Comparison of properties on Orally Disintegrating Tablets (ODTs) produced by direct compression or fluid bed granulation

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Abstract

Orally disintegrating tablets (ODTs) is a popular drug delivery system as they dissolve in the mouth, usually within seconds which enables easy medication for patients with problem swallowing. In this thesis properties of ODTs were compared when produced with direct compression of the excipients or the excipients were pretreated to form granules in a fluid bed granulator prior to tableting.

By altering the excipients used and the process parameters during fluid bed granulation it was concluded that the choice of polyol as the main filler in the tablet mostly affected the properties of both the granules and the produced tablets. This was also concluded for the tablets produced with direct compression. The granulation process increased the flowability of the particles.

The disintegration time was also mostly affected by the filler and not the used super disintegrants. Tablets containing mannitol disintegrate faster than tablets with isomalt or xylitol and is also less friable. From the measured *in vivo* disintegration times an *in vitro* method was developed with the aim to give a better *in vitro-in vivo* correlation (IVIVC) compared to existing methods. The developed method is applicable for tablets containing mannitol as they swell when disintegrating. For this a texture analyzer was used which applied and measured the force on tablets when swelling.

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Thank you,

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Contents

1 Introduction

1.1 Overview

The most common formulation used as a drug delivery system are tablets, due to the easy self-administration and production. Tablets can be produced with different properties, one specific tablet formulation gaining more popularity during the last 20 years is orally disintegrating tablets (ODTs) (Bharawaj et al., 2010). ODTs are solid tablets dissolving rapidly in the mouth, usually within seconds, without additional water. The main advantage of ODTs as a drug delivery system is that there is no need to swallow the tablets. This enables easy medication for children, elderly and patients with problem swallowing. ODTs consists of the active pharmaceutical ingredient (API), often in a small amount together with excipients that increase the volume of the tablet and provide the desired properties for the tablet. ODTs can also improve the bioavailability of the API compared to traditional oral tablets since the uptake starts already in the mouth and throat (Abay and Ugurlu, 2015).

The properties of the ODT such as disintegration time, friability and hardness depend on the excipients used in the tablet and the production method used. By changing the excipients and their concentration the tablet can get desired properties. Tablets can be produced with excipients in powder form directly or the powders can be granulated prior to tableting. The chosen production process and parameters may also affect the properties of the ODT.

1.2 Aim & objective

The aim of the thesis was to examine how the friability, disintegration time and required compression force of ODTs are affected when produced with granules, from a fluid bed granulator, or direct compression, using excipients in powder form. The aim was also to examine differences in particles size, moisture content, flowability and morphology between granules both when altering the excipients used and when altering the process parameters for the fluid bed granulation.

Lastly the aim was to develop an *in vitro* method for detection of disintegration time with a stronger *in vitro-in vivo* correlation (IVIVC) than current methods using a texture analyzer.

1 Background

1.4 Orally Disintegrating Tablets

ODTs are solid tablets disintegrating rapidly in the mouth, usually within seconds to minutes, without additional water. According to the European Pharmacopoeia (2018) ODTs are defined as uncoated tablets disintegrating within 3 minutes in water. The US Pharmacopoeia do not have a specific time limit for ODTs, however, describes them as tablets with characteristics both from liquid and solid tablets (Ghourichay et al., 2021). Neither the Food and Drug Administration (FDA) have a set time defining an ODT, but refer to it as a rapidly dissolving oral tablet and recommends a disintegration within 30 s (Food and Drug Administration, 2008). The ODT formulation consists of the API, often in a small amount together with excipients increasing the volume of the tablet and providing the desired properties for the tablet. ODTs are gaining more popularity as a drug delivery system due to the easy self-administration, the patient can avoid swallowing the tablet (Abay and Ugurlu, 2015).

ODTs can be produced by several different methods, the simplest method is called direct compression where the powder of excipients and API is directly compressed into solid tablets. The powders can also be pretreated to form granules which are further compressed into solid tablets. The advantage of granulating the powder before compression into tablets is that the mixture of excipients is more homogenous and layering of the particles are avoided. Also, the flow properties may be improved with suitable excipients during granulation (Morin and Briens, 2014). The flow properties can also depend on and be modified by the process parameters to control uniformity of the particles, size, density and moisture content.

Another common method to produce ODTs are lyophilization or freeze drying. In lyophilization the formula is dissolved in liquid before froze in vacuum. During freezing the liquid sublime and solid, dry tablets are formed. This method produces tablets with extremely fast disintegration time and often the lack of granules in the tablet provides a better mouth feel for the patient (Anup, Thakkar and Misra, 2018). The drawback with lyophilization is the complex and expensive method (Srivastava and Mishra, 2010) compared to fluid bed granulation which is a wet granulation method where granules are produced and dried in one single container limiting the process steps and decreasing the production cost (Srivastava and Mishra, 2010).

1.5 Direct compression

A common method for making solid tablets is direct compression. Direct compression is a simple method which uses high pressure to compress the powder of all excipients and the API into tablets (Iqubal et al., 2014). In direct compression the number of process steps are limited which makes it more efficient and decreases the production cost. Also, the formula is not exposed to heating or dissolution in a liquid which may affect the characteristics of the API (Dinesh et al., 2012). Another advantage of direct compression compared to wet granulation is that the API is rapidly available for uptake by the body and no disintegration of granules are necessary which may be a rate limiting step for tablets produced by wet granulation (Iqubal et al., 2014). A drawback with direct compression is that the particles may segregate based on size and the homogeneity of the product decreases (Nayak and Manna, 2011). Also drugs with low flowability may need to enhance their flowability with an additional process step to improve the properties of the tablet (Morin and Briens, 2014).

1.6 Fluid bed granulation

Fluid bed granulation is a wet granulation method used to granulate fine particles into larger agglomerates. There are mainly two set-ups for the wet granulation process, top spray and Wurster (bottom) spray. Top spray is the most common set-up for pharmaceutical production of granules while Wurster spray is common for coating of particles. In both processes an air stream sprays the particles up in the container while a liquid stream wets the particle either spraying from the top or the bottom. To optimize the granulation the liquid spray rate and air pressure needs to be controlled (Srivastava and Mishra, 2018).

The granulation process takes place in three different steps starting with wetting and nucleation of the particles. This initiates the formation of agglomerates by liquid coating the particles which enables liquid bridges to be formed between solid particles. Secondly, as more liquid is added the excipients may dissolve and form larger granules (Fig 2.1). Lastly, the liquid spray is switched off and the granules are dried with the air flow. During drying large granules will break down into smaller particles by attrition, however bonds strong enough will remain and solid granule are produced (Agrawal and Naveen, 2011).

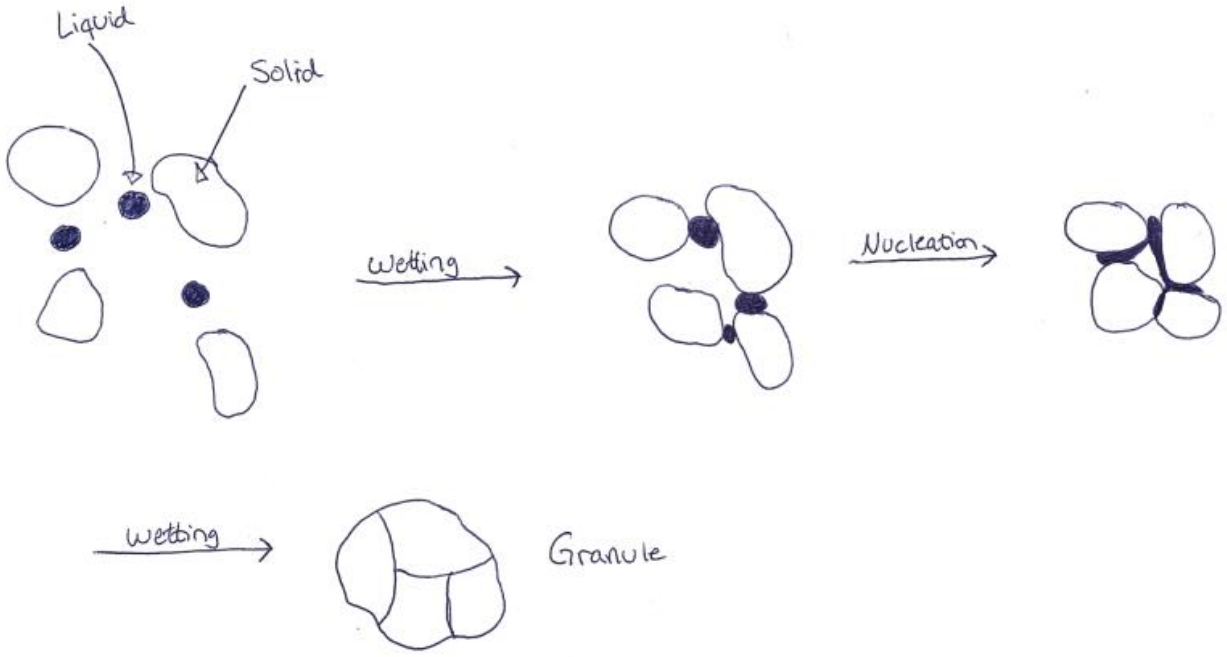


Figure 2.1. Granule growth by wetting the particles.

To produce a granule with properties suitable for tableting excipients are added together with the API. The excipients have several functions, partly they increase the volume of the tablet since the volume of API is usually very small. This is called a filler or diluent. Secondly excipients ensure that the formula is suitable for granulation by acting as a binder to help the particles forming granules. The binder can either be added as a powder or used in the liquid spray. Since ODTs are supposed to easily disintegrate in contact with liquid they also need a disintegrant or super disintegrant which allows fast disintegration in contact with liquid.

2.4 Excipients

2.4.1 Fillers

Polyols can be used as fillers to dilute the concentration of the API in the tablet and to improve the taste of the ODT since they are sweet and inert towards both the API and the body. Mannitol, isomalt and xylitol (Fig. 2.2) are polyols with different properties readily used in the pharma industry for producing solid tablets (Mitchell, 2006).

Xylitol is the sweetest of the three polyols, almost as sweet as sugar while mannitol and isomalt gives about 45-70 % of the sweetness from sugar. (Lenhart and Chey, 2017). Xylitol is also the most soluble, about 67 % (w/w) while mannitol is the least soluble of the three, about 20 % (w/w) and isomalt has a solubility of 25 % (w/w) (Mitchell, 2006). A more soluble excipient makes the granules more uniform in particle size and decreases the friability (Hiremath, Nuguru and Agrahari, 2019). Both mannitol and isomalt are non-hygroscopic which is an advantage when storing the produced tablets since they have a low water absorbance tendency. Again, xylitol differs from the other two and is relatively hygroscopic (Mitchell, 2006). Both mannitol, isomalt and xylitol shows good compressibility which makes them suitable for production of solid tablets (Bin et al., 2020), (Lura et al., 2019).

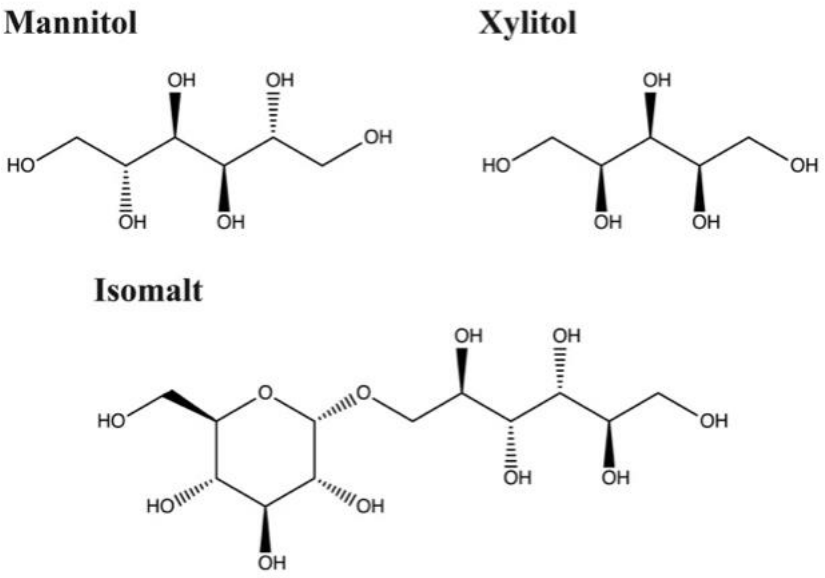


Figure 2.2. Polyols used as fillers and binders (Lenhart and Chey, 2017).

Another type of molecule acting as both filler, binder and disintegrant is microcrystalline cellulose (MCC) (Roquette, 2023). MCC may increase the flow properties of the granules (Yassin et al., 2015). On the contrary to mannitol and isomalt, MCC is highly hygroscopic which enables it to absorb moisture (Hiremath, Nuguru and Agrahari, 2019). MCC, on the contrary to the polyols, is insoluble in water (FAO, 1997).

2.4.2 Binders

Binders enhance the binding between the molecules and facilitates formation of larger agglomerates. The binder can be added as a powder or in liquid form, however the bonds are formed by establishing a wet surface on the particles and make them agglomerate into larger

particles facilitated by the binder. Altering the binder may affect the size of the granule since they can bind them with different strength (Dürig and Karan, 2019).

A commonly used binder is pregelatinized starch which is produced by rupturing the native structure of starch. The modifications increase solubility, flowability and compressibility compared to the native starch and makes it a suitable binder, however it can also act as a disintegrant (Dürig and Karan, 2019). When partially pregelatinized the starch receive both soluble and insoluble properties. Pregelatinized starch is available as Lycatab PGS (fully pregelatinized) from Roquette and Starch 1500 (partially pregelatinized) from Colorcon.

2.4.3 Lubricants

Lubricants are added to the formulation before tableting to enhance the flowability and decrease the friction on the equipment during tableting by coating the particles. A commonly used lubricant is magnesium stearate which consists of a charged magnesium molecule interacting with the powder particles or granules and two fatty acids of stearic or palmitic acid which locates away from the particle and form a hydrophobic surface which gives the particle glidant properties (Hiremath, Nuguru and Agrahari, 2019).

2.4.4 Disintegrants

Disintegrants or super disintegrants ensure that the ODT disintegrate rapidly once in contact with liquid. There are mainly four different mechanisms by which the disintegrants act to make the tablet dissolve, called wicking, swelling, elastic recovery and repulsion.

The first disintegrant used was starch which is still used in different modified forms as both disintegrant and super disintegrant (Desai, Liew and Heng, 2016). Starch can act as a disintegrant if partially pregelatinized, if fully pregelatinized it will dissolve in water and is unable to act as a disintegrant. When partially pregelatinized the starch have both soluble properties from the gelatinization process and insoluble properties from the native starch, the insoluble properties ensuring that disintegration is possible (Hiremath, Nuguru and Agrahari, 2019).

Today, two of the most used disintegrants are croscarmellose sodium (CCS) and sodium starch glycolate (SSG) (Markl and Zeitler, 2017), both are synthetic polymers of modified cellulose and starch respectively (Berardi, Janssen and Dickhoff, 2022). Both CCS and SSG are modified to reduce the solubility and viscosity compared to the native molecule. This results in controlled swelling of the disintegrant in contact with water (Berardi, Janssen and Dickhoff, 2022). SSG acts mainly by swelling, it has a hydrophilic carboxymethyl group which is embedded in a hydrophobic phosphate ester, and in contact with water it swells and breaks the intermolecular bonds of the granules (Dilebo and Gabriel, 2019). CCS have less swelling capacity than SSG due to that the structure of cellulose is more linear while the starch structure of SSG is more branched. This allows less space for water to enter the complex of CCS and thus the swelling decreases (Berardi, Janssen and Dickhoff, 2022). Instead, the dominating disintegration mechanism for CCS is wicking. By wicking, capillary forces draw water inside the tablet where the water disrupts interparticular bonds and dissolve the tablet (Sabath, 2023).

Crospovidone is another typical disintegrant which is hydrophilic, however with poor solubility in water and low viscosity. Due to the lower viscosity and solubility the disintegrant acts mainly by wicking. A lower viscosity enables easier water penetration of the tablet and a

faster disintegration is possible (Berardi, Janssen and Dickhoff, 2022). Crospovidone may also act by swelling and elastic recovery (Sabath, 2023), although the swelling capacity in crospovidone is limited (Berardi, Janssen and Dickhoff, 2022). The swelling effect is limited for soluble particles and for highly porous particles containing void spaces (Zhou et al., 2014). Elastic recovery or shape recovery is when the particles can regain their original shape they had before compression into tablets, once exposed to liquid. When changing shape stored energy is released and the tablet disintegrate (Berardi et al., 2021).

2.5 Disintegration

As mentioned earlier, there are mainly four different mechanisms which contribute to disintegration or dissolution of a tablet, wicking, swelling, elastic recovery and repulsion. Each of them contributes to dissolution of the tablet and the API becomes available for uptake in the body. Wicking is when water penetrates the tablet with help of capillary forces and disrupt it. The wicking can in turn initiate swelling, strain recovery and repulsion (Fig. 2.3). Mostly wicking is the rate limiting step of the disintegration time (Markl and Zeitler, 2017).

Once liquid has penetrated the tablet the disintegrants can absorb the moisture and expand. When expanding the pressure increases which cause van der Waals bonds and intermolecular forces to disrupt (Markl and Zeitler, 2017).

Elastic recovery or strain recovery is when the molecules within the tablet return to their native form and the solid formation is ruptured. These releases stored energy and the entropy increases (Markl and Zeitler, 2017).

Lastly, a mechanism with less impact than wicking and swelling, is electrostatic forces within the tablet. The electrostatic forces can contribute to repulsion within the tablet which also speed up the disintegration time (Mohanachandran et al., 2011).

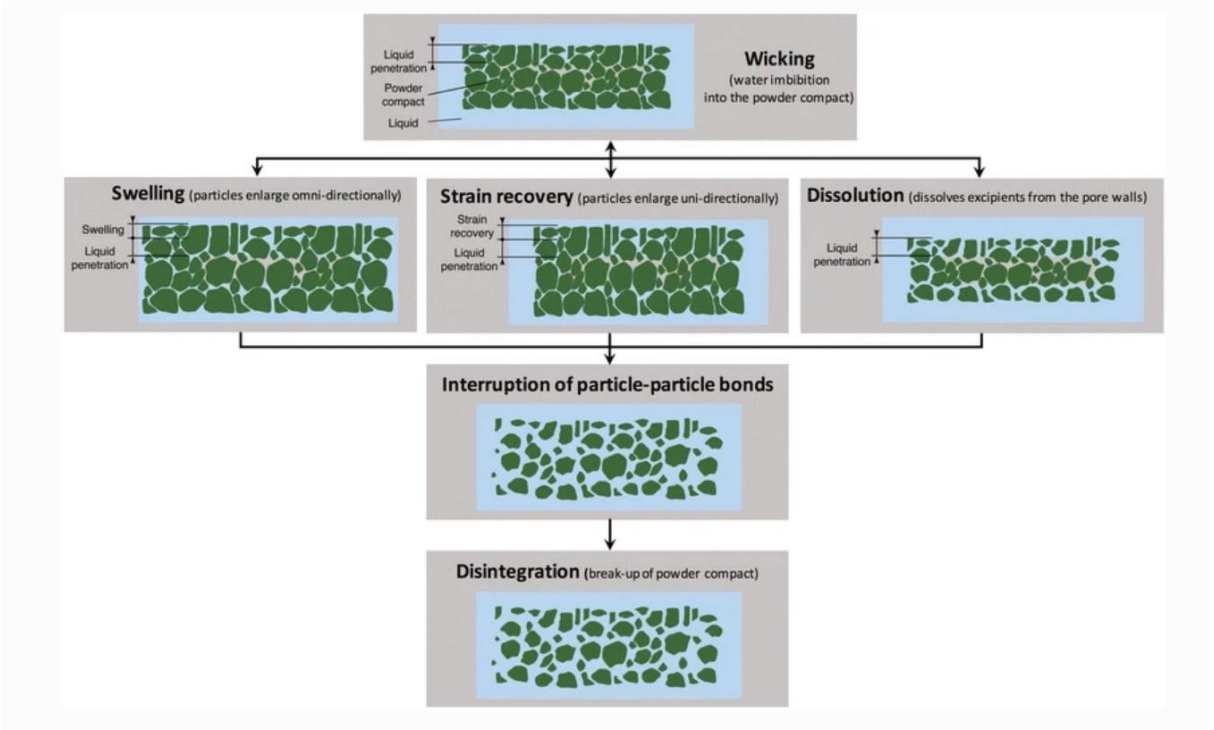


Figure 2.3. The disintegration mechanism wicking, swelling and strain recovery (Markl and Zeitler, 2017).

The *in vitro* method described for measuring the disintegration time of ODTs in the European Pharmacopeia uses a water bath of approximately 800 ml for the dissolution of tablets during agitation (European Pharmacopoeia, 2022). With this method the tablets are dissolved rapidly, and it may be difficult to detect small differences between tablets. According to the Ph. Eur., an ODT should dissolve within 3 min while USP defines it as a tablet dissolving usually within 30 s (European Pharmacopoeia, 2018; FDA, 2008).

Newer methods with parameters more similar to the conditions in the mouth have been tested. A texture analyzer is an instrument which can measure the swelling of the tablet with a probe sensitive to changes in force when the tablet expands after liquid addition. When the tablet is completely dissolved the force on the probe approaches zero and the disintegration time can be detected. This method was shown to give a similar result compared to the *in vivo* disintegration time from healthy people. Therefore, this method shows a good *in vitro-in vivo* correlation (IVIVC) (Szakonyi and Zelkó, 2013).

2 Materials and Methods

3.1 Materials

The raw material of mannitol (Pearlitol 150 SD), MCC (Microcel-101), croscarmellose sodium (Solutab A), xylitol (Xylisorb XTAB 400) and starch (Lycatab PGS) was received from Roquette. Starch 1500 was received from Colorcon and isomalt (GalenIQ 721) was received from Beneo. Crospovidone (Vivapharm XL-10) and sodium starch glycolate (Vivastar P) was received from JRS Pharma.

3.2 Methods

Nine different compositions of the product (Table 3.1) were granulated and pressed into tablets. One batch was produced of each composition except batch number 2 produced in duplicates. To compare the tablets batch 1, 2, 3 and 7 were also tableted using direct compression where batch 1 was produced in duplicates. To analyze the effect of process parameters in the fluid bed granulator batch 1 was granulated with different settings to air flow and spray rate.

Table 3.1. Composition of the evaluated batches.

Batch	Ingredients	Amount (g)
1	Mannitol	156
	MCC	12
	Starch 1500	20
	Croscarmellose	12
2	Isomalt	156
	MCC	12
	Starch 1500	20
	Croscarmellose	12
3	Xylitol	156
	MCC	12
	Starch 1500	20
	Croscarmellose	12
4	Mannitol	156
	Isomalt	12
	Starch 1500	20
	Croscarmellose	12
5	Mannitol	156
	Xylitol	12
	Starch 1500	20
	Croscarmellose	12
6	Mannitol	156
	MCC	12
	Lycatab PGS	20
	Croscarmellose	12
7	Mannitol	156
	MCC	12
	Starch 1500	20
	Crospovidone	12
	Mannitol	156

8	MCC	12
	Starch 1500	20
	Sodium starch glycolate	12
9	Mannitol	168
	Starch 1500	20
	Croscarmellose	12

3.2.1 Granulation

The granulation of the particles was done using the fluid bed granulator Midi-Glatt with the top spray granulation method. Each batch of 200 g was firstly prepared by sieving the powder through a 710 µm sieve before adding it to the product container. The process parameters were controlled and run with the product container at 30 ºC, the inlet air temperature at 50 ºC, the filter blowout rate was 1 s, atomization pressure was set to 0.8 bar and the inlet air flow was started at 20 m^3/h and increased to 30 m^3/h after adding a few ml of liquid. The liquid spray rate was set to 12.5 ml/min.

During granulation 57 % (w/w) of water was added to the product in accordance with a lab protocol for wet granulation received from Colorcon (Appendix 1). Thereafter the product was dried at 30 ºC for 10 min or until the container temperature was above 28 ºC.

Figure 3.1. Fluid bed granulation set up.

To evaluate the influence of the process parameters a design of experiment was set up using Modde, a software from Sartorius which helps planning and analyzing experiments by Design

of Experiment (DoE). Using the recipe for batch 1, two factors were varied, the air flow and spray rate. The factors were varied on two levels, the air flow was set to 30 m^3/h and 60 m^3/h while the spray rate varied between 5 ml/min and 20 ml/min. Modde designed the experiment with four tests varying the process parameters and three center points (Table 3.2). The other parameters remained as described above for granulation of batch 1-9.

Table 3.2. Process parameters changed for batch 1 to evaluate the effect of the process parameters.

