970).

Table 10. Results from both bulk and tapped density, and powder flow rate and angle of repose for the ordered mixtures.

Material [g] Graduated cylinder [ml] Ordered Mixtures	50			
	250	100		
	200SD	300DC	400DC	500DC
Particle size fraction [μm]	180-250	180-250	205-355	355-500
untapped volume	106	79	79	77
10 taps	100	76	76	72
500 taps	94	71	71	68
1250 taps	94	70	70	68
Hausner ratio	1.13	1.13	1.13	1.13
Flow character based On Hausner ratio	Good	Good	Good	Good
Carr Index	11.32	11.39	11.39	11.69
Flow character based on Carr Index	Good	Good	Good	Good
Flow rate [g/sec]	21.68	29.88	27.83	25.82
Angle of repose	26.57	25.84	25.84	26.32
Flow character based on angle of repose	Excellent	Excellent	Excellent	Excellent

4.2.3 Homogeneity

Conventional powder mixture

A powder mixture of high quality should possess high degree of homogeneity. Table 11 (page 52) shows the results obtained for homogeneity of a conventional powder mixture (10 min in Turbula mixer) characterized by sampling randomly 30 samples of $20 \text{ mg} \pm 2 \text{ mg}$. The powder mixture consisted of Pearlitol 300 DC (180-250 μm) and 1 % (w/w) of sodium salicylate screened through a 500 μm sieve. The homogeneity was expressed as the relative standard deviation of the normalised values, and was found to be 48.15 %. This indicates a powder mixture with very poor homogeneity. However, the relative standard deviation of the normalised value decreased approximately 3 times to 16.68 % when the sample size was increased from $20 \pm 2 \text{ mg}$ to $200 \pm 10 \text{ mg}$. It is worth noticing that only 10 random sample units were withdrawn from the powder mixture at the highest mass per unit. The powder mixture showed improved quality due to the increased sample size. It is worth keeping in mind that the variation detected in sampling strongly will depend on the sample size. This is in an agreement of the findings in literature (Sundell-Bredenberg and Nyström., 2001). Despite the lower variation obtained in this particular powder mixture by increasing the sample size, the powder mixture can not be regarded as a homogenous when the relative standard deviation of more than 16%. Possible explanation of the in-homogeneity can due a wide distribution of

particle size of the drug (some very large particles were present) and the fact that the filling load was not optimised in the glass jar used as container within the original container of the Turbula mixer.

The wide particle size distribution is unfavourable for making a homogenous powder mixture taking into consideration that segregation could happen (Hersey, 1975, Poux et al., 1991, Egermann, 1980). Contamination of some very large particles will have a large influence on the variation especially in case of small sample sizes. The effect of sample size is in agreement with results from earlier findings and highly attributed to variables like agglomeration tendencies and wide particle size distribution (Nystrom and Malmqvist, 1980). The results give reason to believe that by increasing the sample size the homogeneity will appear to be improved since the sample investigates a higher number of particles. This further implies that for tablets of high mass 400-500mg it is not as critical that the powder mixture is homogenous down to particle level, but for small units, such as mini-tablets with a mass of 6-8 mg homogeneity is extremely critical. To ensure the homogeneity of powders that will be used for preparation of mini-tablets the sample size is a critical factor. In this Thesis a micro-thief is used and the sample size for 20 mg was chosen. Even smaller sample sizes could be beneficial since the sample size should ideally approximate the size of the final dosage form.

Table 11. The degree of homogeneity of a 1 % w/w conventional powder mixture consisting of sodium salicylate (500 µm) with Pearlitol 300DC (180-250 µm expressed as relative standard deviation of normalised values (n=30)

* n=10

Characteristics	Degree of homogeneity	
	Sample size	
	20 [mg]	200 [mg] *
Relative standard deviation [%]	48.15	16.68

Ordered powder mixture

The filling load of the container (glass jar) and the mixing time were two parameters to optimize in order to prepare mixtures of high homogeneity. Results on filling load are not shown. From the results presented in table 12 (page 54), the ordered mixtures showed a higher relative standard deviation and hence a decreasing tendency of homogeneity moving from the small particle size fraction to the large particle size fraction. The lowest particle size fraction (180-250 μm in diameter) showed very low relative standards deviation (random sampling, $n=30$, sample size $20 \text{ mg} \pm 2\text{mg}$) indicating that a high homogeneity was obtained after 24 hours of mixing. This complies for both the SD and the DC quality. The two carriers of larger particle size fraction (250-355 μm and 355-500 μm in diameter) were not found to have sufficiently low relative standard deviation until after 48 hours of mixing. All ordered mixtures were prepared in duplicate except the 200DC, due to lack of material. The first ordered mixture of 400DC showed a relative standard deviation below 5 % already after 24 h, but upon replication the mixing time was determined to 48 h. The same was seen for the 500DC sample. One mixture was found with a low relative standard deviation after 24 hours, the replication seemed to require even longer mixing times than 24 hours.

