THE EFFECT OF GRANULE SIZE ON THE MINI-TABLET WEIGHT VARIABILITY AND CONTENT UNIFORMITY

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Tiivistelmä – Referat – Abstract

Minitabletit ovat halkaisijaltaan 1-3 mm, ja ne voidaan annostella yhtenä tablettina tai moniannosvalmisteena. Minitabletit ovat houkutteleva vaihtoehto tavanomaisille kiinteille annosmuodoille, koska niiden annostelu on helppoa ja ne mahdollistavat myös joustavan yhdistelmähoidon ja yksilöllisen lääkehoidon. Minitabletien valmistuksessa formulaation hyvä valuvuus on avainasemassa, koska pienet vaihtelut tablettimuotin täyttymisessä voivat johtaa merkittäviin vaihteluihin minitablettien painoissa. Lisäksi painonvaihtelun vähentämiseksi hiukkaskoko ei saa ylittää 1/3 tablettimuotin halkaisijasta. Tämän tutkimuksen tarkoituksena oli määrittää raekoon vaikutus minitabletin painonvaihteluun ja annoksen yhdenmukaisuuteen. Minitabletit valmistettiin käyttäen suorapuristusta sekä high-shear märkärakeistusta ja rullapuristusrakeistusta. Yhdeksästä valmistetusta formulaatiosta määritettiin hiukkaskokojakauma, Hausnerin suhdeluku, Carrin indeksi, kaltevuuskulma ja massavaluvuus. Minitabletit valmistettiin pyörivällä tablettipuristimella käyttäen halkaisijaltaan 3 mm yksittäisiä tablettimuotteja.

Suorapuristusmassan hiukkaskoko oli pienin, kun taas 1,0 mm ja 1,25 mm:n neliön muotoisen seulan läpi seulottujen rullapuristusrakeiden hiukkaskoko oli suurin. Yllättäen RC 0,8 mm:n raastinseulan läpi seulotun formulaation hiukkaskokojakauma oli leveä, ja se luokitellaan lisäksi erittäin hienoksi jauheseokseksi. Leveä hiukkaskokojakauma voi johtua korkeasta täyttöasteesta pakkoseulonnan aikana. Neljällä erilaisella märkäraeformulaatiolla puolestaan oli hyvin samanlainen hiukkaskokojakauma. Hausnerin suhdeluvun ja Carrin indeksiarvojen mukaan formulaatioiden valuvuusominaisuudet vaihtelivat kohtalaisen ja erittäin huonon välillä, kun taas kaltevuuskulman mukaan valuvuussominaisuudet olivat erinomaisen ja huonon välillä. Näistä yhdeksästä formulaatiosta valmistettiin kuitenkin minitabletteja, joiden painonvaihtelu oli Euroopan Farmakopean asettamien rajojen sisäpuolella. Minitablettien painot olivat ± 8,46 % tavoitepainosta, eikä yksikään ylittänyt Ph. Eur:n asettamaa 10 % rajaa. Painonvaihtelu suhteellinen keskihajonta oli pieni, 1,0-2,9 %. Painonvaihtelun erot voivat johtua hiukkasten tai rakeiden koon ja tiheyseron aiheuttamasta segregaatiosta. Tätä tukee se, että tablettipuristimessa ei käytetty pakkosyöttöä tai alipaineimuria, mikä saattoi johtaa formulaation takaisinkiertoon ja rakeiden jauhautumiseen pienemmiksi partikkeleiksi. Lisäksi syöttölaitteen täyttöaste on saattanut vaihdella yhdeksän formulaation tabletointien välillä ja vaikuttaa painonvaihteluun tavalla, jota ei tässä tutkimuksessa ole tunnistettu.

Ainoastaan suorapuristettujen minitablettien annoksen yhdenmukaisuus oli Ph. Eur:n asettamien hyväksymisrajojen sisällä. Märkärakeistetussa formulaatioissa parasetamolin määrä oli 98,5 % ja kuivarakeistetussa 97,7 %. Nämä tulokset viittaavat siihen, että formulaatiot sisälsivät riittävän määrän parasetamolia, mutta eivät selitä sitä, miksi märkärakeista puristetut minitabletit eivät täyttäneet annoksen yhdenmukaisuuskriteerejä. Minitablettien painonvaihtelu ei myöskään välttämättä selitä täysin sitä, miksi annoksen yhdenmukaisuuskriteerit eivät täyttyneet. Yhteenvetona voidaan tiivistää, että suorapuristus soveltuu halkaisijaltaan 3 mm minitablettien valmistukseen, lisätutkimuksia kuitenkin tarvitaan selvittämään märkä- ja kuivarakeistettujen formulaatioiden toimivuutta minitablettien valmistamiseksi.

Avainsanat – Nyckelord – Keywords
Minitabletti,suorapuristus, high-shear märkärakeistus, rullapuristusrakeistus, painonvaihtelu, annoksen yhdenmukaisuus

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Tiivistelmä – Referat – Abstract

Mini-tablets are 1-3 mm in diameter and administered as a single tablet or as a multi-particulate formulation. Mini-tablets are an attractive alternative for conventional solid dosage forms due to the ease of administration and the possibility for combination and individualised drug therapy. In mini-tablet production, good flowability of the formulation is critical as minor variations in die filling can lead to significant changes in mini-tablet weights. In addition, to reduce weight variation, the particle size should not exceed 1/3rd of the die diameter. This study aimed to determine the influence of the granule size on mini-tablet weight variability and content uniformity. The feasibility of direct compression, as well as high-shear wet granulated and roller-compacted formulations, were evaluated. From the nine final formulations manufactured, particle size distribution, Hausner ratio, Carr's index, angle of repose and flowability were determined. The mini-tablets were made on a rotary tablet press using single punches of 3 mm in diameter. Content uniformity and weight variation of the mini-tablets were determined.

The direct compression formulation had the smallest particle size, and the roller-compacted formulation milled through a 1.0 mm and 1.25 mm square screen had the largest particle size. Surprisingly, the RC 0.8 mm grater screen formulation had a very wide particle size distribution and is classified as a very fine blend. The wide particle size distribution might result from a high fill ratio during the milling of the roller-compacted ribbons. The four different high-shear wet granule formulation had a very similar particle size distribution. According to the Hausner ratio and Carr's index values, the flow properties of the formulations varied between fair and very poor, while according to the angle of repose, the flow properties were between excellent and poor. However, all nine formulations were used to make mini-tablets with acceptable uniformity of mass, mini-tablets were within ± 8 % of the target weight, and none exceeded the 10 % limit set by Ph. Eur. The weight variation is small, as indicated by the low RSD of 1.0-2.9 %. The differences in the weight variation may be attributed to segregation due to particle or granule size and density. This is further supported by the fact that no force feeder or vacuum was utilised in the rotary tablet press, possibly causing re-circulation of the formulation and shearing forces. In addition, the fill level of the feeder might have varied between the nine formulations and affect the weight variation in a way that is not recognised in this study.

Only direct compression formulation was within the limits of uniformity of content of single-dose preparations set by Ph. Eur. In the final formulations, the amount of paracetamol was in the HSWG 0.8 mm round screen 98.5 % and in the RC 1.0 mm square screen 97.7 %. These results suggest that the formulations contained an adequate amount of paracetamol, which does not explain why the mini-tablets made from high-shear wet granules did not meet the content uniformity criteria. Furthermore, the weight variation might not entirely explain why high-shear wet granulated formulations performed so poorly in the content uniformity analysis.

In summary, that direct compression is a feasible manufacturing method for mini-tablets of 3 mm in diameter. However, further studies are needed on the content uniformity of mini-tablets made using high-shear wet granulated and roller-compacted formulations as these did not meet the content uniformity criterion. In particular, the content uniformity of the mini-tablets made from the high-shear wet granulated formulations was not acceptable, and the reason for this was not identified.

Avainsanat – Nyckelord – Keywords
Mini-tablet, direct compression, high-shear wet granulation, roller compaction, weight variation, content uniformity

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1 INTRODUCTION

European Union, amongst other authorities, has put effort to encourage pharmaceutical companies to develop paediatric medicines by requiring paediatric investigation plan (PIP) studies and granting a paediatric use marketing authorisation (PUMA) (Regulation (EC) No 1901/2006). An extension of supplementary protection certificate by additional six months or additional two years for orphan medicines is granted when medicines that include the result of PIP studies are authorised. The extension is granted even when the results of the PIP studies are negative. Furthermore, PUMA results in 10 years of market protection for the product. Due to these incentives developing paediatric formulations are of interest to pharmaceutical companies.

Solid oral dosage forms have many benefits compared to liquid oral dosage forms as they have better stability, accuracy of dosing, and improved portability compared to liquid formulations (European Medicines Agency, 2006; Liu et al., 2014). Solid dosage oral forms rarely require excipients inappropriate for paediatric patients, whereas liquid oral dosage forms may require these to enhance stability. With solid dosage forms, the taste can be improved by coating. In addition, the coating also permits the development of modified-release formulations, which have benefits such as wider dosing intervals (Liu et al., 2014). Wider dosing intervals enhance adherence to the treatment, whereas difficulties in taking medicines affect both acceptability and adherence. Further, to aid swallowability, splitting or crushing tablets may occur, leading to changes in bioavailability, toxicity, and stability.

Mini-tablets are one solution developed to overcome the problems associated with liquid formulations. Mini-tablets are 1-3 mm in diameter (Mitra et al., 2017; Ranmal et al., 2016; Tissen et al., 2011), and mini-tablets can be administered as a single tablet or as a multi-particulate formulation packed into a capsule or a sachet (Mitra et al., 2017). The small size enables enhanced swallowability, and thus, mini-tablets are an attractive alternative for conventional solid dosage forms for geriatric and paediatric patients due to their ease of administration and dosing flexibility (Liu et al., 2014). Mini-tablets are suitable formulation for as young as one-month-old infants (Strickley, 2019). Because they are small in size, the swallowability is enhanced (Liu et al., 2014). Thus there should be no need to split or crush mini-tablets into smaller pieces, and problems with dose-dumping of modified-release mini-tablet are unlikely to occur. Moreover, as the dose of mini-tablet formulation is determined by the number of mini-tablets and multiple different mini-tablets that can be packed into one capsule, combination and individualised drug therapy are possible (Mitra et al., 2017). The smaller the mini-tablet, the better is the dosing flexibility provided. However, by decreasing mini-tablet size from 3 mm in diameter to as small as 1 mm in diameter, the handling and dispensing of one single mini-tablet becomes increasingly difficult for patients and carers. Currently, mini-tablet formulations on the market are not administered as a single mini-tablet but as a multi-particulate formulation containing ≥ 20 mini-tablets in a sachet (Strickley, 2019). Nevertheless, Strickley (2019) speculate that the use of mini-tablets will possibly increase in the future and that the trend might be towards administering individual mini-tablets of 2 mm in diameter to children as young as two days of age.

Many of the previous mini-tablet studies have focused on direct compression (Mitra et al., 2017; Mitra et al., 2020), with only a few studying the effect of high-shear wet granulation (Goh et al., 2019; Gupta et al., 2020) and roller compaction (Tissen et al., 2011; Zhao et al., 2018). Moreover, Goh et al. (2019) focused on studying the effects of feed frame parameters and turret speed, and Zhao et al. (2018) focused on studying the effect of particle size on the mini-tablet compression process. The applicability of high-shear wet granulation and roller compaction compared to direct compression to manufacture mini-tablets has not been extensively studied. This study aimed to determine the feasibility of high-shear wet granule formulation, roller compacted granule formulation and direct compression formulation in mini-tablet production. The effect of nine different paracetamol formulations with different granule size distribution on mini-tablet weight variability and content uniformity was studied.