Experiment	**Spray rate (ml/min)**	**Air flow (m^3/h)**
A	5	30
B	20	30
C	5	60
D	20	60
E	12.5	45
F	12.5	45
G	12.5	45

3.2.2 Tableting

All the batches with granules were tableted using the tablet press Korsch XP-1. Also batch 1, 2, 3 and 7 was tableted using direct compression. The granules or powder was sieved through a 710 µm sieve before mixing the formula in a Turbula mixer for 8 minutes at 42 rpm. Next 1 % (w/w) of magnesium stearate was added using a 710 µm sieve and the formula was mixed again for 2 min at 42 rpm. The tablet press was used with round punches with a diameter of 10 mm. The parameters were adjusted to produce tablets weighing 200 mg with a hardness of 20 N.

3.2.3 Granule size distribution

3.2.3.1 Sieving

The size of the granules was determined using a shake sieve (Retsch AS 200 control). Sieves of 710, 500 and 250 µm were stacked on top of each other before the sample of 50-100 g product was added. The shake sieve was run for 10 min with an amplitude of 7 mm/g and the sieves were weighed before and after to determine the ratio of each granule size. The granules were assumed to be evenly distributed so the size distribution of granules was assumed to be represented by one sample since the total product mass was 150-200 g for most batches.

3.2.3.2 Laser diffraction

The laser diffractometer Sympatec Rodos/M was used to characterize the size of granules in the range 4.5-875 µm. A sample of 5-10 ml granules was placed on the platform and transferred with vibrations through the injection vessel before the air pressure accelerate the particles through the laser. The density was estimated to approximately 0.5 g/cm^3, the pressure was set to1 bar and a 4 mm injector was used. Each batch was tested in triplicates except batch 3 which contained too many large particles to be transferred through the injector.

3.2.4 Moisture content

The moisture content was estimated with loss on drying using a Mettler Toledo Moisture analyzer. A sample of 1 g product was dried at 105 ºC and the analysis was done in triplicates.

3.2.5 Flowability

3.2.5.1 Hausner ratio

The flowability was determined from the bulk and tap densities using a stomp volumeter Stav 2003. Before tapping the granules 1250 times a 250 ml cylinder was filled with 220-250 ml granules and the mass was determined. Afterwards, the new volume of granules was noted. The test was performed in duplicates. The mass and the volumes were used to calculate the bulk density (Eq. 3.1) and tap density (Eq. 3.2),

$$\rho_{bulk} = {}^{m}/_{V_{bulk}} \tag{3.1}$$

$$\rho_{tap} = {}^{m}/_{V_{tap}} \tag{3.2}$$

Where ρ_{bulk} is the bulk density, $\rho_{tap}$is the tap density, m is the granule mass, V_{bulk} is the initial volume and V_{tap} is the volume after tapping.

Using the bulk and tap density, the Hausner ratio was calculated (Eq 3.3),

$$Hausner\ ratio = {}^{\rho_{tap}}/_{\rho_{bulk}} \tag{3.3}$$

The Hausner ratio gives an estimate of flowability of the granules (Table 3.3).

Table 3.3. Flow characteristics corresponding to different Hausner ratios.

Flow characteristics	**Hausner Ratio**
Excellent flow	1.00-1.11
Good flow	1.12-1.18
Fair	1.19-1.25
Passable	1.26-1.34
Poor	1.35-1.45
Very poor	1.46-1.59
Very, very poor	>1.60

The porosity of the granules can be calculated using the bulk and tap densities (Eq 3.4),

$$\varepsilon = 1 - {}^{\rho_{bulk}}/_{\rho_{tap}} \tag{3.4}$$

3.2.5.2 Angle of repose

The flowability was also estimated with the angle of repose. Using the angle, the flow characteristics can be estimated from the Carr diagram (Table 3.4). 10 ml of the product was poured through a funnel with a pipe of 3 mm. The height and diameter of poured product was measured (Fig. 3.2).

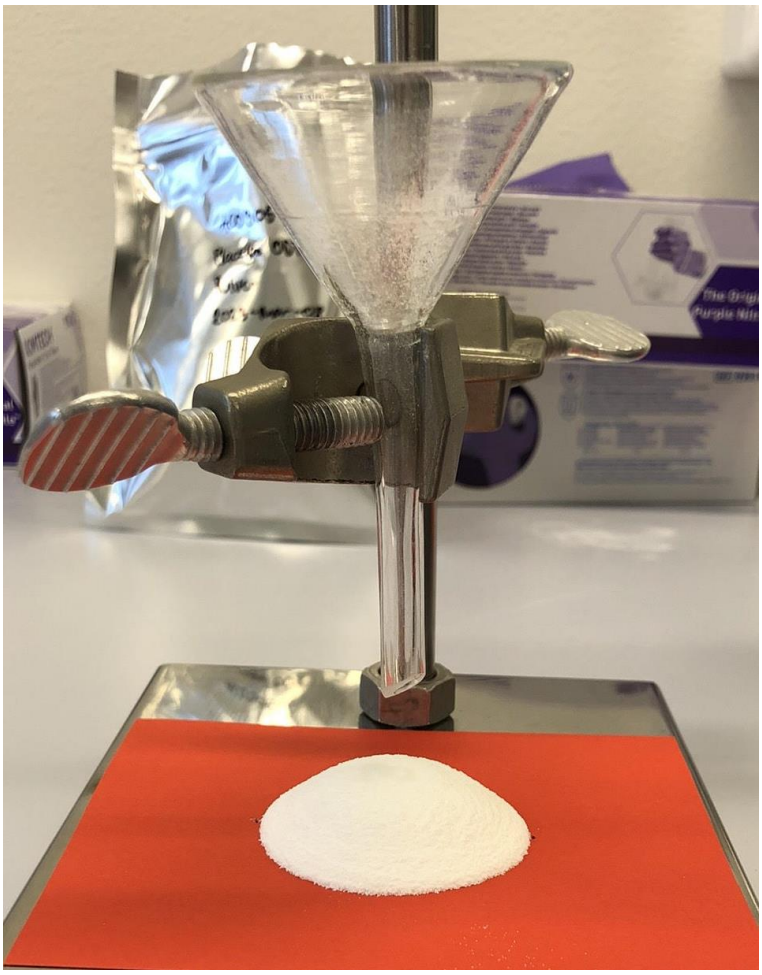


Figure 3.2. Set up for the of angle of repose experiment.

Using the height and radius the angle of repose was estimated (Eq. 3.5),

$$Angle\ of\ repose = \arctan\left(h/r\right) \tag{3.5}$$

Where h is the height of the product and r is the radius.

Table 3.4, Carr diagram showing the flow characteristics of a powder or granulate based on the angle of repose.

Flow characteristics	**Angle of repose**
Very free-flowing	<30º
Free flowing	30-38º
Fair to passable flow	38-45º
Cohesive	45-55º
Very cohesive (non-flowing)	>55º

3.2.6 Scanning electron microscope (SEM)

The granules were viewed in a scanning electron microscope JEOL. Each batch of granules and the raw materials were viewed. The sample was attached to a stump of aluminum which was inserted in the microscope. The images were taken in low vacuum mode at x50, x100, x200, x300 and x650 zooming.

3.2.7 Friability

The friability was determined for all tablets according to Ph. Eur. 2.9.7 (2010) regarding friability of uncoated tablets, using the friabilator Erweka TA 10. Powder and fines were dusted off the tablets before weighing 6.5 g. The friabilator was run for 4 min (100 rotations) before dusting off the tablets again and weighing them, the test was performed in triplicates. The determined weights were used to calculate the friability (Eq. 3.6).

$$F = {(m_{in} - m_{out})}/{m_{in}} \quad (3.6)$$

Where m_{in} is the initial mass and m_{out} is the mass after the run. If F >1.0 % or tablets broke they were considered unsuitable as solid uncoated tablets (European Pharmacopeia, 2010).

3.2.8 *In vitro* disintegration

The disintegration test was performed according to the Ph. Eur. 2.9.1 (2022) describing the disintegration of tablets and capsules using a Disi50 Pharmatron device. The test was performed with a water bath of 800 ml at 37 ºC and 6 tablets with a disc on top to automatically detect the disintegration time. The tablets are classified as ODTs if disintegrating within 3 minutes (European Pharmacopoeia, 2018).

3.2.9 *In vivo* disintegration

The disintegration time was measured *in vivo* using four test people, each testing two tablets per batch. The test person put a tablet in the mouth and measured the time before it was completely disintegrated. The disintegration times measured *in vivo* were used to develop an *in vitro* test giving similar results.

3.2.10 Developed *in vitro* disintegration method

Using the Instron texture analyzer a new *in vitro* disintegration method was developed. The method was developed using a round probe of 10 mm, two filters of 20 mm (Duran filter discs, ε=1) and water for disintegration. The method was developed by testing different water volumes used, different places of adding the water and using different forces from the probe. Also, the use of filters or no filters was considered. The method was considered good when discovering a method giving a disintegration time well correlated to the previously received *in vivo* disintegration times.

3.2.11 Statistical analysis

To calculate the significance of the results statistical calculations were performed on the results from the friability test, the *in vitro* disintegration and the *in vivo* disintegration. A Games-Howell test was performed with the software Minitab statistics using a 95 % confidence interval. The Games-Howell test was used due to variation in sample size between batches. It is a non-parametric test and do not require normal distributed data. However, the sample size is recommended to at least 6 samples per batch why the result is only an indication of the significance.

4 Results

4.1 Granule particle size

4.1.1 Sieving

The granules produced varied in size depending on excipients used in the different batches (Fig. 4.1). The largest granules were produced when the formulation contained isomalt or xylitol as the main filler (batch 2 and 3 respectively). Both batch 2 and 3 had approximately 15 % of their granules larger than 710 µm which was significantly more than any of the other batches. Also, they contained significantly larger ratio of granules between 500-710 µm and 250-500 µm compared to the others. Additionally, batch 2 and 3 contained the smallest fraction, about 10 %, of particles smaller than 250 µm. The batches containing mannitol as the main filler but with isomalt or xylitol in a small volume (batch 4 and 5 respectively) was the second largest with a few percentages of particles between 500-710 µm. Batch 4 containing mannitol and isomalt had 40 % of the particles between 250-500 µm and 57 % smaller than 250 µm. Regarding batch 5, containing mannitol and xylitol, 21 % of the product was between 250-500 µm and 75 % was smaller than 250 µm. It also had 1 % larger than 710 µm.

Comparing batch 1 and 6 which had the same formulation except the binder which was either Starch 1500 (partially pregelatinized starch) or Lycatab PGS (fully pregelatinized starch) they showed very similar particle sizes.

Comparing batch 1 and 7, the super disintegrant was exchanged from croscarmellose sodium to crospovidone. The particle size was smaller when using crospovidone as the super disintegrant, with 90 % of the particles smaller than 250 µm, compared to 85 % using croscarmellose sodium. If instead exchanging the super disintegrant to sodium starch glycolate as done in batch 8, the particles was larger compared to croscarmellose sodium and crospovidone with only 79 % smaller than 250 µm.

In batch 9 no MCC was added, comparing to batch 1 which have the same composition except the MCC shows that batch 9 have more particles ranging from 250-500 µm while batch 1 have more particles <250 µm.

To further analyze the size of the granules, the powder of batch 1 was sieved before granulation. 100 % of the product was smaller than 250 µm before granulation which shows that the fluid bed granulation increases the size of the product.

Altering the process parameters for the air flow and spray rate for the fluid bed granulation for the excipients in batch 1 gives similar particle sizes (Fig 4.2). Batch A produced with an air flow of 30 m^3/h and spray rate of 5 ml/min and batch C (60 m^3/h and 5 ml/min) gave very similar particle sizes, marginally smaller than the particles received from batch 1 which was produced with an air flow of 30 m^3/h and spray rate of 12.5 ml/min. Smaller particles was produced in batch D with both the maximum air flow (60 m3/h) and the maximum spray rate (20 ml/min). The three replicates in batch E-G gave very similar results between batch F and G while batch E gave smaller particles. Batch B could not be measured as the experiment was terminated when the product became too wet and heavy and could not flow in the product container anymore.

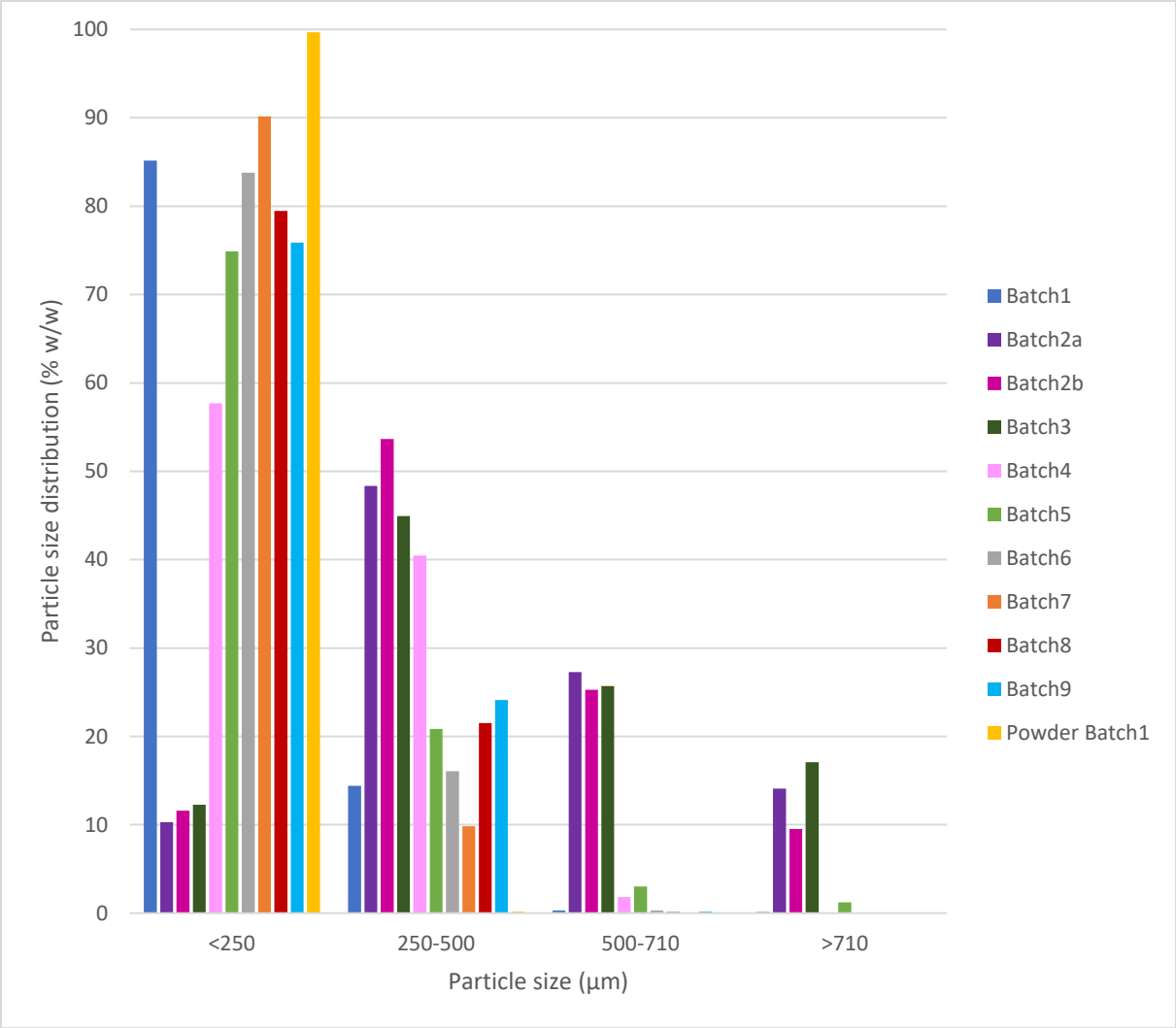


Figure 4.1. Shows the distribution of particle sizes in the 9 different batches of granules, composed of the excipients in table 3.1.

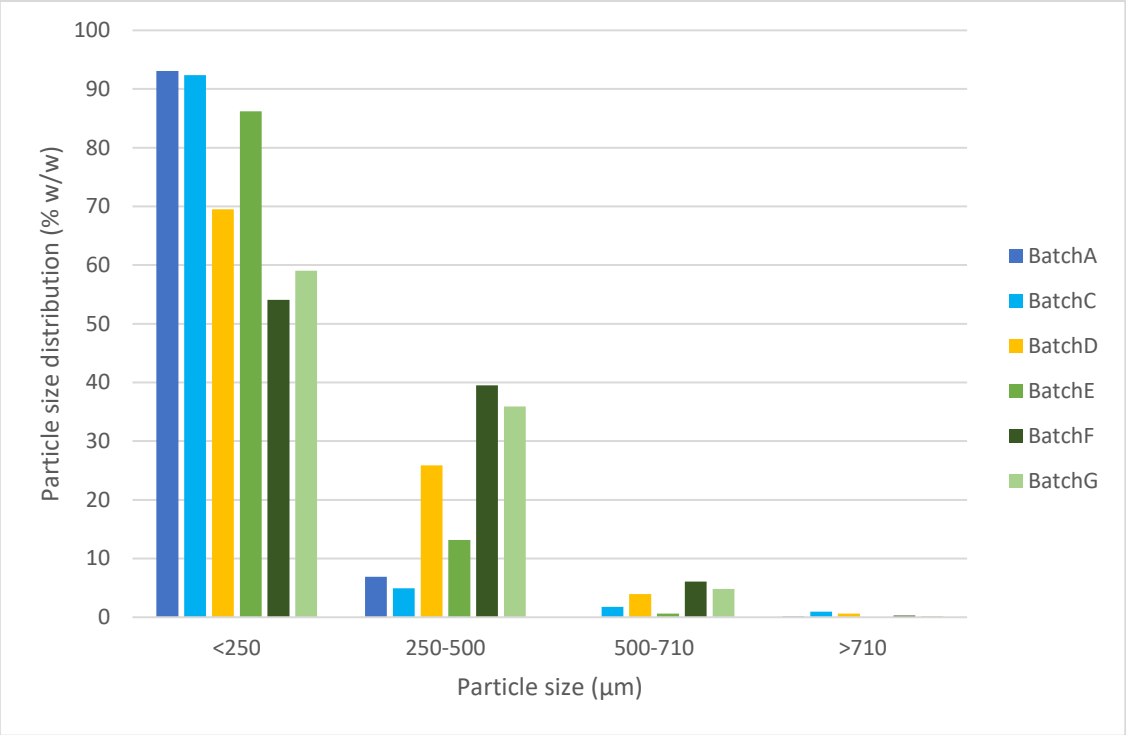


Figure 4.2. Shows the distribution (% w/w) of particles smaller than 250 µm, 250-500 µm, 500-710 µm and larger than 710 µm in batch A-G when altering the process parameters for the fluid bed granulation.

4.1.2 Laser diffraction

The laser diffraction showed that batches containing mannitol as the main filler had similar particle size where 50 % of the particles was smaller than 140-150 µm (Fig. 4.3). Batch 3 could not be measured due to large particles in the granules which clogged the equipment. Batch 2 containing isomalt as the main filler showed larger particles compared to the other batches, with a median value of 360 µm. As the isomalt batch also had larger particles only batch 2a was tested to avoid particles clogging the equipment. Similarly to the sieving results, batch 4 and 5 containing a smaller amount of isomalt and xylitol respectively, had a larger particle size compared to the batches with only mannitol and MCC.

The results from the laser diffraction of batch A-G shows that the median particle size range from approximately 120-140 µm (Fig. 4.4). No distinct difference in particle size could be detected with the alterations in air flow and spray rate.

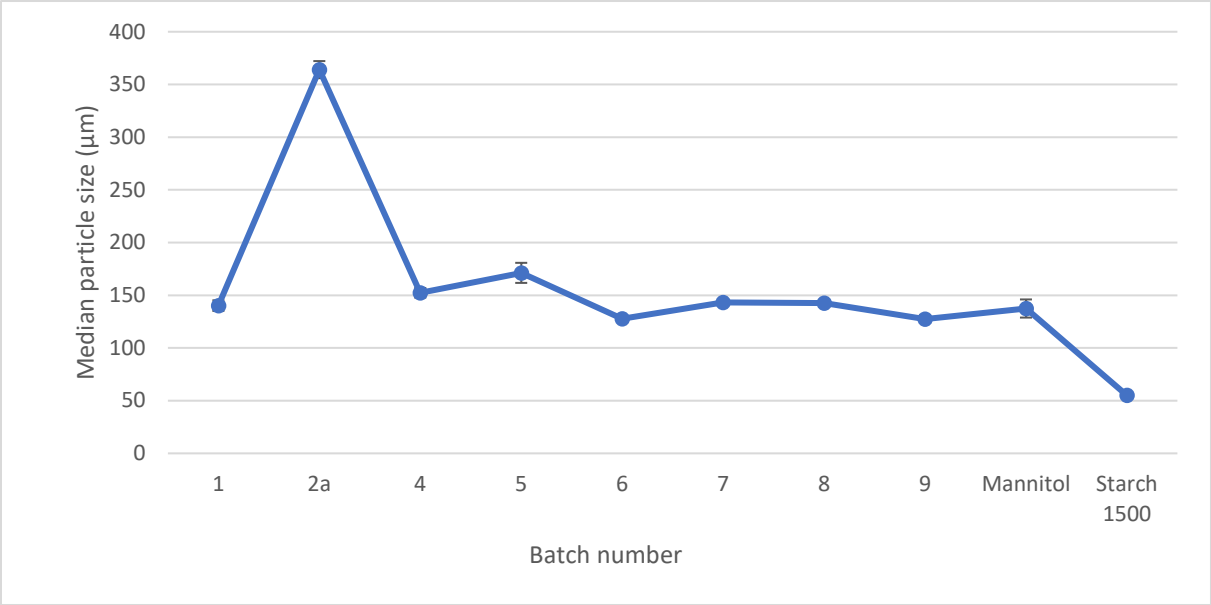


Figure 4.3. Median particle size and standard deviation determined from the laser diffraction for the granules with different excipients.

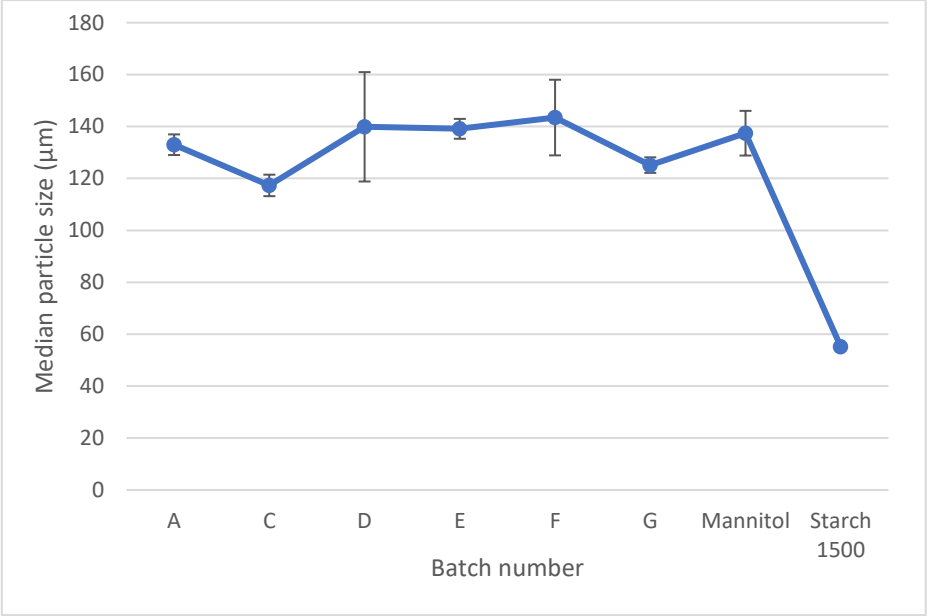


Figure 4.4. Median particle size and standard deviation determined from the laser diffraction for the DoE.

4.2 Moisture content

The powder raw material had a moisture content of 0.9 % to 1.9 % for batch 1, 3 and 7. The one differing was batch 2 containing isomalt as the main filler which had a moisture content of 3.6 % (Fig. 4.5).

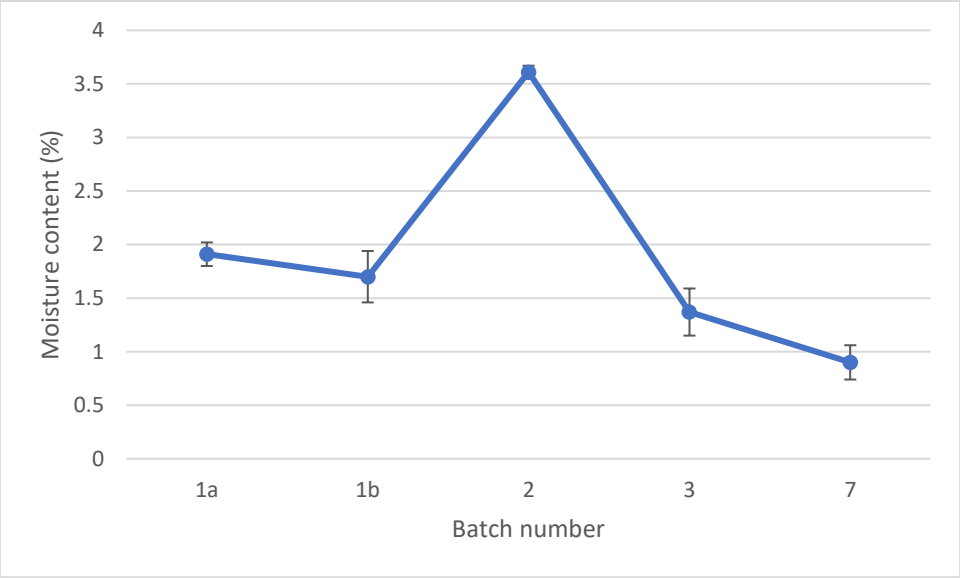


Figure 4.5. Shows the mean moisture content and standard deviation from the triplicate measurement of powders.