From the results it can be seen that utilizing carriers with particle size around 200 μm (180-250 μm) required shorter mixing time compared to the larger particle sizes Sundell-Bredenberg and Nyström were mixing for 72 hours in order to obtain ordered mixtures of 0.15 % (w/w) drug particle size fraction $<10 \mu\text{m}$ and carriers around 200 μm (Sundell-Bredenberg and Nystrom, 2001). They showed low variation in drug content (close to 2 %) after 72 hours. The homogeneity was reported to increase with an increase in drug proportion from 0.015 % (w/w) to 0.15 % (w/w)) (Sundell-Bredenberg and Nystrom, 2001). The results in table 12 showed that less variation in drug content was found using only 48 hours for the best duplicates of particle size fractions 180-250 μm and 250-335 μm . The higher proportion used in this study (1 % w/w) seems to be in agreement with the suggested theory of an increasing tendency of increased homogeneity at higher drug proportions, provided that the drug proportions is less than the definite number of micronized particles that maximally can adhere to the carrier particles. To further reduce the variation in the ordered mixtures of the current study, longer mixing times could be tried out, maybe 72 hours would eliminate the variation seen in the duplicates. Also selection of a more narrow size distribution of the carrier particles could possibly contribute to reduce the variation.

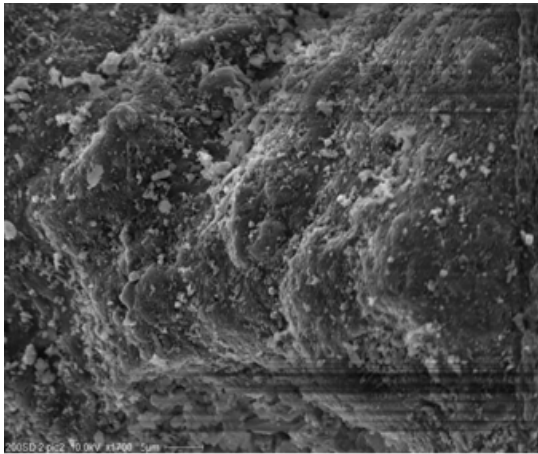
Table 12. The degree of homogeneity of ordered mixtures of 1% w/w sodium salicylate (approximately 3.3 µm in diameter based on external surface area) mixed with different mannitol carriers of defined particle size fractions expressed as relative standard deviation of normalised values (n= 30). (The bold samples were selected for preparation of mini-tablets).

Mixing time [hours]	Degree of homogeneity expressed as relative standard deviation [%]						
	200SD	300DC		400DC		500DC	
	180-250 µm	180-250 µm		250-355 µm		355-500 µm	
24	2.26	5.95	3.54*	4.2	9.82	20.73	3.25
48	1.39	1.20	2.37	1.60	2.24	7.84	2.96

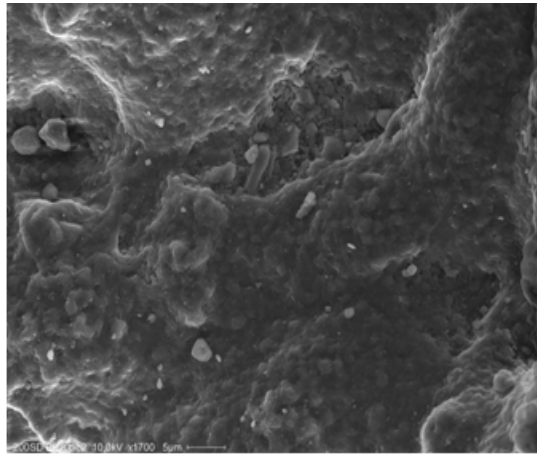
* Additional 30 additional sample units measured; relative standard deviation of 3.12 %

4.2.4 Scanning electron microscopy

SEM micrographs were made of the raw material of the carriers and random samples of what was assumed to be ordered mixtures to look for proof of adhering drug particles on the surface of the carrier particles of the ordered mixtures. Based on earlier findings the sodium salicylate particles are small, with a mean diameter around 3.29 µm and a wide size distribution. The SEM micrographs of the drug (Figure 14, section 4.1.1) indicate that the particles should be flakes or fragments of such. The SEM micrographs of mannitol carriers and ordered mixtures can be seen in figure 22-25, (page 55 and 56). It is hard to differentiate between raw material micrographs and the micrographs of ordered mixtures due to the fact that the surface of mannitol also contain small particles, which may be dust (very fine particles) adhering to the material. The surface of the carrier particles in the ordered mixtures seems to be smoother than for the raw materials, which could be a result of abruption during mixing (analogues to friability test). This makes the micrographs hard to interpret as means of showing physical evidence of adhering particles at the surface of a carrier in the ordered mixtures. With regard to the calculated surface area unit ratio in the powder mixtures, the higher coverage of adhering particles to the carriers were difficult to prove by looking at the micrographs in figure 22-25. At the moment the SEM micrographs are inconclusive. It might have been easier to interpret the micrographs if the raw materials had also been subjected to mixing similar to the ordered mixtures (without addition of drug), thus experiences similar abruption and smoothing of their surfaces.