2 MATERIALS AND METHODS

Paracetamol (Hebej Jiheng Pharmaceutical Co., Ltd, Hengshui City, China) was used as an active substance in this study. The particle size (D_{50}) of paracetamol was 54 µm. Excipients used were mannitol (Pearlitol® 100SD, Pearlitol® 200SD and Pearlitol® 160C, Roquette Frères, Lestrem, France), microcrystalline cellulose (Avicel PH-102 and Avicel PH-102 SCG, Dupont Nutrition, Wallingstown, Ireland), croscarmellose sodium (Ac-Di-Sol® SD-711, Dupont Nutrition, Wallingstown, Ireland), hydroxypropyl methylcellulose (Klucel™ EXF, Ashland Inc., Kentucky, USA), silicon dioxide (Syloid 244FP, W. R. Grace & Co.-Conn., Maryland, USA) and sodium stearyl fumarate (PRUV®, Moehs Cantabra S.L., Polanco, Spain).

Distilled water was obtained from an in-house Milli-Q-Millipore water system (Merck KGaA, Darmstadt, Germany). Phosphate buffer pH 5.8 was made using EMSURE® ISO Sodium Hydroxide pellets for analysis (Merck KGaA, Darmstadt, Germany) and AnalaR NORMAPUR® Potassium dihydrogen phosphate (VWR International BVBA, Leuven, Belgium).

2.1 Formulations

In this study, a total of nine different formulations were made. All nine formulations contained 25 % of paracetamol as an active substance (Table 1). The aim was to use optimised formulations to produce mini-tablets with good quality. Thus, the excipient grade and the amount of excipients vary between the three manufacturing methods: direct compression, high-shear wet granulation (HSWG), and roller compaction (RC).

Table 1. Formulations components used in this study.

	Material	Grade	Role	Amount (%)*
Direct compression	Paracetamol	D50 = 54 µm	Active substance	25
	Mannitol	Pearlitol 200SD	Filler	34
	Microcrystalline cellulose	Avicel PH-102 SCG	Compression aid	34
	Croscarmellose sodium	Ac-Di-Sol SD-711	Disintegrant	4
	Silicon dioxide	Syloid 244FP	Glidant	1+0.5
	Sodium stearyl fumarate	PRUV	Lubricant	2
High-shear wet granulation	Paracetamol	D50 = 54 µm	Active substance	25
	Mannitol	Pearlitol 160C	Filler	33
	Microcrystalline cellulose	Avicel PH-102	Compression aid	33
	Hydroxypropyl cellulose	Klucel EXF	Binder	3
	Croscarmellose sodium	Ac-Di-Sol SD-711	Disintegrant	4
	Silicon dioxide	Syloid 244FP	Glidant	0.5 (extra-granular)
	Sodium stearyl fumarate	PRUV	Lubricant	2 (extra-granular)
Roller compaction	Paracetamol	D50 = 54 µm	Active substance	25
	Mannitol	Pearlitol 100SD	Filler	34
	Microcrystalline cellulose	Avicel PH-102	Compression aid	34
	Croscarmellose sodium	Ac-Di-Sol SD-711	Disintegrant	4
	Silicon dioxide	Syloid 244FP	Glidant	1 (intra-granular) 0.5 (extra-granular)
	Sodium stearyl fumarate	PRUV	Lubricant	1 (intra-granular) 1 (extra-granular)

*Total amount of ingredients is 100.5 % because of late extra-granular addition of 0.5 % silicon dioxide to all batches.

2.1.1 Direct compression

To achieve around 1/2 fill ratio in 3D shaker mixer Turbula T2F (Willy A. Bachofen AG, Basel, Switzerland) with a 2 l jar, the entire batch of 1500 g was divided into three 500 g sub-batches. The manufacturing process is shown in Figure 1. Primary blending was performed using Turbula T2F at 31 rpm for 20 min. Subsequently, the powder was milled using a conical screen mill Quadro Comil U5 (Quadro Engineering, Waterloo, Canada) at 1500 rpm using a 0.8 mm round screen. The milled blend was again blended using Turbula T2F at 31 rpm for 5 min to ensure homogeneity. Lubricant and glidant were sieved through a 500 µm screen and added into milled powder followed by blending in the Turbula T2F at 31 rpm for 10 min.

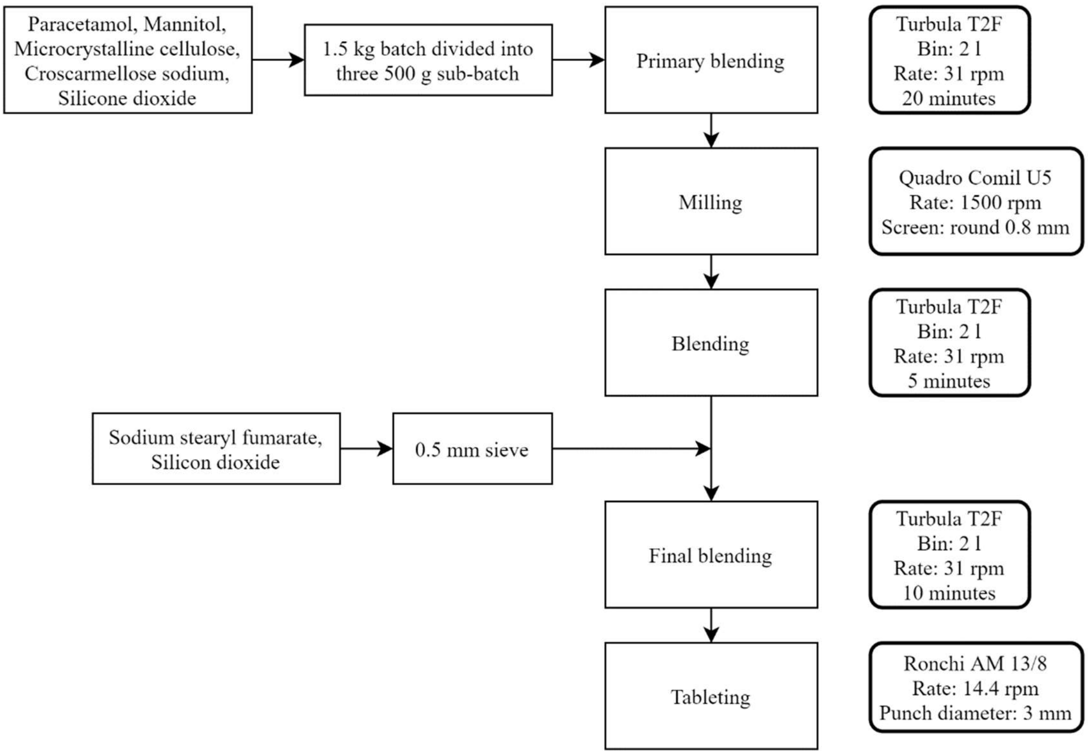

Figure 1. A schematic representation of the direct compression manufacturing process.

2.1.2 High-shear wet granulation

An amount of 4000 g of high-shear wet granulation formulation was divided into eight sub-batch of 500 g. The manufacturing process is shown in Figure 2. The intra-granular materials of the sub-batch were transferred into the 4 l bowl of a high-shear wet granulator (Diosna P 1-6, Dierks & Söhne Gmbh, Osnabrück, Germany) and pre-mixed for 2 min at an impeller rate of 500 rpm. Next, water was added in L/S-ration 0.6 g/g using five 60 ml syringes. The water was added in 5 minutes. During water addition, the powder was constantly mixed at an impeller rate of 500 rpm and a chopper rate of 1500 rpm. The granules were wet massed for 1 min. The wet granules were de-lumped using Quadro mill U5 fitted with a 9525 µm square screen and at an impeller rate of 1000 rpm.

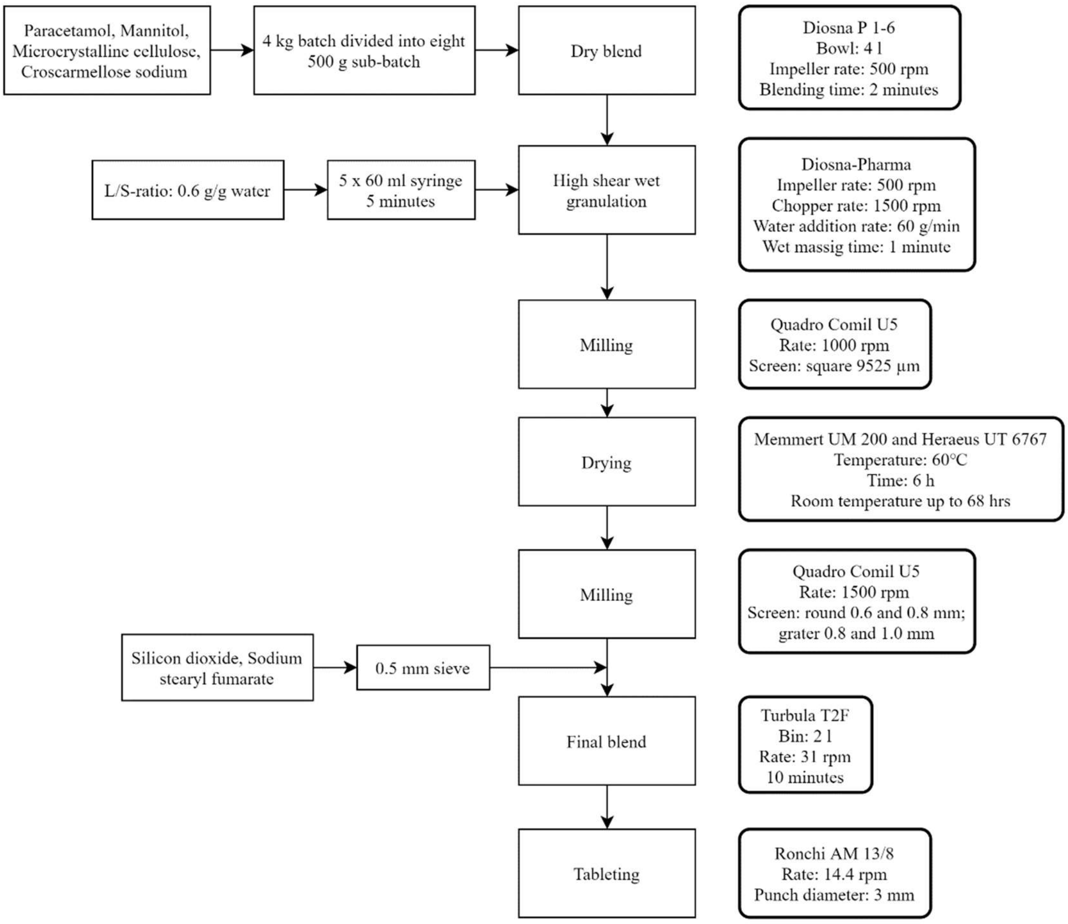

Figure 2. A schematic representation of the high-shear wet granulation manufacturing process.

The granules were tray dried in Memmert UM 200 (Memmert GmbH, Schwabach, Germany) or Heraeus UT 6767 (Heraeus Holding GmbH, Hanau, Germany) oven at 60 °C for 6 hours. After oven drying, granules were allowed to dry at room temperature on tables on the trays for up to 68 hours. The surface water activity of the granules was determined using an AquaLab Model Series 3TE (Decagon Devices Inc., Washington, USA). When the water activity was less than 0.500 $A_{w,}$ the granules were transferred into plastic bags.

