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Orally disintegrating mini-tablets for children: Using interactive mixtures to obtain mini-tablets of high dose-homogeneity

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Abstract

Administration of drugs in children presents several challenges and requires appropriate dosage forms in order to achieve the correct pharmacotherapy. Today, most dosage forms are developed for adults, not children, and therefore new dosage forms are required to improve the administration of drugs in children of all ages. One new and promising system is the orally disintegrating mini-tablets. Using this system, the number of units taken can be personalized in accordance to weight or age. Studies have shown that orally disintegrating mini-tablets can be administered safely in children down to 6 months of age. These systems require high dose-homogeneity because of their small size. In this project, the use of interactive mixtures, where micronized drug particles adhere to the surface of larger carrier particles, is investigated as means to obtain high dose-homogeneity. The effect of different factors on the homogeneity of the interactive mixtures were investigated such as mixing time, mixing method, sampling size and particle size of the carrier particles, using granulated mannitol (Pearlitol® 100SD, Roquette Pharma, France) of three different particle size fractions (63-90 μm, 90-125 μm and 125-180 μm) as carrier particles and 1 % (w/w) micronized sodium salicylate (< 10 μm) as active substance. The results showed that longer mixing times (24 hours or more), use of a tumbling mixer with diffusive mixing as main mixing mechanism and use of the largest investigated particle size fraction (125-180 μm) gave the highest homogeneity in the interactive mixtures. The interactive mixtures were used to prepare orally disintegrating mini-tablets, using a custom-made compaction simulator. The mini-tablets were characterized according to set criteria by the European Pharmacopoeia. Uniformity of mass and content, mechanical strength and disintegration time of the mini-tablets were tested. The prepared orally disintegrating mini-tablets showed high uniformity of mass and content, sufficient mechanical strength and a short disintegration time.

In conclusion, several factors are important for preparation of interactive mixtures. The interactive mixtures gave mini-tablets with high dose-homogeneity, and were suitable for preparation of orally disintegrating mini-tablets for use in children.

1. Background

Historically children have not been considered as potential users during research and development of new medicines, and therefore the formulations are often not appropriate for use in children. The lack of appropriate dosage forms for children can result in off-label use, which means that the drug is used in a way that it is not approved (Ernest *et al*., 2012).

Clinical trials in children have ethical concerns and parents may not be willing to let their child take part in clinical trials (Gill and Kurz, 2003). The financial aspect must also be considered a leading factor for pharmaceutical industry (Thomson *et al*., 2009). To help boost clinical trials in children several steps have been taken by different organizations. The American government launched the "Best Pharmaceuticals for Children Act" in 2002, which gives a prolongation of the patent protection time of six months if the patented drug products are being tested for use in children (National Health Institute, 2002). European Medicines Agency (EMA) launched the European paediatric regulation in 2007. This regulation demands that the company includes paediatric research in development of new medicines in order to get marketing authorisation for the adult population. The manufacturer must present a plan for paediatric research, a so-called paediatric investigation plan (PIP), to EMA, which includes information on child appropriate formulations (Ernest *et al*., 2012).

Recently, several new dosage forms and devices have been presented. A review article describes several new strategies for easier drug-delivery to children (Wening and Breitkreutz, 2010). Pellets, granules, mini-tablets and oral film strips for buccal use are all dosage forms, which are aiming at improved compliance for patients with problems swallowing tablets and more personalized treatment. Orally disintegrating mini-tablets (ODMTs) is a new and promising dosage form that will disintegrate quickly in the mouth, and is then easy to swallow, making this a dosage form that can be used even for small children. This type of dosage form is therefore very interesting to study further in order to improve child drug delivery (Stoltenberg and Breitkreutz, 2011). Clinical studies have shown that mini-tablets of 2 mm diameter were

administered to children down to 6 months of age, without children choking or aspiring the mini-tablets, and it seemed to be equally well, or even better, accepted as glucose syrup by the youngest children (Spomer *et al*., 2012).

In this project the focus was on studies of orally disintegrating mini-tablets with a 2 mm diameter. Due to the small size of the ODMTs, and the fact that they are supposed to be taken as single units, one important issue is to secure high dose-homogeneity. Every ODMT must contain the correct amount of active substance so that the effect of the drug can be predictable. The working hypothesis in the current project is that interactive mixtures can be used as means to obtain high dose-homogeneity. Briefly explained; micronized drug particles are adhered to the surface of larger carrier particles, thereby minimizing segregation and ensuring homogenous distribution of the active substance throughout the powder mixture (Hersey, 1975).

2. Introduction

2.1 Particle and powder characteristics

2.1.1 Particle size and particle size distribution

Particle size affects several factors in a pharmaceutical powder. Powder flow, packing properties, content uniformity, dissolution rate and absorption are all affected by the particle size. Therefore, it is important to characterize the particle size of powders for production of pharmaceutical solid dosage forms. Different particle size in powders can cause volume differences when preparing tablets. This could be a problem because it can influence mass and content uniformity (Venables and Wells, 2001).

A small particle size can cause faster dissolution rate and therefore increased bioavailability as compared to coarser particles, but poor powder flow and segregation issues may occur as a result of the small size. When the particle size is below 100 μm, the van der Waals forces increases and becomes greater than the gravitational forces resulting in more cohesive particles, and below 10 μm particles are strongly cohesive (Venables and Wells, 2001, Aulton, 2007). This can be taken advantage of in the preparation of interactive mixtures; that is e.g. when small, cohesive particles are mixed with larger particles, called the carrier particles. The smaller particles will adhere to the surface of the carrier particles. It was shown in a paper from 2001, that the degree of ordering increased as the size of the adhered particles (micronized drug) was reduced (Sundell-Bredenberg and Nyström, 2001).

Particles in powders are rarely mono-disperse, meaning that all particles has same diameter, therefore, to describe the distribution of particles sizes in a powder, a plot of the particle size distribution (as a histogram or a cumulative frequency plot) is frequently used.

2.1.2 Particle shape

Particle shape is another factor that will affect the mixing quality. Particles can be shaped as spheres, flakes, filaments, crystals and needles, or they can be threadlike (fibrous) or irregularly shaped (Poux *et al*., 1991, Venables and Wells, 2001). Powders with spherical particles have less possible contact points compared to powders with other particle shapes. This will improve powder flow, but segregation issues may occur. Particles with other shapes can interlock and thereby minimize segregation issues (Venables and Wells, 2001). The importance of particle shape with regard to segregation is only significant when the difference in particle shape within the powder mixture is significant (Hogg, 2009).

2.1.3 Particle density

Differences in particle density can cause segregation in powder mixtures. The more dense particles will fall to the bottom because of gravitational forces. There are three different ways of describing particle density. In order to understand the difference one must know the significance of open and closed pores on the density measurement. As described by Venables and Wells, the open pores are "those connected to the particle surface" and closed pores are "those not connected to the surface and irrespective of structure". The *true density* is mass divided by volume excluding all pores. *Effective density* on the other hand is mass divided by volume including all pores. The *apparent density* is calculated in the same way, but includes closed pores and excludes open pores. The bulk density of materials (Hausner Ratio and Carr Index are explained later) cannot be compared to true, effective or apparent density, due to the inclusion of voids between particles in bulk density measurements (Venables and Wells, 2001).

Particle density is said to be less important for mixing powders, due to the similar densities found in pharmaceutical materials. Often, the particle size distribution is much larger than the particle density distribution and will play a much more important role in the powder mixing process (Hogg, 2009).

2.1.4 Powder flowability

2.1.4.1 Powder volume and density

The powder density is related to the mass of the powder divided by its volume. The change in powder density as a result of applied stress can indirectly give information on several factors, such as cohesiveness of the materials, moisture content, size, shape and surface area of the particles. This is normally done by measurements of poured and tapped volume of a powder of known mass. Based on the derived parameters V_{poured} and V_{tapped}, Hausner Ratio and Carr Index (also called Compressibility Index) can be calculated.

Hausner Ratio: V_{poured}/V_{tapped} (Equation 1)

Carr Index: $100 \times ((V_{poured} - V_{tapped})/V_{poured})$ (Equation 2)

The flow character is graded based on their estimated Hausner Ratio and Carr Index (Table 1); where the lowest values are related to the highest flowability and higher values indicating poorer flowability. These related measurement methods are among the simplest methods for characterizing powder flow (European Pharmacopoeia 7.8, chapter 2.9.36 – Powder flow).

Table 1: *Scale of flowability based on Hausner Ratio and Carr Index (European Pharmacopoeia 7.8, chapter 2.9.36 – Powder flow)*

Carr index (per cent)	Flow character	Hausner ratio
1-10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

2.1.4.2 Angle of repose

When the angle of a surface is large enough, powder in a container begins to slide, and the powder will pile on the surface below with a certain angle and radius. How the powder flows from the container and down on the surface, is decided by the adhesive and cohesive forces between particles of the powder bed. The angle of the pile to the surface is called the angle of repose. This will describe how the particles are affected by internal friction or cohesion of the particles. A powder with strongly cohesive particles will give a high angle of repose, a free-flowing powder, i.e. with weaker cohesiveness; will give a low angle of repose (European Pharmacopoeia 7.8, chapter 2.9.36 – Powder flow).

The powder flow properties are classified based on the angle of repose (α), calculated from the following equation:

$$\tan \alpha = h/r \qquad \text{(Equation 3)}$$

h = height of powder pile
r = radius of powder pile

Table 2: *Classification of flow properties based on angle of repose (degrees) (European Pharmacopoeia 7.8, chapter 2.9.36 – Powder flow)*

Flow property	Angle of repose (degrees)
Excellent	25-30
Good	31-35
Fair (aid not needed)	36-40
Passable (may hang up)	41-45
Poor (must agitate, vibrate)	46-55
Very poor	56-65
Very, very poor	> 66

2.2 Powder mixing

Mixing of powder is an important process in the manufacturing of all solid dosage forms. This is done to ensure homogenous distribution of all components of the mixture. The goal is to obtain dose-homogeneity of the drug in all individual units of the dosage form. Important variables that can affect the powder mixing are related to both the particles as well as to the mixing process. The particles can vary in size, shape, charge, surface area and density, which all can affect the quality of the mixing. The concentration of the different components of the mixture can also affect the mixing. When it comes to the mixing process itself, several factors are known to influence the process. Mixing mechanism, equipment, time and intensity will have an influence on the homogeneity of the powder mixture.

Agglomeration and/or segregation of particles are factors that can cause problems in powder mixing (Venables and Wells, 2001). This can result in higher concentrations of drug in some parts of the mixture, causing reduced dose-homogeneity. The ultimate goal of mixing is to get the units of each of the different components to lie as close to each other as possible.

2.3 Types of mixtures

2.3.1 Ideal mixtures

In an ideal mixture, also called perfect mixture, illustrated in Figure 1 (diagram 2), the standard deviation of the sample composition is equal to zero. This means that the concentration of the substances is the same throughout the entire mixture no matter how small the sample size is. The different particles of the mixture will lie as close to each other as possible (Egermann, 1980).

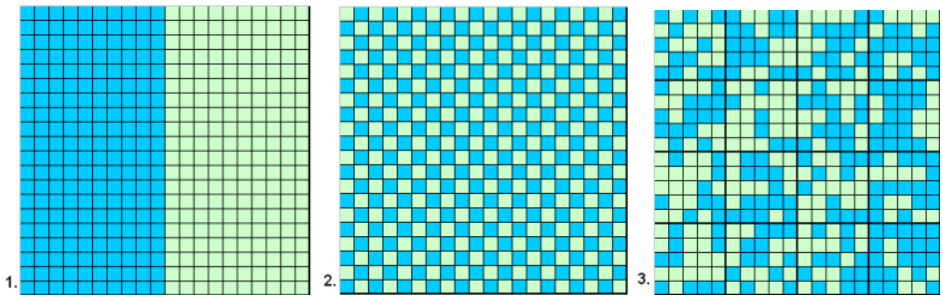


Figure 1: *Illustrations of completely segregated (1), perfect (2) and random mixture (3) (Modified after (Aulton, 2007))*

2.3.2 Random mixtures

Williams stated that a random mixture can be explained as a mixture where the likelihood of finding one specific particle is the same at all positions in the powder mixture (Williams, 1968). See figure 1 (diagram 3) for an illustration. In order to obtain a random mixture the size and weight of the particles cannot differ and they cannot have cohesive properties (Hersey, 1975).

2.3.3 Ordered and interactive mixtures

Travers and White first described the phenomenon of ordered mixtures in 1971, but it was Hersey who first gave it a name, in 1975 (Hersey, 1975). However, since 1980, the term interactive mixtures have been most frequently used and will also be used as the terminology in this thesis (Mihranyan *et al*., 2008).

When micronized particles (< ca. 20 μm) (de Villiers, 1995) are mixed with larger carrier particles, the micronized particles will adhere to the surface of the large particles through adsorption, electrostatic interaction or other forms of adhesion. This inhibits segregation in the powder mixture, which is generally a problem when small particles are mixed with larger particles. In an ideal interactive mixture, a specific amount of micronized particles can adhere to the carrier particles, forming a monomolecular surface layer on the carrier particle. This results in a constant drug content no matter where the samples are taken in the mixture, and the relative

standard deviation of the samples will theoretically reach 0 % (Hersey, 1975, Sundell-Bredenberg and Nyström, 2001).