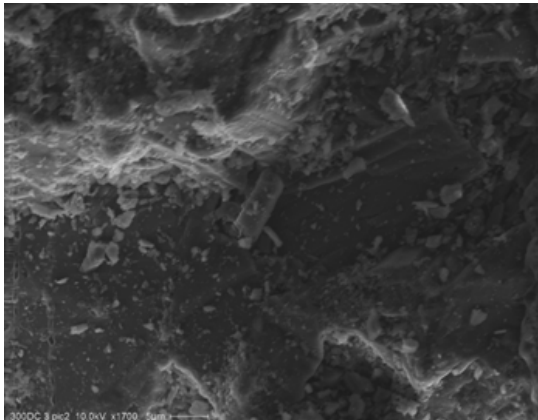


Pearlitol 200 SD
(180-250 μm)

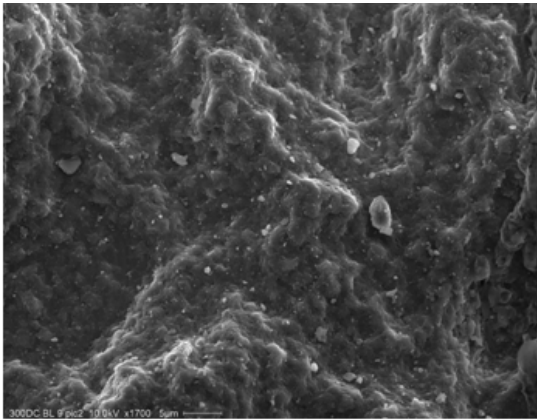


**Ordered mixture of
Pearlitol 200 SD (180-250 μm)
1% Na-salicylate (1% w/w)**

Figure 22. SEM micrographs of Pearlitol 200SD (left) and the surface of the corresponding ordered mixture of Pearlitol 200SD with 1% (w/w) sodium salicylate (right)

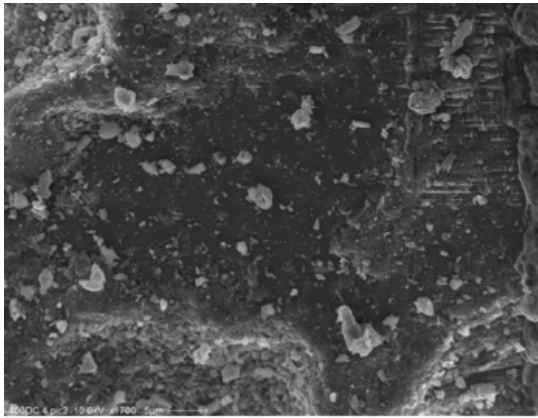


Pearlitol 300 DC
(180-250 μm)

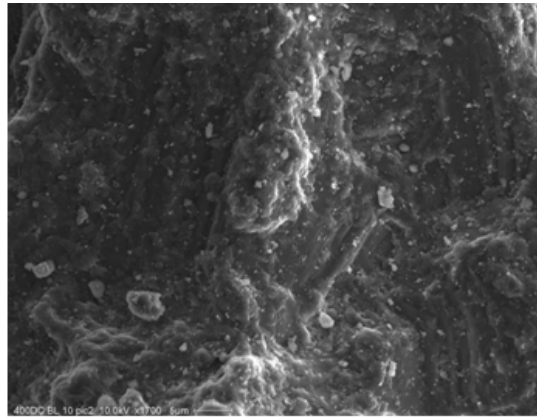


**Ordered mixture of
Pearlitol 300 DC (180-250 μm)
1% Na-salicylate (1% w/w)**

Figure 23. SEM micrographs of Pearlitol 300DC (left) and the surface of the corresponding ordered mixture of Pearlitol 300DC with 1% (w/w) sodium salicylate (right)