Two sub-batches (weight between approximately 430-470 g) of dried granules were pooled together and milled at 1500 rpm impeller rate using a Quadro Comil U5 equipped with 610 µm or 813 µm round screen, or 1016 µm or an 813 µm grater screen. However, half of the HSWG 0.8 mm round screen formulation was milled through the Quadro Comil twice due to an error. This error could potentially impact the HSWG 0.8 mm round screen formulation granule size distribution and decrease it further compared to other high-shear wet granule formulations. The milled granules were weighed, and the extra-granular material was weight-adjusted using the following equation:

$$A = m \times \frac{P_x}{P_m}$$

Where m is the weight of the milled material, P_x the fraction of extra-granular material weighed and P_m the fraction of intra-granular material.

The extra-granular material was sieved through a 500 µm screen and blended in a Turbula T2F at 31 rpm for 10 min. The fill ratio of Turbula T2F was between 2/3-4/5. However, for the HSWG 1.0 mm grater screen formulation, additional manual blending and 5 min in Turbula T2F at 31 rpm were performed. The additional blending was performed because the first blending resulted in an uneven blend with visible lumps of lubricant and glidant. After this, the procedure was slightly changed, and the RC 0.8 mm grater screen and HSWG 0.8 mm grater screen formulations were blended by manually mixing the lubricant and glidant with an equal amount of granules followed by blending in Turbula T2F at 31 rpm for 10 min.

2.1.3 Roller compaction

Roller compaction was performed at AstraZeneca Gothenburg. The manufacturing process is shown in Figure 3. Primary blending was performed using Turbula T10B (Willy A. Bachofen AG, Basel, Switzerland) with a 17 l jar at 30 rpm for 20 minutes. Then lubricant was sieved through a 500 µm screen, and then powders were blended in Turbula T10B at 30 rpm for 10 min. Roller compaction was performed using Alexanderwerk WP120/40 (Donsmark Process Technology A/S, Kopenhagen, Denmark). Compaction pressure was 80 bar, the roll speed was set to 6 rpm, and the gap between the rolls was kept constant at 2 mm. The ribbons were divided into four batches. Three of the four batches were milled in Alexanderwerk in a two-phase milling process at an impeller rate of 60 rpm, first using a 3 mm screen followed by a 0.8, 1.0 or 1.25 mm square screen. Milling of ribbons using an 813 µm grater screen was performed at the University of Helsinki using Quadro Comil U5 at an impeller rate of 1500 rpm. The four final granule batch obtained were weighed, and the extra-granular material was weight-adjusted, sieved through a 500 µm screen and blended in Turbula T2F at 31 rpm for 10 min. The fill ratio in Turbula was between 1/2-3/4.

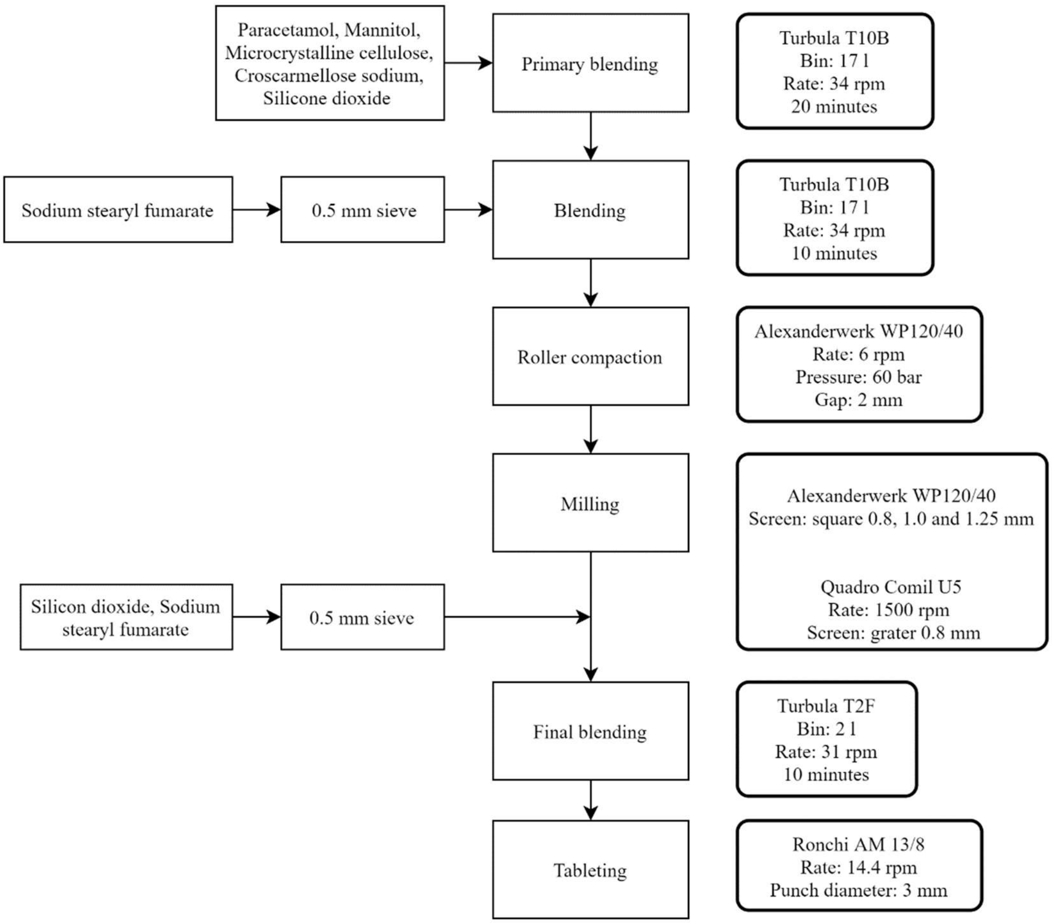

Figure 3. A schematic representation of the roller compaction manufacturing process.

2.2 Final blend characterisation

Before measuring flow properties, the material was left in a room with a regulated relative humidity of 25-35 % for at least 24 hours. The experiments were done in a relative humidity of 17-28 %.

2.2.1 Particle size distribution

Particle size distribution was measured using Parsum Inline Particle Probe Serie IPP 70 (Parsum GmbH, Chemnitz, Germany). The Parsum only allows the setting of ten sieve sizes, which are used to analyse the particle size distribution. Depending on the coarseness of the formulation, ten of these sieve sizes were used: 45, 63, 90, 125, 180, 250, 355, 500, 710, 1000, 1400 and 2000 µm. Four samples (one sample around 5-10 ml) were analysed from one formulation. However, from the RC 0.8 mm and the RC 1.25 mm square screen formulation, eight samples were analysed using two different sieve settings to cover a wider range of granule size distribution. The D_{10}, D_{50} and D_{90} -values obtained from the Parsum were averaged. Span-value was calculated using the following equation:

$$Span = \frac{D_{90} - D_{10}}{D_{50}}$$

In addition, the size distribution of the roller-compacted batch milled through a 1.0 mm square screen was measured by analytical sieving (Ph. Eur. 10.0 2.9.38) to compare with the Parsum data. A single experiment was considered to be enough. Accurately weighed 50.0 g of the final blend was added on the top of the coarsest sieve of a stack of sieves. Sieve size from bottom to top was 71, 90, 125, 180, 250, 355, 500, 710, 1000 and 1400 µm. The stacked sieves were then agitated for 20 min at an amplitude of eight using a Fritsch Vibratory sieve shaker analysette 3 (Fritsch GmbH, Idar-Oberstein, Germany). Each sieve fraction was weighed to calculate the cumulative mass percentage finer than a given sieve, from which the D_{10}, D_{50} and D_{90} were estimated.

2.2.2 Hausner ratio and Carr's index

Bulk and tapped density were measured using the European Pharmacopoeia 10.0 (2.9.34) procedure using Erweka SVM equipment (Erweka Apparatebau GmbH, Germany). A hundred grams of the final formulation was carefully poured into a clean 250 ml graduated cylinder, and the formulation was then carefully levelled without compacting. The apparent volume (V_0) corresponding fill volume was recorded. The same cylinder was then carefully placed on the Erweka SVM equipment, and the formulation was subjected to 10, 490, 750 and 1250 taps to yield a cumulative of 2500 taps. If the difference between 1250 and 2500 taps exceeded 2 ml, repetition of 1250 taps was performed until the difference between successive measurements were less than or equal to 2 ml. The corresponding fill volumes of the tapped powder columns were recorded, and triplicate measurements were performed. Finally, the bulk and tapped densities, as well as, Hausner ratio (HR) and Carr's compressibility index (Carr's index), were calculated using the following equations:

$$HR = \frac{V_0}{V_f} \qquad\qquad Carr's\ index = 100 \times \frac{V_0 - V_f}{V_0}$$

Where V_0 is the apparent volume, and V_f is the final tapped volume of the powder.

2.2.3 Angle of repose

The angle of repose (AoR) was determined as per the European Pharmacopoeia 10.0 (2.9.36). The peak of the powder cone was carefully built by pouring formulation through a funnel on top of a plastic disc. The disc was a fixed diameter of 3.7 cm and had a protruding edge to retain a common base of powder. The funnel was maintained at approximately 2-4 cm above the powder pile to minimise the impact of falling powder on the height of the cone. The pouring was stopped when the cone no longer grew, and the material started to flow over the edge of the base. The height of the cone was measured, and triplicate measurements were performed. The angle of repose (α) was calculated using the following equation:

$$\tan(\alpha) = \frac{height}{0.5 \times base}$$

2.2.4 Flowability

The flowability of the final formulation was measured as per the European Pharmacopoeia 10.0 (2.9.16). A funnel with a stem and orifice of 9.0 mm was used. The funnel was maintained upright, and the assembly was protected from vibrations. Into a dry funnel, which the bottom opening was blocked, accurately weighed 100.0 g of final formulation was introduced without compacting. The bottom opening was unblocked, and the time needed for the entire sample to flow out of the funnel was measured using a stopwatch. Three determinations were carried out. If the formulation failed to flow through entirely, the flowability could not be determined. The results are expressed as both ml/s and g/s.

2.3 Tabletting

Before tabletting, the powders were kept in a regulated relative humidity of 18-36 % on trays for at least 24 hours. Two of the eight stations in the Ronchi AM 13/8 -rotary tablet press (Officine Meccaniche F.lli Ronchi, Milano, Italy) were equipped with single punches. The punches were 3.0 mm in diameter, and the cup depth was 0.3 mm. A gravity feeder was used as the feeding system. The aim was to produce mini-tablets weighing 16 mg and having the tensile strength (TS) of 2 MPa. Mini-tablet tensile strength was calculated using the following equation:

$$TS_{round} = \frac{F_B}{\pi D^2}\left(0.14\frac{H}{D} + 0.36\frac{H - 2H_{cap}}{D}\right)^{-1}$$

Where TS_{round} is the tablet tensile strength of biconvex tablets (MPa), F_B the tablet breaking force (N), D the diameter (mm), H the tablet thickness (mm) and H_{cap} the cup depth (mm) (Shang et al., 2013).

During tabletting, compression force was collected, and no pre-compression was used. The turret speed of the rotary tablet press was 14.4-14.5 rpm, and the speed was kept constant for all batches. The rotary tablet press was run for 22 minutes, and mini-tablets were collected at 0, 5, 10, 15 and 20 minute time points for two minutes to obtain approximately 55-60 mini-tablets. In addition, approximately 40 mini-tablets were compressed and collected using approximately 50 % higher and 50 % lower compression force than used to compress the mini-tablets of the 0-22 minutes run. Before the physical characterisation of mini-tablet properties, the mini-tablets were allowed to rest for at least 24 hours in sealed glass containers to allow viscoelastic recovery.