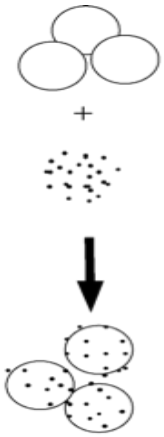


Figure 2: *Illustration of interactive mixing: carrier particles coated with micronized drug particles (modified from (Bredenberg et al., 2003a))*

In the real world, ideal interactive mixtures are difficult to achieve because of several factors affecting carrier particles or the micronized drug component (Sundell-Bredenberg and Nyström, 2001). The mixture will have a certain degree of segregation, due to for example different sizes of the carrier particles (i.e. broad size distribution), lack of carrier particles, or what is called "displacement segregation", where other particles such as lubricants can compete with micronized drug for the "active sites" on the carrier particles. Agglomeration of active substance (micronized particles) can also cause a less interactive mixture. It has been verified that the number or mass of the micronized particles on the carrier particles will vary within an interactive mixture; even uncoated carrier particles may exist in the mixture. Longer mixing times are required to obtain interactive mixtures compared to random mixtures (Hersey, 1975, Sundell-Bredenberg and Nyström, 2001, Sandberg Løding, 2011).

2.4 Mixing mechanisms

In powder mixing the three main mechanisms are convection, shear and diffusion (Williams, 1968). In general, mixing of powders will take use of all these mechanisms (Poux *et al*., 1991). Mixing process conditions, equipment and flowability of the powder will decide which process is most dominant.

2.4.1 Convective mixing

In convective mixing, an amount of powder is moved from one part of the powder bed to another, for example by a paddle. This is mixing on macroscopic level and does not provide mixing inside the powder that is moved, and therefore can give high concentration differences within the powder mixture (Williams, 1968).

2.4.2 Shear mixing

When two layers of powder move on top of each other during mixing, particles in these layers will fall into the voids that arise. Shear mixing is thought to be a combination of convective and diffusive mixing (Poux *et al*., 1991).

2.4.3 Diffusive mixing

When a powder mixture is forced to move by an outer force, like for example the influence of gravity in a tumbling mixer, particles will fall into the empty spaces that are created when the powder is flowing. This is repeated over and over making diffusive mixing a good mixing mechanism to ensure a random mixture, but it is time-consuming. In diffusive mixing single particles are moving, whereas in convective and shear mixing parts of the powder bed are moved (Aulton, 2007).

2.5 Mixing equipment

2.5.1 Tumbling mixers

The tumbling mixer is a mixer that rotates around its own axis. In these types of mixers the powder is mixed inside a locked container (Fan *et al*., 1990). In this particular mixer the most prominent mixing mechanism will probably be diffusive mixing. When the container tumbles, gravity will ensure that particles fall into the spaces that arise when the powder flows from one side of the container to the other. Because of the velocity of the powder, created by the movement of the mixer, the top layer will move faster than the other layers and shear mixing will therefore also occur in tumbling mixers.

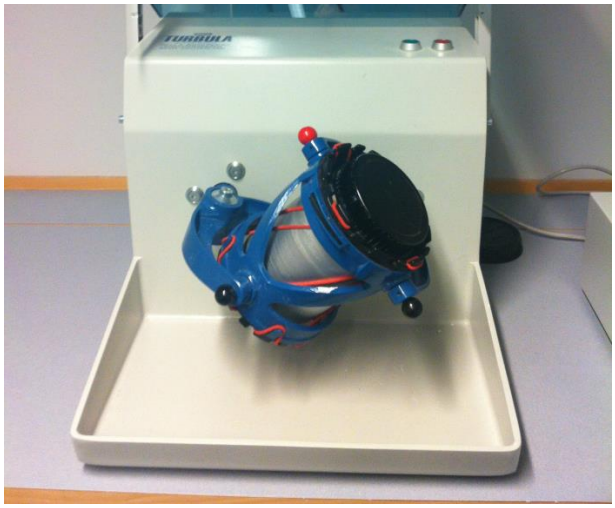


Figure 3: *Example of tumbling mixer (Turbula mixer)*

2.5.2 Planetary mixers

Planetary mixers use a paddle or mixing blade, which is connected in the middle of the mixing bowl. The paddle will spin around its own axis when the mixer is turned on, thereby moving the powder bed. Convective mixing will most likely be the leading mixing mechanism with this mixer; the paddle moves the powder from one powder bed to another.

Figure 4: *Example of planetary mixer (Kenwood mixer)*

2.6 Assessment of quality of mixtures

The quality of a mixture can be evaluated by the homogeneity, which describes the distribution of components in a powder mixture. Several statistical models have been used to describe homogeneity, but they will not be further discussed. The most commonly used method to describe the homogeneity of a powder mixture is using the relative standard deviation of the content of active substance in samples taken from the powder mixture (Williams, 1968, Mihranyan *et al*., 2008). The importance of high dose-homogeneity is clear. An inhomogeneous mixture can result in final products with variations in the content of active substance that can cause either sub-therapeutic levels of active substance or toxicity (Muzzio *et al*., 1997).

2.6.1 Sampling

Testing the homogeneity of powder mixtures requires representative samples to be taken from the mixture. Several factors such as the size, number of samples and location of sampling are important, and can affect the result (Muzzio *et al*., 1997). Although the homogeneity of an ideal interactive mixture should be independent of

sample size, ideal interactive mixtures are often not achievable as explained in 2.3.3. Therefore, the homogeneity of the prepared interactive mixtures may not be independent of sample size, which has also been showed in literature (Sundell-Bredenberg and Nyström, 2001).

The samples will often be taken using a thief probe, also called powder thief, and can either collect powder through several cavities along a hollow cylinder, or just at the end of the probe. The probe is closed upon insertion into the mixture, and is opened when in the right location. The cavities will be filled by powder from that exact location, and then the probe should be closed before it is withdrawn from the mixture. When out of the powder, the sample is released and available for characterization (Muzzio *et al*., 1997).

2.6.2 Homogeneity

The test for uniformity of dosage units in the European Pharmacopoeia can be related to the sampling and testing of homogeneity in powder mixture. According to the European Pharmacopoeia, thirty units should be selected for testing (European Pharmacopoeia 7.8, chapter 2.9.40 – Uniformity of dosage units). This amount of samples is also recommended in literature (Muzzio *et al*., 1997). The samples are quantified and the relative standard deviation of the content of active substance in the thirty samples is calculated. The lower the value of the relative standard deviation is the lower is the degree of variation, i.e. higher dose-homogeneity.

2.7 Optimization of mixing time and conditions

The optimization of the process conditions affecting the mixing process is important in order to ensure the perfect mixing procedure.

2.7.1 Mixing time

In order to get a satisfactory mixture the mixing time is an important parameter. A powder mixture consisting of several components will need to mix for a certain period of time in order to achieve the desired homogeneity (Venables and Wells, 2001). According to Venables and Wells "the mixing time must be optimized for each mix to minimize segregation".

For interactive mixtures longer mixing times are often needed as compared to random mixtures because the carrier particles first have to break up the agglomerates of active substance before the micronized particles will adhere to the surface of the carrier particles. The adhesive property is increased with increased mixing time in interactive mixtures. Mixing times up to 50 hours may be necessary at small scale, but preparation of interactive mixtures on large scale (industry) has been shown to require shorter mixing times (Saharan *et al*., 2008).

2.7.2 Mixing speed

The mixers used in the pharmaceutical powder mixing processes can be set to work at a specific speed. Mixing performance has been shown to be independent of mixing speed for free-flowing mixtures, but not for cohesive materials (Sudah *et al*., 2002). Cohesive materials have shown to mix better with higher rotational speeds in tumbling mixers as shown by previous studies (Chaudhuri *et al*., 2006, Kale *et al*., 2009, Le *et al*., 2012). This is thought to be a result of better de-agglomeration of the micronized active substance at higher speeds (Kale *et al*., 2009, Le *et al*., 2012). The interactive mixing of powders is recognized as mixing of cohesive materials (Saharan *et al*., 2008).

2.7.3 Effect of powder volume in pharmaceutical mixers

When mixing powders in all types of pharmaceutical mixers, the filling volume of powder will affect the mixing process. Too low or too high filling load will both have a negative impact on the mixing process. Improper movement of the powder bed with too high powder load will either prolong the time needed to achieve a proper mixture or obstruct the mixing process (Train, 1960). Too little volume could mean that the powder bed does not move properly, thereby causing improper mixing.

2.8 Appropriate dosage forms for children

Administering drugs to children can be complicated. Children are not small adults (Thomson *et al*., 2009) and can be unable to take the adult dosage form, because of unsuitable dosage or dosage form. Administering the proper age-related dose is also a challenge due to the considerable variation in body mass and developed abilities. Therefore, a flexible dosage form suitable for children of different ages, from neonates to adolescents is desired (Nunn and Williams, 2005).

The lack of appropriate dosage forms for children often results in off-label use. Often pharmacists have to prepare medicines for off-label use, in an extemporaneous manner. This type of preparation is not without risk. Analysing the final product, and also the shelf life, is not as easy compared to full-scale industrial products (Nunn, 2003).

The perfect dosage form for children contains according to Krause and Breitkreutz among others the following characteristics: It should be suitable for children of all ages, have a good safety and toxicity profile, have sufficient bioavailability and be easily administered (Krause and Breitkreutz, 2008).

Liquid solutions or suspensions are the most common dosage form used in children of low age when not able to take tablets or capsules. These dosage forms presents several challenges such as taste masking issues, stability issues, excipients not suited for children and inaccurate dosing (Thomson *et al*., 2009, Breitkreutz and Boos, 2011, Spomer *et al*., 2012).

New dosage forms fitting children are therefore required. In a recent review Breitkreutz and Boos states that orally disintegrating mini-tablets and thin film-strips for oro-mucosal use are the most promising dosage forms for children (Breitkreutz and Boos, 2011).

2.9 Mini-tablets as single units suitable for children

Traditional tablets or capsules are not well suited for most children, especially not for the youngest children. There are no specific age limit for when children are able to swallow tablets or capsules safely, although the most common perception is that from 6 years of age, children can swallow equally well as adults and training the child to swallow tablets will often help (Thomson *et al*., 2009).

Recently, the preparation and use of mini-tablets as a new dosage form for children have been described (Thomson *et al*., 2009, Stoltenberg and Breitkreutz, 2011, Spomer *et al*., 2012). Mini-tablets are defined as tablets with a diameter of 3 mm or less, and are made by direct compaction using a multiple-tool (Lennartz and Mielck, 1998). Mini-tablets down to 1 mm diameter have been successfully prepared with acceptable properties (Tissen *et al*., 2011). Reports on mini-tablets with normal (Lennartz and Mielck, 1998), sustained (De Brabander *et al*., 2000) or biphasic drug release (Lopes *et al*., 2006), but also orally disintegrating systems (Stoltenberg and Breitkreutz, 2011) are found in literature.

Figure 5: *Illustrating the small size of 2 mm mini-tablets in a 96-well titer plate*

Mini-tablets have several positive features such as uniform size, low porosity and an even surface. There are reports indicating that poorly compactable materials may obtain improved mechanical strength when the tablet diameter is reduced to mini-tablet size, compared to conventional tablet sizes (Lennartz and Mielck, 1998).

Mini-tablets can either be filled into capsules (Lennartz and Mielck, 1998) or used as single units, where the number of mini-tablets taken is personalized in accordance to weight or age (Thomson *et al*., 2009). Special dosing devices, that count the tablets, may be necessary to get a safe and user-friendly way of administering the mini-tablets (Bredenberg *et al*., 2003b, Stoltenberg and Breitkreutz, 2011).

Thomson and co-workers investigated how well mini-tablets (placebo, 3 mm diameter, 19-21 mg) were accepted in children of pre-school age (2-6 years). The study demonstrated that mini-tablets are indeed well accepted and swallowed safely by children in the age of 2 to 6 years (Thomson *et al*., 2009). In this study the children had to swallow 1 tablet each, given with the drink of their choice. The results did not indicate how children would respond to multiple dosing, which will be necessary in most cases to reach the wanted therapy. Spomer and co-workers compared mini-tablets (placebo, 2 mm diameter, 7 mg) with 3 ml glucose syrup (15 %) in 60 children from 6 months to 6 years in an open cross-over study. The results showed that the mini-tablet was equally well accepted as the glucose syrup by children of all ages, even down to 6 months (Spomer *et al*., 2012).

2.10 Orally disintegrating mini-tablets as a new dosage form for children

Mini-tablets are a promising dosage form that is suitable for children as outlined above (2.8 and 2.9). The use of tablets in general, in children under the age of 2, is however not accepted by the drug regulatory agencies, as it is viewed as unsuitable (Spomer *et al*., 2012). Therefore orally disintegrating mini-tablets may represent an even better and safer way of administering drugs to children down to 6 months of age, as they are able to swallow solid food and also multi-particulates from this age (Bowles *et al*., 2010).