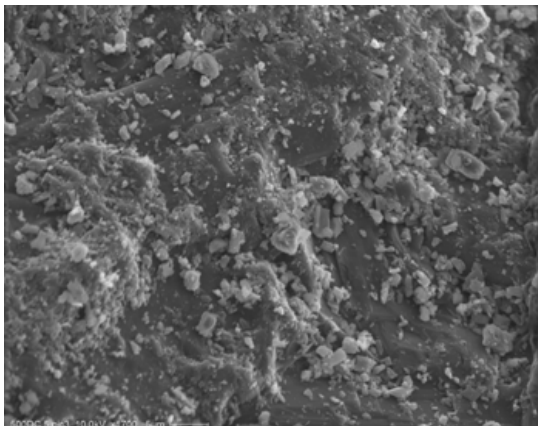


Pearlitol 400 DC
(250-355 μm)

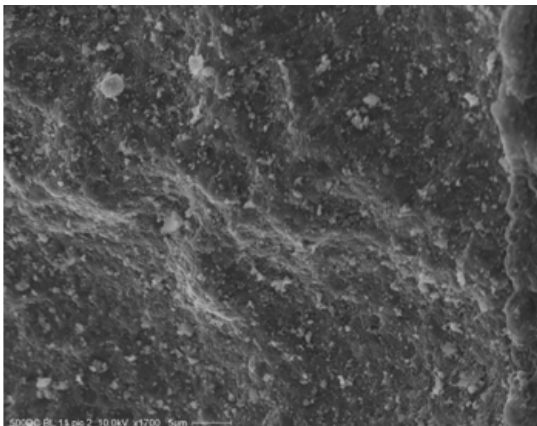


**Ordered mixture of
Pearlitol 400 DC (250-355 μm)
1 % Na-salicylate (1 % w/w)**

Figure 24. SEM micrographs of Pearlitol 400DC (left) and the surface of the corresponding ordered mixture of Pearlitol 400DC with 1 % (w/w) sodium salicylate (right)



Pearlitol 500 DC
(355-500 μm)



**Ordered mixture of
Pearlitol 500 DC (355-500 μm)
1 % Na-salicylate (1 % w/w)**

Figure 25. SEM micrographs of Pearlitol 500DC (left) and the surface of the corresponding ordered mixture of Pearlitol 500DC with 1 % (w/w) sodium salicylate (right)

4.3 Mini-tablet characterisation

4.3.1 Mini-tablet mass and hardness.

Mini-tablets should have a very low mass variation since this is connected to dose variation. This is especially important for low dose mini-tablets. The results from the test of uniformity of mass (European Pharmacopeia, Ch.2.9.5. Uniformity of mass of single unit dose preparation) is shown in table 13 and showed that all the 4 batches of mini-tablets complied with the uniformity of mass test, with a good margin. The uniformity of mass test allow not more than one mini-tablet to be outside the deviation of 10 percentage of the average mass, and none should deviate more than 20 % from the average mass. The highest percentage deviation found for the mini-tablets (4.00 %) was found in the batch of mini-tablets made from ordered mixture of Pearlitol 300DC.

Table 13. Uniformity of mass in mini-tablets of ordered mixtures of 1 % (w/w) sodium salicylate and different mannitol carriers (Eur.Pharm. 7.0, chapter 2.9.5 Uniformity of mass of single dose preparations; tablets less than 80 mg), n=20

Carrier	200 SD	300 DC	400 DC	500 DC
Particle size fraction [μm]	180-250	180-250	250-355	355-500
Mean mass in mg (n=20)	7.98	8.03	7.99	8.04
Max % deviation	1.71	4.00	3.41	3.93
Number of mini-tablets deviating 10 % from average mass	0	0	0	0
Number of mini-tablets deviating 20 % from average mass	0	0	0	0
Comply with the requirements	yes	yes	Yes	yes

The mini-tablets should possess a sufficient mechanical stability in order to assure stability during handling. Table 14 (page 58) shows a summary of the compression conditions and the resulting mini-tablets. The compression force was tried kept at 8.00 kN. Nevertheless, the compression force varied a little. The mean compression force from the lowest to the highest was 7.93 and 8.04 kN. Aiming at developing ODT one requirement of the mini-tablets is that it should dissolve rapidly in the mouth; the mini-tablets should still have a satisfying hardness. All mini-tablets showed a mean crushing force above 11 Newton (see table 14) (page 58). The highest crushing force was measured for the mini-tablets made of an ordered

mixture of 200SD. The crushing forces (200SD, particle size fraction 180-250 μm) showed a mean value that was twice as high as for the other formulations. Even though mini-tablets of 200SD and 300DC were compressed from the same particle size fraction, very different tablet hardness was obtained. The higher crushing strength seen in mini-tablets of 200SD compared to 300DC is expected to be related to the increased external surface area (twice as high), and thus being able to create more bonds. Further results showed a decreasing crushing force tendency as the particle size fractions increased for the DC mixtures. The decrease in crushing force with an increase in particle size fraction gives an indication of the decreased bonding sites between larger particles compared to small particles.