2.4 Characterisation of mini-tablets

Mini-tablets collected at 0, 10 and 20 minute time points were selected for further testing, in addition to the mini-tablets made using 50 % higher and 50 % lower compression force. From these, randomly selected ten mini-tablets were analysed. The mini-tablet thickness and diameter were measured using Sony Digital indicator U30-F (Magnescale Europe GmbH, Wernau, Germany). The weights of the mini-tablets were measured using Precisa Balance type 290-9829/D 100A-300M (PAG Oerlikon AG, Switzerland). Mini-tablet breaking force was measured using a Tablet Hardness Tester TBH 125 (Erweka GmbH, Langen, Germany). The tensile strength was calculated using the equation mentioned in section 2.3. The compression pressure was calculated using the cross-sectional area of the tablet and the mean compression force of the two punches used in the rotary tablet press during the two-minute collection at the specific time point.

To determine the uniformity of mass, 20 mini-tablets were taken at random from the mini-tablets collected at 0, 10 and 20 minute time points and individually weighed as per European Pharmacopoeia 10.0 (2.9.5.). To analyse the content uniformity, phosphate buffer pH 5.8 (Ph. Eur. 10.0 5.17.1) was prepared. The standard solution was done by diluting 15 mg paracetamol into 1.0 litre of the phosphate buffer. From this solution, four dilutions of 3/4, 1/2, 1/4 and 1/8 were made, and the absorbances were determined using Genesys 10S UV-Vis Spectrophotometer (Thermo Fisher Scientific Inc., Massachusetts, USA). The absorbance was determined using a quartz cuvette, and the wavelength was set to 243 nm.

From all nine formulations, three mini-tablets were randomly selected from time point 0 and 10 min, and four mini-tablets from time point 20 min. Individual mini-tablet was dissolved into 100 ml phosphate buffer, mixed, and the solution was allowed to stand for 6-32 hours. From this solution, 1/5 dilution into phosphate buffer was made using Proline® Plus single channel mechanical pipette 500-5000 µl (for HSWG 0.8 mm round Proline® Plus mechanical pipette 100-1000 µl) (Sartorius Lab Instruments GmbH & Co. KG, Goettingen, Germany). The sample was taken from this dilution using HSW SOFT-JECT® 5 ml syringes (Henke-Sass, Wolf GmbH, Tuttlingen, Germany) and filtered through a 0.2 µm cellulose acetate membrane (VWR International BVBA, Leuven, Belgium). The filter was changed between every formulation and after every five filtrations. The acceptance value was calculated as per the European Pharmacopoeia 10.0 (2.9.40).

The content uniformity of the final formulations HSWG 0.8 mm round screen and RC 1.0 mm square screen was determined by diluting 160 mg of the blend into a 200 ml of phosphate buffer. The solution was mixed and allowed to stand for 24 hrs. A sample of 1 ml was diluted into 100 ml of phosphate buffer. From this dilution, triplicate samples were filtered into a quartz cuvette, and the absorbance was determined.

3 RESULTS AND DISCUSSION

3.1 Particle size

Direct compression RC 1.0 mm square screen HSWG 0.8 mm round screen

Figure 4. Pictures of direct compression, RC 1.0 mm square screen and HSWG 0.8 mm round screen formulations.

The appearance of the three final formulations is seen in Figure 4. The D_{50} particle size of the final formulations varied from 95 to 907 µm (Table 2). As expected, the direct compression formulation had the smallest particle size, and the roller-compacted formulation milled through a 1.25 mm square screen had the largest particle size. Surprisingly, the RC 0.8 mm grater screen had a very wide particle size distribution (Span 4.09) and is classified as a very fine formulation (Ph. Eur. 10.0 2.9.35). The wide particle size distribution might result from a high fill ratio during the milling of the roller-compacted ribbons in Quadro Comil U5 (Figure 5). The high fill ratio might have led to increased residence time and thus into smaller particles and to an increased amount of fines.

Table 2. Particle size distribution of the nine formulations.

	D10 (µm)	D50 (µm)	D90 (µm)	Span	Ph. Eur. 10.0 2.9.35	Particles above 1.0 mm (%)
Direct compression	69	95	210	1.49	Very fine	0
HSWG 0.6 mm round screen	87	230	393	1.33	Moderately fine	0
HSWG 0.8 mm round screen	102	263	446	1.33	Moderately fine	0
HSWG 0.8 mm grater screen	112	300	555	1.48	Moderately fine	0
HSWG 1.0 mm grater screen	107	285	524	1.46	Moderately fine	0
RC 0.8 mm grater screen	68	116	544	4.09	Very fine	0
RC 0.8 mm square screen	77	444	893	1.84	Coarse	7.0
RC 1.0 mm square screen	98	711	1108	1.42	Coarse	19.1
RC 1.25 mm square screen	149	907	1383	1.36	Coarse	40.3

Figure 5. The RC 0.8 mm grater screen milling process in Quadro Comil U5. The fill ratio was high, which might have led to increased residence time and smaller particles.

The four different high-shear wet granule formulation had a very similar particle size distribution (Figure 6), and the different mill screens did not have a statistically significant impact on the granule size (p=0.95). This similar particle size indicates that the original granules obtained from the high-shear wet granulation process were small and passed the screen readily. However, the high-shear wet granule formulation granule size before milling was not analysed to confirm this speculation. Besides, the error of milling half of the HSWG 0.8 mm round screen formulation twice does not seem to have caused a significant impact on the granule size distribution.

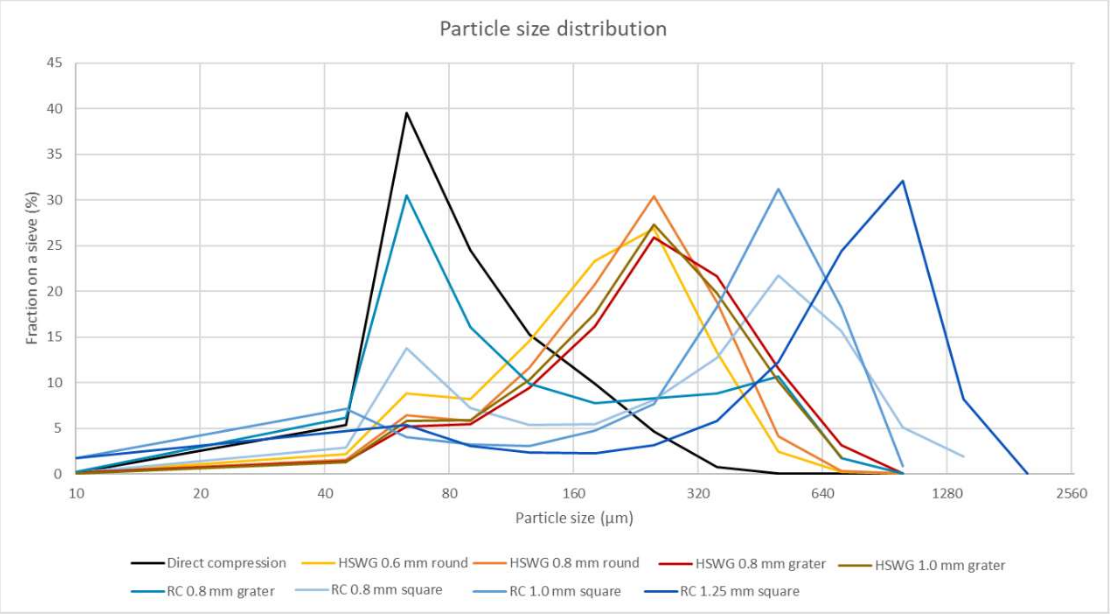

Figure 6. Particle size distribution of the formulations.

Essential parameters for successful mini-tablet production are particle size distribution and flow properties because using a fine blend with a small particle size distribution and poor flowability can cause inconsistent die filling (Zhao et al., 2018). In a successful mini-tablet process to reduce weight variation, the particle size should not exceed 1/3 of die diameter, and the particle size should be controlled independently of its impact on flowability (Flemming and Mielck, 1995; Zhao et al., 2018). In this study, 3.0 mm punches were used, and therefore the particles above 1.0 mm would exceed the 1/3rd ratio. As seen from Table 2, the RC 0.8 mm square screen, RC 1.0 mm square screen and RC 1.25 mm square screen formulations had 7.0 %, 19.1 % and 40.3 % of particles above 1.0 mm, respectively. The high ratio of particles above 1.0 mm suggests that with the RC 1.0 mm square screen and RC 1.25 mm square screen formulations, a high weight variation of the mini-tablets might be detected.

The granule size distribution of the RC 1.0 mm square screen was measured by analytical sieving (Ph. Eur. 10.0 2.9.38) to compare with the Parsum data. The Parsum gave a slightly different granule size distribution compared to the analytical sieving (Figure 7). The different granule size distribution might be due to the inaccuracy of the scale used in analytical sieving compared to the automated Parsum. For example, it was visible that a few granules were retained on the coarsest sieves in analytical sieving, but the granules were too light in weight to be detected on the scale used.

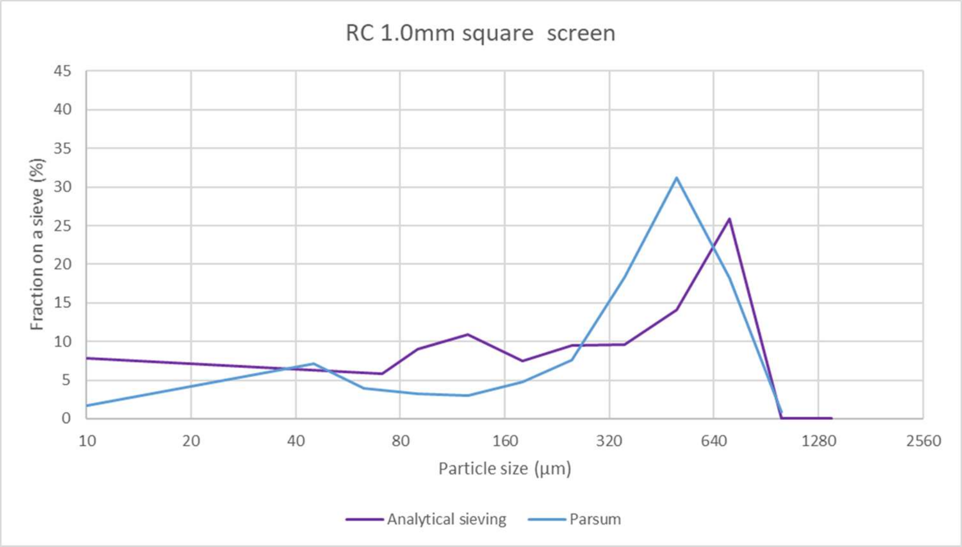

Figure 7. The particle size distribution measured using the Parsum Inline Particle Probe Serie IPP 70 compared to the analytical sieving method (Ph. Eur. 10.0 2.9.38).

In general, dry granulation is associated with a higher amount of fines compared to wet granulation methods (Šantl et al., 2011). Small particle size increases the particles' specific surface area, causing more interaction between the particles, thus hindering the flowability. Nordström and Alderborn (2015) observed that the external surface area varied between granules of similar size – in general, higher porosity led to a larger surface area. The roller compaction can lead to granules with higher density than high-shear wet granulation (Bacher et al., 2008; Nordström and Alderborn, 2015). The higher density is likely due to the differences in porosity, shape and surface structure of the granules (Nordström and Alderborn, 2015). Generally, the high-shear wet granules are more spherical than the roller-compacted granules, which are more irregular in shape (Bacher et al., 2008; Nordström and Alderborn, 2015). As a result, high-shear wet granulation usually results in better flow properties compared to roller compaction and direct compression formulation (Šantl et al., 2011; Taipale-Kovalainen et al., 2020). Enhanced flowability can be attributed to the more spherical shape and a smaller amount of fines.