The moisture content was about 1.5 to 2.0 % for all batches of granules, again batch 2 deviated with a higher moisture content of 4.2 % (Fig. 4.6).

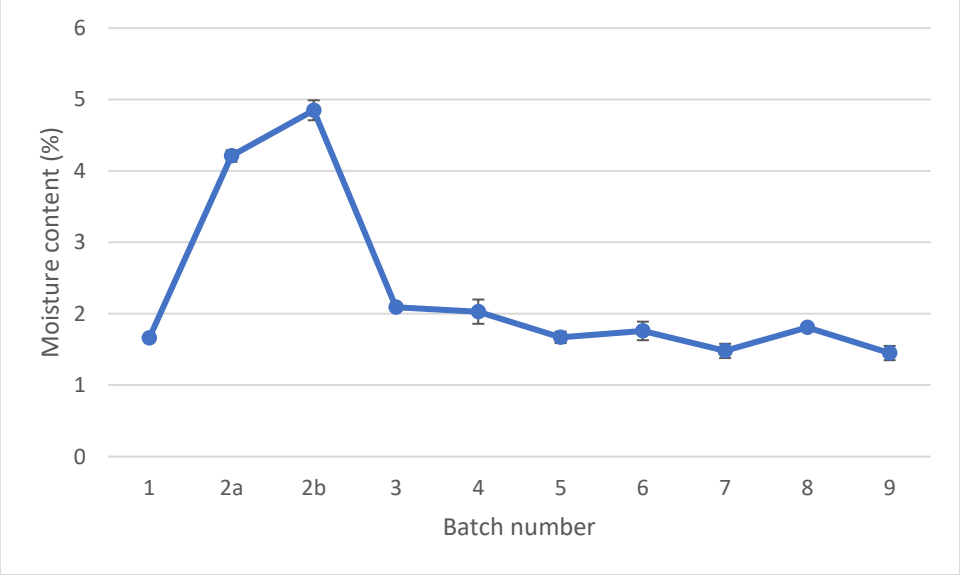


Figure 4.6. Shows the mean moisture content and standard deviation from the triplicate measurement of granules.

The granules produced when varying the air flow and spray rate had similar moisture content, ranging from 1.4-2.2 % moisture content for all batches except batch B (Fig 4.7). Batch B had a much higher moisture content as the spray rate was too fast and the product could not flow in the container after adding 50 ml of the water. The fluid bed granulation was terminated and the moisture content was determined, however any further testing of this batch was canceled.

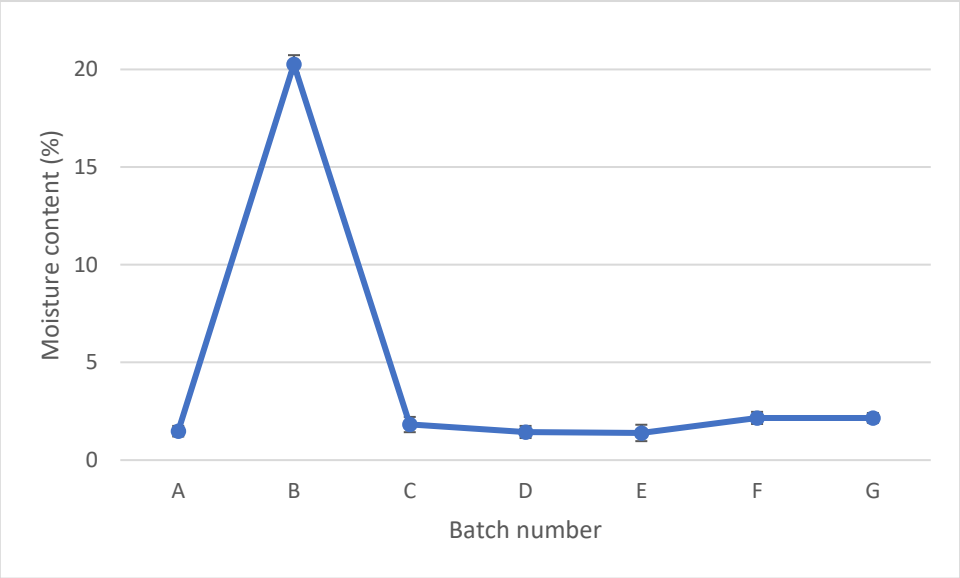


Figure 4.7 Shows the mean moisture content and standard deviation from the triplicate measurement of granules produced with different process parameters.

4.3 Flowability

4.3.1 Hausner ratio

The flowability for batch 1, 2, 3 and 7 tested as powders was determined to be fair according to the Hausner ratio (Fig. 4.8). The porosity for the powder beds ranged between 0.18-0.20. Complete results and raw data are presented in Appendix 9.2.

The flowability was also determined to be fair for all the granules except batch 2 and batch 6 which had a passable flowability (Fig. 4.9). Adding the magnesium stearate the flowability of the granules increase, the become more free flowing than both the powder with lubricant and granules without added lubricant.

From the Hausner ratio the porosity of the granules was calculated according to equation 3.4. The porosity for all batches was similar, ranging from 0.18-0.22. Complete results and raw data are presented in Appendix 9.3.

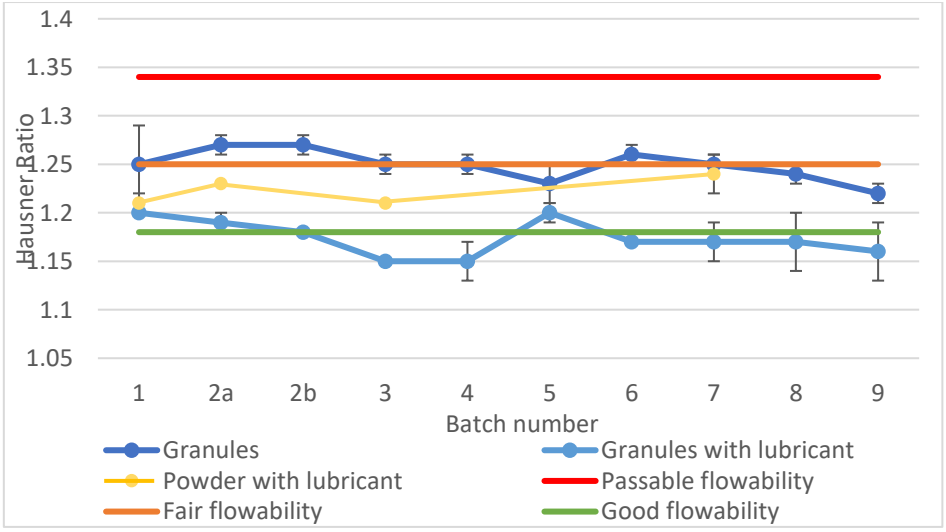


Figure 4.8. Shows the flowability and standard deviation of the granules with limits for the flowability ranges according to the Hausner ratio.

The Hausner ratio without added lubricant for the granules produced in batch A-G shows passable flowability for all granules (Fig. 4.9).

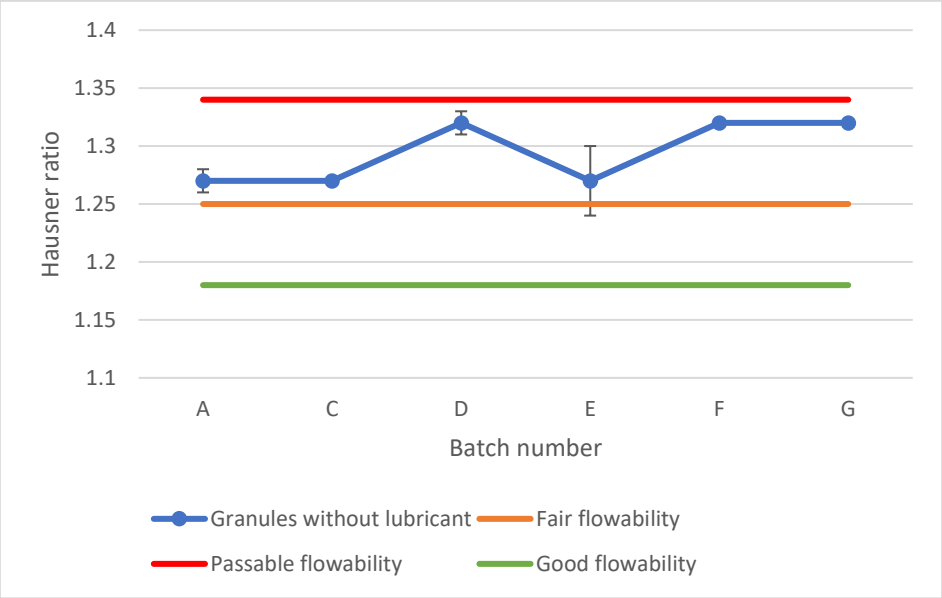


Figure 4.9. Shows the flowability and standard deviation of the granules produced with different process parameters. Limits for the flowability ranges according to the Hausner ratio are shown with lines.

4.3.2 Angle of repose

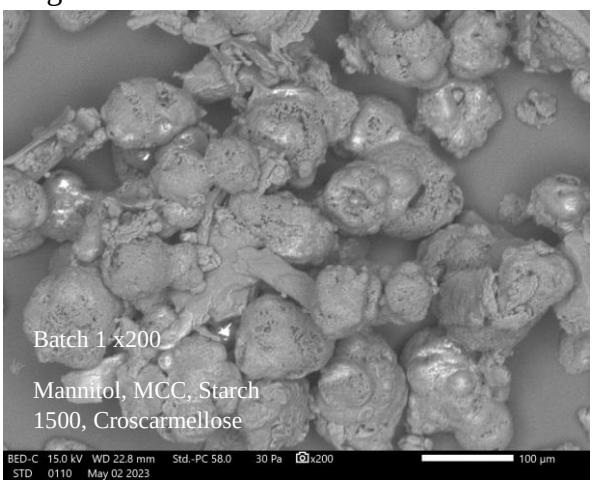
The angle of repose indicates a free-flowing product both among the powders and all the granules produced with different excipients. The powder of batch 7, containing crospovidone as the super disintegrant showed the highest flowability and was considered very free flowing. The diagrams with the angle of repose are presented in Appendix 9.4.

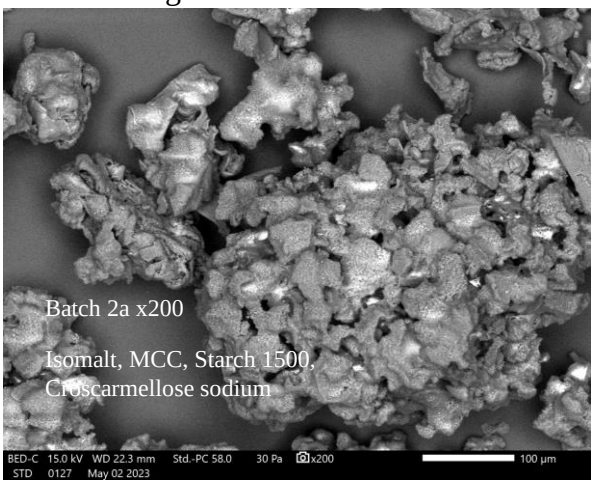
4.4 Scanning electron microscope

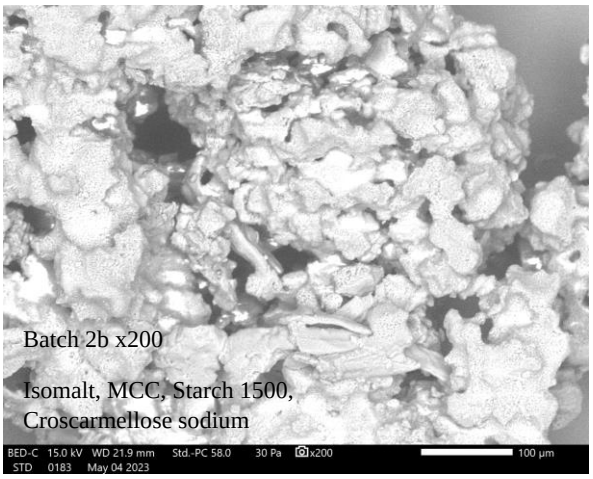
The images received with the SEM demonstrated the differences in structure among the granules with x200-300 zooming (Fig. 4.10). The granules containing mannitol as the main filler had a smoother surface compared to the granules with either isomalt or xylitol as the main filler. The mannitol batches seemed to be similar in structure regardless of the other excipients added. The isomalt granules in batch 2a and 2b showed the roughest surface while the largest granules were observed in batch 3 with xylitol. However only a few granules from the batch were observed why the size of one granule is not representing the entire batch. Images of the granules with x50 zooming are presented in Appendix 9.5.

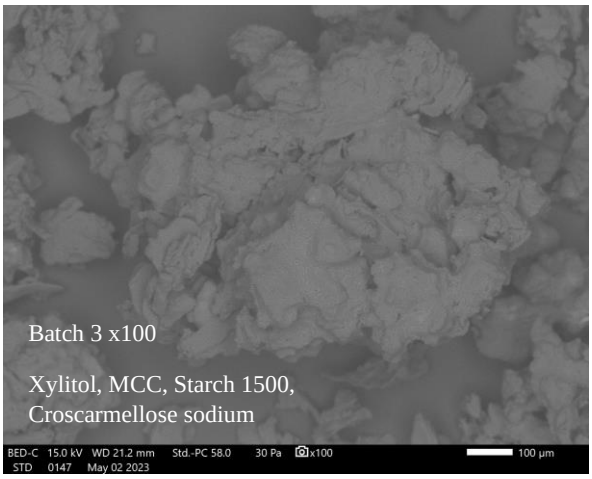
The images from the DoE trial and the raw materials are presented in Appendix 9.6 and Appendix 9.7 respectively. The granules produced with different process parameters in batch A-G showed similar structures with round and rather smooth surfaces resembling the structure of mannitol raw material. All batches A-G had visible granules where the mannitol particles had formed bindings with each other. A few other structures can also be determined, attached to the larger structures. Both smaller particles and longer straws of particles, similar to the images of croscarmellose sodium and Starch 1500. In the images the particle size seems to differ, however as this is only a few particles of the whole batch it is impossible to determine the size differences between the granules from these images.

The images of the raw materials was used to compare the structures visible in the granules. For the raw materials croscarmellose sodium shows different particle structures compared to most other particles by having “straws” instead of round particles. Isomalt and xylitol have rougher surfaces also as raw materials before the fluid bed granulation.









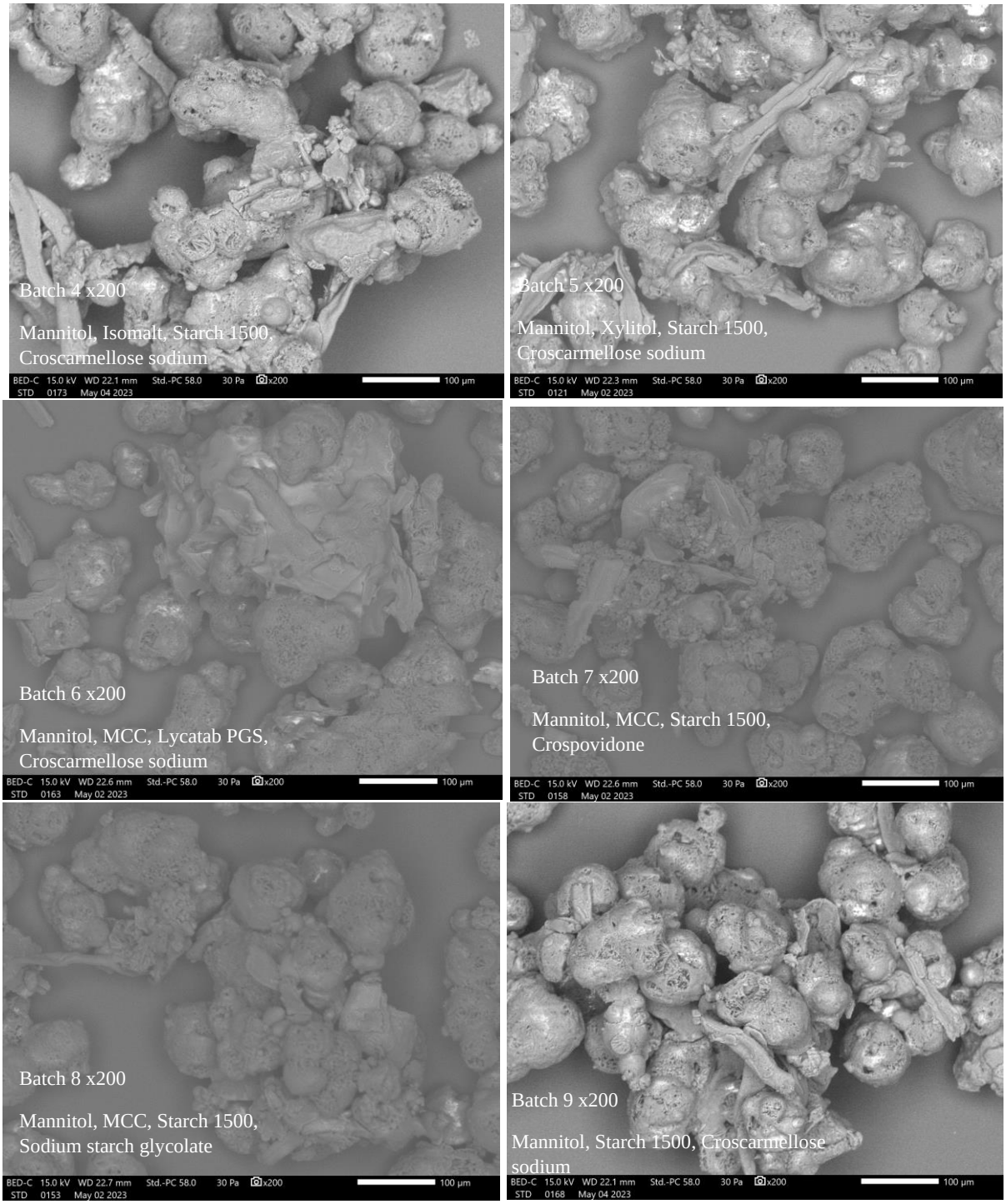


Figure 4.10. Images of the granules from the electron microscope, focusing on one granule with x100-x200 zooming.

4.5 Compression force

The compression force varied between the produced batches, largest was the compression force for xylitol tablets (batch 3) produced with direct compression (Fig 4.11). The lowest compression force was used when producing tablets with isomalt as the main filler (batch 2).

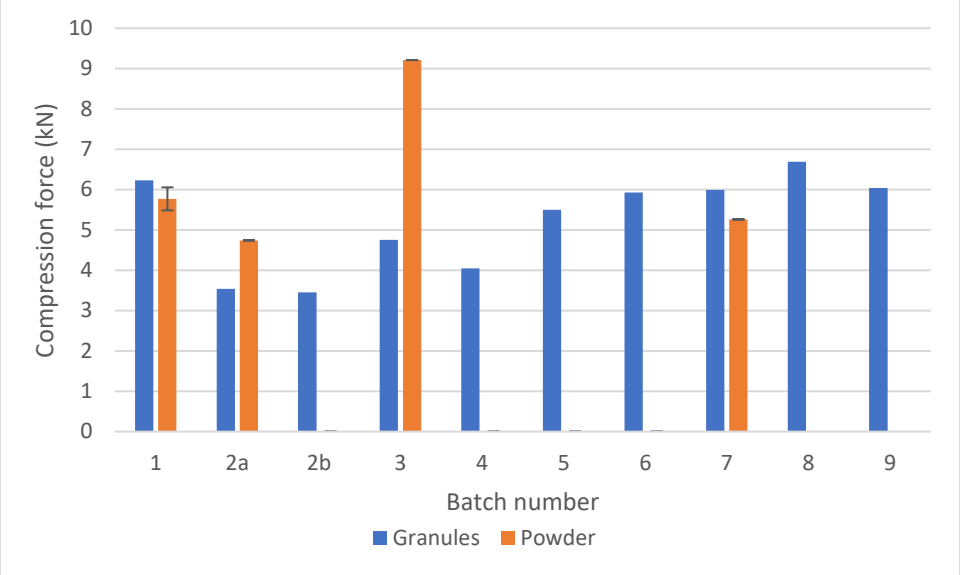


Figure 4.11 Shows the compression force used for the tablets pressed with granules compared to tablets produced with direct compression using powders. For batch 1a and 1b of the direct compressed tablets a mean and standard deviation is presented.

For the tablets produced from granules produced with altering process parameters the compression force was similar (Fig. 4.12). The compression force varied between 5-6.5 kN which was similar to the compression forces applied to the other batches produced with mannitol and MCC as fillers (e.g. batch 1 and 6-9).

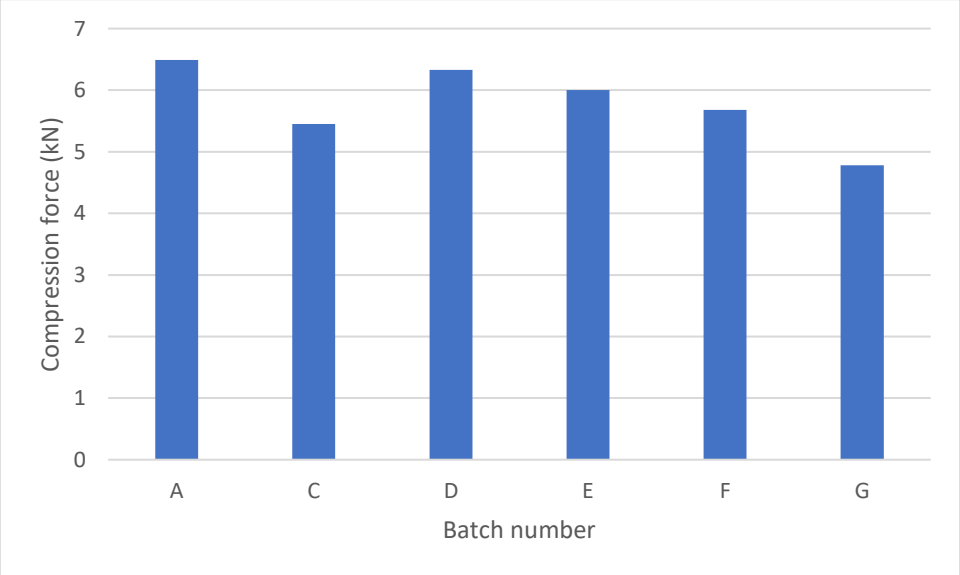


Figure 4.12. Shows the compression force used for the tablets pressed with granules produced with different process parameters.

4.6 Friability

Most tablets had a friability <1 %, whether they were produced by direct compression of the powder (Fig. 4.13) or from granules (Fig. 4.14). In total, four batches had tablet breakage during the run in the friabilator, batch 3 and 7 using direct compression and batch 2a and 6 from the granules. Considering the unbroken tablets, only the tablet with isomalt or xylitol as the main filler had a friability above 1 %.

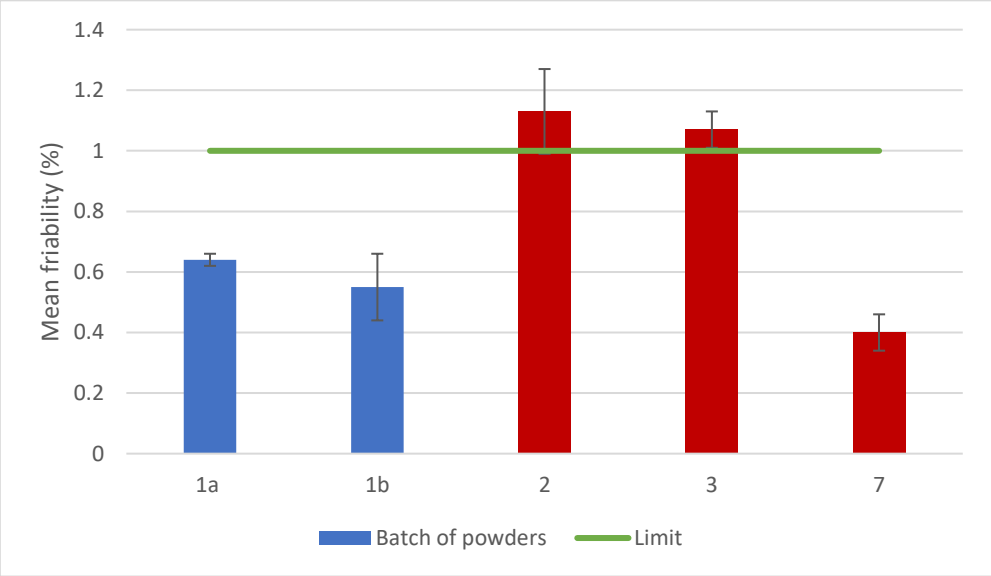


Figure 4.13. Shows the mean friability and standard deviation for the tablets pressed with direct compression of powders. In case of broken tablets or a friability > 1 % the batch do not fulfill the requirements of Eur. Ph. and are colored red.