The European Pharmacopoeia defines oro-dispersible tablets (ODT) as; "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed", and also state that they should disintegrate within 3 minutes (European Pharmacopoeia 7.8, Monographs of dosage forms). According to the US Drug and Food Administration, however, orally disintegrating tablets should have an *in vitro* disintegration time of 30 seconds or less (Park *et al*., 2008). Desired characteristics of drugs for ODT, which also are relevant to orally disintegrating mini-tablets (ODMT), are for example no bitter taste of the drug, good solubility in water and saliva and that it is present in the non-ionized form in the pH of the oral environment (Pfister and Ghosh, 2005).

For the preparation of ODTs many factors should to be considered in order to obtain the desired properties. For example the ODT should disintegrate quickly upon contact with the saliva in the mouth without the aid of extra water, be comfortable for the patient in terms of taste and mouth feel, be minimally sensitive to humidity and temperature with respect to storage stability, and have sufficient mechanical strength to ensure that the product will survive manufacturing, storage and handling by the patient (Kraemer *et al*., 2012).

Spomer *et al*. have studied the acceptability of orally disintegrating mini-tablets in children as described earlier (in 2.9). Although this study was not specifically describing the acceptance of ODMTs, the fact that the mini-tablets used in the study were disintegrating makes the result directly applicable to ODMTs. This is promising

for the future use of ODMTs, considering the drawbacks of using liquid preparations as discussed in 2.8.

2.11 Preparation of orally disintegrating tablets and mini-tablets

Orally disintegrating tablets are supposed to disintegrate quickly in the mouth as explained in 2.10. Manufacturers are faced with several challenges when preparing ODTs; for example optimizing disintegration time, mechanical strength, moisture protection and taste masking. The properties of the active substance, excipients and the chosen formulation technology will affect these characteristics (Bandari *et al*., 2008).

Excipients are chosen based on their properties such as flowability, compactability, disintegration ability, hygroscopicity, safety and taste. There are also several ready-to-use co-processed excipients on the market, that includes disintegrants which expand and dissolve upon contact with the saliva in the mouth, and thereby shortening the disintegration time (Stoltenberg and Breitkreutz, 2011). These excipients are often based on the water-soluble sugar alcohol mannitol co-processed with maize starch as in Pearlitol® Flash from Roquette (France), croscarmellose sodium as in Parteck® ODT from Merck (Germany) or crosslinked polyvinylpyrrolidone and polyvinyl acetate as in Ludiflash® from BASF (Germany).

The properties of the active substance can also affect tablet characteristics such as disintegration time, mechanical strength and taste. Particle size, hygroscopicity, compressibility and solubility of the active substance are properties that must be taken into account (Parkash *et al*., 2011).

There are also several technologies available for the preparation of orally disintegrating tablets. Freeze-drying, direct compaction, moulding, granulation, the cotton candy process and spray drying are all techniques, which are used to prepare ODTs (Bandari *et al*., 2008, Parkash *et al*., 2011, Stoltenberg and Breitkreutz, 2011). Direct compaction is a cheap and easy technique, but requires the drug and excipient to have good flow and compactability. Stoltenberg and Breitkreutz have successfully

prepared orally disintegrating mini-tablets by the direct compaction method (Stoltenberg and Breitkreutz, 2011).

2.12 Characterization of tablets and mini-tablets

2.12.1 Criteria for mass and dose variation of single unit dosage form

In order to get a predictable effect of a drug, the finished dosage form must pass certain tests to ensure the quality. Therefore, the European Pharmacopoeia provides tests for mass and dose variation of single unit dosage forms.

For uniformity of mass the European Pharmacopoeia states that, out of the 20 (randomly selected) units not more than 2 of the individual masses should deviate from the average mass more than the percentage shown in Table 3, and none must deviate more than twice that percentage (European Pharmacopoeia 7.8, chapter 2.9.5 – Uniformity of mass of single-dose preparations).

Table 3: *Criteria for the test for uniformity of mass of single-dose preparations (European Pharmacopoeia 7.8, chapter 2.9.5 – Uniformity of mass of single-dose preparations)*

	Average mass	**Percentage deviation**
Tablets (Uncoated or film-coated)	80 mg or less	10
	More than 80 mg or less than 250 mg	7.5
	250 mg or more	5

Further, for the test of uniformity of content, the European Pharmacopoeia states that the content of active substance in 10 randomly selected units should be individually analysed. For tablets the criteria is met if each of the individual contents are between 85 % and 115 % of the average content. The test fails if more than one of the individual contents are outside these limits or if one is outside 75 % to 125 % of the average content (European Pharmacopoeia 7.8, chapter 2.9.6 – Uniformity of content of single-dose preparations).

2.12.2 Mechanical strength of tablets and mini-tablets

The mechanical strength of a tablet depends on the behaviour of each of the different components and how it is prepared (van Veen *et al*., 2000). The mechanical strength should be sufficient to withstand handling related to production (e.g. packaging), transportation as well as by patient. The mechanical strength is often correlated to the dissolution rate of the tablet, which again will affect the onset time of the therapeutic effect of the drug. The mechanical strength is decided by the number, type and strength of bonds formed between particles during powder compaction (Nyström *et al*., 1993).

The European Pharmacopoeia describes the test of mechanical strength as measuring the force (F) needed to crush the tablet in a crushing test (European Pharmacopoeia 7.8, chapter 2.9.8 - Resistance to crushing of tablets). However, the force is influenced by the tablet dimensions (mass, diameter, height), and force measurements cannot be used for direct comparison of tablets of different dimensions. The calculation of tensile strength, however, takes tablet dimensions into consideration and makes it possible to compare the mechanical strength of different tablets (Fell and Newton, 1970). Tensile strength (σ) of flat-faced tablets is calculated by the following equation:

$$\sigma = \frac{2F}{\pi dh} \qquad \text{(Equation 4)}$$

where
d = tablet diameter (mm)
h = tablet thickness (mm)

This equation has also been used to determine tensile strength in biconvex mini-tablets by several authors. Although a modified equation for convex tablets have been proposed in literature (Pitt *et al*., 1988), the dimensions of the mini-tablets favour the original equation (Lennartz and Mielck, 1998, Tissen *et al*., 2011).

2.12.3 Test of disintegration time for orally disintegrating tablets

The purpose of ODTs is to rapidly dissolve upon contact with saliva in the oral cavity, making the drug easy to swallow. As with all other pharmaceutical dosage forms several tests has to be performed to ensure the quality of the ODTs and that they meet the quality standards (Kraemer *et al*., 2012). Since ODT is still a relatively young dosage form, and has gained increased attention during the last couple of years, there are not yet a specifically designed disintegration test described in the United States Pharmacopoeia or the European Pharmacopoeia. There are however several non-compendial disintegration tests available in literature (Park *et al*., 2008, Kraemer *et al*., 2012). In 2008 Park *et al*. described the simulated wetting test (Park *et al*., 2008), which has also been used by the group of Breitkreutz in Germany (Stoltenberg and Breitkreutz, 2011).

2.12.3.1 Simulated wetting test

The simulated wetting test takes into consideration the small volume of saliva that is available, in which the ODT should dissolve. This method is presented as a simple method that requires minimal equipment and is easily reproducible and quick. The simulated wetting test has shown good correlation to *in vivo* conditions (Park *et al*., 2008).

The test requires a fitted circular cellulose filter to be put in the wells of a titer plate. A specific volume of a coloured solution (blue dye) is used to wet the cellulose filter. The volume is decided by the size of the ODT. The tablet is placed gently on top of the wetted surface of the cellulose filter. The time for the blue dye to diffuse through the ODT and colour the entire tablet, is called the simulated wetting time. This time is suggested used as a substitute for the disintegration time for orally disintegrating tablets (Park *et al*., 2008).

Stoltenberg and Breitkreutz have used this method to evaluate the wetting time for 2 mm biconvex orally disintegrating mini-tablets of mannitol-based formulations. The authors commented that one drawback of using this method is that it does not include

the influence of mechanical stress in the oral cavity when administering ODMTs (Stoltenberg and Breitkreutz, 2011).

2.12.3.2 Other disintegration tests

The disintegration test described in the European Pharmacopoeia involves a "disintegration test apparatus", in which the tablets are inserted. The bottom of the apparatus consists of meshes of stainless steel with the mesh size (openings) of 2 mm. The apparatus is moved up and down in a beaker containing the test medium at 37°C. The test is performed by placing the tablets in the baskets, and covering them with discs. The discs are pierced with five 2 mm holes to allow passing of the medium. The basket is moved up and down until all the tablets are fully disintegrated (European Pharmacopoeia 7.8, chapter 2.9.1 – Disintegration of tablets and capsules).

The reason why this test is not applicable for disintegration testing of ODTs is the large volume available for disintegration in this specific test, which would not correlate with the *in vivo* conditions. The volume of the saliva is much smaller. Moreover, the test is also unsuitable for mini-tablets of 2 mm because of the size of the mesh covering the basket. The mini-tablets would pass through the openings unhindered.

Park and co-workers also mentions two additional methods for testing *in vitro* disintegration time that might correlate better to *in vivo* conditions for ODTs (Park *et al*., 2008). One method is very similar to the simulated wetting test described above. The tablet is placed on a cellulose filter wetted with a coloured dye-solution, which is placed in a Petri dish. The time until the tablet is disintegrated is measured. The second method involves a texture analyser with a flat-ended cylindrical probe. The tablet is placed in a given volume of water and the probe will push the tablet until disintegration, which is recognised by the instrument as a change in resistance. The probe is moved with a predetermined force for a given period of time. The computer software then calculates the disintegration based on the distance the probe has travelled (Park *et al*., 2008).

3. Aim of the study

The overall aim of the project was to prepare orally disintegrating mini-tablets with high dose-homogeneity appropriate for children. The working hypothesis was that preparation of interactive mixtures would be a suitable means to obtain high dose-homogeneity in mini-tablets. The project was divided in the following sub goals:

- Test the effect of mixing time, mixing method, sampling size and carrier particle size on the homogeneity of the powder mixture.

- Preparation and characterization of orally disintegrating mini-tablets (2 mm) based on interactive mixtures, with focus on dose-homogeneity, disintegration time and mechanical strength.

- Study the effect of compaction pressure on mechanical strength and disintegration time. For this purpose 6 mm flat-faced tablets were employed.

4. Materials and methods

4.1 Materials

Granulated mannitol (Pearlitol® 100SD, Roquette Pharma, France) was used as carrier material and sodium salicylate (Sigma Life Science, Germany) as active substance.

4.2 Characterization of raw material

100 g of Pearlitol® 100SD was sieved with a mechanical sieve shaker (Retsch VE 1000, Retsch GmbH & Co. KG, Germany) to assess the particle size distribution. Sieves (Retsch GmbH & Co. KG, Germany) with the following sizes were used: 45, 63, 90, 125 and 180 µm. The material was sieved until not more than approximately 0.2 % of the material went through each sieve per 5 minutes of sieving. The percentage of material left on each sieve was noted and a histogram showing particle size distribution was made. Three parallels were included.

***Figure 6**: Retsch mechanical sieve shaker and sieves used for particle size analysis*

4.3 Separation of particle size fractions

Pearlitol® 100SD was sieved as described in 4.2.

Collected particle fractions:
63-90 µm, 90-125 µm and 125-180 µm

Sodium salicylate was previously estimated by laser diffraction to have mean particle size < 10 µm (Sandberg Løding, 2011).

4.4 Characterization of the particle fractions of mannitol

The mannitol fractions listed in 4.3 were characterized separately using the following methods.

4.4.1 Poured and tapped volume

A 250 ml volumetric cylinder was filled with 100 g powder. The poured volume was noted. By using a tapped density tester (Erweka SVM, Erweka GmbH, Germany) the cylinder was tapped 10 000 times and the tapped volume was noted. Three parallels were done. The Hausner Ratio and Carr Index were then calculated according to Equation 1 and 2, respectively.

4.4.2 Angle of repose and flow time

100 g of powder was poured into a glass funnel (Figure 7). The bottom opening was closed during pouring. When the bottom opening was opened the powder went through the funnel and down on a metal plate covered with paper. The height and radius of the powder pile was measured and the angle of repose was calculated. Five parallels were performed.

The flow time (rate) was estimated by measuring the time from when the powder was released from the funnel until all of the powder reached the plate.

Figure 7: *Showing equipment used for the test of angle of repose and flow time*

4.4.3 Powder densities

The true density of the carrier particles was determined using helium pycnometer (AccuPyc 1330, Micromeritics Instrument Corporation, USA). The particle fractions were mixed before testing to ensure that eventual segregation of smaller particles to the bottom of the container did not affect the density result. The apparatus tested the particle density in triplicate.

4.5 Preparation of powder mixtures

4.5.1 Tumbling mixer

100 g of 1 % (w/w) mixture of micronized sodium salicylate and mannitol carrier particles was prepared in a glass jar. Only for the size fraction with the largest particle size (125-180 μm) the mass had to be adjusted to 80 g. This was due to differences in volume as a consequence of particle size and density. The powder was mixed in a Turbula mixer (Willy A. Bachofen AG Maschinenfabrik, Switzerland) at 96 rpm. At predetermined time points the mixing was stopped and samples were withdrawn. Time points were selected from 10 minutes up to 48 hours. All powder mixtures were prepared in duplicate.