As seen from Figure 6, due to the small particle size, it is expected that the worst flow properties are found from the direct compression and RC 0.8 mm grater screen formulations. In comparison, the high-shear wet granulated formulations might have better flowability than the RC 0.8 mm, the RC 1.0 mm and the RC 1.25 mm square screen if the possibly more spherical shape compensates the effect of smaller particle size. In further studies, it would be beneficial to determine the particle shape and morphology.

3.2 Flow properties

The smaller the mini-tablet die, the more difficult it is to fill uniformly as the decreasing die orifices challenge the rapid and homogenous die filling (Kotlowska et al., 2020; Tissen et al., 2011). In mini-tablet production, good flowability of the formulation is key as even minor variations in die filling can lead to significant changes in mini-tablet weights. Thus, it is essential to study the flowability of the formulation. The mini-tablet manufacturing process has better capability when free-flowing and non-cohesive materials are used (Kotlowska et al., 2020). Despite this, more cohesive powders have been successfully compressed into mini-tablets of acceptable mass uniformity. Better flowability, however, may allow increased production efficiency and reduced risks during scale-up and high-speed tabletting.

In this study, the Hausner ratio, Carr’s index, as well as the angle of repose and flowability were determined as indicators of the final blend flow properties. According to the Hausner ratio and Carr’s index values, the flow properties of the formulations varied between fair and very poor, while according to the angle of repose, the flow properties were between excellent and poor (Table 3) (Ph. Eur. 10.0 2.9.36). In the study made by Gupta et al. (2020), a formulation with the Hausner ratio higher than 1.43 could not be compressed using multi-tip tooling due to poor flow. Therefore, in terms of flow, all formulations used in the present study, except the RC 0.8 mm grater screen, might be successfully tabletted using multi-tip tooling. However, this needs to be confirmed in further studies.

Table 3. Flow properties of the formulations.

	Bulk density (g/ml)	Tapped density (g/ml)	Hausner ratio	HR and Carr's index	Carr's index (%)	Angle of repose (°)	Angle of repose
Direct compression	0.50	0.64	1.29	Passable	22.7	41	Passable (may hang up)
HSWG 0.6 mm round	0.48	0.60	1.25	Fair	19.9	33	Good
HSWG 0.8 mm round	0.50	0.62	1.23	Fair	18.8	30	Excellent
HSWG 0.8 mm grater	0.46	0.57	1.24	Fair	19.2	34	Good
HSWG 1.0 mm grater	0.43	0.54	1.26	Passable	20.5	35	Good
RC 0.8 mm grater	0.48	0.72	1.51	Very poor	34.0	54	Poor (must agitate)
RC 0.8 mm square	0.58	0.79	1.37	Poor	26.9	40	Fair (aid not needed)
RC 1.0 mm square	0.59	0.77	1.30	Passable	23.3	41	Passable (may hang up)
RC 1.25 mm square	0.60	0.78	1.31	Passable	23.5	41	Passable (may hang up)

Table 4. Flowability of the formulations.

	Flowability (g/s)	Flowability (ml/s)	%RSD
Direct compression	14.0	28.2	18
HSWG 0.6 mm round	12.6	26.2	33
HSWG 0.8 mm round	8.7	17.3	4
HSWG 0.8 mm grater	7.8	17.0	16
HSWG 1.0 mm grater	9.7	22.4	30
RC 0.8 mm grater	-	-	-
RC 0.8 mm square	-	-	-
RC 1.0 mm square	12.8	21.7	14
RC 1.25 mm square	15.4	25.8	9

The bigger the flowability value, the better flow it indicates. In this study, the flowability results are contradictory to the other flow results (Table 3 and 4). The flowability results suggest that the RC 1.0 mm square screen and the RC 1.25 mm square screen would have better flowability than the HSWG 0.8 mm round screen and the HSWG 0.8 mm grater screen. However, according to Carr's index and angle of repose values, these HSWG formulations had one of the best flow properties amongst the nine formulations. These contradictory results and the high %RSD of the flowability tests might be explained by the insufficient human reaction time and relative humidity differences during the measurement of flowability. Interestingly, the RC 0.8 mm grater screen and the RC 0.8 mm square screen formulations were in line with other flow studies as they failed to flow through the funnel, suggesting very poor flow properties.

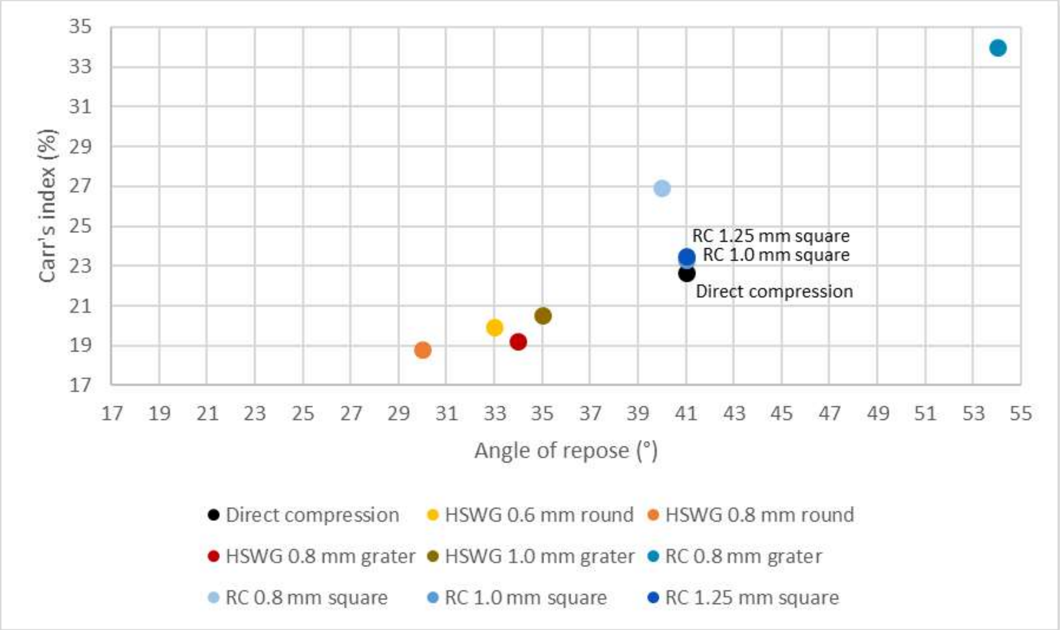

Figure 8. Illustration of the flow properties of the formulations. The higher the Carr's index or angel of repose value is, the poorer is the flow properties. The HSWG formulations had the best flow properties, whereas the RC 0.8 mm grater screen had the poorest flowability.

In general, larger particles have better flow properties (Mills and Sinka, 2013; Šantl et al., 2011). However, as discussed previously, generally, high-shear wet granules are more spherical, whereas roller-compacted material is more irregular in shape (Bacher et al., 2008; Nordström and Alderborn, 2015). The spherical shape enhances the flow properties, which might explain why high-shear wet granules had better flowability than roller-compacted formulations of larger particle size (Figure 8). The poor flow of the RC 0.8 mm grater screen may be attributed to the wide particle size distribution and high amount of fines. The poor flow properties of the RC 0.8 mm grater screen indicate that the grater screen is a poor choice for milling the roller-compacted ribbons. However, the large fill ratio in the milling process might explain the poor flow as it may be the reason behind the large particle size distribution and high amount of fines.

3.3 Physicomechanical properties of the mini-tablets

The mini-tablets were smooth and shiny on the surface, and no visible sticking or capping occurred, as seen in Figure 9. The mini-tablet diameter was 3.0 mm, and the mean height varied between 1.9-2.2 mm.

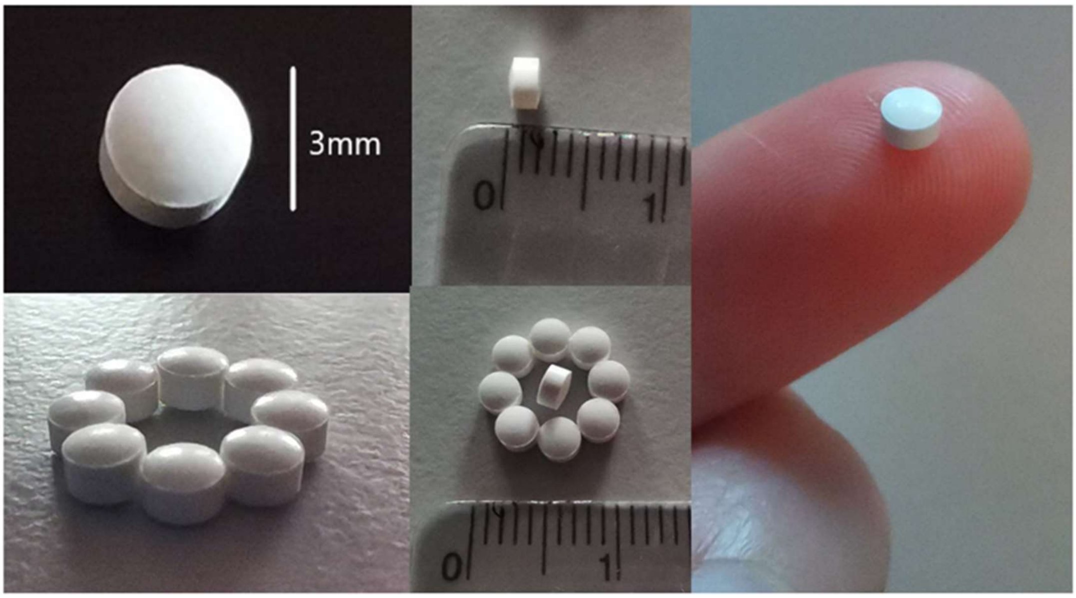

Figure 9. Pictures of the mini-tablets.

3.3.1 Uniformity of mass

The mean weight of 20 mini-tablets collected at time point 0-2 min was set to be the target weight because the rotary tablet press used in this study was only equipped with a gravity feeder, and the manual fill depth control was not precise enough to control the mini-tablet weight of 16 mg. This target weight allowed a better view of the possible weight change during tabletting. As per European Pharmacopoeia 10.0 (2.9.5.), when the tablets are lighter than 80 mg, not more than two of the individual masses of uncoated mini-tablets can deviate from the mean mass by more than 10 %, and none can deviate by more than twice this percentage. In this work, mini-tablets collected at 0, 10 and 20 minute time points were selected for further testing, and a total of 60 mini-tablets from all nine formulations were weighed to determine the weight change during the tabletting. Determination of the weight variation was performed to evaluate the robustness of the formulations in the mini-tabletting process. The individual weight of the 20 mini-tablets collected at 0, 10 and 20 min time point and the average weight of the given time point are expressed in Figure 10.