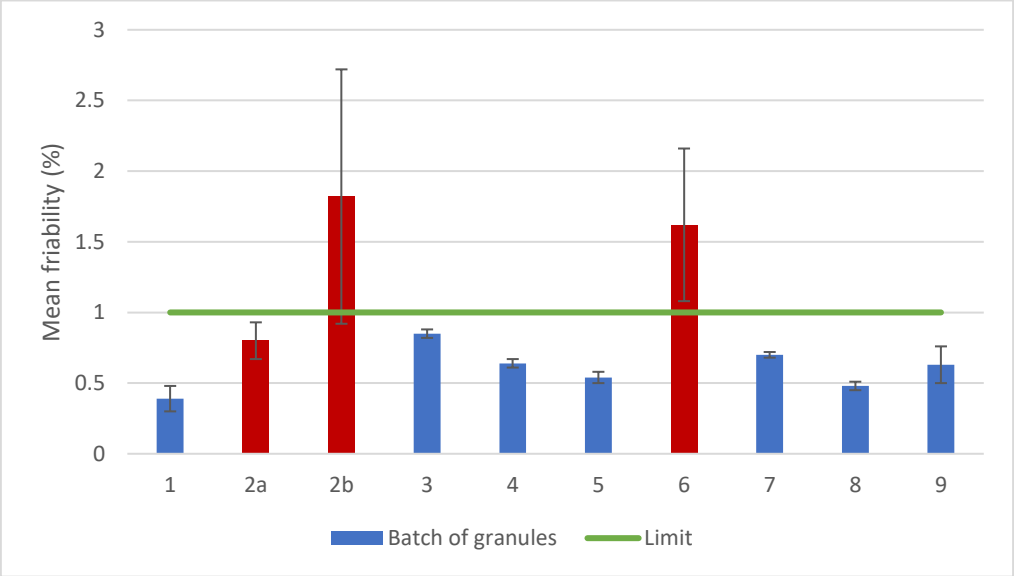


Figure 4.14. Shows the mean friability and standard deviation for the tablets pressed from granules. In case of broken tablets or a friability > 1 % the batch do not fulfill the requirements and are colored red.

Batch 3 and 5 containing xylitol as the main filler or a smaller amount of xylitol together with mannitol showed significantly different friability (p= 0.009) using Games-Howell test and a confidence level of 95 %. On the contrary, batch 2 and 4 containing only isomalt or a smaller amount of isomalt showed no significant difference (p=0.808) in friability.

The tablets pressed with granules produced from batch 1 with different process parameters all had acceptable friability except for batch C (Fig. 4.15). The statistical test however gave no significant difference between any of the tablets.

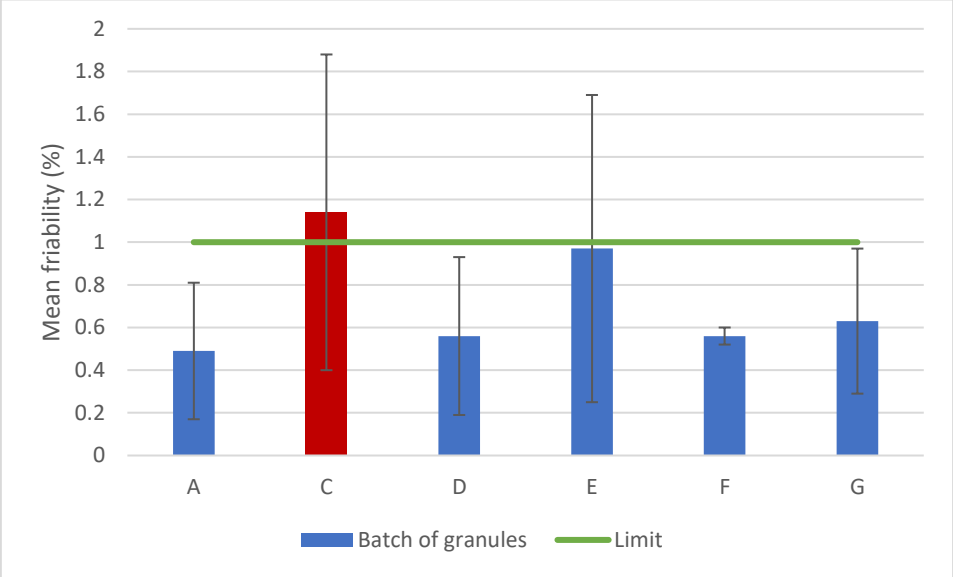


Figure 4.15. Shows the mean friability and standard deviation for the tablets pressed from granules produced with different process parameters. In case of broken tablets or a friability > 1 % the batch do not fulfill the requirements and are colored red.

All tablets tested from the experiment where the process parameters were altered showed no tablet breakage. This indicates that the excipients and ratios used in batch 1 is suitable for tableting. There was no significant difference between the batches determined from the statistical test, this is probably due to the large standard deviation for many of the batches.

4.7 Disintegration time

4.7.1 *In vitro* disintegration Ph. Eur. method

Using the Pharmathron disintegration test the *in vitro* disintegration times was determined for each batch. As some tablets tended to stick to the disc which hindered the disintegration of the tablets all batches do not have six replicates tested, if the tablets were visible attached to the disc during the test the tablet data was removed before calculating the mean disintegration time for each batch.

The disintegration time was longest for batch 3 with xylitol as the main filler both for the direct compression (Fig. 4.16) and granules (Fig. 4.17). For the direct compression method, the tablets in batch 7 containing crospovidone as super disintegrant had the fastest disintegration time. For the granules several batches had similar disintegration time, the ones considered among the fastest are batch 1, 5, 6, 7 and 9.

There was no significant difference between batch 9 without the filler MCC or batch 1, 7 and 8 containing the super disintegrants croscarmellose sodium (p=0.951), crospovidone (p=1.000) and sodium starch glycolate (p=0.995) respectively.

Batch 3 containing xylitol had a significantly longer disintegration time than batch 2 containing isomalt (p=0.002) and batch 1 containing mannitol (p=0.003). The same trend was

determined for the tablets pressed with direct compression. Comparing with xylitol, isomalt was significantly faster (p=0.042) similar to the results for mannitol (p=0.049).

The *in vitro* and *in vivo* method gave some variation in disintegration time, however no significant trend whether one method increases or decreases could be seen (Fig. 4.18).

The *in vitro* disintegration time for batch A-G varied between 17-30 s (Fig. 4.19). The standard deviation was rather larger compared to the standard deviation for the *in vivo* disintegration time.

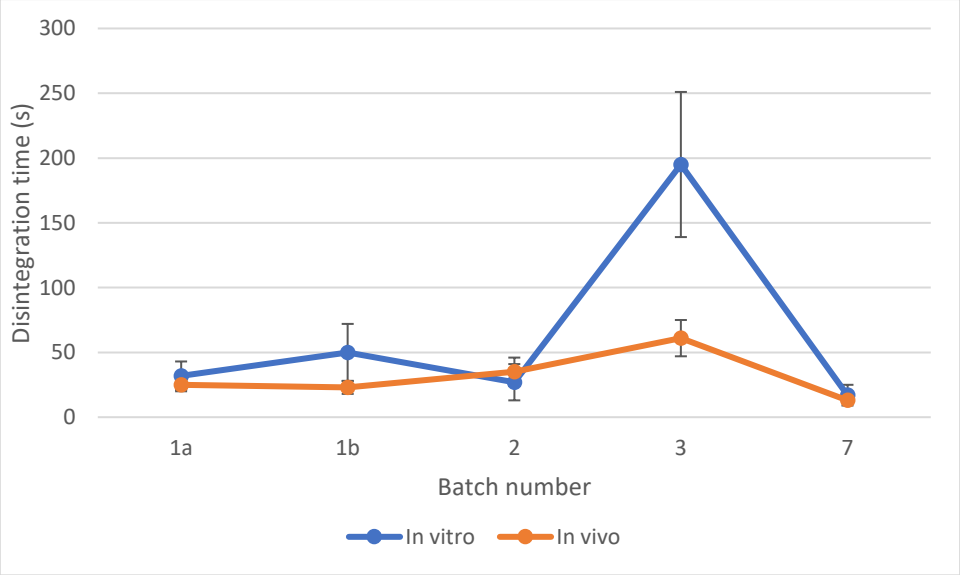


Figure 4.16. Shows the disintegration times and standard deviation using the *in vitro* Eur. Ph. disintegration method and using *in vivo* disintegration for the tablets produced with direct compression.

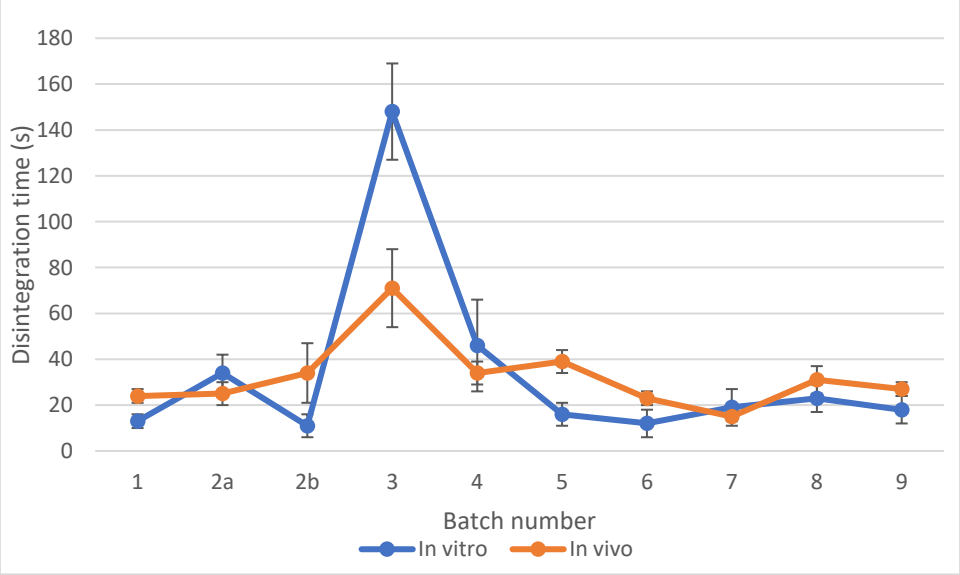


Figure 4.17. Shows the disintegration times and standard deviation using the *in vitro* Eur. Ph. disintegration method and using *in vivo* disintegration for the tablets pressed from granules.

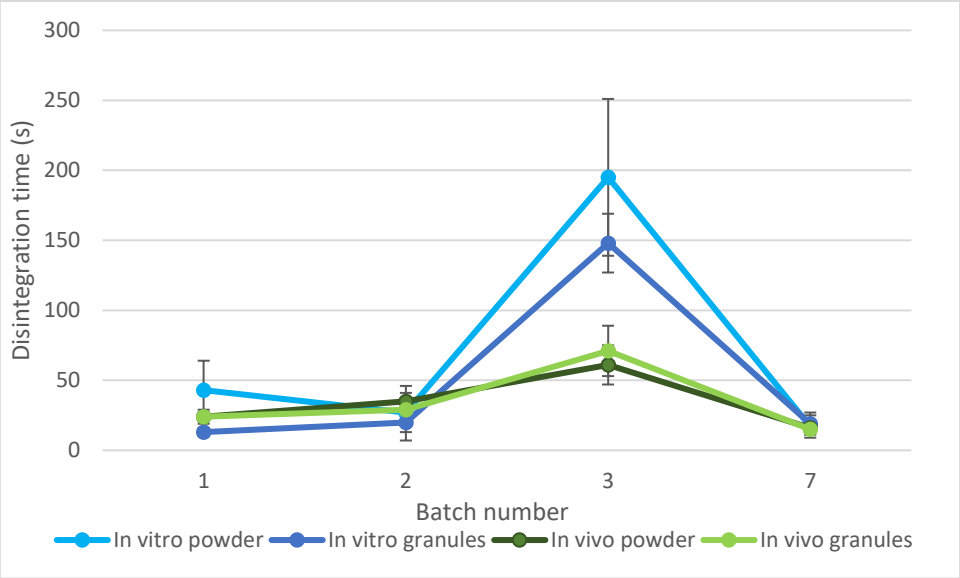


Figure 4.18. Compares the disintegration time and standard deviation for the batches produced with both granules and powders. Where duplicates are produced the mean value is presented.

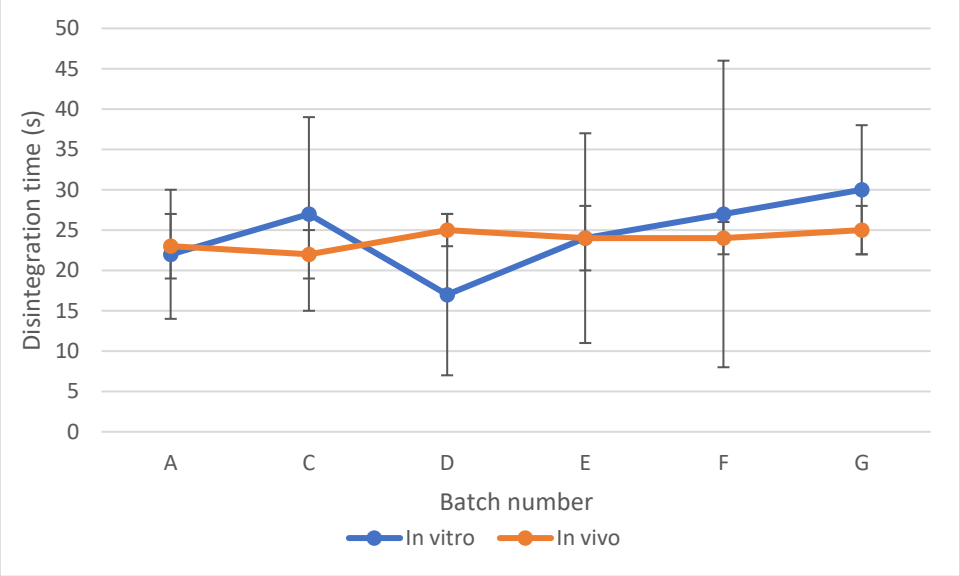


Figure 4.19. Shows the disintegration times and standard deviation using the *in vitro* Eur. Ph. disintegration method and using *in vivo* disintegration for the tablets pressed from granules when altering the process parameters for the granulation.

4.7.2 *In vivo* disintegration

The *in vivo* disintegration times for tablets produced with direct compression (Fig. 4.16) were relatively similar to the *in vivo* disintegration times for tablets made of granules (Fig. 4.17) for all batches. There were two batches differing slightly among the powders, batch 2 containing isomalt as the main filler and batch 3 containing xylitol as the main filler. The tablets with isomalt showed a slower disintegration time *in vivo* while the batch containing xylitol had a faster disintegration time *in vivo.*

The *in vivo* disintegration time for the tablets pressed with granules (Fig. 4.17) also indicated some variation between the *in vivo* and *in vitro* test. Batch 1, 2, 5, 6, 7, 9 had a slower

disintegration time *in vivo,* batch 8 had a similar disintegration time in both tests and batch 3 and 4 had faster disintegration times *in vivo.*

Comparing batch 2 and batch 4 containing isomalt as the main filler or isomalt together with mannitol there was no significant difference (p=0.808), however there was a significant difference between batch 3 and 5 (p=0.009) containing xylitol as the main filler and xylitol together with mannitol. Similarly to the *in vitro* results, the xylitol tablets had a significantly longer disintegration time than both mannitol (p=0.005) and isomalt (p=0.005) for tablets with granules. Another result complying with the *in vitro* result is the effect of MCC, comparing batch 1 with MCC and batch 9 without MCC no significant effect was determined (p=0.926).

On the contrary to the *in vitro* results, the tablets had a significantly faster *in vivo* disintegration time when containing crospovidone as the super disintegrant instead of croscarmellose sodium. This trend was observed both for tablets produced using direct compression (p=0.003) and from granules (p=0.008). This is remarkable as the same trend was not detected with the Eur. Ph. *in vitro* test. Comparing to SSG, crospovidone had a faster disintegration time (p=0.009) as well.

4.7.3 Developed *in vitro* disintegration method

The tablets disintegrated with two different mechanisms due to different excipients used in the composition. The tablets containing mannitol as the main filler swelled, which was detected from the increase in force on the texture analyzer when adding water to the tablet. On the contrary, the tablets containing isomalt or xylitol as the main filler (batch 2 and 3) melted. No increase in force on the probe was detected due to no increase in volume when adding water.

A new disintegration method was developed for the tablets containing mannitol. The method which gave the best IVIVC was detected when a filter of 20 mm was placed under and above the tablet and a probe of 10 mm was lowered onto the top filter until a force of 0.01 N was reached (Fig 4.20). Then 1 ml of water was added around the lower filter. The water was absorbed by the filter and once in contact with the tablet it started to disintegrate and swell. During the swelling the force on the probe increased until a maximum force was reached, then the force decreased gradually. The disintegration time was detected at the maximum force and during the decrease in force at 90, 80, 70, 60 and 50 % of the maximum force (Fig 4.21). The *in vivo* time did not show a consistent correlation with either fraction of the max force as shown in Appendix 9.7. However, plotting the time until max force against the *in vivo* disintegration time showed a linear correlation with the slope 2.45, $R^2 = 0.91$ (Fig 4.22). The R^2 value indicates a good correlation between the measured disintegration times *in vivo* and *in vitro*.

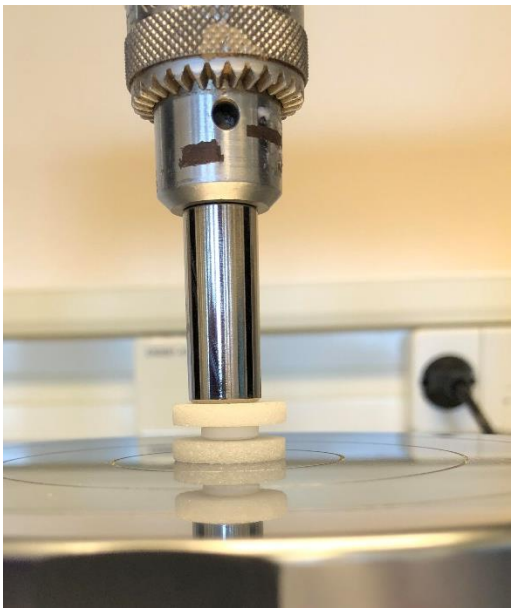


Figure 4.20. Set up of the texture analyzer with filters above and under the tablet and a probe applying and measuring the force on the ODT.

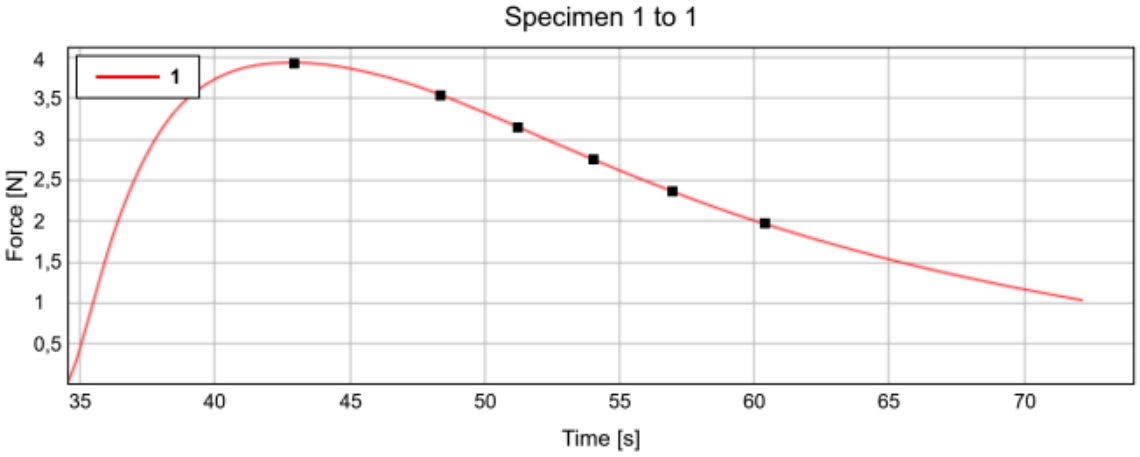


Figure 4.21 Shows the graph received from the texture analyzer. The graph begins when the ODT begins to swell and the time was recorded at the maximum force and at 90, 80, 70, 60 and 50 % of maximum force.

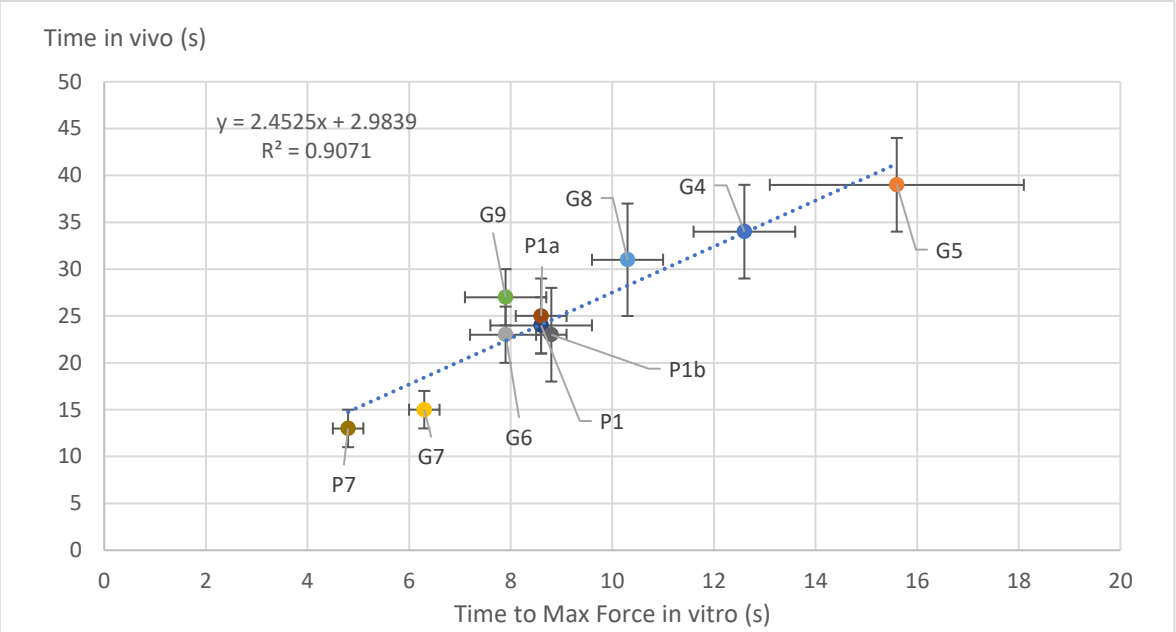


Figure 4.22. Shows the relation between the time to maximum force for the tablets containing mannitol plotted against their *in vivo* disintegration time including standard deviation. The linear regression shows a correlation between the disintegration times of 2.45. Each data point is labeled if produced from powders (P) or granules (G) and batch number.

The tablets in batch 2 and 3 containing isomalt and xylitol respectively showed a different dissolving mechanism, both when produced from powders and granules. The tablets dissolved when water was added both on the top and bottom filter, however only the outer layer dissolved and the inside remained a solid tablet. When the water rinsed off the tablet became stable again and no further disintegration was observed unless more water was added. These tablets were tested with several different methods using the texture analyzer. As the tablets did not swell the probe was set to follow the tablet with a constant force between 0.5-3 N. When water was added and the tablet started to melt the displacement of the probe was measured to detect the dissolving mechanism. The water volume was varied between 200-2000 µl and added both through the top and bottom filter, the tablets showed similar behavior and melted for a few seconds while the probe displaced before becoming stable again. To try and change this behavior the bottom filter was exchanged for a sieve/net of 2000 µm to make the tablet dissolve or break through the net. This resulted in a little longer displacement time for the probe, however a solid tablet was remaining once the water rinsed of. Lastly the net was removed, and a cylinder was placed around the tablet to try and keep the water around the tablet making it dissolve more, unfortunately neither this method showed a full dissolution of the tablet.

4.8 Design of experiment granulation process parameters

In experiment B (air flow 30 m^3/h and spray rate 20 ml/min) the product became too wet resulting in a wet mass in the bottom and along the walls of the container which was too dense to flow from the air flow, the experiment was terminated and the moisture content checked (Table 4.1). Apart from this the other combinations of process parameters successfully produced granules which were further pressed into solid tablets.

Table 4.1. Shows the parameters and resulting characteristics of the granules and tablets produced from the DoE.