4.5.2 Planetary mixer

200 g of 1 % mixture of micronized sodium salicylate and mannitol carrier particles (90-125 μm fraction only) was prepared in a Kenwood mixer (Kenwood Ltd., UK). The powder was mixed with a mixing paddle speed of 3.5. At predetermined time points the mixing was stopped and samples were withdrawn. Time points were selected from 10 minutes up to 48 hours. The powder mixture was prepared in duplicate.

4.6 Buffer solution

The chosen buffer solution used in the entire project was phosphate buffered saline pH 6.8 (European Pharmacopoeia 7.8, chapter 4.1.3 – Buffer solutions).

1.0 g of potassium dihydrogen phosphate, 2.0 g of dipotassium hydrogen phosphate and 8.5 g of sodium chloride were dissolved in ca. 980 ml of distilled water. The pH was adjusted if necessary and the solution was then diluted to 1000 ml with distilled water.

4.7 Homogeneity of the powder mixture

Thirty random samples of 3.0±0.5 mg and a varying number of 20.0±2.5 mg were withdrawn from the powder mixture at each time point, using a powder micro-thief (Sampling systems Ltd., UK). The samples were dissolved in 1.50 ml or 10.0 ml phosphate buffer pH 6.8, respectively. For quantification standard solutions were made from a stock solution of 1 mg/ml sodium salicylate. The following concentrations were used for the standard solutions: 10, 15, 20, 25 and 30 µg/ml.

The samples were quantified by UV-spectrophotometry at the wavelength of 295 nm. In the beginning of the project the samples were measured with the Agilent 8453 UV-visible Spectroscopy system (Agilent Technologies GmbH, Germany), with manual filling of the cuvette. The samples were measured and quantified based on the calibration curve made from the standard solutions (R^2=0.97571).

To get a more efficient measuring procedure a UV-spectrophotometer with a plate-reader (Spectramax 190 Absorbance microplate reader, Molecular Devices LLC, USA) was used. A 96-well titer plate (Polystyrene round bottom 96-well plates for BCA-RAC assays, Thermo Scientific Inc., U.S.A.) was used and 250 µl of the samples and standards were added in separate wells. The samples were measured and quantified based on the calibration curve made from the standard solutions within each of the plates (R^2>0.98566).

For each sampling time the standard deviation, mean, median, minimum and maximum value, relative standard deviation and 10, 25, 75 and 90-percentile were calculated. From this a scientific “stock-plot” was made. In addition, the degree of homogeneity was expressed as the relative standard deviation of the normalized values (i.e. the ratio of the measured content to the theoretical content).

4.8 Preparation of mini-tablets of 2 mm diameter

4.8.1 Addition of lubricant

1 % (w/w) magnesium stearate was added to the powder mixtures by light manual mixing.

During the compaction procedure a 5 % (w/v) suspension of magnesium stearate in acetone was used for lubrication of the die and punches before every stroke to avoid sticking of powder.

4.8.2 Compaction of mini-tablets

The final powder mixtures (48 hours) were used for preparation of 2 mm mini-tablets. 105.0±0.8 mg of powder was manually filled into the dies of the multiple-tool, which allows preparation of 15 mini-tablets per stroke. The concave punches with a diameter of 2 mm are positioned in two lines, with 7 in the front row and 8 in the back. A total of 98 mini-tablets were made from each powder mixture batch. The powder mixtures (parallels) with the lowest relative standard deviation of the normalized values were used for the preparation of the mini-tablets.

Special care was taken that the manual filling of the dies of the multiple-tool was done in a reproducible way. The powder was gently moved into the die using a predetermined technique to ensure homogenous mass of the mini-tablets. After appropriate filling, the powder was compressed into biconvex 2 mm in diameter mini-tablets, by the custom-made compaction simulator (Schmidt ServoPress 450 Schmidt Technology GmbH, Germany; with compaction module from IBR, Germany) (Figure 8). The velocity of the upper punch was 10 mm/s, while the lower punch was stationary. The compaction force was calculated as the mean of the maximum upper and lower force. These values were measured with Kistler Instrumente AG force sensor 9363 (Kistler Group, Switzerland).

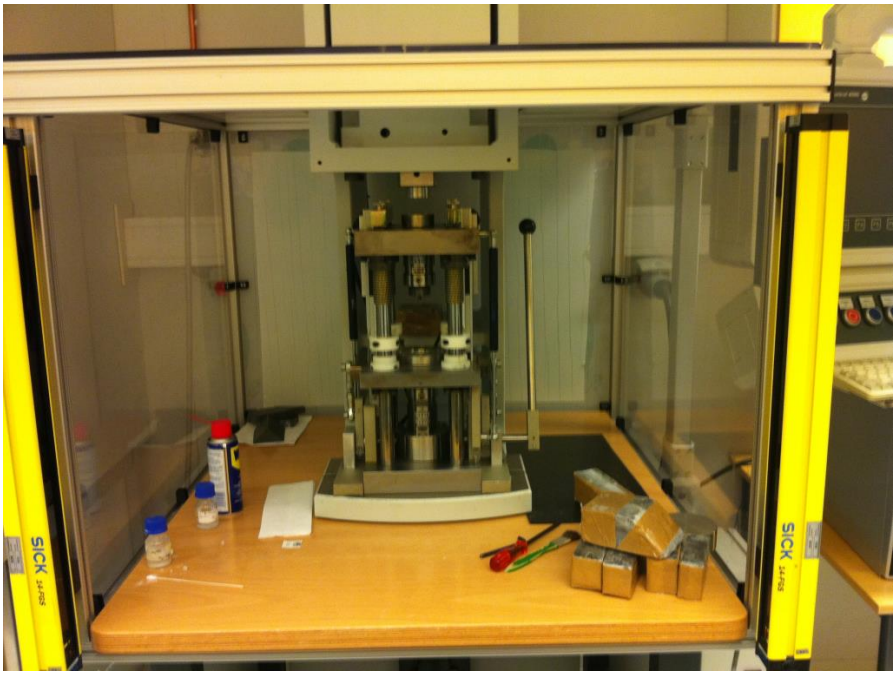


Figure 8: *Compaction simulator used for preparation of all tablets*

A pressure of 100 MPa was used for preparation of the mini-tablets, which equals a force of 4.7 kN. The compaction pressure can be calculated from the force from the following equation.

$$P = F/A = F/ (\pi * r^2 * 15) \qquad \text{(Equation 5)}$$

*Where 15 is the number of mini-tablets made per stroke.

The mini-tablets were removed by forceps and placed in a titer plate for convenient storage. The titer plate was covered with paper when not in use, in order to protect the mini-tablets from light exposure.

4.9 Preparation of flat-faced 6 mm tablets

The final powder mixtures (48 hours) were used for preparation of the 6 mm tablets by the custom-made compaction simulator (Schmidt ServoPress 450 Schmidt Technology GmbH, Germany; with compaction module from IBR, Germany) (Figure

8). 75.0±0.5 mg of powder was filled manually into the die. Between 30-40 tablets were made at 35, 50 and 100 MPa, respectively (corresponding to 1.0, 1.4 and 2.8 kN).

A 5 % (w/v) magnesium stearate in acetone suspension was used for lubrication and applied on the die walls after approximately every second stroke.

4.10 Characterization of mini-tablets (2 mm) and tablets (6 mm)

4.10.1 Uniformity of mass

Test was done according to the European Pharmacopoeia. For the 2 mm mini-tablets 30 tablets were randomly selected and weighed, and for the 6 mm tablets all prepared tablets prepared were weighed. The average and standard deviation were calculated and it was checked whether the batch complied with the European Pharmacopoeia requirements (European Pharmacopoeia 7.8, chapter 2.9.5 – Uniformity of mass of single-dose preparations).

4.10.2 Uniformity of content

Test was done according to the European Pharmacopoeia. Ten tablets or mini-tablets, selected randomly, were separately weighed and dissolved in 50.0 or 5.0 ml, respectively, of phosphate buffered saline (pH 6.8) in volumetric flasks (European Pharmacopoeia 7.8, chapter 2.9.6 –Uniformity of content of single-dose preparations). These solutions and the standard solutions were all filtered using 0.2 µm syringe filter (Bulk Acrodisc® 25 mm syringe filter w/0.2 µm Supor Membrane, Pall Life Sciences, USA) to ensure that the samples were not contaminated with magnesium stearate. The samples and standard solutions were quantified by UV-spectroscopy at 295 nm as described in 4.7. The amount of added magnesium stearate (as in 4.8.1) was taken into consideration in the calculations. The average and standard deviation were calculated and it was checked whether the batch complied with the European Pharmacopoeia requirements (European Pharmacopoeia 7.8, chapter 2.9.6 – Uniformity of content of single-dose preparations).

4.10.3 Height measurement

The height of 30 randomly selected mini-tablets was measured using a texture analyzer (TA.XTplus, Stable Micro System, UK). A 4 mm in diameter probe was used. The equipment was calibrated using standard height blocks, and the height measurements were corrected in order to determine the actual height of the mini-tablets. The height of all of the prepared flat-faced 6 mm tablets was measured using a micrometer screw (Micrometer screw IP54, Wilson Wolpert, the Netherlands).

4.10.4 Crushing strength

Crushing strength of 30 mini-tablets (the same as subjected to height measurements in 4.10.3) was measured using the texture analyser (TA.XTplus, Stable Micro System, UK), with the same 4 mm in diameter probe used in 4.10.3. One single mini-tablet was placed with the horizontal side facing down on the metal plate on the texture analyser. The probe moved down at a speed of 2 mm/sec until it made contact with the mini-tablet. The trigger force was 5 g. The test speed then changed to 0.03 mm/sec until the mini-tablet was crushed. Maximal force used to crush the mini-tablet was identified in the force-distance diagram. The crushing strength was registered in kg and converted to Newton by multiplying with 9.8. The tensile strength was then calculated for each mini-tablet according to Equation 4.

Crushing strength of flat-faced 6 mm tablets was measured as according to the European Pharmacopoeia using a tablet hardness tester (Erweka TBH 20, Erweka GmbH, Germany). The individual crushing force (N) of ten tablets was measured (European Pharmacopeia 7.8 chapter 2.9.8 – Resistance to crushing of tablets). The tensile strength was calculated according to Equation 4.

4.10.5 Friability test

The friability of the mini-tablets was tested using the method from European Pharmacopoeia, and a standard friability apparatus (Erweka Tar-20, Germany). 20 randomly selected mini-tablets were weighed and placed in the drum, which was rotated for 4 minutes at a speed of 25 rpm. The mini-tablets were dedusted and weighed again. The percentage weight loss was then calculated (European Pharmacopoeia 7.8, chapter 2.9.7 – Friability of uncoated tablets).

4.10.6 Disintegration testing

Three different methods were used to test the disintegration properties of the tablets.

Disintegration test apparatus: Method (1) used for 6 mm flat-faced tablets

By using a tablet disintegration tester (Erweka ZT 42, Erweka GmbH, Germany) six 6 mm flat-faced tablets were put in separate and dry cylindrical baskets. A beaker with approximately 750 ml phosphate buffer pH 6.8 was warmed up to 37°C. The apparatus was turned on, and by movement of the baskets up and down at a regular speed; the time for the tablets to reach full disintegration was measured.

Shaking water bath: Method (2) used for 6 mm flat-faced tablets

50 ml phosphate buffer pH 6.8, in a beaker, was warmed in a water bath to 37°C. One 6 mm flat-faced tablet was placed in a basket taken from the dissolution equipment (basket apparatus) and then immersed in the beaker fixed in a shaking water-bath. The time until the tablet had fully disintegrated was measured. A total of six tablets were tested.

Simulated wetting test – used for 2 mm mini-tablets

Cellulose filter was cut in small circular shapes to fit into the wells in a 96-well titer plate (Polystyrene round bottom 96-well plates for BCA-RAC assays, Thermo

Scientific, U.S.A.) and then covered with 30 µl of 0.1 % (w/w) Brilliant Blue dye solution (Coomassie® Brilliant Blue R-250, Bio-Rad Laboratories, USA) (Figure 9). One mini-tablet was placed on top of the filter with the horizontal part facing down, using forceps. The solution only covered the filter and the bottom of the mini-tablet. The time the dye needed to completely colour the entire mini-tablet blue was measured. A total of 10 mini-tablets were included for each batch.