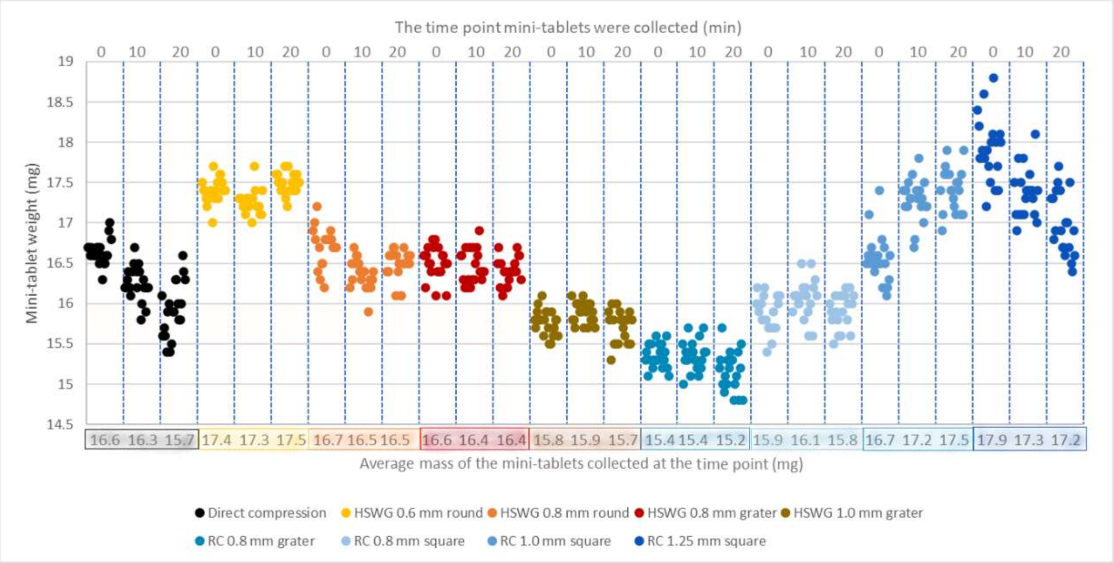

Figure 10. The individual weight of the 20 mini-tablets collected at 0, 10 and 20 min time point and the average weight of the given time point are expressed in the figure.

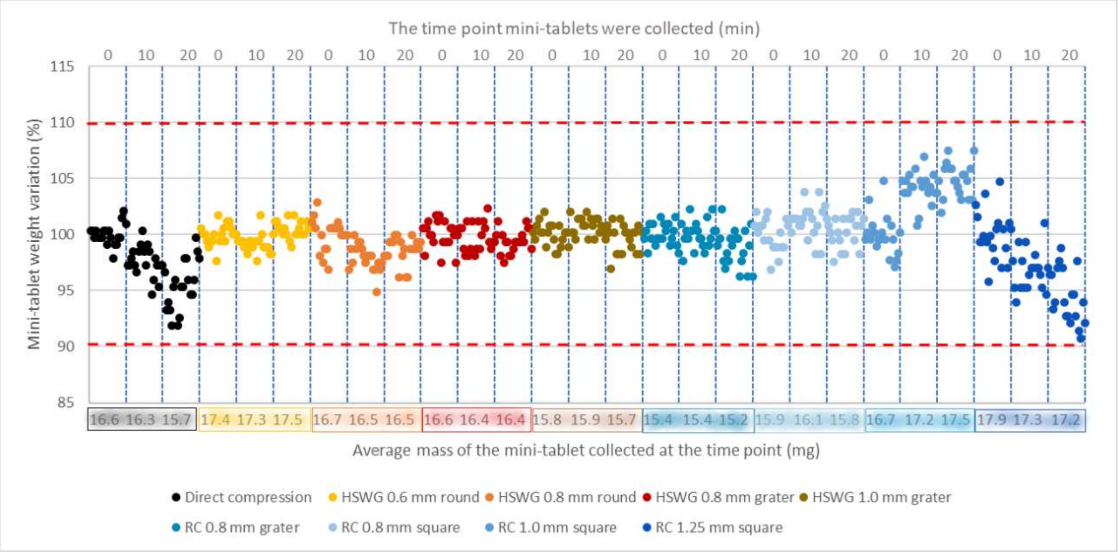

Figure 11. Uniformity of mass of 60 mini-tablets normalised using the mean weight of 20 mini-tablets collected at time point 0 min. The average weight of 20 mini-tablets collected at time point 0-2 min is indicated as the average weight in the figure.

The individual weights of 60 mini-tablets normalised to the target weight are expressed in Figure 11. All mini-tablets were within ± 8.5 % of the target weight, and none exceeded the 10 % limit. The mean change was within ± 3.6%. The relative standard deviation (%RSD) values of the weight variation are expressed in Figure 12. The weight variation is small, as indicated by the low RSD of 1.0-2.9 %, indicating reasonable weight control. There is a statistically significant relationship between the D_{50} and the weight variation (%RSD), r(9)=0.71, p=0.03. However, there is no statistically significant relationship between Carr's index and the weight variation (%RSD), r(9)=0.11, p=0.78. Instead, the angle of repose and the weight variation (%RSD) has a statistically significant relationship, r(9)=0.78, p=0.01. In other words, the flow properties measured using the angle of repose correlate with the weight variations of the mini-tablets, but Carr's index does not depict a similar trend.

The direct compression formulation had the third-highest weight variation (RSD 2.3 %). As seen in Figure 10, the directly compressed mini-tablets weights decreased during tabletting which explains the relatively high weight variation. One possible explanation for the decreased weight might be the segregation of the formulation. Even though the aim was to match the particle size and powder densities to prevent segregation, the density of microcrystalline cellulose and paracetamol is around 0.3 g/cm^3, and the density of croscarmellose sodium and mannitol is around 0.5 g/cm^3. Similarly, the particle size of croscarmellose sodium and paracetamol is around 50 µm, while microcrystalline cellulose and mannitol are around 150 µm in size. Thus, the size difference of the particles was as high as threefold, which could lead to segregation during the tabletting process. However, the segregation could not be studied as there was no remaining material from the process available.

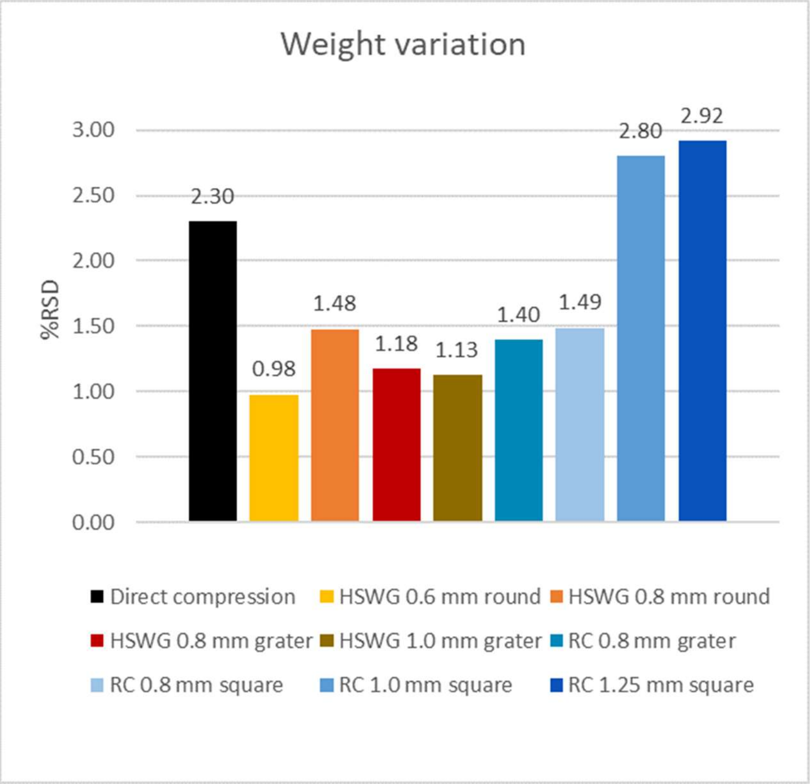

Figure 12. The relative standard deviation of the mini-tablet weights.

The HSWG 0.8 mm round screen formulation had the highest RSD (1.5 %) amongst high-shear wet granulated formulations. The explanation for the relatively high %RSD might be that the amount of formulation in the gravity feeder decreased during the process. Due to the decreased amount of formulation, there might not have been enough granules at the vicinity of the die opening to fill the die uniformly. The decreased amount of formulation in the feeder is supported by the fact that more granules were added after 13 minutes of tabletting. The addition of the formulation caused the decreased compression force to increase again, as seen in Figures 13. In addition, according to the angle of repose, the HSWG 0.8 mm round screen formulation is labelled "excellent" in terms of flow, whereas the other high-shear wet granule formulations are labelled "good" (Ph. Eur. 10.0 2.9.36). The slightly better flowability of the HSWG 0.8 mm round screen formulation suggests that flow properties are not the reason behind the higher weight variation compared to the other high-shear wet granule formulations.

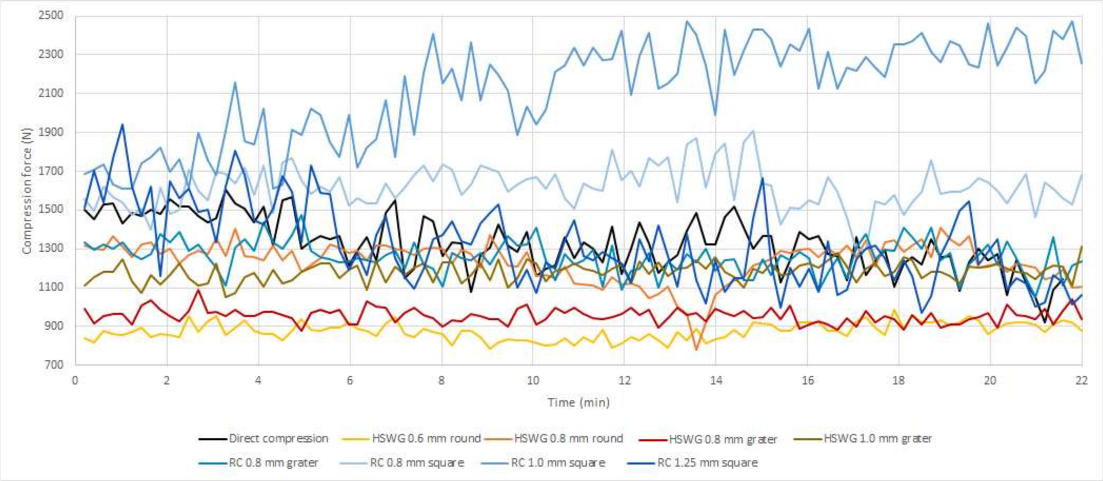

Figure 13. Compression forces during the mini-tabletting. During the compression force collection, few disturbances were detected. These disturbances were attributed to the measuring device and not to the mini-tablet compression process. Thus, these disturbances detected as a compression force below 100 N were deleted from the data and are not shown in the figure.

It was surprising that the weight variation of the RC 0.8 mm grater screen was so small as it had the poorest flow properties compared to the other formulations. One explanation might be that, because Carr's index, angle of repose and flowability do not comprehensively depict the flow properties, the formulation may exhibit better flow in the tabletting process than what these flow results suggest. The low turret speed of around 14.4. rpm might also explain the small weight variation because it allows the die to fill a longer time, decreasing the effect of poor flow. Moreover, the entire process was relatively short, only 22 minutes. Therefore, some problems might not have had time to develop to the level to be detected.

In the suction fill, the downward motion of the punch reduces the pressure inside the die resulting in a pressure gradient in the direction of powder flow (Baserinia and Sinka, 2019). Towards the end of the suction fill, the pressure in the die starts to increase. Eventually, the die fill mechanism changes to gravity fill, where the increasing pressure opposes the further flow of particles into the die. The efficiency of the die fill increases significantly when suction fill is employed compared to gravity fill alone. During die fill, the air pressure in the die can dissipate through the powder bed and the clearances in the system. Large particle size and small bulk density indicate high permeability of the material, which reduces the efficiency of suction fill. The reduced suction fill efficiency is due to increased air permeation into the die resulting in a smaller negative pressure gradient to the same direction as the powder flow. However, large permeability is beneficial in gravity fill as the increasing pressure opposing further flow of particles into the die is smaller.