Batch	Spray rate (ml/min)	Air flow (m^3/h)	Median particle size (µm)	*In vivo* disinte-gration time (s)	Moisture content (%)	Compression force (kN)	Friability (%)	Process time (min)
A	5	30	133	23	1.48	6.49	0.49	26
B	20	30			20.26			
C	5	60	117	22	1.82	5.45	1.14	38
D	20	60	140	25	1.44	6.33	0.56	26
E	12.5	45	139	24	1.39	6.00	0.97	13
F	12.5	45	143	24	2.16	5.68	0.56	13
G	12.5	45	125	25	2.16	4.78	0.63	12

The model showed that the spray rate significantly affected the *in vivo* disintegration time, using a 95 % confidence interval (Fig. 4.23). An increase in spray rate seems to increase the *in vivo* disintegration time. The small difference between R2 (0.88) and Q2 (0.70) indicates a good model for the parameters (Fig. 4.24). Further the replicates are closely centered which also indicates a reliable result and model (Fig. 4.25).

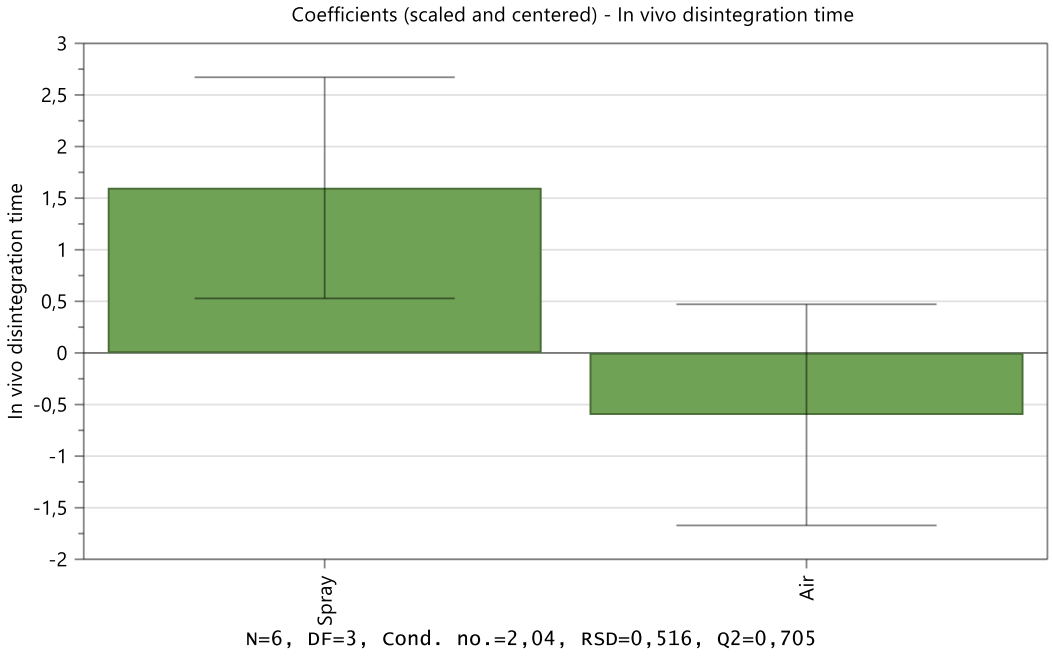


Figure 4.23. The coefficients shows that the spray rate significantly affects the disintegration time while the effect of air flow is not significant.

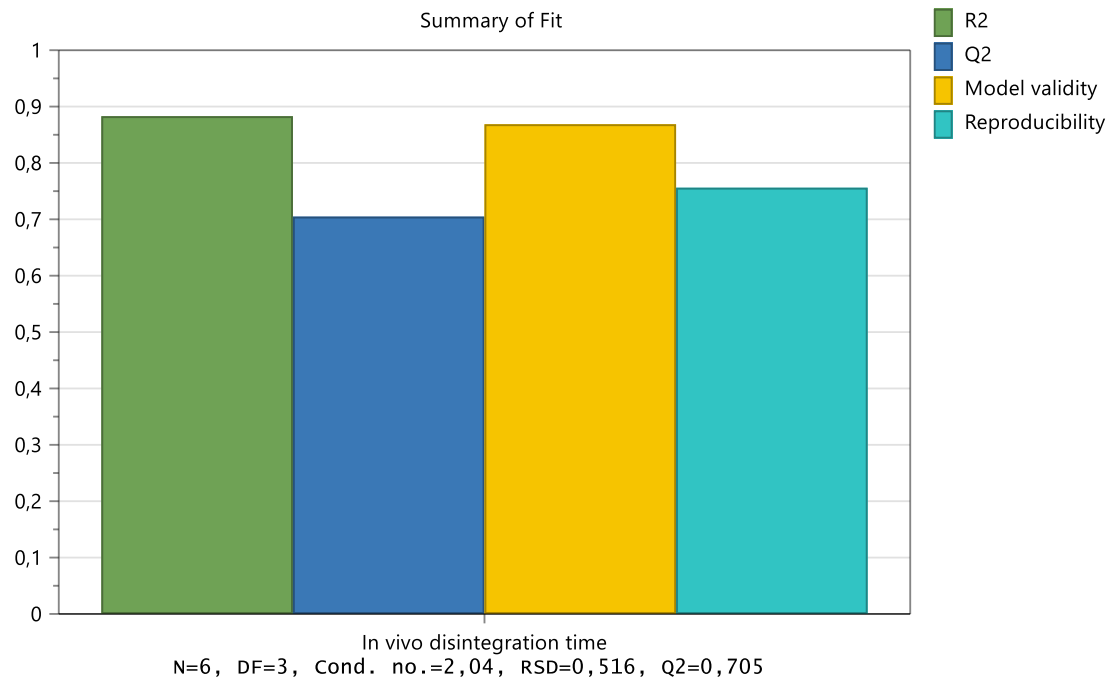


Figure 4.24. The summary of fit plot shows the goodness of fit (R2), goodness of prediction (Q2), validity and reproducibility of the model.

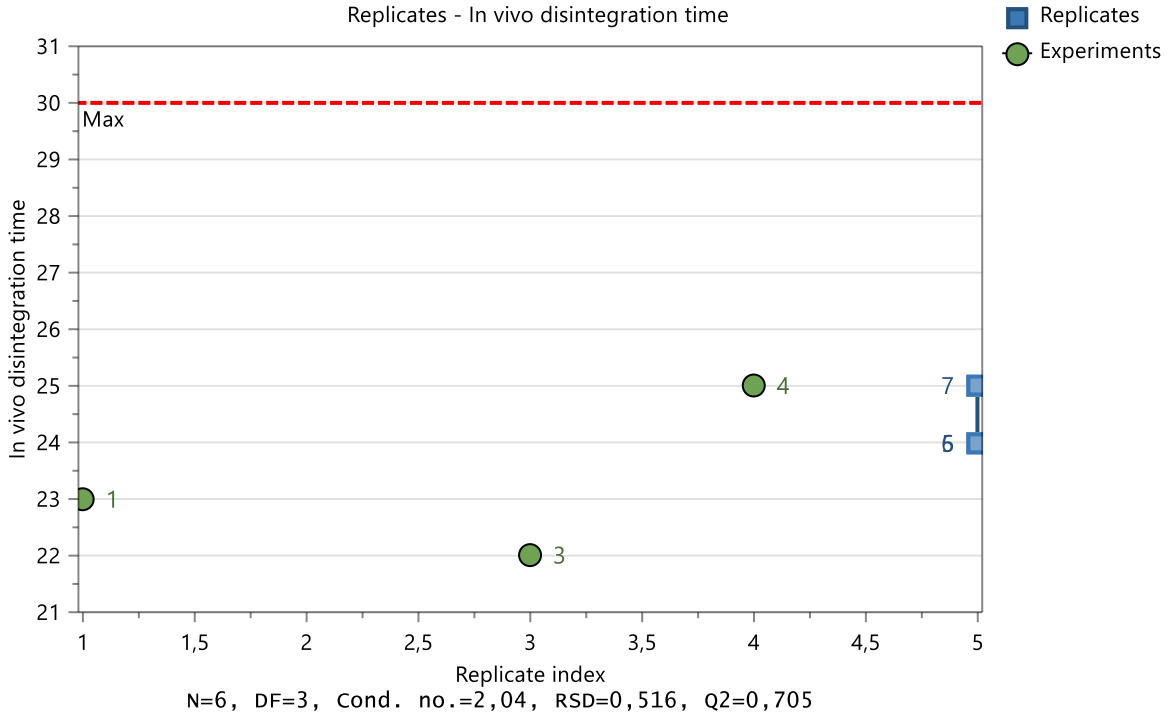


Figure 4.25. Shows the distribution of the replicates.

Also, the process parameters significantly affected the process time for the fluid bed granulation (Fig. 4.26). A decrease in spray rate increases the process time while an increase in air flow also increases the process time (Fig 4.27). However, the model is difficult to evaluated due to few degrees of freedom.

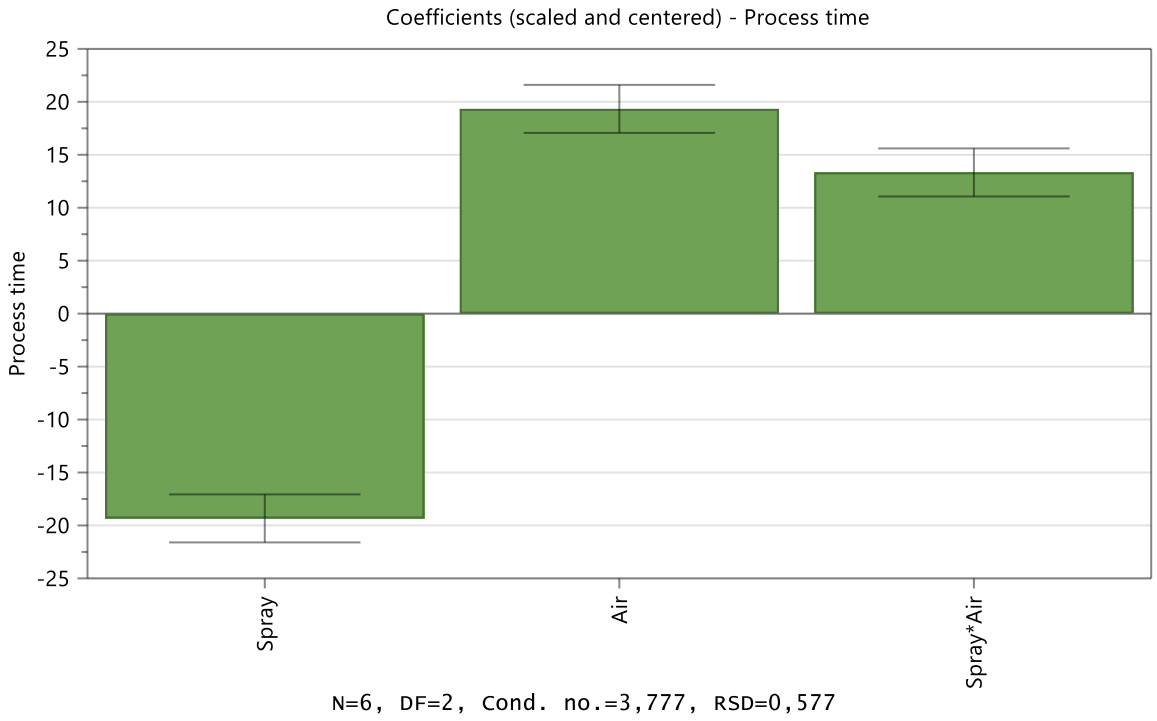


Figure 4.26. Coefficients for the process time, shows that spray rate, air flow and spray rate*air flow significantly affect the process time with a 95 % confidence interval.

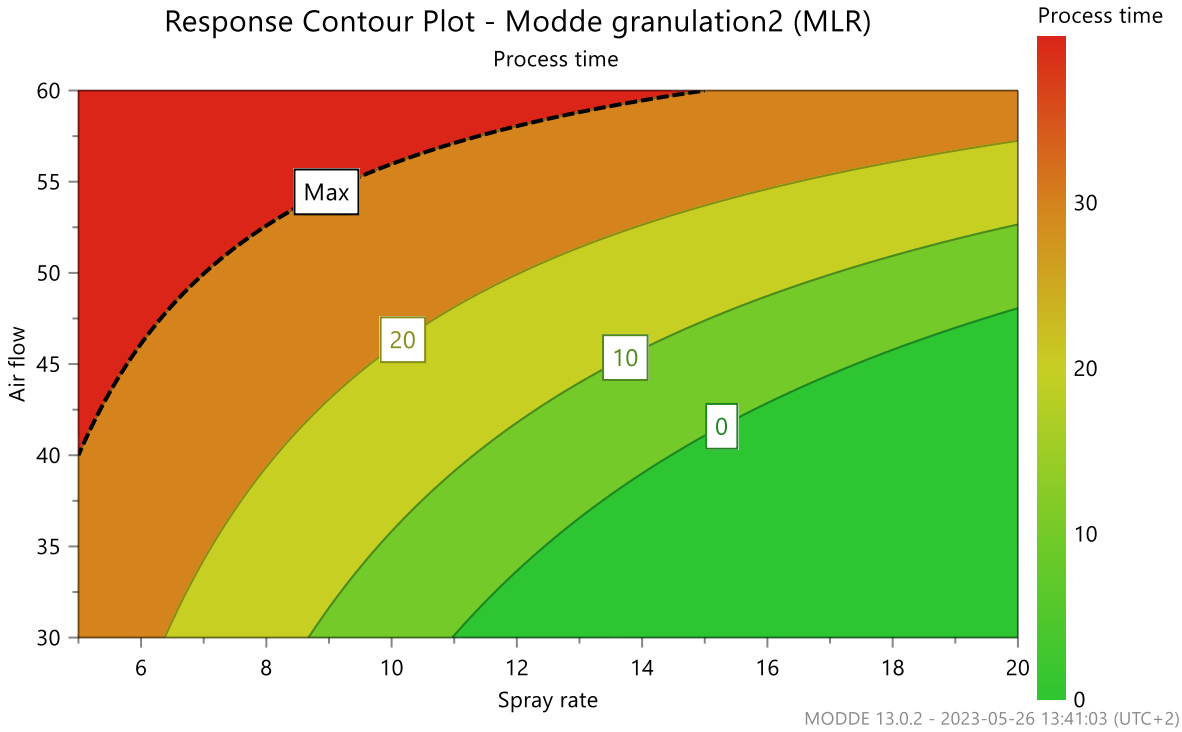


Figure 4.27. The contour plot shows that an increase in air flow increases the process time and a decrease in spray rate increases the process time.

4.9 Statistical analysis

The results from the friability test, the *in vitro* and *in vivo* disintegration time was evaluated with a Games Howell test and 95 % confidence interval (Table 4.2). The results shows that many differences between the batches are insignificant. The largest differences are seen between batches with different polyols as the main filler.

Table 4.2. Shows the statistical probability of significant data calculated with Games Howell test and 95 % confidence interval. The batches are distinguished with letter "P" for powders pressed with direct compression and "G" for tablets with granules.

Batch	**Friability (*p*)**	***In vitro* (*p*)**	***In vivo* (*p*)**
P1a/G1	0.234	0.276	1.000
P1b/G1	0.804	0.288	1.000
G1/G2	0.595	0.175	1.000
P1a/P2	0.171	1.000	0.702
G1/G3	0.066	0.003	0.005
P1/P3	0.041	0.049	0.702
G2/G3	0.840	0.002	0.005
G2/G4	0.808	0.995	0.311
G3/G5	0.009	0.002	0.051
G1/G6	0.362	1.000	1.000
G1/G7	0.163	0.537	0.008
G1/G8	0.875	0.295	0.530
G7/G8	0.009	1.000	0.530
P1a/P1b	0.915	0.946	1.000
G2a/G2b	(0.818)	0.123	0.874

5 Discussion

5.1 Granule particle size

5.1.1 Sieving

The largest granules were produced when using isomalt or xylitol as the main filler, the seven batches with mannitol as the main filler had significantly smaller granules. This could be explained by the solubility differences between the polyols. Mannitol is the least soluble of the three as it is reasonable that the molecules form smaller aggregates. The more soluble polyols dissolve to a larger extent which enables larger aggregates to be formed during the liquid state. If strong enough the bonds remain when dried and large granules are produced. The replicate of batch 2 shows that the particle size is similar for both 2a and 2b which indicates that the granulation process is somewhat reproducible.

Although xylitol is more than twice as soluble as isomalt there is no significant difference between the particle sizes produced with the two fillers. This indicates that the granules might have a maximal size which is independent of the solubility of the excipients. The particle size may be determined by the process parameters which was set to be constant for all batches produced. Adding a small amount of a more soluble filler such as isomalt or xylitol as a complement to the main filler mannitol (batch 4 and 5) shows an increase in granule particle size if comparing to the insoluble filler MCC (batch 1). In conclusion the solubility of the excipients plays an important role for the particle size of the granules, however it seems like the particles have a maximum particle size independently of the solubility.

The smallest granules were produced in batch 7, containing crospovidone as the super disintegrant instead of croscarmellose sodium. Both batch 1 and 7 containing croscarmellose sodium and crospovidone decreased the particle size compared to using sodium starch glycolate (batch 8) as the super disintegrant. A possible explanation to this could be the high porosity of crospovidone which makes the particles more susceptible to attrition during drying. As sodium starch glycolate mainly acts by swelling it is non-porous why it is reasonable it can resist the drying conditions better than crospovidone.

Comparing batch 1 and 6 the effect of fully pregelatinized starch and partially pregelatinized starch can be evaluated. As both batches have almost identical size distribution (Fig. 4.1) the conclusion is drawn that the pregelatinized state of the binder do not affect the particle size of the granules. As Lycatab PGS is fully pregelatinized and more soluble than Starch 1500 it would be expected that batch 6 with Lycatab as the binder have larger granules compared to batch 1 with Starch 1500 since the solubility seems to alter the granule size when using mannitol or isomalt/xylitol. The reason why no difference in granule particle size are detected is probably due to the small amount % (w/w) used and that Starch 1500 also is partially soluble in water.

The granules produced with excipients from batch 1 with altered process parameters shows rather similar particle size distribution. The largest particles were produced in batch F and G, when the parameters are set to the middle values (air flow 45 m^3/h and spray rate 12.5 ml/min). The second largest particles were produced in batch D with air flow 60 m^3/h and spray rate 20 ml/min. The smallest particles are produced in batch A and C which both had the lowest spray rate (5 ml/min). This indicates that the spray rate affects the particle size the most, which is reasonable as a low spray rate prevents the product from wetting and agglomerates are more difficult to be formed. A larger air flow should also affect the particle

size as a higher flow causes more attrition to the particles however such relationship is not detected from the results (Fig. 4.2) which indicates that the granules are rather strong.

5.1.2 Laser diffraction

From the laser diffraction the median particle size was determined. Similarly to the results from the shake sieve batch 2 containing isomalt had the largest granules, more than twice the size of the batches containing mannitol as the main filler. This again proves that the solubility of the excipient determines the size of the granules. The excipients besides the main filler seems to play a minor role regarding the particle size. This is probably due to the smaller amount % (w/w) added of these excipients.

Comparing the batches with mannitol (1 and 4-9) to the raw material of mannitol it was seen that the median particle size was similar between both the granules and the raw material. As seen in the SEM, granules are formed in all batches. The reason the median particle size is similar is probably because everything in the batch is not granulated, there is still small particles free in the batch.

Batch 1, 7 and 8 with the super disintegrants croscarmellose sodium, crospovidone and sodium starch glycolate respectively have almost identical median particle size. This shows that the super disintegrant have no effect on the granule particle size.

The granules from batch A-G have particle sizes similar to each other and similar to batch 1, all with the same excipients added. Batch C has the smallest median particle size in accordance with the results from the shake sieve where batch C (together with batch A) also had the smallest granules. Batch C have the highest air flow and lowest spray rate why it is reasonable that the granules formed are small. The process parameters make the product drier during the granulation process and less dissolved particles can bind to each other and form aggregates. The aggregates that are formed have less possibility to attach to each other as the product mass in the container will be kept drier during the process. The particles in batch B should have the largest particles according to this theory, however the product became too wet during granulation and the particles were unable to flow which resulted in a wet mass in the bottom of the container. Batch D has high air flow and high spray rate resulting in larger median particle size compared to batch C with lower spray rate.

The median value is also a good measurement to estimate how well the granulation went, a small median particle size indicates that many particles have not been granulated and are still in powder form, e.g. smaller particles.

5.2 Moisture content

The moisture content was similar for the batches before and after granulation if comparing the raw materials of powders to the granules. This indicates that the drying after granulation was efficient and successful. Batch 2 containing isomalt was more difficult to dry compared to the others and had the highest moisture content. This may be due to larger particles formed, holding more water inside.

It is previously shown that the moisture content may affect the flowability of the granules which could explain why batch number 2 had a the poorest flowability and highest moisture content with 4.21 %. It is also shown that tablets produced from granules with a higher moisture content result in harder tablets and lower porosity (Gabbott, Al Husban and Reynolds, 2016). The same study also concluded that the most important factor for porosity

was the moisture content of the granules. This could explain why the granules had very similar porosity, since all of the granules except batch 2 had only 1-2 % moisture content. Batch 2, with a higher moisture content, also had slightly higher porosity than the rest of the batches, with a porosity of 0.22 compared to 0.18-0.21 for the others.

5.3 Flowability

The powders with added magnesium stearate in batch 1, 2, 3 and 7 all had a fair flowability. After granulation of the powders and addition of lubricant the flowability was improved and the Hausner ratio decreased which shows that the granulation process was successful in increasing the flowability of the product. The flowability for granules with lubricant was good for most batches and fair for a batch, 1, 2a and 5.

Considering the granules without any added lubricant, all batches had fair flowability except batch 2 and 6 which had passable flowability. This indicates that all excipient used for the project had similar flowability properties after granulation despite differences in solubility or particle size. As seen in the images from the electron microscope (Fig. 4.10) batch 2a and 2b had a rougher surface while the batches with mannitol as the main filler had a smoother surface which could explain the slight difference in flowability. Also batch 3 with xylitol had a rougher surface which could explain the poorer flow compared to some of the batches containing mannitol. Surprisingly, the results indicates that the lubricant have no effect on batch 3 as the Hausner ratio is very similar before and after the addition. The other have improved flow properties when adding the magnesium stearate. Also, the magnesium stearate seems effective in used concentration (1 % (w/w)) and helps improving the flowability of the product before tableting.

The granulation process is often used to improve the flowability of poorly flowing APIs to increase the homogeneity of the product. In this project the flowability was successfully improved during the wet granulation process which is an advantage of the process. To increase the flowability further, the fluid bed granulation would need to be further optimized to produce larger particles with a narrower size distribution and even shape of the particles as these factors mainly affects the flowability of particles (Liu et al., 2008).

The results from the angle of repose experiment shows similar results as the flowability determined with the Hausner ratio for granules without added lubricant and powders with magnesium stearate. The only batch standing out is batch 4 with mannitol and isomalt as fillers, the flow is poorer with the angle of repose method compared to the stomp volumeter method. Overall though the results seems to align and it is expected that the angle of repose would show improved flow for granules with added lubricant as well. However, this was not tested due to time limitations.

The granules produced in batch A-G all had passable flowability without any lubricant added, this shows that the process parameters have no effect on the flowability of the granules. Since all granules contain mannitol and have similar structures visible in the SEM (Appendix 9.6) it is reasonable that the flowability is similar.

A study showed that the binder concentration mostly influenced the porosity of the granules (Rajniak et al., 2007), and since all the batches have the same concentration of binder added it is reasonable and expected that the porosity should be similar. Also, the bulk and tap densities

were shown to be related to the concentration of binder (Rajniak et al., 2007), which could explain the similarities among the densities of the granules.

5.4 Scanning electron microscope

Comparing the batches of granules containing mannitol to the image of mannitol raw material the structures are similar with round particles and a smooth surface. The larger particles in batch 1 and 4-9 are therefore believed to be clusters of mannitol which have successfully formed granules during fluid bed granulation. The diameter of the granules is rather small, 200 µm for many granules viewed, which corresponds to the particle sizes determined with the shake sieve. Although small, the image shows that many agglomerates are formed with several mannitol particles. A few particles are unattached and have not been granulated in the process but are laying free on the image. To receive a more granulated product the granulation process might have to be slower to ensure that the entire mass gets wet. However, a remaining problem with lower air flow is the risk of wetting the product too much which makes it more dense and limits the flow, leading to snowballing and difficulties with the drying process.

As all batches containing mannitol are similar the conclusion can be drawn that the main filler plays the most important role when forming granules. This is reasonable as the main filler consists of more than 75 % (w/w) of the total raw materials and the excipient varied between the batches consists of 6-10 % (w/w) each.

Batch 2, containing isomalt seems to give the most irregular granules with spikes on them, however the center of the granule is somewhat spherical for many of the granules while the surface is more irregular. The more irregular surface could explain why the flowability was “passable” for batch 2 while it was “fair” for most of the other batches according to the Hausner ratio. Also batch 3 containing xylitol seemed to have a more irregular and rougher surface compared to mannitol observing the SEM images. However, the flowability was still “fair” according to the Hausner ratio. From the Carr index it is determined that all granules are “free flowing” which surprisingly indicates that the flowability is unaffected by the different surface structures. This might be due to larger particle size of isomalt and xylitol particles as it is previously determined that larger particles have increased flowability (Goh, Heng and Liew, 2018). The increase in size might compensate for the rougher surface which should decrease flowability.