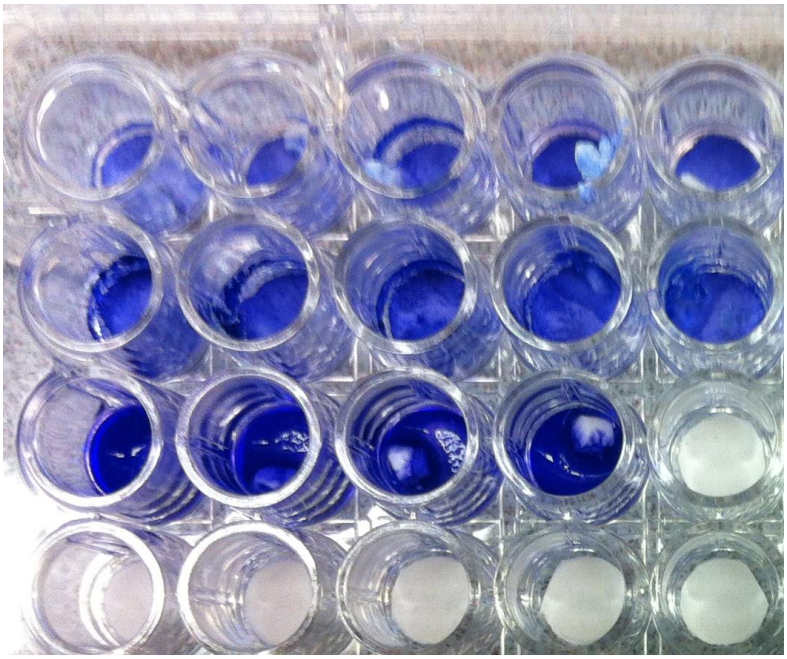


Figure 9: *Illustration of the simulated wetting test*. *Mini-tablet is put gently down on the filter covered with blue dye*

5. Results and discussion

5.1 Characterization of raw materials

5.1.1 Particle size distribution

The particle size distribution of the raw material (Pearlitol® 100SD) is shown in Figure 10. It illustrates the fact that even though a material is delivered with a mean particle size (here: 100 µm), the distribution can still be quite wide.

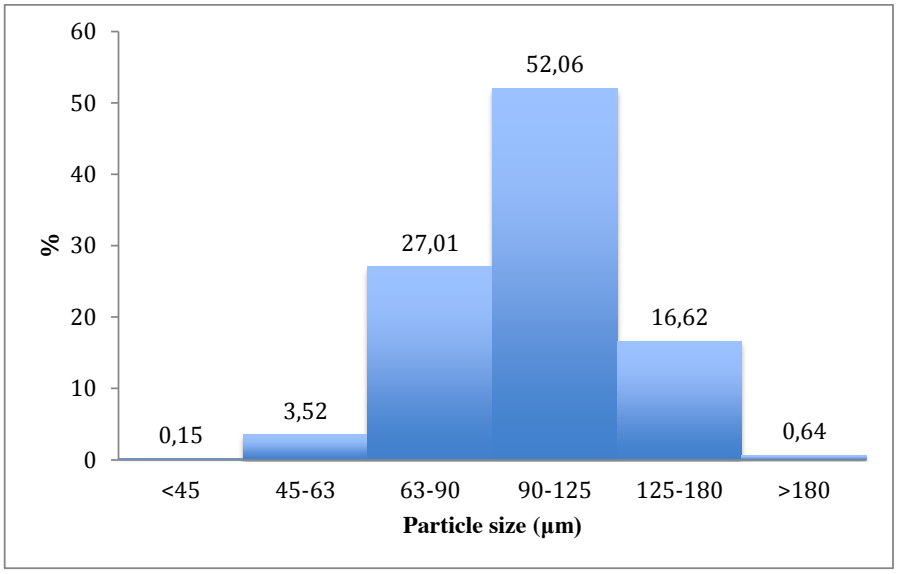


Figure 10: *Particle size distribution of Pearlitol® 100SD as determined by sieving analysis*.

In an ideal interactive mixture the carrier particles should be mono-sized. This will help to ensure even distribution of micronized drug particles on the surface of the carrier material. Smaller carrier particles that have higher surface area than larger carrier particles have the potential of carrying more micronized drug particles per particle. Carrier particles that are not mono-disperse can segregate, as commented in literature (Yip and Hersey, 1977b), which will result in a lower degree of order in the

interactive mixture. Experiments done by Bredenberg and co-workers supported this theory; the narrower the particle size distribution, the more mechanically stable will the interactive mixture be (Bredenberg *et al*., 2012). It is therefore important to analyse the raw materials and take out the fractions with the desired particle size for the preparation of the interactive mixture.

The particle size of the micronized drug (sodium salicylate) was estimated by laser diffraction to have a mean size < 10 µm (Sandberg Løding, 2011).

5.1.2 Other powder characteristics

The powder flow characteristics are important in order to predict the results of powder mixing and the compressibility of the powder. Hausner Ratio, Carr Index, angle of repose and flow time all give an indication of the powder flow and packing characteristics. All the respective values of the investigated mannitol samples are presented in Table 4.

Table 4: *Powder characteristics of the mannitol particle size fractions investigated*

Particle size fraction (µm)	**Carr Index**	**Hausner Ratio**	**Angle of repose (°)**	**Flow time (s)**	**True density (g/cm^3)**
63-90	15.30±1.65	1.18±0.02	28.2±1.4	3.3±0.3	1.4696±0.0003
	Fair	Good	Excellent		
90-125	12.37±0.67	1.14±0.01	27.7±1.2	2.9±0.2	1.4703±0.0003
	Good	Good	Excellent		
125-180	15.08±1.36	1.18±0.02	32.3±2.5	3.1±0.1	1.4729±0.0003
	Fair	Good	Good		

Hausner Ratio and Carr Index illustrate the packing properties of the different mannitol fractions selected as carrier material for preparation of interactive mixtures. Taking the standard deviation of the results into consideration, they can generally be

classified as materials with good flow characteristics. Taking testing errors into consideration, there do not seem to be any noteworthy differences in flow properties between the three particle size fractions.

The fraction with the smallest particle size (63-90 μm) showed much more electrostatic behaviour than the other two particle fractions. A significant amount of powder stuck to and stayed in the funnel after the test on flow time and angle of repose. This is not so clearly seen in the result, as the most cohesive particles (the smallest) were not leaving the funnel and never reached the powder pile on the plate below. Therefore, based on the results of flow time and angle of repose, it is difficult to judge whether there is a difference in flow properties of this powder fraction compared to the other two. The electrostatic behaviour of the carrier particles is not desirable for preparation of an interactive mixture. Although there are no specific requirements for flow time in the European Pharmacopoeia, the results can give an indication of differences in powder flow between the particle size fractions. There was no significant difference ($p>0.05$) in flow time identified for the three particle size fractions investigated.

Overall, the 90-125 μm particle size fraction have shown slightly better results in terms of powder flowability and packing properties, but the difference between the tested fractions are low. The only concern with respect to preparation of the interactive mixtures from the three mannitol samples is the significant electrostatic behaviour experienced for the 63-90 μm particle size fraction.

The difference in true density of the three different particle size fractions is so small (though significant, $p<0.05$) that it should not affect the ability to compare the results of the interactive mixtures made from each of these particle size fractions. According to Hogg, the difference in particle size is more important in terms of segregation issues than difference in particle density. The difference in particle size is often much larger, and therefore more important, than the difference in particle density (Hogg, 2009).

5.2 Effect of mixing time on the homogeneity of the interactive powder mixture

Figure 11 shows the homogeneity of a powder mixture consisting of 1 % (w/w) sodium salicylate and mannitol of the 90-125 µm particle size fraction. The powder was mixed in Turbula mixer, and samples of 3.0±0.5 mg were withdrawn at different time points. After 20, 30 and 60 minutes of mixing, the relative standard deviation (RSD) of the normalized values was 7-9 % (n=30 at each time interval), which was higher than what was expected for an interactive mixture. Therefore, the mixing time was increased. In general, Figure 11 shows that, the longer the mixing time, the higher degree of homogeneity was obtained in the powder mixture. The RSD gradually decreased for each time point up to 48 hours. The same powder mixture was prepared twice and for the longer time intervals (> 1 hour), the mean of the two mixtures was calculated (Figure 11). Therefore, at 2 hours, where the error bars indicate large variation, the difference between the two mixtures was large: one mixture showed similar level of variation as the shorter mixing times (7.6 %), whereas the other showed much lower variation (4.9 %). From 24 hours it seemed like a plateau was formed and the variation stabilized around 3.7-4.2 %. It may be that 24 hours is enough to accomplish the achievable homogeneity in this particular powder mixture. The error bars are clearly overlapping when comparing samples between 24 and 48 hours.

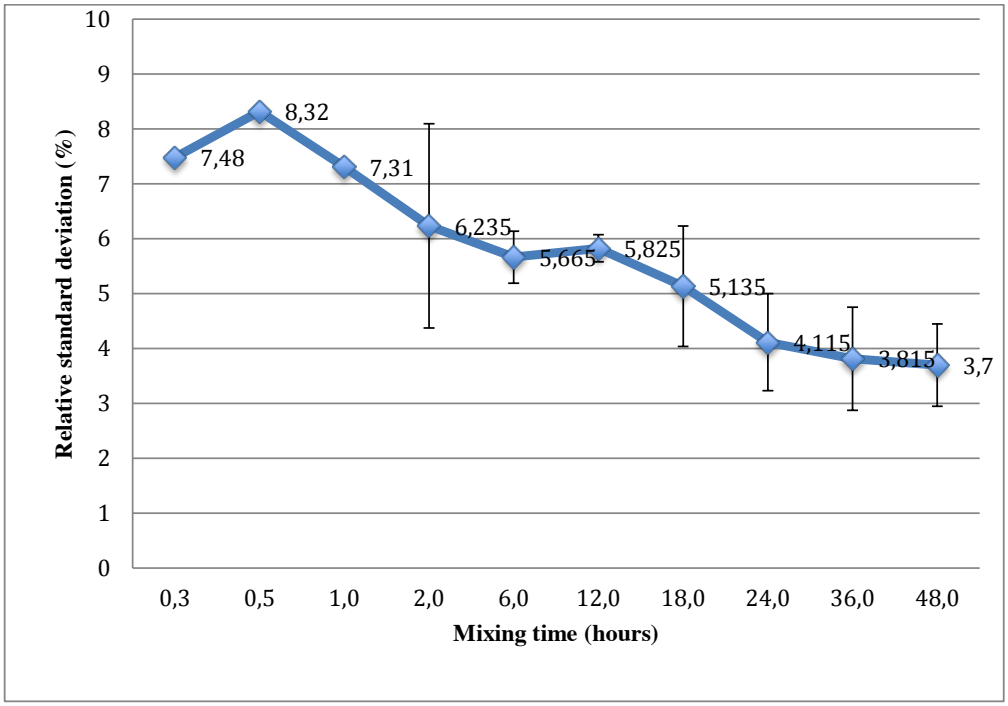


Figure 11: *Homogeneity of 1 % (w/w) sodium salicylate in mannitol (fraction 90-125 µm) represented by relative standard deviation (%) of the normalized values as a function of mixing time (hours) for Turbula mixer. Sampling size 3 mg (n=30 for each time point in all parallels. n=2 for the number of powder mixtures prepared (time points without error bars represents only one powder mixture)*

Figure 12 shows the variation in detected content of sodium salicylate in the samples at each time point. The stock-plot is used to better display the variation since it depicts the average (mean), median, different percentiles (10, 25, 75 and 90) as well as the minimum and maximum content of each series of samples. The figure confirmed that the variation is high at the short mixing time-points, showing a large difference between maximum and minimum values. Longer mixing times give less variation in the values. There seemed to be a continuous decrease in variation up to 36 hours of mixing. The series of samples taken after 48 hours showed once more some variation towards higher values. Whether this is just random variation or start of demixing or segregation has not been investigated.

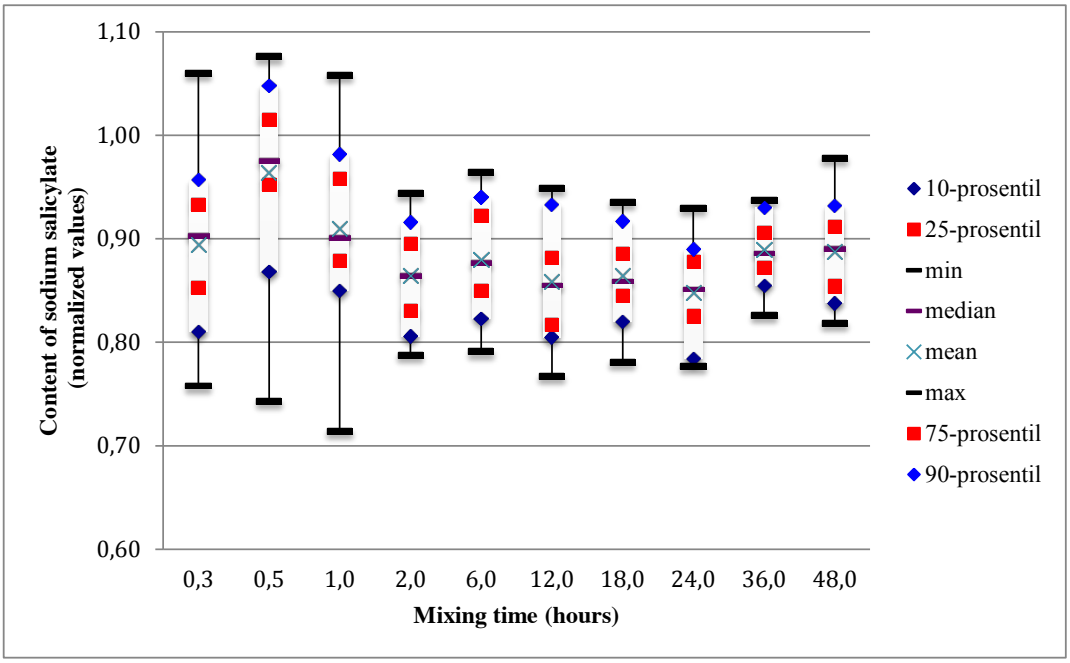


Figure 12: *Scientific stock-plot for 1 % (w/w) sodium salicylate in mannitol (fraction 90-125 µm) showing the variation of the measured content as a function of mixing time (hours) for powders mixed in Turbula. Sample size 3 mg (n=30 for each time point). Result is showing one of the parallels in Figure 11*

Sundell-Bredenberg and Nyström reported that a mixing time of 24 hours was sufficient in order to achieve a stable interactive mixture with high homogeneity (Sundell-Bredenberg and Nyström, 2001). The interactive mixture that was comparable to those used in this project was prepared from 0.15 % micronized sodium salicylate (size less than 10 µm) and mannitol (particle size 250–425 µm), and mixed in Turbula mixer (120 rpm). The mean RSD-value of two parallels was 3.92 % for samples of 25 mg. Longer mixing time than 24 hours had little effect on homogeneity for their interactive mixture. This supports our findings.