Further, the friability testing showed that all mini-tablets had a low friability with less than 0.2 % loss of mass (Table 14). This complies with adequate resistance against abrasion. An effect of particle size could be recognised in the values of percentage friability. The percentage of mass lost during testing increased with increasing particle size fraction in the powder mixture. The friability percentage was lowest for the fraction 180-250 μm (200SD) and highest for 355-500 μm (500DC). With regard to the results for crushing strength of the mini-tablets the results of friability correlated with crushing force. Comparing the two carriers of same particle size fractions (200SD and 300DC) the friability percentage was twice as high for 300DC compared to 200SD. This could be explained by the higher external surface area of 200SD compared to 300DC, which is available for bonding between the finer particles (Weyenberg et al., 2005). This is the same tendency as seen above for the crushing strength.

Table 14. Characteristics of mini-tablets

	Particle size fraction [μm]	Mass single mini-tablet [mg] \times		Compression force on multi-tooling* [N]		Crushing force of single mini-tablets [N]		Friability [%]
		mean	stdev	mean	stdev	mean	stdev	
200SD	180-250	7.98	0.08	7.98	0.18	23.54	3.73	0.0627
300DC	180-250	8.03	0.18	8.04	0.07	12.595	2.84	0.1255
400DC	250-355	7.99	0.12	7.93	0.08	11.435	2.15	0.1257
500DC	355-500	8.04	0.18	7.89	0.09	11.535	2.80	0.1887

* 15 mini-tablets in one stroke

\times 20 random picked mini-tablets from the final batch (same as tested in table 13)

Compared to the orally disintegrating mini-tablets (ODMTs) in the study of Stoltenberg and Breitzkreutz all the presented ODMTs in this study passed what they call sufficient crushing strength >7 N and low friability <1% (Stoltenberg and Breitzkreutz, 2011).

4.3.2 Homogeneity

The mini-tablet batches did all comply with the uniformity of content of single dose preparations test (European Pharmacopeia, Ch. 2.9.6.). For one of the mini-tablet batches, the one prepared from 400DC, one mini-tablets was outside the content drug limit of 115 % of the average content (drug content 1.027 %), but the content drug of the mini-tablet was still inside the limit of 125 % (drug content 1.117 %) of the average content (table 15). Since it was only 1 mini-tablet that was outside 115 %, and it was not outside the 125% limit, the batch complies with the test. The other batches had no problem to comply with the uniformity of content of single dose preparations test.

Table 15: Uniformity of content of mini-tablets (European Pharmacopeia 7.0, chapter 2.9.6 Uniformity of content of single dose preparations; tablets), n=10

Carrier	200SD	300DC	400DC	500DC
Particle size fraction [μm]	180-250	180-250	250-355	355-500
Average content (n=10)	0.9007	0.9009	0.8933	0.9833
Min value; % deviation from average (limit 85%)	98.68	97.79	97.77	92.74
Max value; % deviation from average (limit 115%)	101.46	103.11	102.87	103.52
Number of mini-tablets deviating 15 % from average dose	0	0	1	0
Number of mini-tablets deviating 25 % from average dose	0	0	0	0
Comply with the requirements	yes	yes	yes	yes

The results presented in table 16, show the degree of homogeneity in the ordered mixtures and the corresponding mini-tablets. According to table 16, the high dose homogeneity from the ordered mixtures was also proven in mini-tablets. The same increasing tendency of the relative standard deviation with the particle size of the powder mixture could be recognised in the mini-tablets as previously seen for the ordered mixtures.

Table 16: The homogeneity of the 1 % (w/w) ordered mixtures of sodium salicylate with different mannitol carriers characterised by the relative standard deviation of normalised values

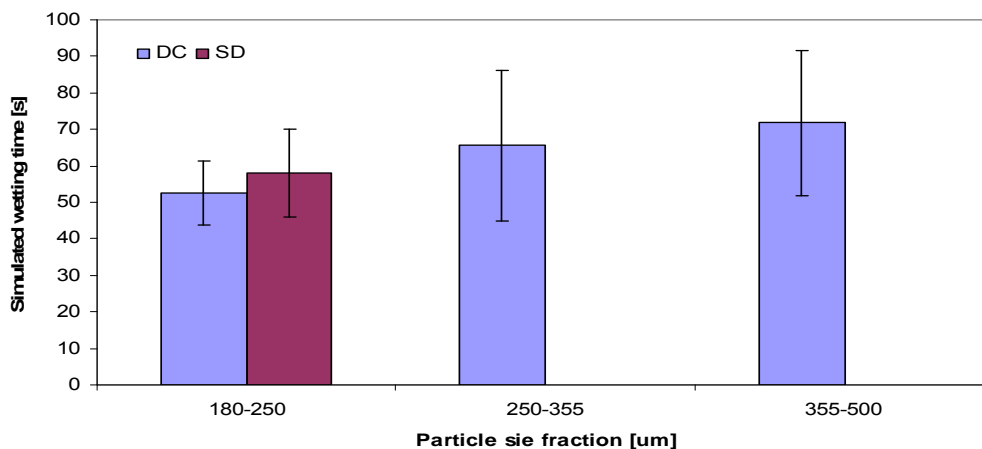
Type of sample	Degree of homogeneity expressed as relative standard deviation [%]			
	200SD 180-250 µm	300DC 180-250 µm	400DC 250-355 µm	500DC 355-500 µm
Ordered mixture [48 hours] *	1.39	1.20	1.60	2.96
Mini-tablet**	0.94	1.77	1.79	3.39