The granules in batch A-G are similar to batch 1 and batch 4-9 with mannitol as the main filler. They have distinct round mannitol particles agglomerated together to form larger granules. Again the granules found with the SEM are rather small for all batches but it is visible that granules are successfully produced. There is no clear difference between the granules when produced with different air flow or spray rate. In conclusion the most important factor for the morphology of the granules seems to be the choice of main filler.

5.5 Compression force

The compression force varied between the batches. In general the powders required a larger compression force to form tablets weighing 200 mg with a hardness of 20 N from powders compared to granules. This is reasonable as the powders are smaller and more dense compared to the granules. Also, the larger granules containing isomalt or xylitol seems to require a smaller compression force compared to most batches with mannitol as the main filler. The compression force also seems to decreases with increasing particle size.

5.6 Friability

Most tablets had a friability <1 % in accordance with the European Pharmacopoeia's demand on solid tablets (European Pharmacopoeia, 2010). Out of the tablets produced from granules there were two batches (batch 2 and 6) considered inadequate since they had tablets breaking during the friability test. These batches were containing isomalt as the main filler or Lycatab PGS instead of Starch1500 as the binder. Batch 2 containing isomalt had the highest moisture content which may be the reason for the high friability. Comparing batch 2b and 4 containing only isomalt compared to mannitol and isomalt in a smaller amount showed no significant difference in friability according to Games-Howells test (p=0.808). Neither batch 2b nor batch 4 had broken tablets which makes them comparable. However, batch 2a had broken tablets which indicates that isomalt might not be the best choice for tableting. As the isomalt batches either had broken tablets or a friability > 1% isomalt is considered a poor choice, when using only isomalt and MCC as fillers.

Comparing batch 3 containing xylitol and batch 5 containing mannitol and xylitol showed a significant difference in friability (p=0.009). This indicates that a larger amount of xylitol increases the friability of the ODT. However, to conclude this hypothesis more than 3 samples would be needed and preferably more replicates of the entire batches would be granulated and tableted.

From the tablets produced by direct compression only batch 1 containing mannitol as the main filler was considered adequate as solid ODTs since the other batches either had a friability > 1 % or tablet breakage. This indicates that the tablets might be more sensitive for breakage when produced with direct compression compared to using granules. Batch 2 containing isomalt as the main filler was inadequate both when produced with direct compression, due to a friability above 1 %, and using granules, due to tablet breakage for one batch and friability > 1 % for the other batch. However, batch 3 containing xylitol and batch 7 containing crospovidone as the super disintegrant showed decrease in friability when granulated before pressed into tablets compared to direct compression. This indicates that the granulation process could enhance the strength of the tablets.

From this trial it could not be concluded that a more soluble excipient decreases the friability as stated by Hiremath, Nuguru and Agrahari (2019). They stated that a more soluble excipient gives more uniform granules in size distribution which will decrease the friability of the tablet. As isomalt and xylitol have higher solubility compared to mannitol it was expected that the ODTs containing isomalt or xylitol have lower friability. However, that was not discovered here which probably is because the particle size varied in the batch, although there were larger particles due to higher solubility there was also a large amount of smaller particles. Although smaller, the granules were more homogenous in size for the batches containing mannitol.

All batches produced with different process parameters, except batch C, had a friability < 1 %. As all of them contains the same excipients and proportions and are similar in other experiments it was expected that all tablets have similar friability as well. Although the friability is above the Eur. Ph. limit of 1 % for batch C there is no significant difference between any of the batches A-G according to the statistical Games-Howell test. The granules from batch C are among the smallest, however the particle size is not remarkably smaller.

5.7 Disintegration

5.7.1 *In vitro* disintegration Ph. Eur. method

The *in vitro* disintegration results from the replicates (batch 1a and 1b produced with direct compression and batch 2a and 2b produced from granulation) showed some difference in the disintegration time (Fig. 4.16, Fig. 4.17). However, the difference was not significant which indicates a reproducible result (p=0.946) and (p=0.123). To further assure that the tablets are similar and the results reproducible more batches should be produced.

Batch 2 containing xylitol as the main filler differs the most from the other batches, both when producing the tablets from direct compression and granules. This indicates that xylitol is more difficult to disintegrate compared to mannitol and isomalt. This is remarkable as xylitol has the highest solubility of the three polyols. The reason xylitol disintegrate slower could be that the water does not penetrate the tablet, instead the tablet dissolve one layer at a time and the dissolution is too fast for the water to penetrate and the super disintegrant is unable to perform the super disintegration effect. This concept also explains why isomalt, with a solubility between mannitol and xylitol also has a disintegration time in between the two.

There seems to be no difference between the disintegration time for tablets produced from granules or direct compression. This indicates that the disintegration of the granules is not rate limiting but a fast process, not affecting the total disintegration of the ODT. Comparing both the *in vivo* and *in vitro* disintegration time for batch 1, 2, 3 and 7, which are produced both with granules and powders (Fig. 4.18) there is no clear trend showing one measurement giving higher or lower disintegration times. For batch 1 produced with direct compression and granules p=0.276 (Batch 1a) and p=0.288 (Batch 1b) indicating no significant difference between the methods. This increases the reliability of the method and measured values as no method seems to increase or decrease the disintegration time. Again, to ensure this more batches should be tested.

From the results (Fig. 4.16) it is visible that batch 7 containing crospovidone has a faster disintegration time compared to croscarmellose, used in batch 1, when produced with direct compression. When produced with granules, the tablets containing croscarmellose and crospovidone shows a more similar disintegration time (Fig. 4.17). However, the difference is not significant neither for tablets produced from granules or direct compression. To conclude whether crospovidone is a better super disintegrant or not more samples would be needed. Regarding sodium starch glycolate the same trend is detected, SSG seems to give the tablets a longer disintegration time compared to crospovidone, however the difference is not significant (p=1.000). If comparing batch 1 with croscarmellose sodium and batch 8 with SSG no significant difference is detected although the results indicate a slightly faster disintegration time for batch 1 (p=0.295).

In summary, the three different super disintegrants seems to give similar disintegration times for the tablets, crospovidone might be the faster one, croscarmellose the second fastest one and SSG the slowest one, however this is not proven with the statistical test. The statistical test is uncertain as only one batch is produced of each tablet and the sample size is rather small. This indication from the *in vitro* test do however comply with the results from the *in vivo* test. Regardless the difference between the super disintegrants is small which indicates that the choice of super disintegrant have minimal effect on the tablet, maybe due to the small % (w/w) of the total tablet. In the future, it would be interesting to produce tablets without any

super disintegrant to examine the effect of any super disintegrant at all and increase the % (w/w) of super disintegrant to optimize the disintegration time.

Lycatab PGS is fully pregelatinized starch and will dissolve in contact with water. On the contrary Starch 1500 is only partially pregelatinized and may act as a disintegrant in contact with water. Therefore, it was expected that batch 1 containing starch 1500 would disintegrate fasted than batch 6 containing Lycatab PGS. However, there was no significant difference between the batches (p=1.000). This could either be explained by the granulation as the granules must dissolve before the disintegration is finished which may be the rate limiting step in this case. Another possible explanation is that the super disintegrant affects the disintegration rate much more. Both batches have the same amount of the super disintegrant croscarmellose sodium added and the rather small amount of partially pregelatinized starch may not make a significant difference.

From batch 9 the effect of MCC can be evaluated. As batch 9 and batch 1 have similar disintegration times both *in vivo* and *in vitro* the conclusion is that MCC have no effect on the disintegration time. This is reasonable as MCC acts as a filler and is added in a small % (w/w).

The standard deviation is larger for the *in vitro* disintegration time compared to the *in vivo* or the developed *in vitro* method. This again motivates the need for another method. The larger standard deviation could be explained by the discs which can increase the disintegration time. Although tablets visible stuck to the disc are removed from the experiment there could be tablets stuck for a little while which increase the variation between the tablets.

There was no significant difference in disintegration time between any of the tablets produced with granules from batch A-G. All of the batches had similar disintegration times which was expected as the characterization of the granules, compression force and friability was similar for all batches. If the granules had a larger difference there would probably be a larger variation of disintegration times as well.

5.7.2 *In vivo* disintegration

The *in vivo* disintegration test showed that batch 7, containing crospovidone as the super disintegrant had the fastest disintegration time both for the tablets produces from granules and direct compression. As crospovidone had a faster disintegration time than both croscarmellose sodium and SSG this indicates that crospovidone is the most effective super disintegrant. However, to determine this with more security more replicates would be needed as the statistical method is more reliable using more samples.

Batch 6 containing Lycatab PGS and batch 1 containing Starch 1500 showed almost identical disintegration times in agreement with the *in vitro* method from Eur. Ph. This indicates that the starch solubility do not affect the disintegration of the tablets. This might be because the super disintegrant affect the disintegration time more and a larger amount would be needed. In this experiment only 10 % (w/w) is added of the starch. According to previous experiments by Colorcon (2009), a larger amount of Starch 1500 compared to a super disintegrant, is required to give similar disintegration times.

From the *in vivo* test it was determined that MCC had no effect on the disintegration time when comparing batch 1 with MCC and batch 9 without MCC. This was also indicated from the *in vitro* result.

The *in vivo* disintegration time was almost identical for batch A-G which strongly indicates that the differences during the fluid bed granulation had no effect on the final tablets. This indicates that the granulation parameters can be chosen to minimize the time for each batch.

Interestingly, the *in vivo* trial gave some different results compared to the *in vitro* method using the disintegration bath in this trial. This could depend on having few replicates and a small sample size which makes the results more uncertain. To further increase the reliability of the results more replicates would be needed for each batch. Also, more samples should be tested to give a more accurate results and increase the reliability of the statistical calculations. However, the results give an indication of the trends for the different batches. As it seems the *in vivo* and *in vitro* method gives different results for some batches the interest in formulating a new *in vitro* method with a stronger IVIVC.

5.7.3 Developed *in vitro* disintegration method

The new method developed had mainly two difficulties, firstly the tablets acted in two different ways once water was added. The tablets containing isomalt or xylitol as the main filler shrunk immediately once liquid was added which made it difficult to measure the disintegration mechanism with the texture analyzer. The force immediately approached zero although only a small part of the outer layer was disintegrated which gave a false measure of only a few seconds disintegration time since the force on the probe of the texture analyzer disappeared. When the method was changed so the probe displaced and followed the tablet with a constant force the disintegration time was between 3-5 s. This mechanism could be explained by the high solubility of isomalt and xylitol which makes the tablets dissolve from the outside, layer for layer instead of disintegrate using swelling, wicking, elastic recovery or repulsion.

The reason the tablets only dissolved the outer layer of the tablet when using a cylinder and keeping the tablet in 1-2 ml of water could be that the water was saturated with sugars and could not dissolve more of the tablet.

The other batches (1 and 4-9) containing mannitol as the main filler and MCC, isomalt or xylitol in a smaller volume all swelled when adding water to the tablet. This was detected by the increased force on the probe, the swelling reached the maximum after 5-10 seconds for most tablets, then the force on the probe slowly decreased when the tablet started to shrink, this is called the relaxation phase. The disintegration time showed a linear correlation with the *in vivo* disintegration time, by a factor 2.5 of the time to maximum force. This shows that the relaxation time is approximately 1.5 times as long as the swelling time. Comparing the force on the probe with the mouth feel of the tablet, after the finished *in vivo* disintegration time there are still a force larger than 50 % of the maximum force on the probe for most tablets (Appendix 9.8), indicating that the tablet is not fully dissolved into particles when considered fully disintegrated *in vivo*, however a wet soft mass remains. The motions of the tongue are probably mixing the soft material of the tablet before swallowing why there is still a detected force on the probe when finishing the new *in vitro* disintegration test.

A study by Popescu et al. (2010) used a texture analyzer to measure the *in vitro* disintegration time. The method used a probe of 5 mm, 2 ml water and 3 N pressure from the probe before adding the water. They did also emphasize that the method was only appliable for tablets containing mannitol.

5.8 Design of experiment granulation process parameters

Due to a high spray rate and low air flow in batch B the product became wet and heavy which resulted in the product collecting in the bottom and along the walls of the product container. This shows that a certain spray rate requires a certain minimum air flow to ensure sufficient flow of the product and even distribution of the liquid. From this study it can be concluded that a spray rate of 20 ml/min requires more than 30 m^3/h air flow. It would be interesting to further try different combinations of spray rate and air flow to determine the limit of sufficient air flow when adding specific amount of liquid per min.

The *in vivo* disintegration time was significantly increased when increasing the spray rate during fluid bed granulation. This indicates that the spray rate should be limited to ensure a short disintegration time. Limiting the spray rate also decrease the risk of over wetting the product during granulation, however the process time increases when decreasing the spray rate.

It was expected that an increase in air flow would decrease the process time as a higher air flow should speed up the drying process. However, a higher air flow increased the total process time. This could be because the air flow of 60 m^3/h was too high and forced particles into the spray nozzle which could make it drip rather than spray the liquid. If the spray nozzle drip completely the product would form a large mass in the bottom, maybe the spray nozzle formed droplets for a short while which formed some larger particles increasing the drying time. It would be interesting to decrease the air flow to 50 m^3/h and see if the same trend is recognized. From this trial it is concluded that the center replicates have the fastest process time and seems to be an effective production method.

To counteract this the air flow also needs to decrease as this significantly reduces the process time.

To make the model more reliable and give better correlations between the granule/ODT properties and the process settings more samples are needed. As batch B was unsuccessful there was only three different batches and 3 replicates used in the model.

5.9 Statistical analysis

The Games Howell test was chosen as the data is not known to be normal distributed which makes the test applicable. Also, a rather small sample size is required, 6 samples are recommended. However only the *in vivo* disintegration time have more than 6 samples for each batch. The *in vitro* disintegration time have 6 samples for most batches, however some have fewer due to tablets getting stuck on the disc in the disintegration bath. The friability test was performed in triplicates why the statistical analysis is more of an indication if the results is significant. To make the statistical analysis more reliable more replicates should be performed of each batch.

6 Conclusions

There are many similarities between ODTs produced with direct compression and ODTs produced from granules. The main difference was the improved flowability of the granules produced with fluid bed granulation compared to the excipients in powder form.

The variation between the granule's particle size, moisture content, flowability and morphology were larger when altering the added excipients compared to when altering the process parameters during fluid bed granulation. Mainly the characteristics were affected by the choice of polyols used while the effect of excipients in a smaller amount (% w/w) had a less significant effect.

The used polyols disintegrated with different mechanisms and the polyol with the fastest disintegration and lowest friability was concluded to be mannitol. Regarding the binder, partially pregelatinized starch was the most suitable option as it lowered the friability compared to fully pregelatinized starch. The tested super disintegrants gave no significant difference in the *in vitro* disintegration time when examined, however, *in vivo* it is indicated that crospovidone has a faster disintegration time compared to croscarmellose sodium and sodium starch glycolate.

A texture analyzer measuring the force from the tablet was an effective method to determine the *in vitro* disintegration time for ODTs with mannitol. The texture analyzer was used with a 20 mm probe applying a constant force of 0.1 N to the tablet which was embedded in a filter above and under it. When the force was constant 1 ml of water was added around the lower filter and the change in force was determined. The *in vitro* disintegration time seemed to be proportional to the time of swelling with a factor 2.5, for ODTs containing mannitol.

7 Future outlook

To further develop this experiment and be able to draw more conclusions more replicates would be needed for all batches. This would give a better accuracy of the conclusions, better reliability of the statistical analysis and a more trustworthy model with Modde. Also, it would be interesting to compare the batches of granules with tablets produced with direct compression from powders instead of only a few selected batches.

More process parameters could be varied during the fluid bed granulation to further evaluate the effect of the process and optimize the granulation. First of all the atomization pressure could be varied so the spray nozzle sprays larger or smaller liquid particles. Also, the total amount of water added could be altered, a smaller amount of water would for example decrease the process time. Regarding the excipients it could be interesting to compare the disintegration times received in this experiment with disintegration times when adding the super disintegrant extra granularly. This would prevent the water from having to penetrate the granules before the disintegration mechanism can start and might improve the disintegration time.

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9 Appendix

9.1 Lab protocol from Colorcon used to calculate suitable amount of water added in fluid bed granulation

Fluid Bed Wet Granulation

Granulation

Ingredient	Percent	mg / tablet	g / batch
Magnesium Carbonate	10.00	20.0	70.00
Microcrystalline Cellulose [50 micron]	59.50	119.0	416.50
Pregelatinized Starch [Starch 1500®] – Dry	20.00	40.0	140.00
Pregelatinized Starch [Starch 1500®] - Slurry	10.00	20.0	70.00

Dry Additions

Ingredient	Percent	mg / tablet	g / batch
Magnesium Stearate	0.50	1.0	3.50
Total	**100.00**	**200.0**	**700.00**

Process Steps

Prepare the granulation binder fluid by hydrating a portion of the Starch 1500 (equal to 10% of the final formulation) in water (at room temperature) to achieve a concentration of 15% (w/w). In an appropriately sized container, position a low-shear propeller mixer so that the blade is close to bottom of the container and off-centre. Increase the speed of the mixer to create a vortex. Add the Starch 1500 and allow it to mix at high speed for 30 minutes.

Add granulation ingredients to fluid-bed.
Measure LOD after blending.
Top-spray set-up with target bed temp of 24-30°C.
Inlet air set point – 60-65°C.
Begin spraying after 2-3 minutes; spray rate = 25-35 g/min.
When the slurry is exhausted, continue with water.
Measure LOD when spray is complete.
Dry at 65°C to an LOD close to the initial LOD.
Pass the granulation through comil if necessary.
Pass Mg St through 60-mesh screen prior to weighing.
Add Mg St & blend for 5 minutes.

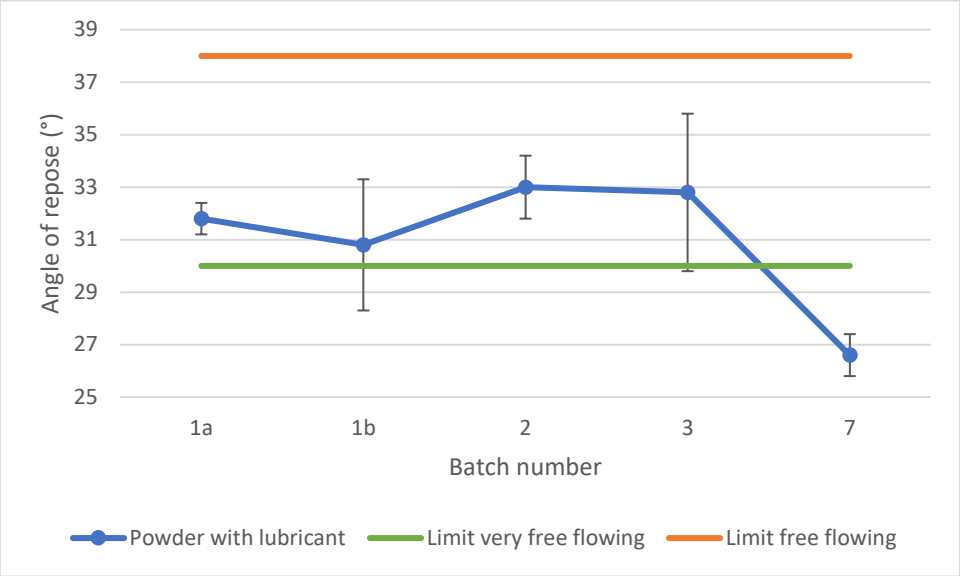
9.2 Complete measured and calculated data of the flowability for the powders with lubricant using the stomp volumeter.

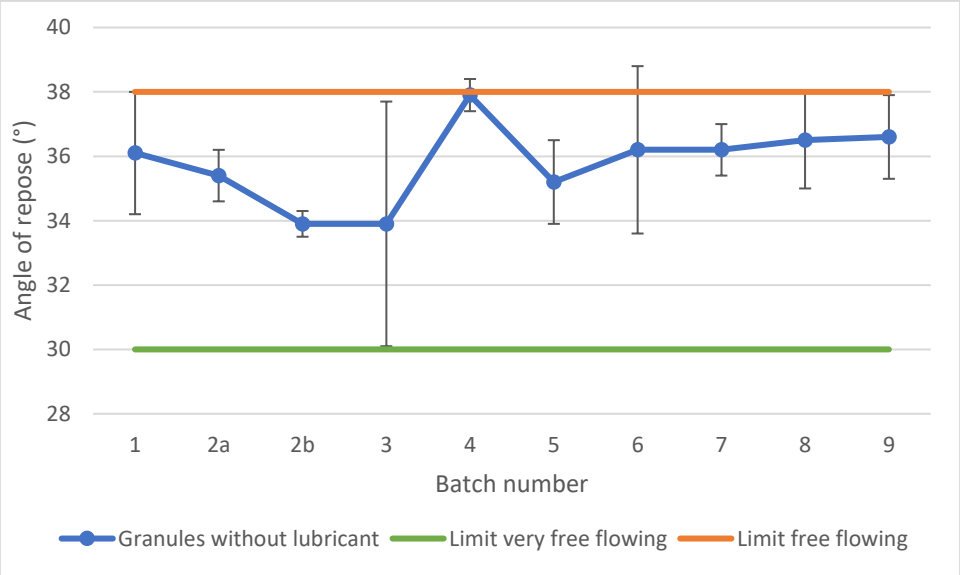
Batch nr	**Mass (g)**	**Bulk volume (ml)**	**Shake volume (ml)**	**Bulk density (g/cm^3)**	**Shake density (g/cm^3)**	**Hausner ratio**	**Flowability**	**Porosity (ε)**
1a	113.6	230	192	0.49	0.59	1.20		
1a	109.6	222	185	0.49	0.59	1.20		
Mean (including standard deviation):						**1.20± 0.00**	**Fair**	**0.18**
1b	96.9	200	163	0.48	0.59	1.23		
1b	96.8	198	163	0.49	0.59	1.21		
Mean (including standard deviation):						**1.22± 0.01**	**Fair**	**0.18**
2	102.1	230	188	0.44	0.54	1.22		
2	97.4	220	179	0.44	0.54	1.23		
Mean (including standard deviation):						**1.23± 0.00**	**Fair**	**0.18**
3	141.3	223	184	0.63	0.77	1.21		
3	140.4	221	182	0.64	0.77	1.21		
Mean (including standard deviation):						**1.21± 0.00**	**Fair**	**0.18**
7	102.6	237	188	0.43	0.55	1.26		
7	98.1	220	179	0.45	0.55	1.23		
Mean (including standard deviation):						**1.24± 0.02**	**Fair**	**0.20**

9.3 Complete measured and calculated data of the flowability for the granules using the stomp volumeter.

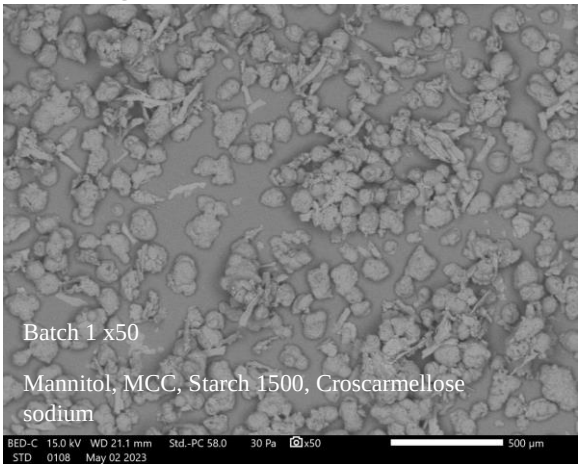
Batch nr	**Mass (g)**	**Bulk volume (ml)**	**Shake volume (ml)**	**Bulk density (g/cm^3)**	**Shake density (g/cm^3)**	**Hausner ratio**	**Flowability**	**Porosity (ε)**
1	75.3	220	170	0.34	0.44	1.29		
1	83.4	236	195	0.35	0.43	1.21		
1	79.7	231	185	0.35	0.43	1.25		
Mean (including standard deviation):						**1.25 ± 0.04**	**Fair**	**0.20**
2a	54.5	221	174	0.25	0.31	1.27		
2a	54.2	220	172	0.25	0.32	1.28		
Mean (including standard deviation):						**1.27± 0.01**	**Passable**	**0.22**
2b	62.6	221	175	0.28	0.36	1.26		
2b	70.5	242	190	0.29	0.37	1.27		
Mean (including standard deviation):						**1.27± 0.01**	**Passable**	**0.21**
3	82.2	230	183	0.36	0.45	1.26		
3	85.3	234	189	0.36	0.45	1.24		
Mean (including standard deviation):						**1.25 ± 0.01**	**Fair**	**0.20**
4	78.1	235	187	0.33	0.42	1.26		
4	84.1	247	198	0.34	0.42	1.25		
Mean (including standard deviation):						**1.25 ± 0.01**	**Fair**	**0.20**
5	87.4	241	198	0.36	0.44	1.22		
5	82.8	232	187	0.36	0.44	1.24		
Mean (including standard deviation):						**1.23 ± 0.02**	**Fair**	**0.19**
6	77.7	231	182	0.34	0.43	1.27		
6	79.5	234	187	0.34	0.43	1.25		
Mean (including standard deviation):						**1.26 ± 0.01**	**Passable**	**0.21**
7	85	239	192	0.36	0.44	1.24		
7	84.4	240	190	0.35	0.44	1.26		
Mean (including standard deviation):						**1.25 ± 0.01**	**Fair**	**0.20**
8	85.1	237	190	0.36	0.45	1.25		
8	85.2	236	192	0.36	0.44	1.23		
Mean (including standard deviation):						**1.24 ± 0.01**	**Fair**	**0.19**
9	84.3	232	191	0.36	0.45	1.25		
9	79.8	220	179	0.36	0.44	1.23		
Mean (including standard deviation):						**1.22 ± 0.01**	**Fair**	**0.18**

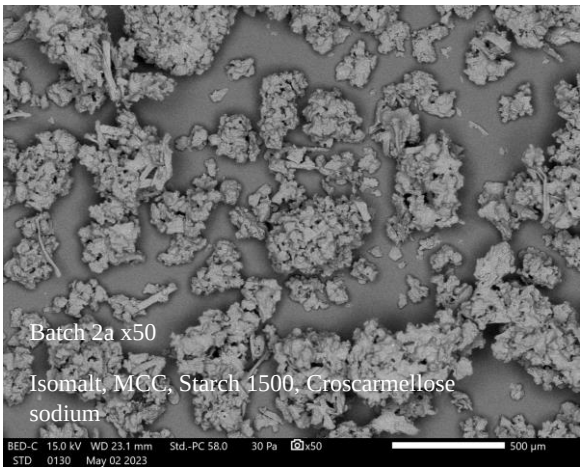
9.4 Angle of repose estimated with the Carr index.