5.3 Effect of sampling size on the homogeneity of the interactive powder mixture

The detected homogeneity is expected to depend on the size of the samples examined, as was explained in 2.6.1. In the current project two different sampling sizes were studied: 3 mg and 20 mg. From Table 5 we can see that the 20 mg sample size showed in general a lower value of the relative standard deviation, but that there does not seem to be a clear difference. However, 20 mg samples are still small samples. The difference in the sample sizes may have to be larger and more parallels completed, to conclude whether sample size has a significant effect on the relative standard deviation that represents the homogeneity of the mixture.

Table 5: *Effect of sampling size (3 mg and 20 mg) on detected homogeneity of 1 % (w/w) sodium salicylate in mannitol (fraction 90-125 µm), represented by relative standard deviation of normalized values, for Turbula mixer. n=30 for each time point*

Mixing time (hours)	Relative standard deviation (%)		
	3 mg sample size		20 mg sample size
	Parallel 1*	Parallel 2	Parallel 2
18	4.36	5.91	5.04
24	4.74	3.49	3.22
36	3.14	4.48	2.59
48	4.23	3.17	2.68

*same powder mixture as shown in Figure 12

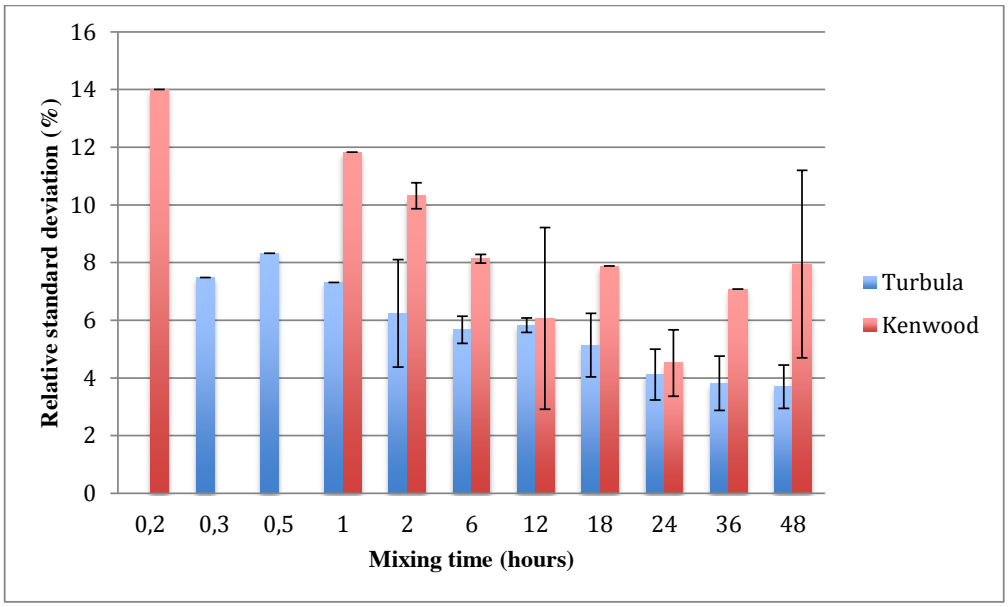
The goal of the current project was to prepare 2 mm mini-tablets from the interactive mixtures, and the mass of one mini-tablet is low; typically in the size range 6-8 mg per unit (Stoltenberg and Breitkreutz, 2011, Sandberg Løding, 2011, Spomer *et al*., 2012). The sample size of 3 mg was chosen in order to be able to test the homogeneity of the powder mixture at a level comparable to inside the mini-tablet. A 20 mg sample size is approximately three times larger than one mini-tablet and by using this sample size we cannot say with certainty that there was not more variation within the sample. Therefore, the sample size of 3 mg is recommended to check the

homogeneity for preparation of mini-tablets, which then can be reliable to the actual finished dosage form.

5.4 Effect of different mixing mechanisms on the homogeneity of the interactive powder mixture

By using different mixing equipment, the effect of different mixing mechanisms on the homogeneity of an interactive mixture could be determined. As seen from Figure 13, the planetary mixer (Kenwood) had a tendency to form less homogeneous interactive mixtures than with the tumbling mixer (Turbula). The variation was higher both in 3 mg samples (Figure 13A) and 20 mg samples (Figure 13B), and also more fluctuating if one looks at the 3 mg samples compared to the results obtained with the tumbling mixer. While the RSD values decreased continuously for the tumbling mixer, the RSD values for the planetary mixer did show a decrease in RSD up to 24 hours, but from 24 hours onward the increasing RSD values could indicate demixing. It might be concluded that it is more difficult to achieve high homogeneity of interactive mixtures using planetary mixers. One explanation for these results can probably be connected to the fact that the convective mixing mechanism is dominant in planetary mixers. Venables and Wells described that convective mixing is expected to give a more crude powder mixture than diffusive mixing, which is the dominant mixing mechanism in tumbling mixers (Venables and Wells, 2001). This is most likely due to the moving of larger sections of powder in convective mixing, compared to moving of single particles in diffusive mixing. In addition, the risk of dead spots is higher in planetary mixers, therefore, the choice of tumbling mixers for the mixing of interactive mixtures have been highly recommended (Yip and Hersey, 1977a). The larger carrier particles need to break up agglomerates of the fine micronized particles in order to achieve a stable interactive mixture.

A)



B)

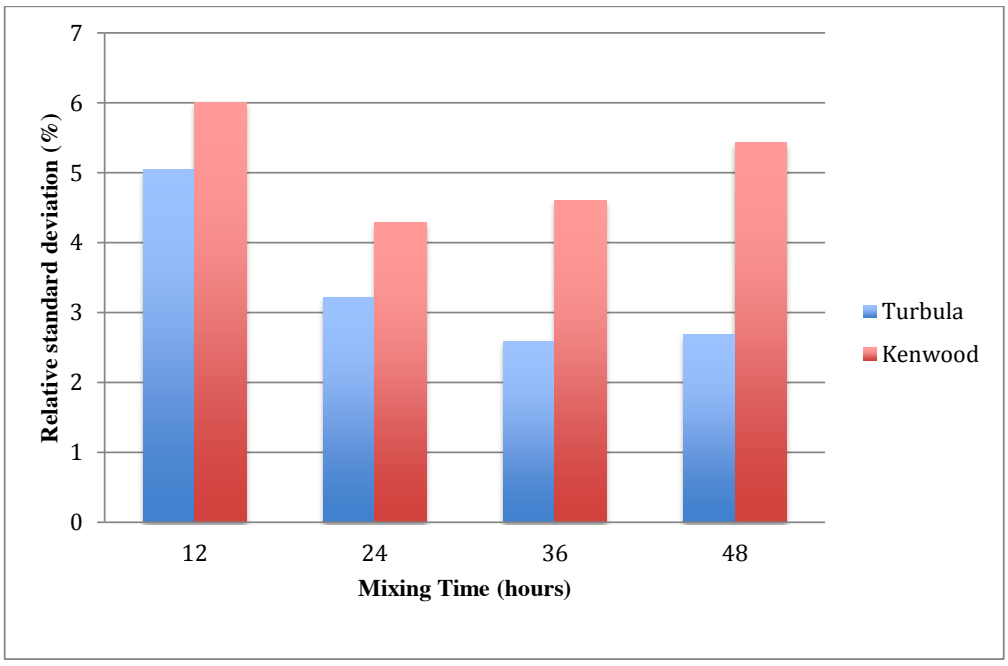
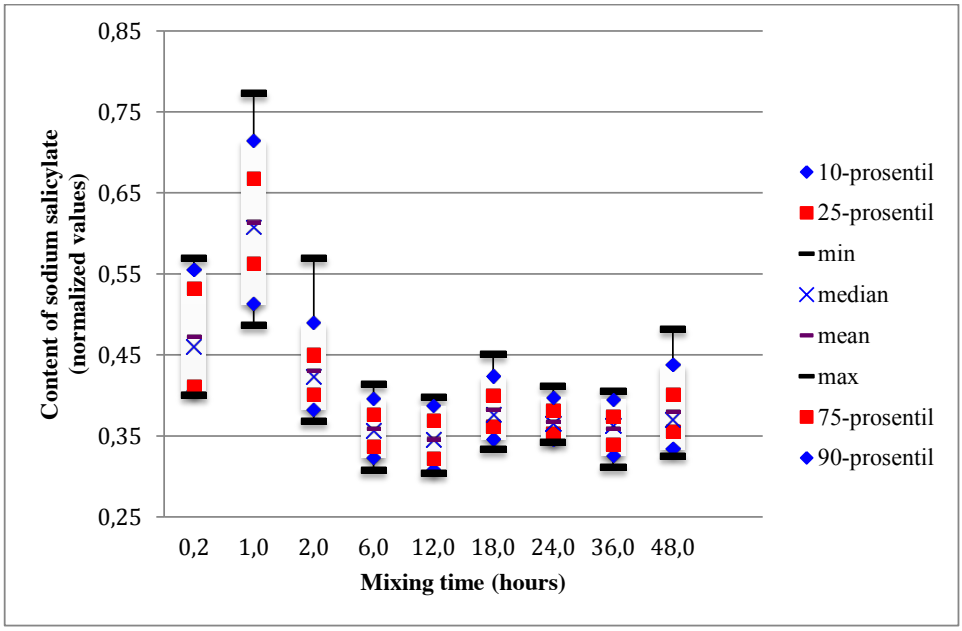


Figure 13: *Effect of different mixing equipment (Turbula tumbling mixer and Kenwood planetary mixer) on the homogeneity of 1 % (w/w) sodium salicylate in mannitol (fraction 90-125 µm), represented by relative standard deviation (%) of normalized values. n=30 in each time point. A) Sample size of 3 mg (average of two parallels where error bars are showed) B) Sample size of 20 mg*

It is important to point out that much of the theory on mixing equipment and mixing mechanisms in general are based on random mixtures, not interactive mixtures, and therefore some of the knowledge cannot be directly transferred. However, with respect to diffusive versus convective mixing, the above mentioned explanations should be comparable in both random and interactive mixing (Yip and Hersey, 1977a).

There was a significant loss of the active substance (over 60 %) observed during mixing in the planetary mixer in the first parallel, as can be seen in Figure 14A. Compared to the tumbling mixer (Figure 12), the loss of active substance was substantial for the planetary mixer. Two strategies were tried out in the second parallel (Figure 14B) in order to reduce the loss of active substance in the planetary mixer; a "slow start"-procedure, where the mixer was run at reduced speed for the first 30 seconds, as well as placement of the drug in between the mannitol powder before the mixer was started. These strategies were not able to prevent the loss of the active ingredient, which still was at approximately 50 %. It was observed that the powder showed high electrostatic properties after mixing in the planetary mixer, as it would easily stick to different parts of the mixing equipment (cover, blade, bowl), and therefore substantially lowering the amount of active substance in the powder mixture. The significant electrostatic properties of the powder after mixing were also recognised, as the powder would stick to the thief probe during sampling. This phenomenon did not occur when samples were withdrawn from the powder mixtures prepared in the tumbling mixer.