*n=30, ** n=10

4.3.3 Simulated wetting test

Orally disintegrating tablets should be fast dissolving drug formulation with a disintegration time of less than 3 minutes according to the European pharmacopoeia. All mini-tablets complied with this time. The simulated wetting test was developed by Park et al. as a supplementary test to disintegration time especially for ODTs (Park et al., 2008). The mean values of the simulated wetting times (SWT) are presented in figure 26 (page 61) and was 52.5, 58.1, 65.6 and 71.8 seconds. The mini-tablets were ranked in following previous order 300DC, 200SD, 400DC and 500DC. Only mini-tablets made of ordered mixtures 300DC and 200SD with respect to mean values passed the test for possessing fast dissolving ODT properties with less than 60 seconds as categorized by Krause and Breitzkreutz (Krause and Breitzkreutz, 2008). The standard deviation values for the two were 8.64 and 12.03 proving differences within the 10 randomly examined tablets of each batch. It is worth noticing that the mini-tablets in the current study does not contain any disintegrant, which is often used in ODTs. The specialized ODT materials (Pearlitol Flash and Parteck ODT) did not make it to the mini-tablet stage due to lack of time. It would have been interesting to see whether they would have obtained lower SWTs in our studies. An increased SWT with increasing particle

size fraction of the carrier was shown. However, the standard deviations did overlap (figure 26).



Figur 26. Mean simulated wetting time for mini-tablets of ordered mixtures of different size fraction of mannitol carriers. The simulated wetting times time is taken as the time when the blue dye solution cover the entire surface of the mini-tablets

The passing of the test for being a fast dissolving ODT based on mean times, indicated that 200SD and 300DC would be the most suitable choices for making appropriate paediatric formulations. However, when referring to the European Pharmacopoeia it was given a disintegration time, but no further specifications related to hardness or friability. So in principle all mini-tablets could have been made with a lower pressure and thus a faster disintegrating time. Despite of that it is though in general agreement that a fast disintegrating time together with high crushing strength and low friability is the most desirable. In fact, brittle tablets require peel able blister packing which is related to higher production costs (Abdelbary et al., 2004). The results from testing of friability and crushing force indicated that 200SD ODTs could have been made with a lower compression force and still having a suitable compactibility, but a faster dissolution time being even more appropriate dosage form for children. Stoltenberg and Breitzkreutz made a preliminary experiment showing sodium stearyl fumarate to be a beneficial lubricant over magnesium stearate related to simulated wetting times and crushing strength (Stoltenberg and Breitzkreutz, 2011). Stoltenberg and Breitzkreutz showed simulated wetting times of less than 25.2 seconds (n=10) using superdisintegrants at compression force of 8 kN (Stoltenberg and Breitzkreutz, 2011).

5. Conclusion

Ordered mixtures were obtained from different qualities of mannitol as carrier particles and micronized sodium salicylate as drug particles. All the ordered mixtures showed high dose homogeneity after 48 hours of mixing. The lowest particle size fraction (180-250 μm) resulted in ordered mixture after 24 hours and the larger particle size fractions (250-355 μm and 355-500 μm) required 48 hours mixing to obtain satisfying low variation. The homogeneity of the ordered mixtures showed a slight decrease with increasing particle size of the carrier particle size, which is probably related to the lower external surface area of the larger particles. No difference was found in the homogeneity between batches of similar particle size, but different external surface area (200SD vs. 300DC).

The same high dose homogeneity as found for the ordered mixtures was seen in the mini-tablets. All the produced batches of mini-tablets complied with the European Pharmacopeia requirements for uniformity of mass and content for single dose preparations.