The four RC formulations had the highest bulk and tapped density differences (18-24 g/ml) compared to the HSWG formulations (11-12 g/ml) (Table 3). The direct compression had a bulk and tapped density difference of 14 g/ml. These values indicate that the RC formulations had the highest permeability, thus those are expected to perform well under gravity fill. In comparison, the direct compression and the HSWG formulations are expected to perform well under suction fill conditions. In the present study, the smaller weight variation of the HSWG formulations might be explained by the suction fill mechanism, which could have enhanced the die fill performance. However, the slow turret speed of 14.4 rpm used in this study might not allow suction fill conditions to develop. In future, studying the effect of gravity and suction fill on the mini-tablet properties on a rotary tablet press would be beneficial.

The weight variation was the highest for the RC 1.0 mm square screen (RSD 2.8 %) and RC 1.25 mm square screen formulations (RSD 2.9 %). The high weight variation was expected as these formulations had the largest percentage of particles above 1.0 mm, 19.1 % and 40.3 %, respectively. However, as seen in Figure 10, the weight of the mini-tablets produced from the RC 1.0 mm square screen formulation increases towards the end of the process, whereas the weight of the mini-tablets produced from the RC 1.25 mm square screen decreases towards the end of the process. If the reason behind the non-uniform die filling and high weight variation is the large particle size, it would be expected to detect a similar trend in the weight variation between these formulations. However, this was not the case.

Segregation of the formulation can cause increased mini-tablet weights during the tabletting process because better flowing larger particles fill the die less densely compared to smaller particles. Hence, when the larger particles fill the die less densely, the minitablet weights are smaller compared to mini-tablet weights compressed from smaller particles later in the tabletting process. Therefore, segregation can explain why the mini-tablet weights of the RC 1.0 mm square screen formulation increased towards the end of the process.

Another reason to explain the increased mini-tablet weights of the RC 1.0 mm square screen formulation during the process might be that the granules are sheared into smaller on the die table. As the amount of granules above 1.0 mm is reduced, the smaller particles fill the small die more uniformly and densely, causing the mini-tablet weights to increase during the tabletting. In this study, no force feeder or vacuum was utilised in the rotary tablet press, causing a high amount of formulation on the die table during the tabletting. The high amount of formulation on the die table might have caused re-circulation of formulation, and the moving die table and other toolings might have sheared the granules into finer particles. Similarly, the re-circulation of powders and the moving die table could also have aid segregation.

The effect of the tabletting process on the particle size was studied by taking a sample from the die table after tabletting the RC 1.25 mm square screen formulation. The particle size was analysed using the Parsum. As seen in Figure 14, the particle size distribution changes, and the amount of large particles reduces. The explanation might be segregation of the granule formulation, shearing of granules into finer particles or both. To conclude, these reasons might explain why the mini-tablet weight of the RC 1.0 mm square screen formulation increased but do not explain why an opposite trend was seen in the mini-tablet weights made from the RC 1.25 mm square screen formulation.

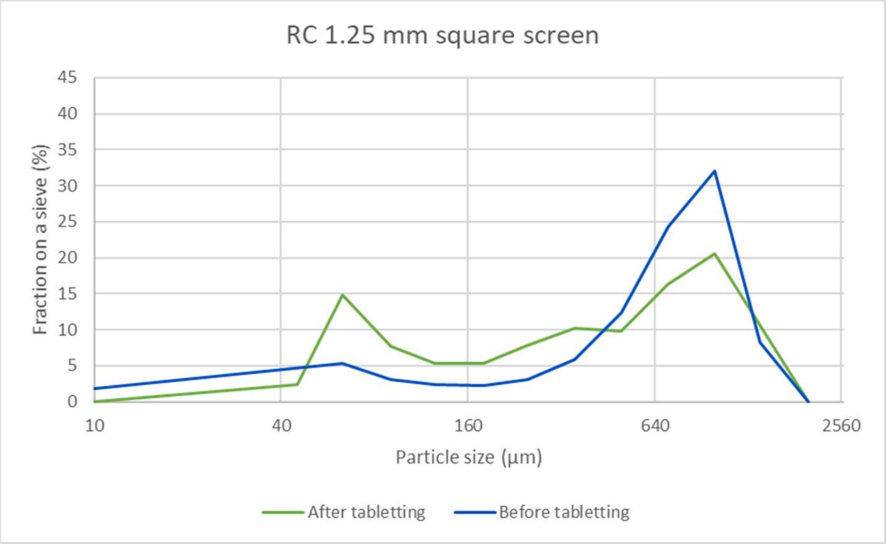

Figure 14. The change of particle size distribution before and after tabletting.

One explaining factor for the decreased weight of the RC 1.25 mm square screen formulation is that the fill ratio in the gravity feeder decreased too much towards the end of the process. Thus, the reduced amount of the formulation at the vicinity of the die opening would explain the decreased weight. On the contrary, however, a high fill ratio causing a large self-weight of powder can lead to local densification and particle interlocking, which reduces the permeability of the powder bed (Baserinia and Sinka, 2019). Densification of the powder bed inhibits powder flow into the die under gravity fill. However, the amount of formulation in the gravity feeder was not determined prior to or after the tabletting process in any of the tabletting processes. As a result, the fill level of the feeder might have varied between the nine formulations and affect the weight variation in a way that is not recognised in this study. In the future, the fill level of the feeder would be important to record. Despite the reason behind the decreased weight, if the tabletting process of the RC 1.25 mm square screen formulation would have been continued beyond the 22 minutes, the mini-tablet weight would have most likely decreased below acceptable limits set by the European Pharmacopoeia.

In this study, the collection of mini-tablets was started almost immediately after adjusting the fill depth and compression force. Thus in future studies, a longer tabletting time than 22 minutes should be considered, or the tablet press should be run a longer time before starting the collection of samples. These changes would allow a more accurate insight into the feasibility of the tabletting process. In addition, to enhance the mini-tabletting process and have more uniform die filling, using a force feeder and accurate control of the fill depth using a digital fill depth control should be considered (Mitra et al., 2017).

3.3.2 Tensile strength

The aim was to produce mini-tablets of tensile strength 2 MPa, as it is sufficient for the mini-tablets to persist the stresses of downstream processes like coating, packaging and handling. The tensile strength was calculated from ten randomly selected mini-tablets collected at 0, 10 and 20 minute time points and all nine batches of mini-tablets had tensile strength above 2.0 MPa. Tensile strength of direct compression (RSD 11.4 %), HSWG 0.8 mm round screen (RSD 4.7 %), RC 1.0 mm square screen (RSD 12.4 %) and RC 1.25 mm square screen (RSD 15.7 %) mini-tablets changed considerably during 0-22 min collection run (Table 5). The tensile strength variation is probably due to the weight change during the tabletting process, which changed the compression force and mini-tablet thickness. It should be noted that the tensile strength values are means, and deviations in thickness and breaking force measurement cause variability in the tensile strength.

Table 5. The mean mini-tablet weight and tensile strength during 0-22 minutes collection run. The trend of the weight and tensile strength change is depicted in the table.

		Weight (mg)	TS (MPa)	TS %RSD
Direct compression	0 min	16.6	2.3	11.4
	10 min	16.3	2.3	
	20 min	15.7	1.9	
				
HSWG 0.6 mm round	0 min	17.4	2.1	0.7
	10 min	17.3	2.1	
	20 min	17.5	2.1	
				
HSWG 0.8 mm round	0 min	16.7	2.5	4.7
	10 min	16.5	2.4	
	20 min	16.5	2.3	
				
HSWG 0.8 mm grater	0 min	16.6	2.5	1.2
	10 min	16.4	2.5	
	20 min	16.4	2.5	
				
HSWG 1.0 mm grater	0 min	15.8	2.5	1.9
	10 min	15.9	2.6	
	20 min	15.7	2.5	
				
RC 0.8 mm grater	0 min	15.4	2.3	1.6
	10 min	15.4	2.3	
	20 min	15.2	2.2	
				
RC 0.8 mm square	0 min	15.9	2.4	1.5
	10 min	16.1	2.4	
	20 min	15.8	2.4	
				
RC 1.0 mm square	0 min	16.7	2.1	12.4
	10 min	17.2	2.6	
	20 min	17.5	2.6	
				
RC 1.25 mm square	0 min	17.9	3.0	15.7
	10 min	17.3	2.4	
	20 min	17.2	2.2	
				

For wet and dry granulated formulations, a higher granule porosity results in a higher tensile strength of the tablets (Nordström and Alderborn, 2015). Thus, granule porosity is an essential parameter for tabletting. In general, roller-compacted formulations need higher compression pressure than direct compression and high-shear wet granulated formulations to be successfully compressed into tablets (Bacher et al., 2008; Perez-Gandarillas et al., 2016; Taipale-Kovalainen et al., 2020). As seen in Figure 15, the roller compacted granules indeed need higher compression pressure than direct compression and high-shear wet granulated formulations. These results are in accordance with literature as roller compaction has been associated with the work-hardening of granules (Herting and Kleinebudde, 2008). In general, with higher compaction force during roller compaction, the granule size increases and the amount of fines decreases. The increased particle size is due to stronger ribbons with lower porosity. Thus, the higher the compaction force during roller compaction, the higher compression pressure is needed to compress tablets. In addition to compaction force, lubrication and formulation affect the reduced compactibility of roller-compacted granules (Mosig and Kleinebudde, 2015).

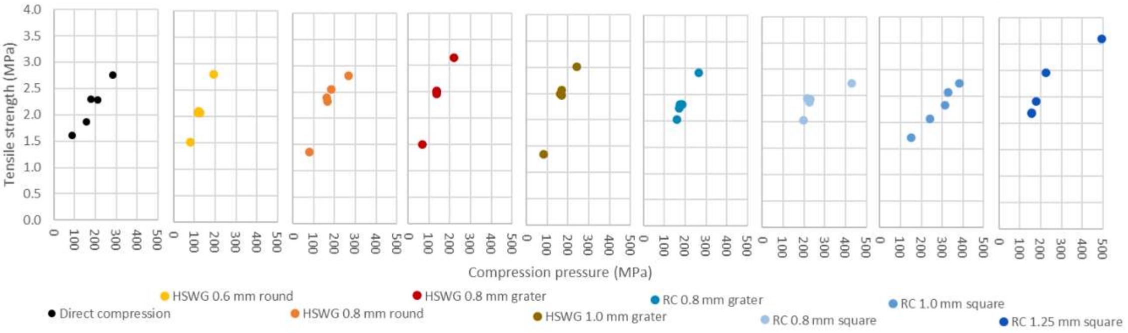

Figure 15. The effect of compression pressure on mini-tablet tensile strength. The tensile strength and compression pressure were calculated from mini-tablets collected at 0, 10 and 20 minute time points and from the mini-tablets made using 50 % higher and 50 % lower compression force.

However, some studies contradict these results showing that roller-compacted formulations have a higher degree of compactibility than high-shear wet granules and direct compression formulation (Šantl et al., 2011). The higher degree of compactibility of roller-compacted granules was attributed to small particle size and a high amount of fines enabling more bonds during tablet production. In the study conducted by Nordström and Alderborn (2015), wet and dry granulation caused a loss in compactibility compared to direct compression of the original powder. Moreover, the dry granulated granules were used to produce tablets of higher tensile strength compared to the high-shear wet granules of corresponding granule porosity. However, as said earlier, the present study does not support these findings as the roller-compacted formulations needed higher compression pressure than high-shear wet granulated formulations. The high-shear wet granulated formulations were also compressed using smaller compression pressure than the direct compression formulation. Besides, the compactibility of direct compression formulation was relatively similar to the RC 0.8 mm grater and the RC 0.8 mm square screen formulations. The good compactibility of the high-shear wet granule formulation might be due to the large porosity of the granules. This, however, should be confirmed in further studies.