A)



B)

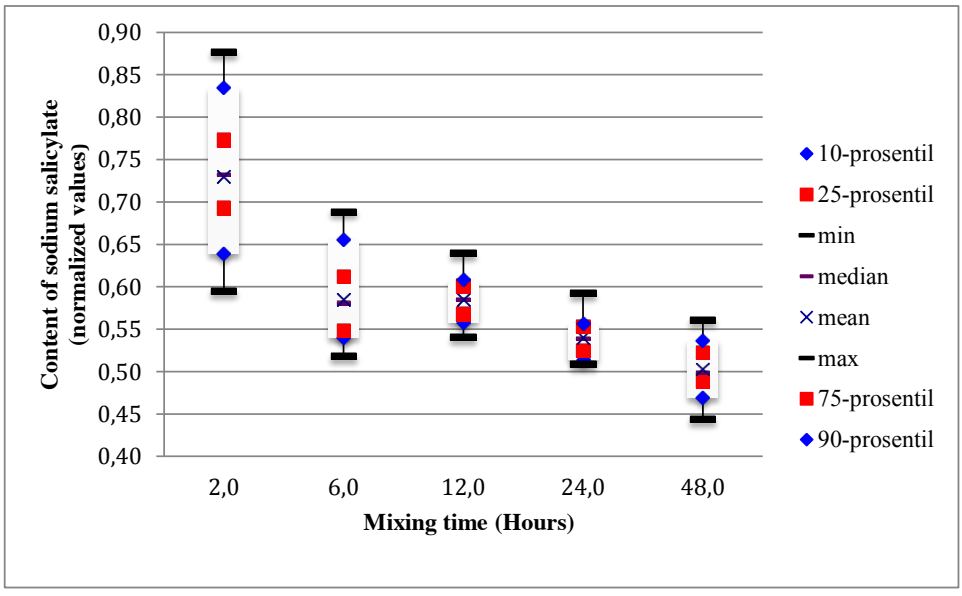


***Figure 14**: Scientific stock-plot for 1 % (w/w) sodium salicylate in mannitol (fraction 90-125 µm) showing the variation of measured content as a function of mixing time (hours) for powders mixed in planetary mixer (Kenwood); 3 mg samples, n=30 in each time point. A) First parallel – drug added last and continuous speed of mixer from start B) Second parallel – drug placed between mannitol powder and reduced speed of mixer in first 30 seconds*

5.5 Effect of carrier particle size on the homogeneity of the interactive powder mixture

Powder mixtures were prepared with three different particle size fractions. In addition to the 90-125 µm fraction described above, one fraction with higher particle size (125-180 µm) and one with lower particle size (63-90 µm) were used. All mixtures were prepared in duplicate using the tumbling mixer. The three different particle size fractions showed some differences with respect to homogeneity as showed in Figure 15. There seemed to be a correlation between carrier particle size and the degree of homogeneity of the interactive mixtures. The higher the mean particle size the higher the degree of homogeneity could be obtained in the mixture. At first glance this seems to contradict what is found in literature where other researchers have concluded that higher particle size gives a *lower* degree of homogeneity (Sandberg Løding, 2011, Bredenberg *et al*., 2012). However, it is important to notice that in their studies the particle sizes of mannitol-carrier particles were from 180 µm and up. They concluded that their lower particle size fractions (180-250 µm) gave interactive mixtures with the highest degree of homogeneity. Sandberg Løding achieved a relative standard deviation of around 1.40 % with a sample size of 20 mg (Sandberg Løding, 2011).

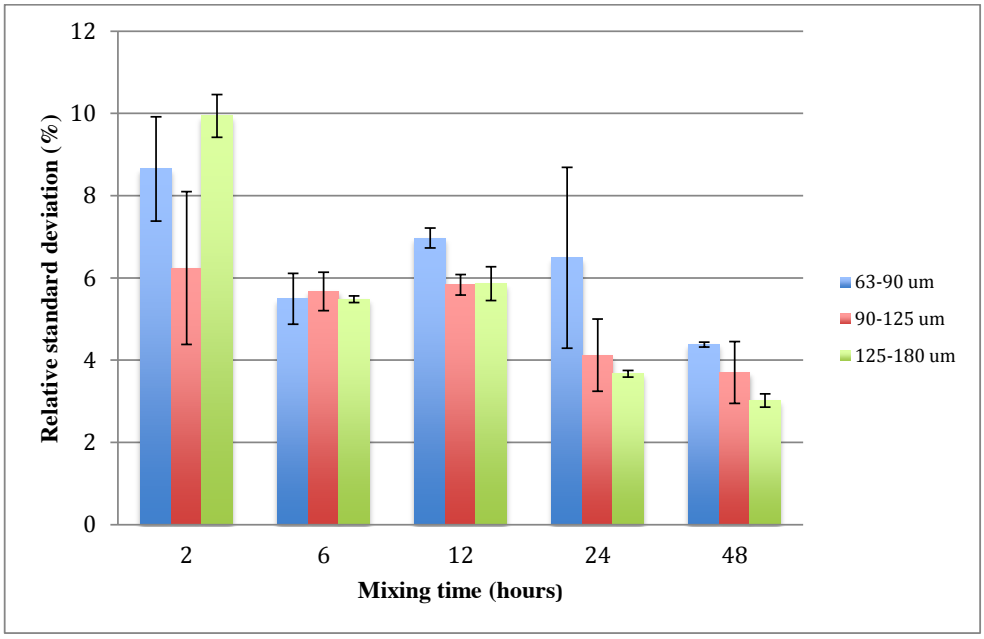


Figure 15: *Effect of the size of the carrier particles on homogeneity of 1 % (w/w) sodium salicylate in mannitol (fraction 63-90, 90-125 and 125-180 µm), represented by the relative standard deviation (%) of normalized values. Mixed in Turbula mixer: sample size 3 mg and n=30 in each time point*

It is widely recognized, that the lower the particle size, the higher the surface area will be. Particles with a diameter below 100 µm is known to be more cohesive and this leads to agglomeration, which can affect the mixing process and also the homogeneity of the interactive mixtures (Bridgwater, 1976, Venables and Wells, 2001). This may explain why the mixture with the lowest carrier particle size showed the poorest degree of homogeneity. This phenomenon has also been described for interactive mixtures (Swaminathan and Kildsig, 2002), where mixing of micronized drug (1 %) with carrier particles with mean sizes of 36, 60 and 103 µm, showed that the mixture containing the largest particle size fraction showed better homogeneity than the others. The electrostatic behavior was also observed in the current project as previously described during the powder characterization of the 63-90 µm particle size fraction. All together it may be concluded that the highest degree of homogeneity can be obtained for an interactive mixture using micronized drug and carrier particles somewhere between 125 and 250 µm, since both size fractions below as well as above obtained lower degree of homogeneity.

5.6 Characterization of 2 mm mini-tablets

5.6.1 Uniformity of mass and content

Mini-tablets were prepared from the interactive mixtures (48 hours) of the three different carrier particle sizes. It is important that the mass variation of the mini-tablets (ODMTs) is low, to ensure low variation in the amount of active substance in the mini-tablets (content uniformity). According to the European Pharmacopoeia not more than 2 tablets can deviate from the average mass by more than 10 % and no tablets can deviate from the average mass by more than 20 %, when the tablet mass is 80 mg or less (European Pharmacopoeia 7.8, chapter 2.9.5 – Uniformity of mass of single-dose preparations). As seen by the highest percentage of deviation from average mass in Table 6, no deviations came close to 10 %, which means that all batches complied with the test. The difference observed in average mass was most probably due to a difference in volume or density of the carrier particles. The tablets were made by volumetric filling of the die at a constant fill-depth. When filling with the powder mixture of the two largest particle size fractions (90-125 μm and 125-180 μm), some of the powder would not fit into the die and was pushed aside. This is the reason for the differences in average mass. The low standard deviation shows that the filling method used was appropriate.

Table 6: *Test of uniformity of mass of 2 mm mini-tablets tablets prepared from mannitol of different particle size fractions and 1 % (w/w) sodium salicylate (European Pharmacopoeia 7.8, chapter 2.9.5 – Uniformity of mass of single-dose preparations)*

Particle size fraction (μm)	Average mass (mg)	Highest deviation (%)	Comply with the test?
63-90	6.98±0.11	2.84	Yes
90-125	6.77±0.08	2.97	Yes
125-180	6.61±0.11	4.49	Yes

Analyzing the uniformity of content of the mini-tablets was important, especially because of the small size of the single units. The test of uniformity of content of single dose preparations will be approved if all of the individual contents are between 85 % and 115 % of the average content (European Pharmacopoeia 7.8, 2.9.6 – Uniformity of content of single-dose preparations). Table 7 showed that all three mini-tablet batches complied with this test by a clear margin. In general, the average content of sodium salicylate (%) was closest to the theoretical value in the mini-tablets made from the 125-180 μm particle size fraction. This fraction also showed the best homogeneity results. The result is however, not statistically significant ($p>0.05$) due to the low number ($n=10$) of mini-tablets tested.

Table 7: *Test of uniformity of content of 2 mm mini-tablets prepared from mannitol of different particle size fractions and 1 % (w/w) sodium salicylate (European Pharmacopoeia 7.8, chapter 2.9.6 – Uniformity of content of single-dose preparations)*

Particle size fraction (μm)	**Average content of sodium salicylate (%)**	**Highest deviation from average content (%)**	**Comply with the test?**
63-90	0.979±0.048	7.26	Yes
90-125	0.982±0.032	4.44	Yes
125-180	1.001±0.041	6.87	Yes

5.6.2 Mechanical strength of the orally disintegrating mini-tablets

The pressure used during preparation of the mini-tablets was constant at approximately 100 MPa (4.7 kN) as seen in Table 8, with low standard deviation, which is preferable in order to compare the different batches.

Table 8: *Characteristics of 2 mm mini-tablets prepared from 1 % (w/w) sodium salicylate and mannitol of different particle fractions; all values are given as mean+SD (n=30)*

Particle size fraction (µm)	**Compaction force (kN)***	**Average mass (mg)**	**Average height (mm)**	**Crushing strength (N)**	**Tensile strength (N/mm^2)**
63-90	4.74±0.06	6.98±0.11	2.18±0.01	12.70±1.81	1.85±0.26
90-125	4.67±0.12	6.77±0.08	2.14±0.03	12.63±1.64	1.88±0.25
125-180	4.68±0.11	6.61±0.11	2.08±0.02	14.70±2.52	2.25±0.39

* n=6 (number of strokes to prepare mini-tablets)

The average height of the mini-tablets is decreasing with increasing particle size. This is due to the difference in mass of the tablets, which is a result of difference in volume/density as discussed under 5.6.1. The low standard deviation support that the chosen filling method was suitable.

The measured crushing strength and the calculated tensile strength showed no difference between the tablets made from powder mixtures based on the particle size fraction 63-90 µm and 90-125 µm. The tablets made from powder mixture based on the particle size fraction 125-180 µm showed a statistically significant difference ($p<0.05$) in tensile strength compared to the other two. In theory, one might have expected the opposite tendency. The lower the particle size, the higher the surface area. This increases possible contact points between particles, which usually gives higher crushing and tensile strength (Weyenberg *et al*., 2005). All of the mini-tablets

were prepared on the same day, stored under equal conditions and were also tested on the same day. Therefore it is difficult to explain why these results did not comply with theory.

The measured crushing strength values are however acceptable for all the individual batches and well above the crushing strength of 7 N as Stoltenberg and Breitkreutz suggested as acceptable for this type of disintegrating mini-tablets (Stoltenberg and Breitkreutz, 2011). All batches of the current study have accomplished this goal.

The friability test is another test of the mechanical strength of tablets. This will test the tablets' strength against abrasion when mechanical stress is applied. When performing the test as described earlier, in 4.10.5, there was no measurable loss of mass after the friability test of 20 mini-tablets. The results were the same for all three batches. It should however be kept in mind that the very low losses can be hard to detect, even with the use of analytical balances. The mass of the 20 mini-tablets was very low (appx. 0.1315 - 0.1385 g), and 1 % of this is only approximately 0.0013 g (1.3 mg). According to the European Pharmacopoeia, the maximum accepted loss of mass during the friability test is 1 %. It is therefore not possible to conclude if the test was passed (European Pharmacopoeia 7.8, chapter 2.9.7 – Friability of uncoated tablets).

In order to get a better measurement of friability a different method could have been used. Mini-tablets are so small that they are more similar to multi-particulates like pellets than regular tablets. Therefore a method that takes this into consideration, like the one used by Stoltenberg and Breitkreutz could have been a more suitable procedure. According to Stoltenberg and Breitkreutz the alternative friability method was first described by Sucker and co-workers in 1982 (Stoltenberg and Breitkreutz, 2011). In principle they place a given amount of mini-tablets (1 g) in a snap-vial on a mechanical shaker, and shake the vial for a given period of time at a given vibration-intensity before the mini-tablets are dedusted and the weight loss determined. A 1 % maximum loss of mass was seen as acceptable.

5.6.3 Test of disintegration time of the orally disintegrating mini-tablets

As explained above in the introduction (2.12.3) conventional disintegration tests are generally not applied for mini-tablets since their size is so small that they will slide through the meshes in the bottom of the pharmacopoeial disintegration tester. Therefore, the simulated wetting time was used as an approximation. The result of the simulated wetting time (s) is illustrated in Figure 16.