Further, the mini-tablets demonstrated low friability's, high crushing strengths and a suitable simulated wetting time compared to literature. The simulating wetting test (all batches were fully wetted within 80 seconds, implies that the formulations also comply with the European Pharmacopoeia requirements for ODTs of disintegration within 3 minutes. All batches of mini-tablets proved suitability as orally disintegrating mini-tablets. The most suitable among the formulations might be the mini-tablets prepared of ordered mixture 200SD; it showed the lowest friability, the highest crushing strength and had a simulated wetting time of less than one minute.

6. Future perspectives

For further studies it would have been included the co-processed mannitol qualities for preparation of ordered mixtures and mini-tablets. Then it would have been interesting to prepare ordered mixtures using both higher and lower coverage of micronized adhering to carriers. All mini-tablets could have been made using two more compression forces for comparisons and to look for tendencies. Further, tablets could have been compacted using the ordered mixtures and characterised. The mini-tablets could have been compacted into larger tablets and those tablets could have been characterised.

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8. Appendix

8.1 Steady state permeametry

Example shows one of three external surface area measurements for 200SD sample.

KONSTANT FLÖDESPERMEAMETRI

Sample : Pearlitol 200 SD

DATE: 02.11.10

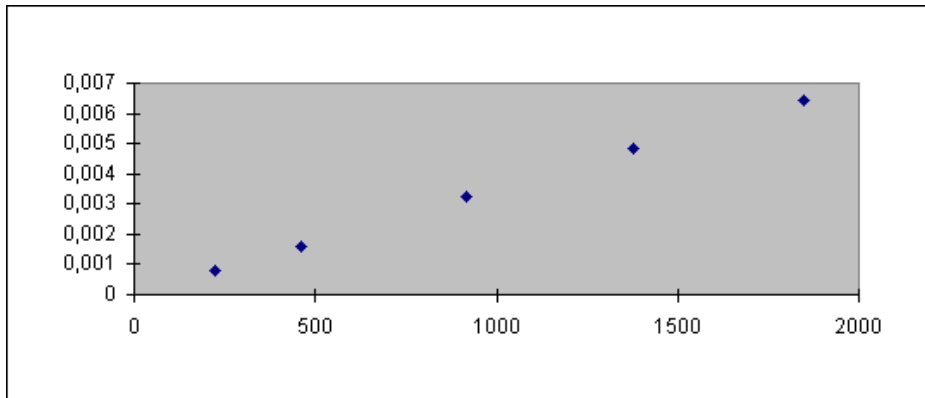
Example 1

Flowmeter 0-50

Cylinder diameter (mm):	11,47	Weight (g):	5,47	Voidage:	0,6751282
height (mm):	111,01	Density (g/ml):	1,4679		
	<i>hållt</i>				

Flödesmätare:	% flöde:	Flow (ml/min):	Flow (m/s):	P (Pa):	P/L (Pa/m):
>50ml/min	9,9	4,95	0,0007984	24,9	224,30412
>50ml/min	19,9	9,95	0,0016049	50,9	458,51725
>50ml/min	39,9	19,95	0,003218	101,6	915,23286
>50ml/min	60	30	0,004839	152,9	1377,3534
>50ml/min	80,0	40	0,006452	205	1846,6805
>50ml/min	100,0	50	0,008065	257,0	2315,1067

1-20ml/min:	SLOPE: 3,5E-06	Intercept: 1,42408E-05	Korr.koeff: 0,9999761	External surface area: 874,598745
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8.2 Blaine permeametry

Example shows the three measurements for sodium salicylate

Determination of specific surface area by air permeametry (Blaine)

Formatted Table

Date

Material

Primary data:

U-tube-

manometer:

Density of liquid (g/cm³)

1

Diameter of arm (cm)

0,697

Start point (cm)

7

Stop point (cm)

1,5

Permeability-

cell:

Diameter (cm)

1,27

Sample:

Material density (g/cm³)

I 1,5682

II 1,5682

III 1,5682

III

III

Particle density (g/cm³)

1,5682

1,5682

1,5682

Weight (g)

1,3154

1,2881

1,2429

Height (cm)

1,47

1,47

1,47

1,47

1,47

Time for measurement (s)

237,7

205,7

162,1

Constant for slip flow equation!!

0,96

0,96

0,96

0,96

0,96

Results:

Total porosity:

(-)

0,5495

0,5589

0,5744

#DIV/0!

#DIV/0!

(%)

54,95

55,89

57,44

#DIV/0!

#DIV/0!

Means:

St_e

de

0,5609

0,0

56,0932

1,2

Kozeny-Carman surface area:

Volume (cm⁻¹)

24858,35

24219,90

23214,37

#DIV/0!

#DIV/0!

Weight (cm²/g)

15852,02

15444,89

14803,67

#DIV/0!

#DIV/0!

24 097,54

82:

15 366,86

52:

Slip flow surface area:

(SM)

12591,50

11509,15

9927,37

#DIV/0!