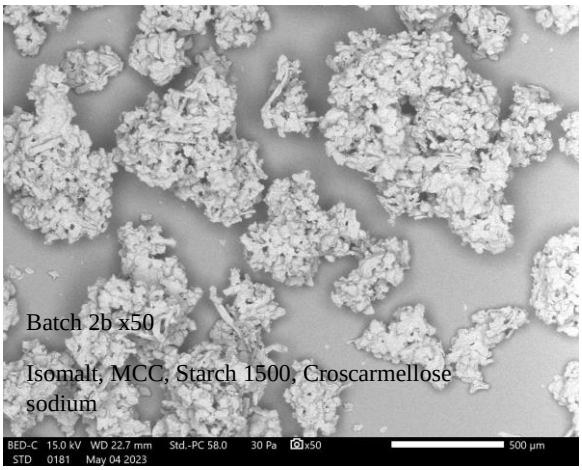


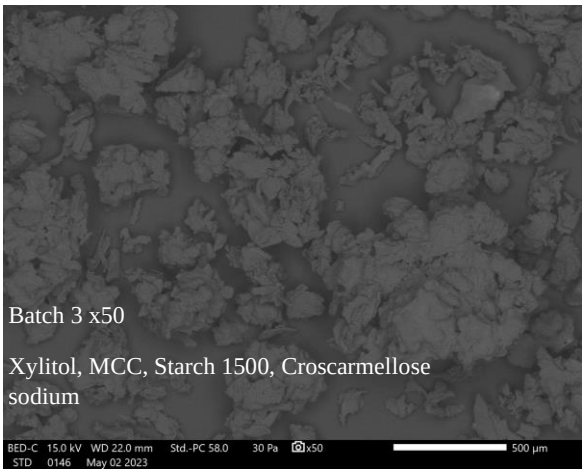


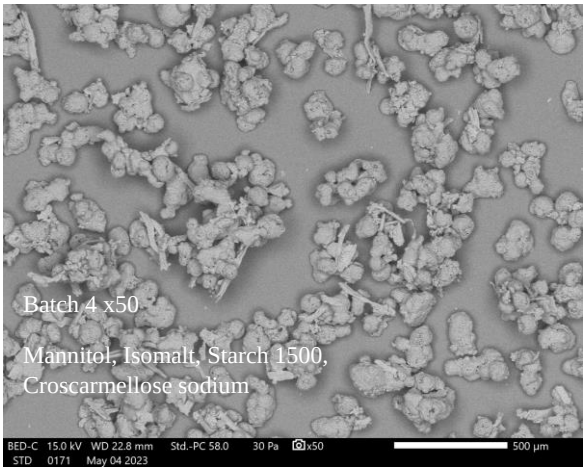
9.5 Images of the granules in batch 1-9 received from the SEM with x50 zooming

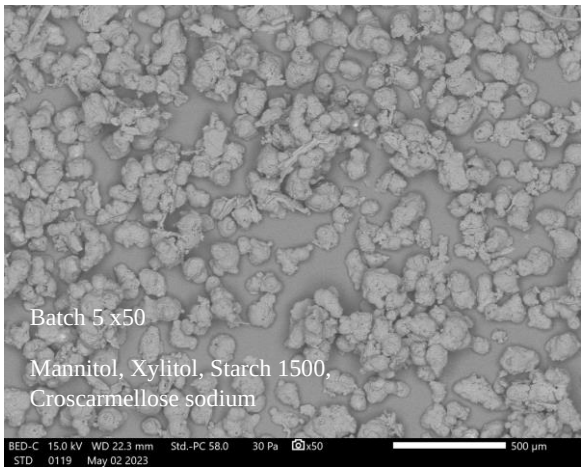


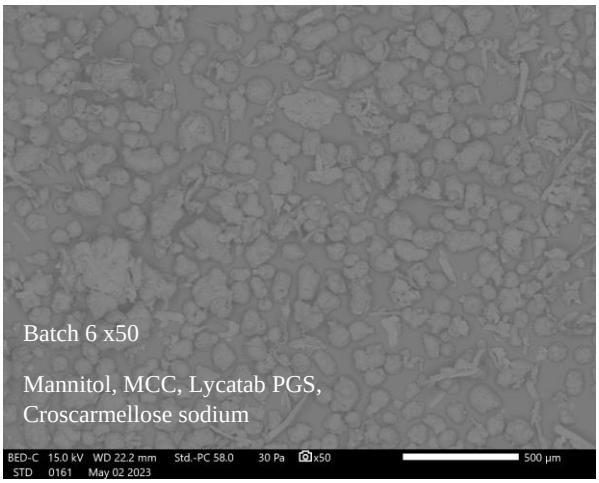


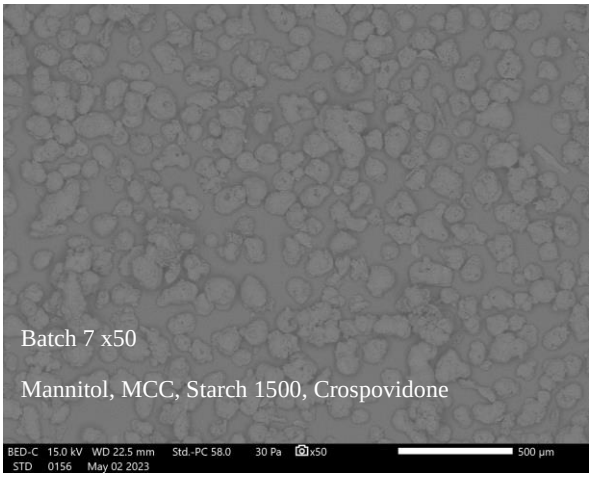


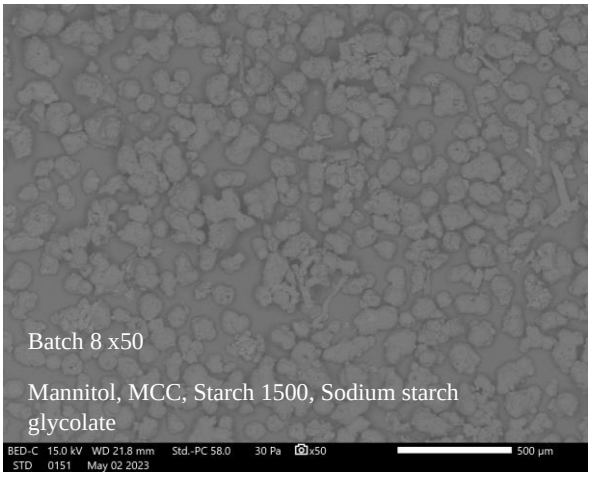


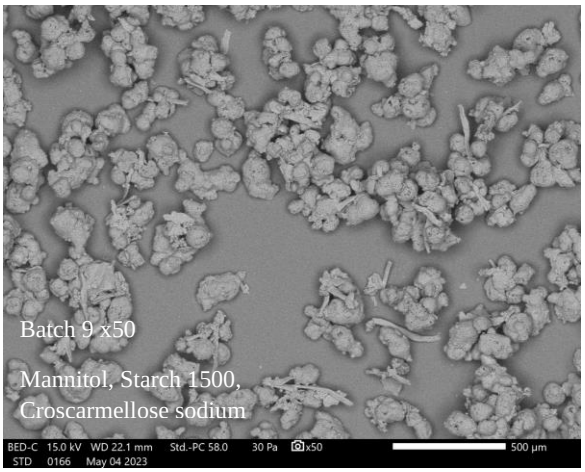




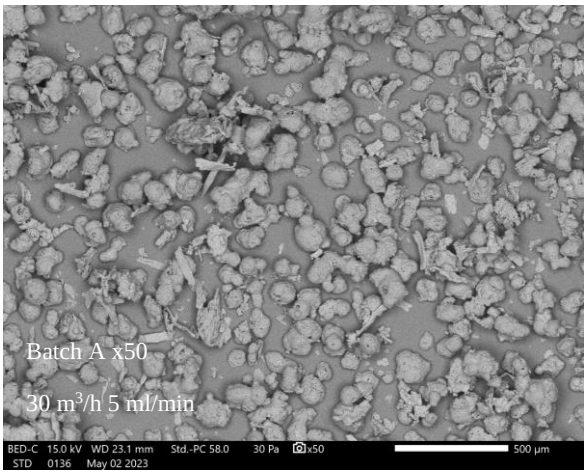

Batch 6 x50
Mannitol, MCC, Lycatab PGS, Croscarmellose sodium
BED-C 15.0 kV WD 22.2 mm Std.-PC 58.0 30 Pa x50 500 µm
STD 0161 May 02 2023

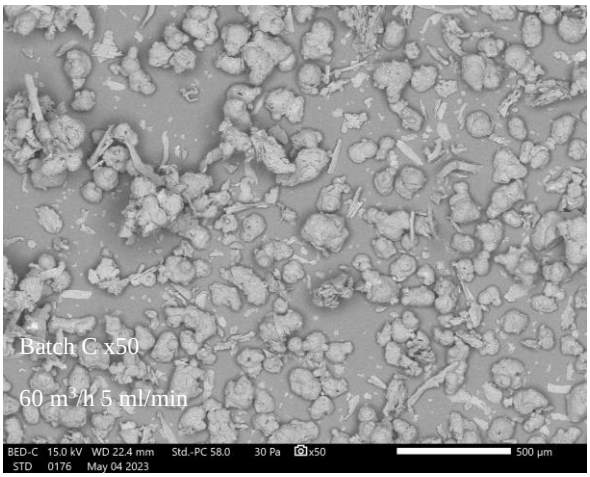

Batch 7 x50
Mannitol, MCC, Starch 1500, Crospovidone
BED-C 15.0 kV WD 22.5 mm Std.-PC 58.0 30 Pa x50 500 µm
STD 0156 May 02 2023

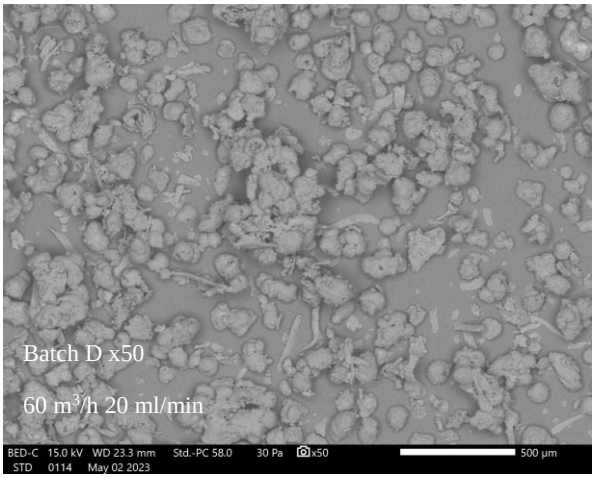

Batch 8 x50
Mannitol, MCC, Starch 1500, Sodium starch glycolate
BED-C 15.0 kV WD 21.8 mm Std.-PC 58.0 30 Pa x50 500 µm
STD 0151 May 02 2023

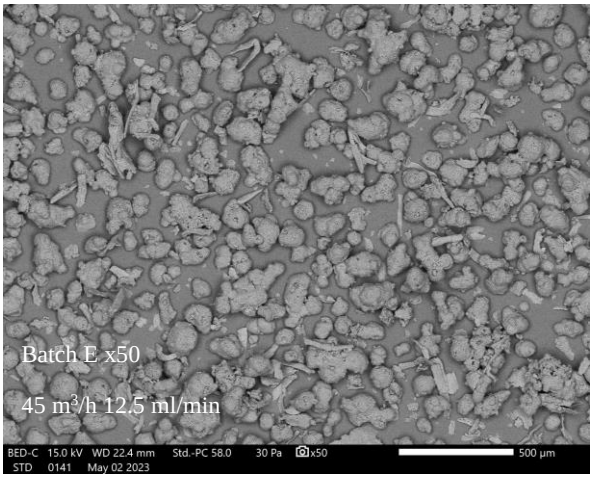

Batch 9 x50
Mannitol, Starch 1500, Croscarmellose sodium
BED-C 15.0 kV WD 22.1 mm Std.-PC 58.0 30 Pa x50 500 µm
STD 0166 May 04 2023

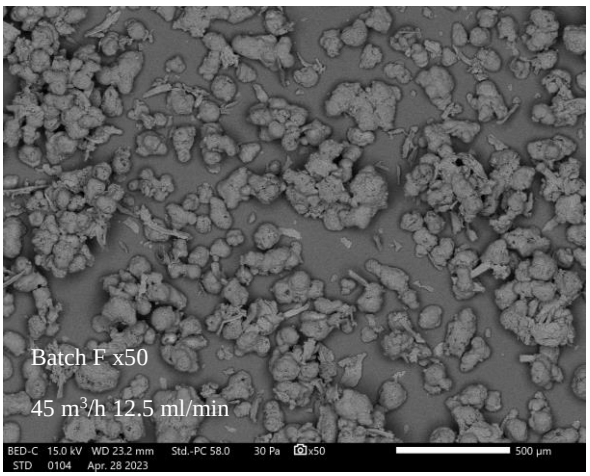
9.6 Images of the granules in batch A-G received from the SEM with x50 and x200-300 zooming

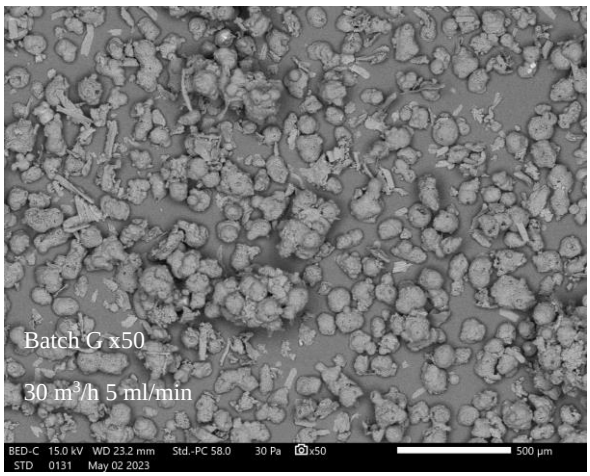


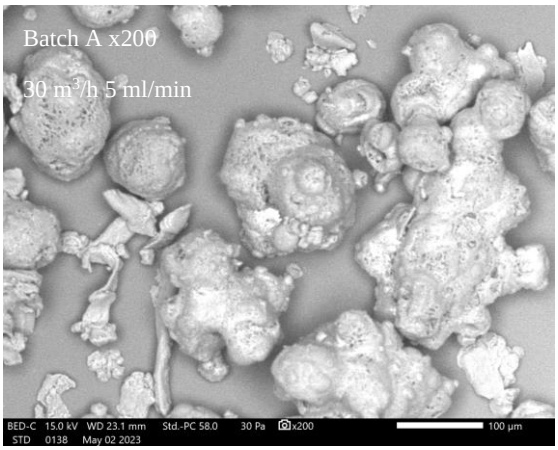


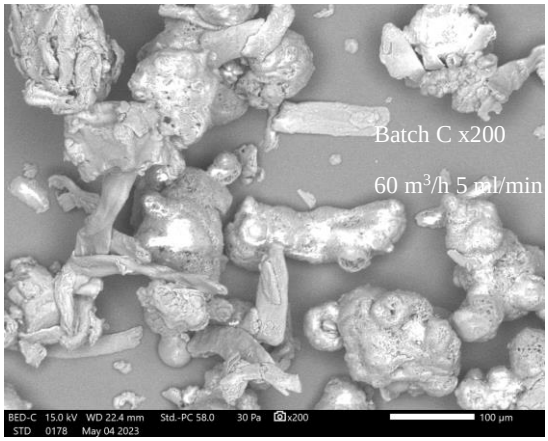


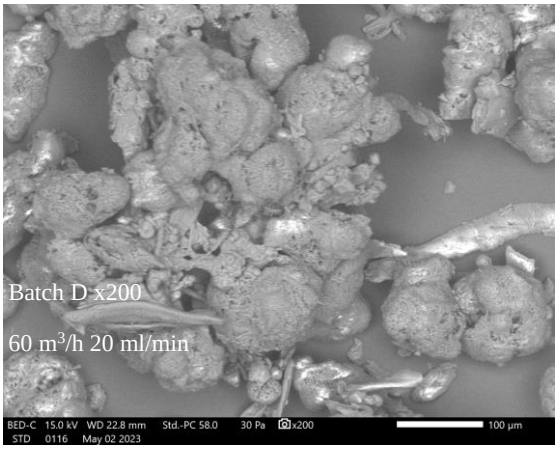


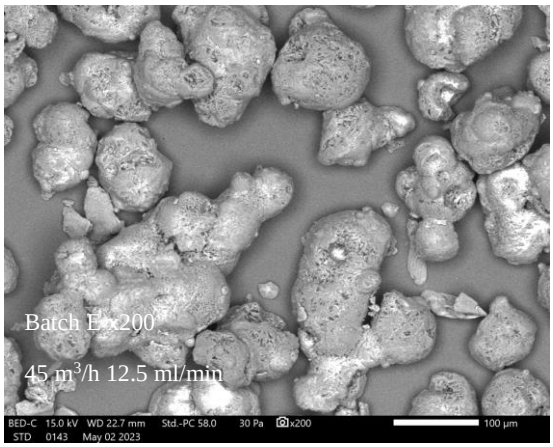


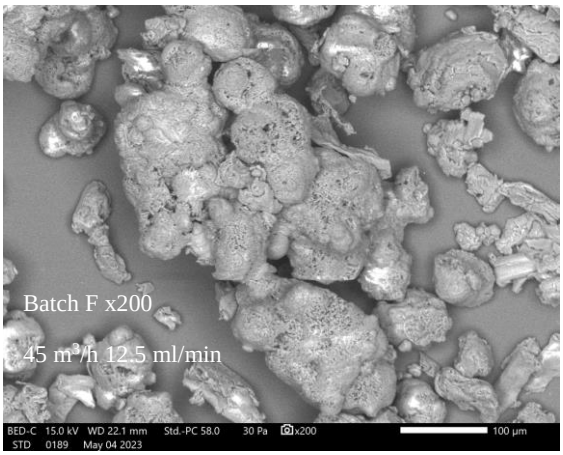


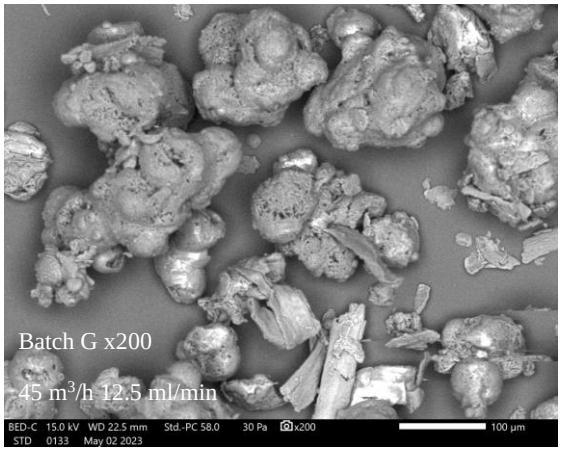

Batch A x200
30 m3/h 5 ml/min
BED-C 15.0 kV WD 23.1 mm Std.-PC 58.0 30 Pa x200 100 µm
STD 0138 May 02 2023


Batch C x200
60 m3/h 5 ml/min
BED-C 15.0 kV WD 22.4 mm Std.-PC 58.0 30 Pa x200 100 µm
STD 0178 May 04 2023

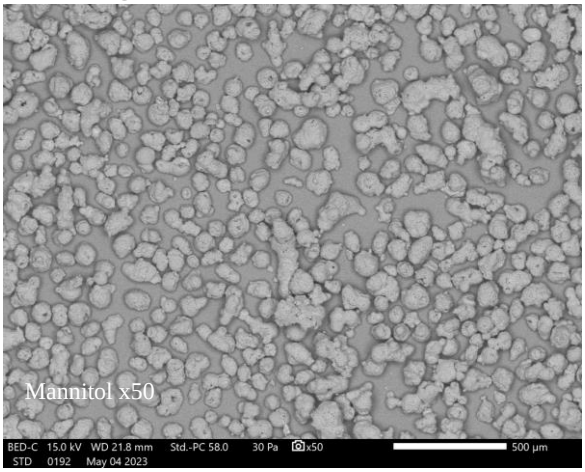

Batch D x200
60 m3/h 20 ml/min
BED-C 15.0 kV WD 22.8 mm Std.-PC 58.0 30 Pa x200 100 µm
STD 0116 May 02 2023

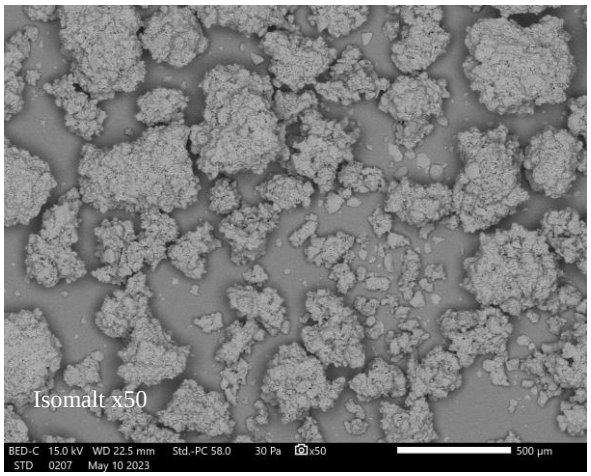

Batch E x200
45 m3/h 12.5 ml/min
BED-C 15.0 kV WD 22.7 mm Std.-PC 58.0 30 Pa x200 100 µm
STD 0143 May 02 2023

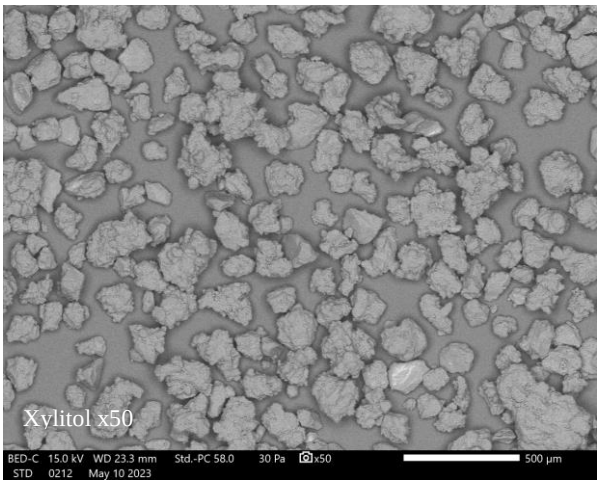

Batch F x200
45 m3/h 12.5 ml/min
BED-C 15.0 kV WD 22.1 mm Std.-PC 58.0 30 Pa x200 100 µm
STD 0189 May 04 2023