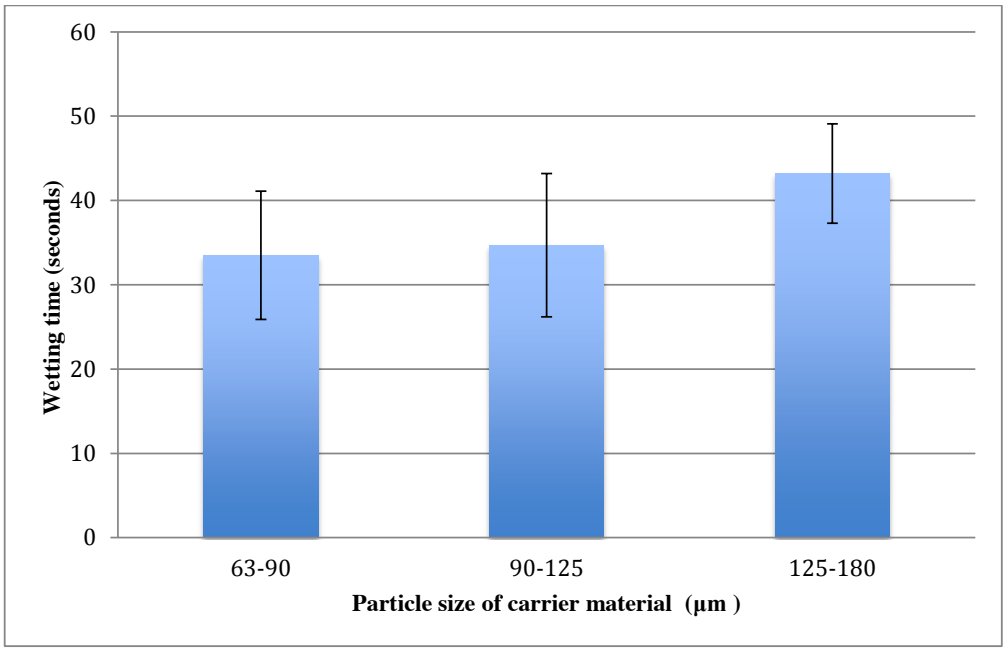


Figure 16: *Simulated wetting time (seconds) as a function of the particle size of the carrier material (µm) used in the different batches of 2 mm ODMTs (n=10)*

The results showed similar wetting time for the batches of mini-tablets prepared from the two lowest particle size fractions of carrier material and a significantly ($p<0.05$) higher wetting time was observed for the mini-tablets prepared from the carrier material of the largest particle size fraction (125-180 µm) compared to the other two. This correlates well to the difference in mechanical strength described above (5.6.2). As stated earlier (in 2.10), the European Pharmacopoeia and US Food and Drug Administration have different criteria for disintegration time of orally disintegrating tablets. The criteria of disintegration within 3 minutes set by the European Pharmacopoeia was fulfilled for all batches, but the criteria of disintegration within 30

seconds set by the US Food and Drug Administration was not fulfilled. Although the simulated wetting time of the similar mini-tablets prepared by Stoltenberg and Breitkreutz showed shorter wetting times, even for the highest pressure used, there were differences in the composition of the tablets that can explain the difference in simulated wetting time (Stoltenberg and Breitkreutz, 2011). The chosen carrier materials used in their studies were specifically made for disintegration purposes since they used mannitols that were co-processed with disintegrants. Disintegrants are included because they swell and expand upon contact with water, resulting in a faster disintegration of the tablet. Pearlitol® 100SD, the carrier material used in this project, is a pure mannitol quality. Therefore, slower disintegration and simulated wetting time must be expected. Another factor that may have an effect on the simulated wetting time is the choice of lubricant. The chosen lubricant in the current project was magnesium stearate, which is a hydrophobic substance. Magnesium stearate will prolong the simulated wetting time in aqueous medium (blue dye also has hydrophilic nature). Stoltenberg and Breitkreutz used sodium stearyl fumarate as lubricant, which according to tests of simulated wetting time was superior to magnesium stearate.

5.7 Effect of compaction pressure on mechanical strength and disintegration time

To further study the effect of compaction pressure on mechanical strength and disintegration time, 6 mm flat-faced tablets were prepared from the interactive mixture prepared from 1 % (w/w) sodium salicylate and the 90-125 µm particle size fraction of mannitol, using different pressures (35, 50 and 100 MPa corresponding to forces of 1.0, 1.4 and 2.8 kN). The results are summarised in Table 9.

Table 9: *Characteristics of 6 mm orally disintegrating (flat-faced) tablets prepared from 1 % (w/w) sodium salicylate and mannitol fraction 90-125 µm. Mixed in Turbula, 48 h. Results are given as mean±SD; n=30-40*

Compaction pressure (MPa)	**Crushing strength (N)**	**Tablet height (mm)**	**Tensile strength (N/mm^2)**	**Disintegration time (s)****	
				Method 1 (disintegration test apparatus)	Method 2 (shaking water bath)
35	16.2±2.4	2.66±0.02	0.65±0.10	5-12	17-58
50	18.2±2.8	2.53±0.02	0.76±0.12	50-63***	21-57
100	44.1±3.5	2.26±0.01	2.07*	16-64	26-73

*Tensile strength was calculated based on average height and average crushing strength for all characterized tablets. This value is therefore given without SD. For 35 and 50 MPa each of the ten tablets used to calculate tensile strength were characterized individually.

**Time (s) until first and last tablet were fully disintegrated, n=6.

***n=5 tablets.

The results of average crushing strength, tablet height and the calculated tensile strength reflect the different pressures used to prepare the tablets. The higher the pressure, the stronger the tablets get. This result was expected, but we can see from the results of the two lowest pressures that the difference was small. It does not seem to be a linear relationship between pressure and tensile strength (Figure 17).

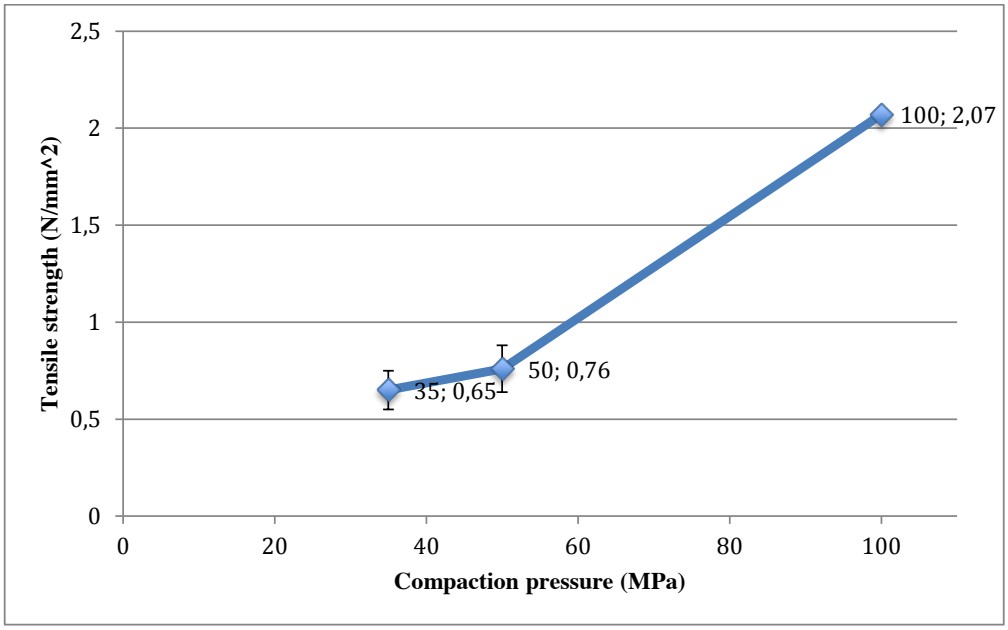


Figure 17: *Effect of compaction pressure (MPa) on the tensile strength of 6 mm flat-faced tablets prepared from 1 % (w/w) sodium salicylate and mannitol fraction 90-125 µm mixed in Turbula mixer for 48 hours; n=10*

According to several other researchers the crushing strength is expected to increase significantly, even exponentially, at lower pressures but reaches a constant level at higher pressures (Riippi *et al*., 1998, Marais *et al*., 2003). In the current project the increase in pressure does result in higher mechanical strength (in Figure 17 showed as tensile strength). More tests are necessary to conclude how the relationship between compaction pressure and mechanical strength develops from low to high compaction pressures with this particular formulation.

As seen in Table 9 no clear differences could be determined in disintegration time related on the compaction pressure using the shaking water bath method (method 2). The mechanical stress the tablets were subjected to in this test may have been too small to achieve reliable results. The standard pharmacopoeial method (method 1), where the stress on the tablets are higher showed lower disintegration times for the tablets prepared at 35 MPa as compared to method 2. Also, detectable differences were found in disintegration between tablets prepared at high and low pressure. In theory, the disintegration should lower at lower compaction pressure. Higher porosity

of the tablet will allow enhanced penetration of the surrounding liquid (Marais *et al*., 2003). The results on disintegration time in this study supports the idea presented by (Park *et al*., 2008) that the current pharmacopoeial disintegration method is not capable of capturing small differences in fast disintegrating tablets and that new methods should be investigated. The proposed simulated wetting test, which was used for the 2 mm orally disintegrating mini-tablets, seems like a suitable alternative.

5.8 Using interactive mixtures to prepare orally disintegrating mini-tablets with high dose-homogeneity for use in children

In the current project interactive mixing was used as a mean to achieve high dose-homogeneity in powder mixtures for the preparation of 2 mm orally disintegrating mini-tablets. As stated earlier, high dose-homogeneity is essential when administering drugs to children and since the single unit of this particular dosage form is so small, it is extremely important to ensure that each mini-tablet contains the stated amount of drug with little variation. The reason for this is so that the effect of the drug can be highly predictable in order to get the wanted effect and lower the risk of side effects and toxicity issues. One limitation is the fact that both interactive mixtures and orally disintegrating mini-tablets are most suited for potent drugs, which are given in a low dose.

Based on the characterization of the interactive powder mixtures prepared from 1 % (w/w) sodium salicylate and mannitol of different size fractions, it was seen that even with small sample sizes (3 mg), the standard deviation of the normalized values were small (down to 3.02±0.16 %) after a mixing time of 48 hours. High homogeneity was also seen in the characterization of the prepared 2 mm mini-tablets, where all batches complied with the criteria of the European Pharmacopoeia without problems. An average content of 1.001±0.041 % sodium salicylate was found in the best batch and this showed that the interactive mixing process was highly successful at achieving mini-tablets with high dose-homogeneity. The mini-tablet characteristics such as the test of disintegration time and mechanical strength also met the desired quality criteria, with the exception of the friability test. The test of disintegration time showed disintegration well within 60 seconds and a better (shorter) disintegration time could

most likely have been accomplished by using a hydrophilic lubricant instead of the hydrophobic magnesium stearate. In real life though, the *in vivo* disintegration time will probably be shorter because of the lack of mechanical stress applied in the simulated wetting test.

Using interactive mixtures to obtain orally disintegrating mini-tablets showed promising results and should soon be ready for testing on an industrial scale so that this dosage form, with the potential of better personalized treatment, can reach the market and ensure more fitted pharmacological treatment of children of all ages.

6. Conclusion

High dose-homogeneity is a prerequisite for the use of mini-tablets as single units, which is the ultimate goal of the project. Interactive mixtures were investigated as a means to obtain high dose-homogeneity.

The effect of mixing time on the homogeneity of the interactive mixtures was clearly seen. On the investigated scale, mixing times of at least 24 hours was required in order to ensure stable interactive mixtures with high homogeneity. Mixing in tumbling mixer (predominately diffusive mixing) was found to be superior over planetary mixer (predominately convective mixing). Also, the carrier particle size had an effect on the homogeneity of the interactive mixtures. The highest particle size fraction (125-180 μm) showed better results of homogeneity (lower degree of variation) than the other two particle size fractions (63-90 μm and 90-125 μm). Based on comparison of these results and literature, it was suggested that the optimal particle size for preparation of interactive mixtures of this kind is in the size range between 125 μm and 250 μm. Two sampling sizes (3 mg and 20 mg) were investigated, but no significant difference was identified on the degree of homogeneity. However, based on the small size of the mini-tablets to be made from the interactive mixtures, the 3 mg sample size is regarded as the safer choice.

The orally disintegrating mini-tablets (2 mm diameter), prepared from the interactive mixtures, showed high mass and dose uniformity, sufficient mechanical strength and disintegration times below 60 seconds for all investigated formulations. All tests, with the exception of test of friability (due to inappropriate testing method), met the standards of the European Pharmacopoeia.

In addition, the effect of compaction pressure on the mechanical strength and disintegration time was studied by the use of 6 mm flat-faced tablets. The results showed that an increase in compaction pressure gave an increase mechanical strength, but the effect on disintegration time gave no conclusions most likely because of unsuitable testing methods.

In conclusion, interactive mixtures are suitable means to prepare mini-tablets with high dose-homogeneity. Orally disintegrating mini-tablets of high dose-uniformity, suitable mechanical strength and disintegration times, which might serve as an appropriate dosage form for children, were successfully prepared.

7. Future perspectives

- Investigate whether co-processed mannitol carrier particles can be advantageous in preparing the interactive mixtures, with respect to degree of homogeneity of the mixture and improved disintegration time of the orally disintegrating mini-tablets, without sacrificing the mechanical strength.

- Include other excipients in the powder mixture that improves disintegration time and taste.

- Study the acceptability of multiple dosing of orally disintegrating mini-tablets in children and look into which dosage devices are most suitable for administration of this dosage form.

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