#DIV/0!

Volume (cm⁻¹)

31938,96

30648,73

28702,79

#DIV/0!

#DIV/0!

Weight (cm²/g)

20367,28

19544,51

18303,60

#DIV/0!

#DIV/0!

11342,6717

1:

30430,1590

16:

19405,1328

10:

Mean pore diameter

Kozeny-Carman (μm)

1,96

2,09

2,33

#DIV/0!

#DIV/0!

2,1269

0:

Slip flow (μm)

1,53

1,65

1,88

#DIV/0!

#DIV/0!

1,6873

0,1

8.3 Temperatures and humidity's during compressions

Table 17. Shows the average values of 6 compressions:

Batch	RH	Temp
	%	C
minitablet 200SD	22.6	22.71
minitablet 300DC	18.7	22.8
minitablet 400DC	17.8	22.4
minitablet 500DC	16.8	22.8

8.4 Example relative standard deviation powder mixture

Table 18. Shows the example of powder mixture 200SD

Sample	weight of sample (mg)	Absorbance (au)	constant a	constant b	teoretical weight drug (µg)	drug concentr. in flask (µ/ml)	measured drug in sample (µg)	normalised (µg)
13	18,3	0,37198	0,0224	0,0025	183	16,71786	167,1786	0,9135441
18	18,68	0,38367	0,0224	0,0025	186,8	17,23973	172,3973	0,9228979
27	19,01	0,3873	0,0224	0,0025	190,1	17,40179	174,0179	0,9154017
9	19,16	0,40324	0,0224	0,0025	191,6	18,11339	181,1339	0,9453754
5	19,18	0,40098	0,0224	0,0025	191,8	18,0125	180,125	0,9391293
6	19,2	0,39886	0,0224	0,0025	192	17,91786	179,1786	0,9332217
2	19,22	0,39608	0,0224	0,0025	192,2	17,79375	177,9375	0,9257934
26	19,29	0,39092	0,0224	0,0025	192,9	17,56339	175,6339	0,9104921
20	19,34	0,38808	0,0224	0,0025	193,4	17,43661	174,3661	0,9015826
19	19,43	0,40614	0,0224	0,0025	194,3	18,24286	182,4286	0,9389016
25	19,45	0,40185	0,0224	0,0025	194,5	18,05134	180,5134	0,9280894
23	19,45	0,40558	0,0224	0,0025	194,5	18,21786	182,1786	0,9366508
11	19,47	0,40031	0,0224	0,0025	194,7	17,98259	179,8259	0,923605
1	19,48	0,40362	0,0224	0,0025	194,8	18,13036	181,3036	0,9307165
7	19,6	0,40349	0,0224	0,0025	196	18,12455	181,2455	0,9247221
30	19,61	0,40674	0,0224	0,0025	196,1	18,26964	182,6964	0,9316493
3	19,69	0,41676	0,0224	0,0025	196,9	18,71696	187,1696	0,9505822
12	19,7	0,41153	0,0224	0,0025	197	18,48348	184,8348	0,9382478
29	19,77	0,41676	0,0224	0,0025	197,7	18,71696	187,1696	0,9467357
16	19,91	0,41474	0,0224	0,0025	199,1	18,62679	186,2679	0,9355493
10	19,96	0,42126	0,0224	0,0025	199,6	18,91786	189,1786	0,9477884
14	20	0,40909	0,0224	0,0025	200	18,37455	183,7455	0,9187277
24	20,03	0,42296	0,0224	0,0025	200,3	18,99375	189,9375	0,9482651
28	20,16	0,40849	0,0224	0,0025	201,6	18,34777	183,4777	0,9101075
4	20,26	0,42086	0,0224	0,0025	202,6	18,9	189	0,9328727
15	20,26	0,41445	0,0224	0,0025	202,6	18,61384	186,1384	0,9187482
8	20,35	0,42888	0,0224	0,0025	203,5	19,25804	192,5804	0,9463408
17	20,5	0,42158	0,0224	0,0025	205	18,93214	189,3214	0,9235192
21	20,53	0,42492	0,0224	0,0025	205,3	19,08125	190,8125	0,9294325
22	20,84	0,4256	0,0224	0,0025	208,4	19,11161	191,1161	0,9170637
Average	19,661				196,61	18,27637	182,7637	0,9295251
Max	20,84				208,4	19,25804	192,5804	0,9505822
Min	18,3				183	16,71786	167,1786	0,9015826
Median	19,605				196,05	18,25625	182,5625	0,9300745
Stdev	0,566101916				5,661019	0,612016	6,120157	0,0129315
Relstdev	2,879313952				2,879314	3,348672	3,348672	1,3911985