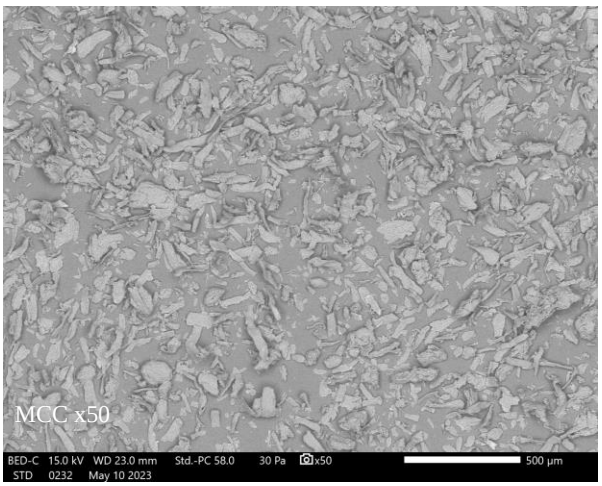

Batch G x200
45 m3/h 12.5 ml/min
BED-C 15.0 kV WD 22.5 mm Std.-PC 58.0 30 Pa x200 100 µm
STD 0133 May 02 2023

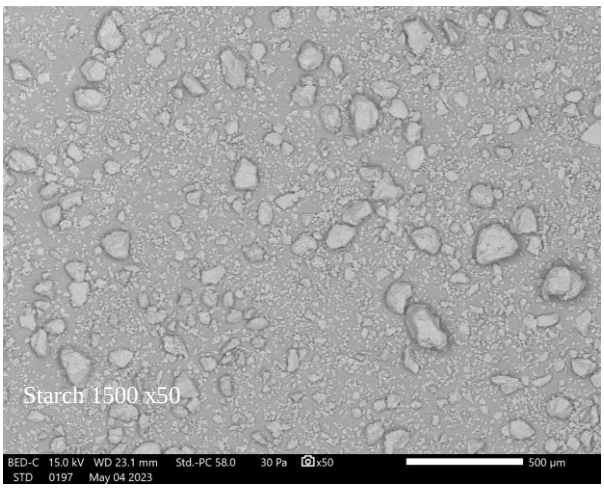
9.7 Images of the raw materials received from the SEM with x50 and x200-300 zooming

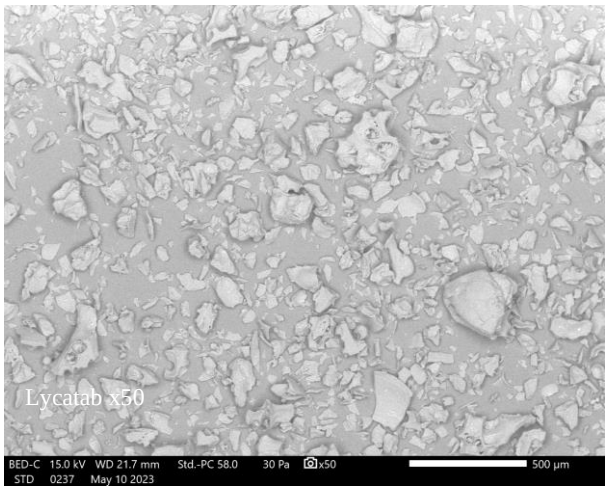


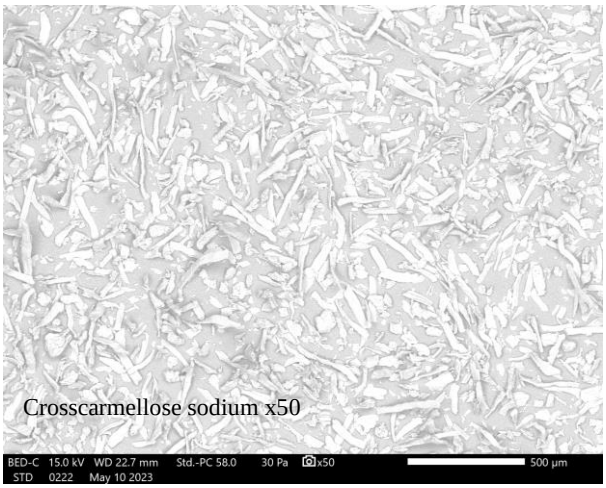


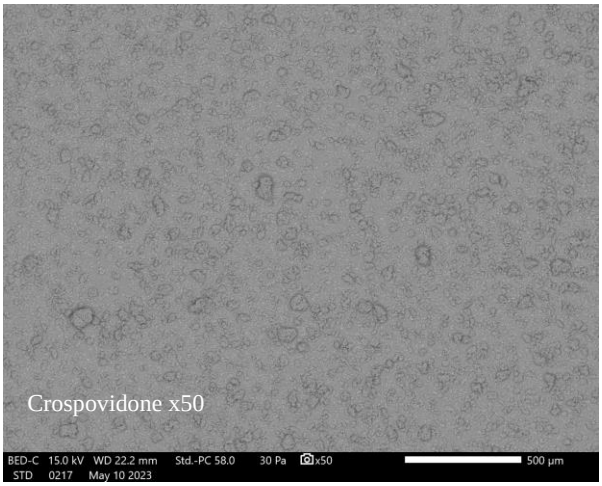


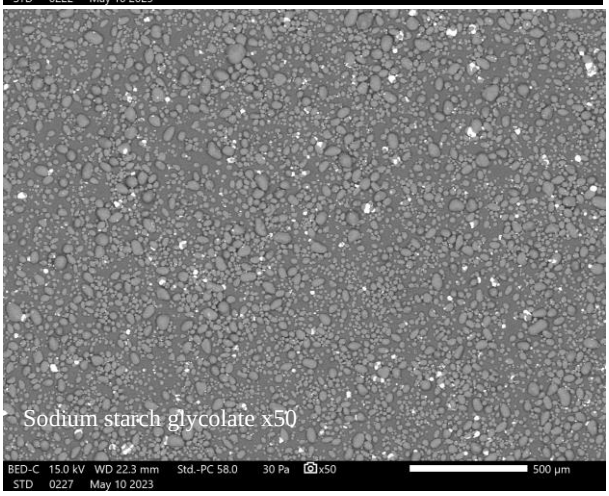


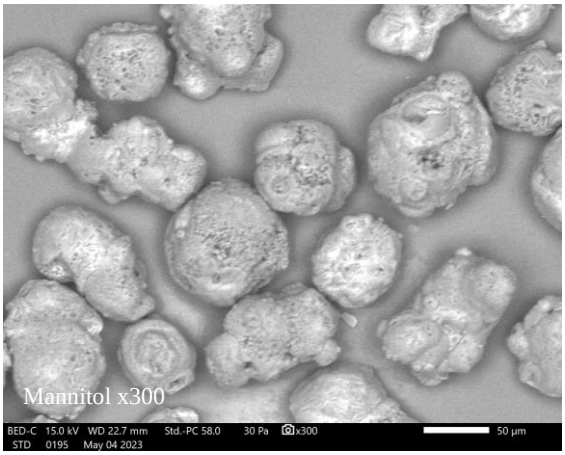


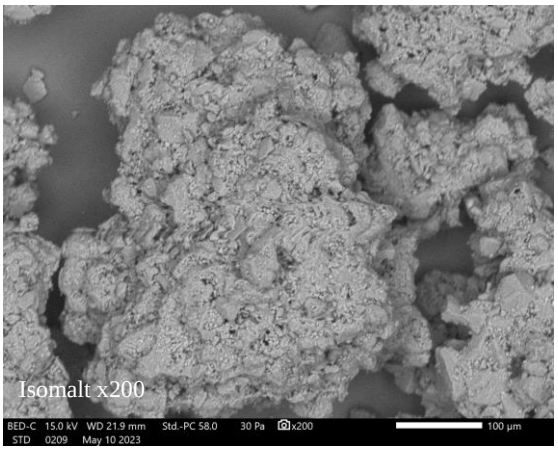


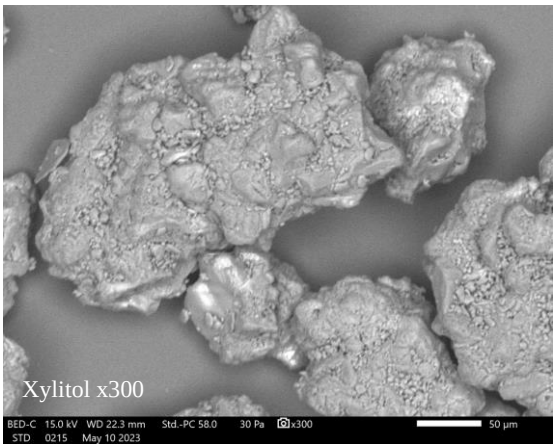

Crosscarmellose sodium x50
BED-C 15.0 kV WD 22.7 mm Std.-PC 58.0 30 Pa x50 500 µm
STD 0222 May 10 2023

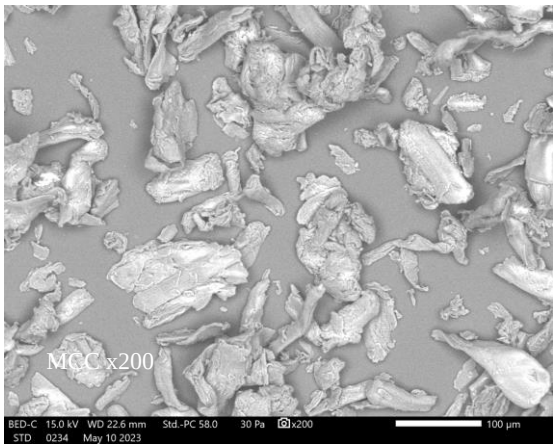

Crospovidone x50
BED-C 15.0 kV WD 22.2 mm Std.-PC 58.0 30 Pa x50 500 µm
STD 0217 May 10 2023

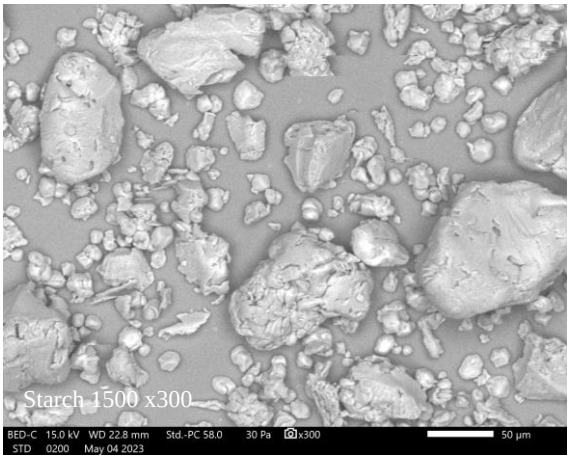

Sodium starch glycolate x50
BED-C 15.0 kV WD 22.3 mm Std.-PC 58.0 30 Pa x50 500 µm
STD 0227 May 10 2023

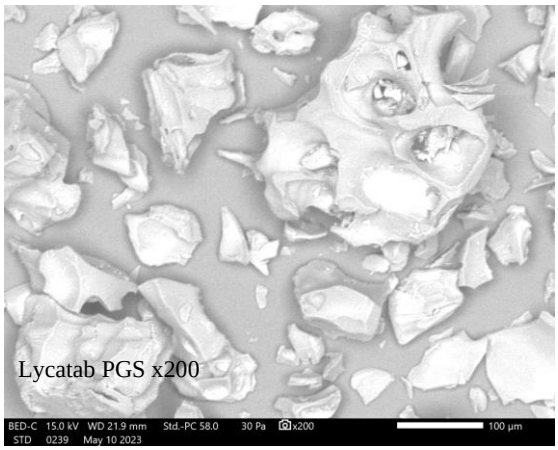

Mannitol x300
BED-C 15.0 kV WD 22.7 mm Std.-PC 58.0 30 Pa x300 50 µm
STD 0195 May 04 2023

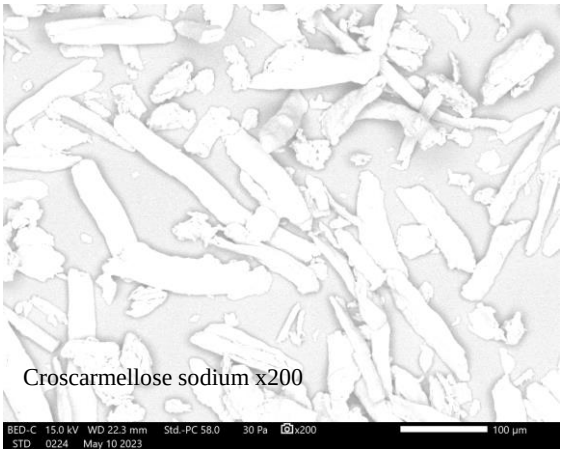

Isomalt x200
BED-C 15.0 kV WD 21.9 mm Std.-PC 58.0 30 Pa x200 100 µm
STD 0209 May 10 2023

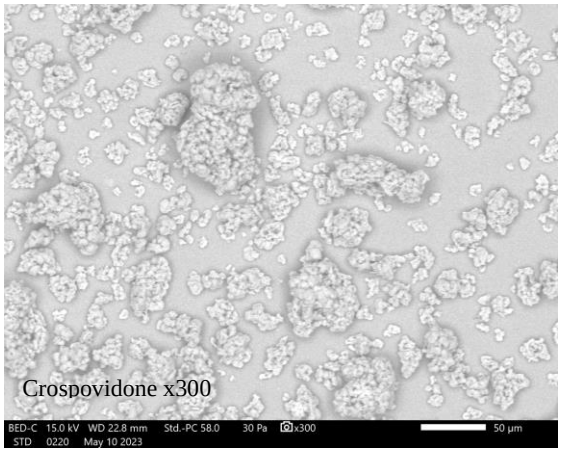

Xylitol x300
BED-C 15.0 kV WD 22.3 mm Std.-PC 58.0 30 Pa x300 50 µm
STD 0215 May 10 2023

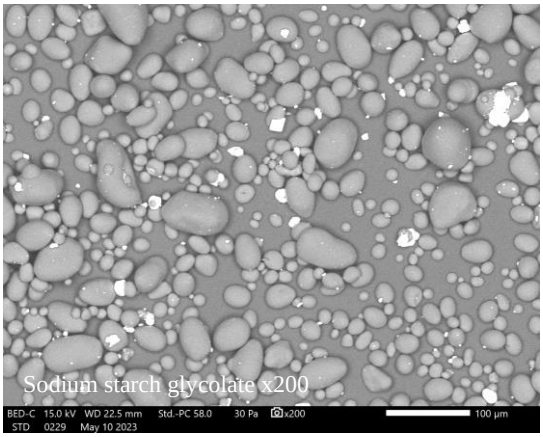

MCC x200
BED-C 15.0 kV WD 22.6 mm Std.-PC 58.0 30 Pa x200 100 µm
STD 0234 May 10 2023


Starch 1500 x300
BED-C 15.0 kV WD 22.8 mm Std.-PC 58.0 30 Pa x300 50 µm
STD 0200 May 04 2023

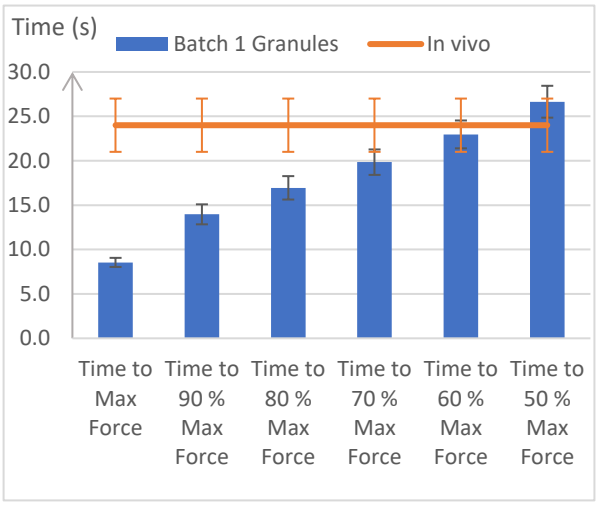

Lycatab PGS x200
BED-C 15.0 kV WD 21.9 mm Std.-PC 58.0 30 Pa x200 100 µm
STD 0239 May 10 2023

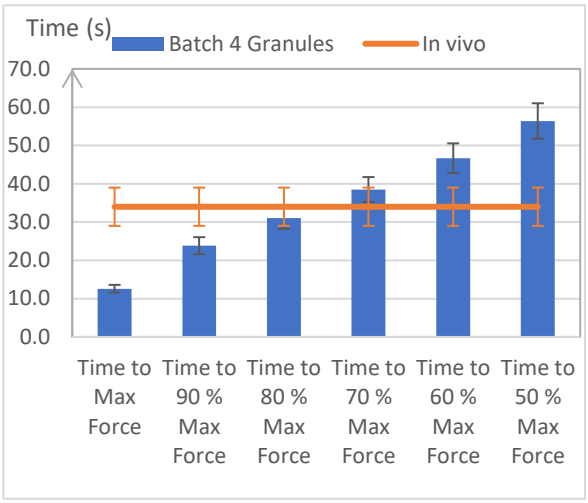

Croscarmellose sodium x200
BED-C 15.0 kV WD 22.3 mm Std.-PC 58.0 30 Pa x200 100 µm
STD 0224 May 10 2023

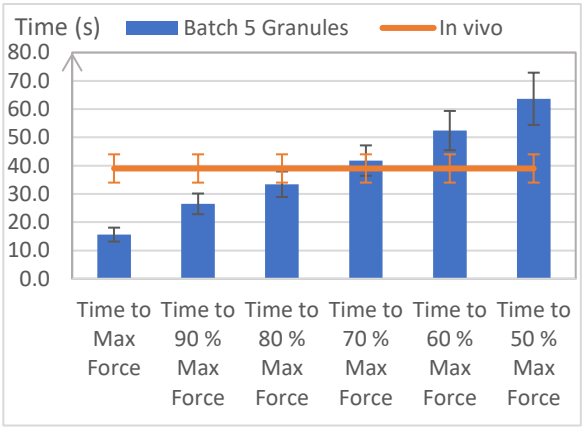

Crospovidone x300
BED-C 15.0 kV WD 22.8 mm Std.-PC 58.0 30 Pa x300 50 µm
STD 0220 May 10 2023

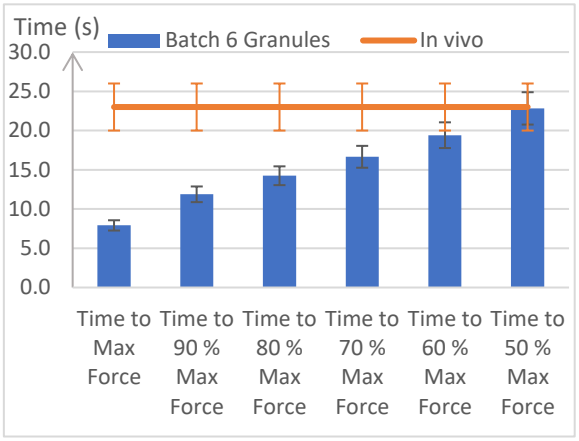

Sodium starch glycolate x200
BED-C 15.0 kV WD 22.5 mm Std.-PC 58.0 30 Pa x200 100 µm
STD 0229 May 10 2023

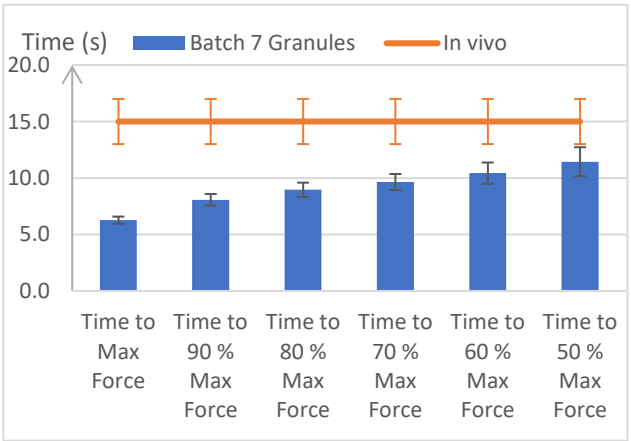
9.8 Disintegration times calculated from the texture analyzer and the correlating *in vivo* disintegration time

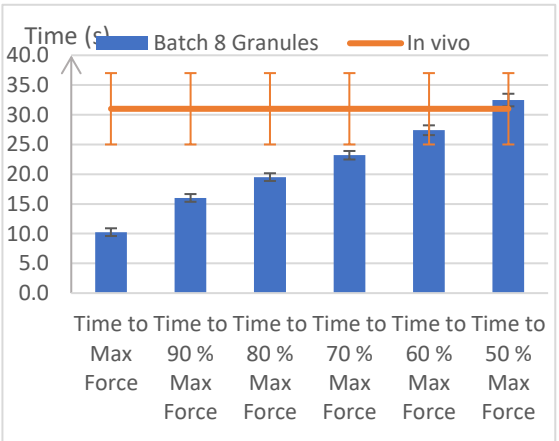


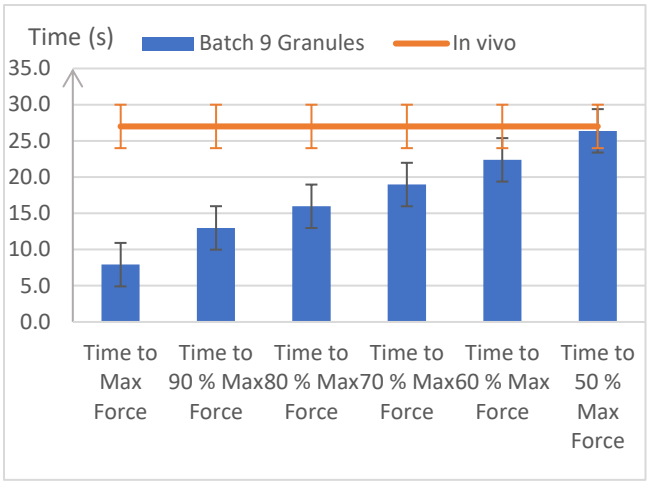


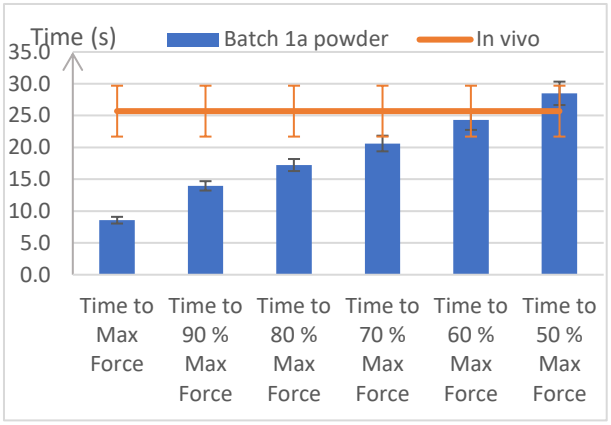


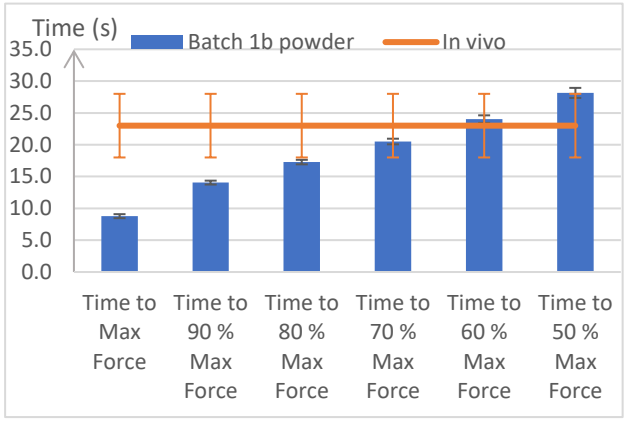


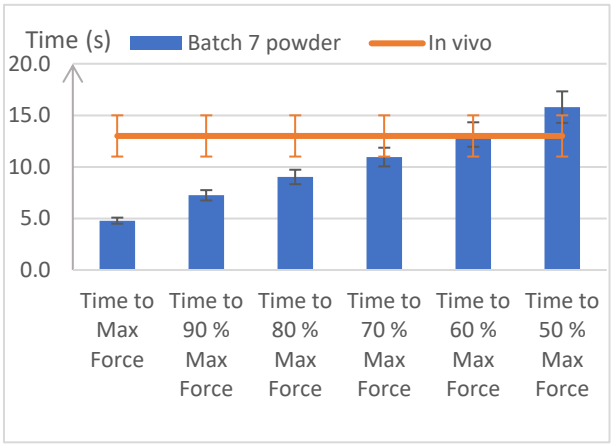





Time (s)
Batch 9 Granules
In vivo
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
Time to Max Force
Time to 90 % Max Force
Time to 80 % Max Force
Time to 70 % Max Force
Time to 60 % Max Force
Time to 50 % Max Force


Time (s)
Batch 1a powder
In vivo
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
Time to Max Force
Time to 90 % Max Force
Time to 80 % Max Force
Time to 70 % Max Force
Time to 60 % Max Force
Time to 50 % Max Force


Time (s)
Batch 1b powder
In vivo
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
Time to Max Force
Time to 90 % Max Force
Time to 80 % Max Force
Time to 70 % Max Force
Time to 60 % Max Force
Time to 50 % Max Force


Time (s)
Batch 7 powder
In vivo
20.0
15.0
10.0
5.0
0.0
Time to Max Force
Time to 90 % Max Force
Time to 80 % Max Force
Time to 70 % Max Force
Time to 60 % Max Force
Time to 50 % Max Force