3.3.3 Content uniformity

The mean of mini-tablet drug content is expressed in Table 7. Only the direct compression formulation was within the limits of uniformity of content of single-dose preparations set by European Pharmacopoeia 10.0 (2.9.6). The HSWG 0.6 mm round screen, RC 0.8 mm grater screen, RC 0.8 mm square screen, RC 1.0 mm square screen and RC 1.25 mm square screen had one mini-tablet outside the 85-115 % limit but within the 75-125 %. Therefore, the content uniformity of 20 more mini-tablets should be determined in further studies. In addition, the uniformity of dosage units was determined as per European Pharmacopoeia 10.0 (2.9.40). The acceptance values are presented in Table 7. As ten mini-tablets were analysed, the maximum acceptance value allowed is 15.0. Thus, only directly compressed mini-tablets met this criterion.

Table 6. The mini-tablet drug content, the uniformity of dosage units and the number of mini-tablets outside the 85-115 % limit but within 75-125 %. The HSWG 0.8 mm round screen drug content has been calculated using the individual mini-tablet weights in the weight correction. Others are calculated using the mean weight of 20 mini-tablets at 0-2 min time point.

	Mean drug content (%)	**Acceptance value (Ph. Eur. 10.0 2.9.40)**	**Number of mini-tablets outside the 85-115 % limit but within 75-125 %**
Direct compression	99.3	13.3	0
HSWG 0.6 mm round screen	93.0	17.7	1
HSWG 0.8 mm round screen	83.6	23.2	6
HSWG 0.8 mm grater screen	88.3	24.0	2
HSWG 1.0 mm grater screen	91.3	21.4	3
RC 0.8 mm grater screen	93.4	17.1	1
RC 0.8 mm square screen	91.8	19.6	1
RC 1.0 mm square screen	90.3	16.8	1
RC 1.25 mm square screen	90.9	20.9	1
HSWG 0.8 mm round screen (final formulation)	98.5	-	-
RC 1.0 mm square screen (final formulation)	97.7	-	-

All mini-tablet drug contents, except the HSWG 0.8 mm round screen, were calculated using the mean weight of 20 mini-tablets at 0-2 min time point. The HSWG 0.8 mm round screen is weight corrected using the individual weights of the mini-tablets. The acceptance value for the HSWG 0.8 mm round screen was 23.2 % when the weight correction was done using the individual weights. The acceptance value calculated using the mean weight of 20 mini-tablets at 0-2 min time point was 22.8 %. In the future, it would be beneficial to determine the individual weight of the mini-tablet before analysing the drug content to detect better the effect of weight variation on the content uniformity.

The high-shear wet granulated formulations had 1-6 mini-tablets outside the 85-115 % limit but within 75-125 % (Table 6). Hence, these formulations did not meet content uniformity criteria. The roller-compacted formulations had only one mini-tablet outside the 85-115 % limit but within 75-125 %, having better content uniformity. To get a deeper insight into the differences in content uniformity, an analysis of the drug content of the final formulation was performed. For this analysis, the HSWG 0.8 mm round screen and the RC 1.0 mm square screen were selected. An amount equal to the weight of 10 mini-tablets was taken and analysed using UV-Vis-spectrophotometer. In the final formulations, the amount of paracetamol was for the HSWG 0.8 mm round screen 98.5 % and for the RC 1.0 mm square screen 97.7 %. These results suggest that the formulations contained an adequate amount of paracetamol, which does not explain why the mini-tablets made from high-shear wet granules did not meet the content uniformity criteria. Furthermore, the weight variation might not entirely explain why high-shear wet granulated formulations performed so poorly in the content uniformity analysis as the weight variation of these mini-tablets were well within limits set by the European Pharmacopoeia 10.0.

All the content uniformity analysis was done using the same procedure and equipment. No step was identified that would explain the difference in the content uniformity of mini-tablets made using the high-shear wet granulated and roller-compacted formulations. Although human error is always possible, another explanation could be that the single granules contain a heterogeneous amount of paracetamol and fill the die non-uniformly, causing inadequate content uniformity and a high acceptance value. For example, Gupta et al. (2020) speculate that the fine particles of ibuprofen (D_{50} 6 µm) might not have gotten uniformly entrapped within the granules because the major formulation components, Pearlitol 50C (D_{50} ~ 50 µm) and Avicel PH101 (D_{50} ~ 50 µm), had around ten times larger particle size. The different particle size may have caused the formation of heterogeneous particles during high-shear wet granulation. Thus, if segregation of these heterogeneous granules happens due to the size or density in downstream processes, mini-tablets of low drug content are tabletted.

As mentioned previously in section 3.3.1, there were differences in the density and particle size between paracetamol and the excipients used in the present study. These differences support the theory that the granules made by high-shear wet granulation might contain a heterogeneous amount of paracetamol. Previously, however, better content uniformity of mini-tablets has been achieved using high-shear wet granulated formulation compared to direct compression when ibuprofen has been used as an active substance proving the benefits of granulation in mini-tablet manufacture (Gupta et al. 2020; Maitra et al. 2020). Thus, formulation components such as size, shape and density should be optimised in addition to the process parameters to avoid problems of heterogeneous granules and segregation in mini-tablet manufacture (Gupta et al. 2020).

Suppose segregation is the cause behind the high acceptance values of high-shear wet granulated formulations, the content uniformity analysis of the final granule formulation using an amount equal to ten mini-tablets will average the results. For that reason, analysis of ten randomly taken samples from the final formulation, which size is equal to one mini-tablet, would give better insight into the content uniformity of the final formulation. As an alternative, samples from the die table or the feeder could be taken during tabletting, and the content uniformity analysed to determine whether segregation occurs. Analysing paracetamol drug content of different size fractions of granule formulations would also give insight into the content uniformity in case of segregation occur.

Another reason for the high acceptance value of the high-shear wet granulated formulations could be that, for some reason, the paracetamol in the granules compressed to the mini-tablets did not dissolve entirely. As directly compressed tablets disintegrate directly into particles, it allows faster dissolution compared to the tablets made from granules, as those first disintegrate into granules and then into particles (Gohel and

Jogani, 2005). This difference might explain why only directly compressed mini-tablets met the content uniformity criterion. In fact, the dissolution rate of tablets made from high-shear wet granules has been demonstrated to be lower compared to roller-compacted granules (Taipale-Kovalainen et al., 2020). The lower dissolution rate was attributed to the stronger granule and tablet structure of high-shear wet granulated formulation.

3.4 Future prospectives

Mitra et al. (2020) remark that the excipient burden for paediatric patients needs to be considered when designing paediatric formulation. High drug load enables the manufacture of smaller mini-tablets, which in addition reduces the excipient burden. A high drug load also enables the administration of fewer mini-tablet in one multi-particulate dose, which is especially advantageous with paediatric formulations as this might aid the swallowability and administration of the multi-particulate formulation. On the other hand, it is more difficult to achieve adequate weight control and content uniformity of smaller mini-tablets compared to larger mini-tablets (Mitra et al., 2020). Nevertheless, in the literature, mini-tablets as small as 1 mm and 1.2 mm in diameter have been successfully manufactured with acceptable weight variability, tensile strength, disintegration time and dissolution properties using a direct compression process and drug load up to 90 % (Mitra et al., 2020; Tissen et al., 2011). However, as per the best knowledge of the author, the studies have mainly concentrated on the direct compression process, and the effect of granulation and the shape of the particle has not been extensively studied (Gupta et al., 2020; Mitra et al., 2017; Mitra et al., 2020; Tissen et al., 2011). In later studies, it would be essential to determine the performance of wet and dry granulated formulations when the size of the mini-tablet is reduced from 3 mm in diameter to as small as 1 mm in diameter. In addition, the effect of granule shape, higher drug loading, and the performance of the formulations when using multi-tip tooling needs to be studied.

4 CONCLUSIONS

In this study, the high-shear wet granule formulations had better flowability, compactibility and uniformity of mass than direct compression and roller-compacted formulations. The roller-compacted formulations containing more than 19 % of particles above 1/3rd of the die diameter had the highest weight variations. These results might support the findings of previous studies suggesting that in mini-tablet production, the particle size should not exceed the 1/3rd ratio. Nonetheless, all nine formulations were used to make mini-tablets with acceptable uniformity of mass. The directly compressed mini-tablets of 3 mm in diameter and 25 % paracetamol loading manufactured in the present study had acceptable uniformity of mass and content, suggesting that direct compression is a feasible manufacturing method for mini-tablets of 3 mm in diameter. However, further studies are needed on the content uniformity of mini-tablets made using high-shear wet granulated and roller-compacted formulations as these did not meet the content uniformity criterion. In particular, the content uniformity of the mini-tablets made from the high-shear wet granulated formulations was not acceptable, and the reason for this was not identified. Further, the optimum formulation type for multi-tip punches with a small diameter should be addressed.

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ANNEX 1 PROV-002A Literature review

MINI-TABLET MANUFACTURING PROCESS

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May 2021

TABLE OF CONTENT

1 INTRODUCTION

Solid oral dosage forms such as tablets and capsules are the most common formulations (Liu et al. 2014). Due to developmental stages or deteriorating conditions, physiological and cognitive responses are different in young and elderly patients compared to adults. This can lead to problems with swallowing solid oral dosage forms. Difficulties in taking medicines affect the acceptability and adherence to the treatment. Besides, to aid swallowability, splitting or crushing of tablets may occur, which can lead to changes in bioavailability, toxicity, and stability. Therefore, special consideration to suitable formulation is required in patient populations with swallowing difficulties.

To aid the development of paediatric medicines, European Union has decided that all marketing authorisation applications for new medicines must include the results of paediatric investigation plan (PIP) studies (Regulation (EC) No 1901/2006). This can only be exempted if the medicines are freed due to a deferral or waiver. A paediatric investigation plan must also be followed when a marketing authorisation holder wishes to add a new indication, formulation or route of administration. When medicines are authorised due to studies from a paediatric investigation plan, they are eligible to extend their supplementary protection certificate by additional six months or additional two years for orphan medicines. The six months are granted even if the results of the studies are negative. In addition, a paediatric use marketing authorisation (PUMA) can be granted for authorised medicines that are not protected by a patent or supplementary protection certificate if they are developed specifically for children. PUMA results in 10 years of market protection for the product. Due to these incentives developing paediatric formulations are of interest to pharmaceutical companies.

Mini-tablets are an attractive alternative for conventional solid dosage forms for geriatric and paediatric patient populations due to the ease of administration and dose flexibility. This literature review will examine the use of mini-tablets as well as mini-tablet production. The focus will be on the general principles of tablet manufacturing processes in conjunction with mini-tablet production and the powder characteristics affecting the tabletting process.

2 PAEDIATRIC AND GERIATRIC PATIENT POPULATIONS

In general, paediatric patients have one condition, usually acute, whereas, in elderly patients, several co-morbidities and chronic illnesses are more prevalent (Liu et al. 2014). Therefore, polypharmacy, that is, the use of more than five medicines concurrently, is more common in elderly patients. Polypharmacy can affect adherence – especially if administration of the drug is difficult. In addition, one important aspect to consider is a caregiver's ability and willingness to administer the drug to the patient because children and some elderly patients are dependent on the caregiver.

2.1 Paediatric patients

Swallowability and taste are key factors contributing to the difficulty to intake tablets and capsules (Liu et al. 2014). In fact, in paediatric patients, swallowability is the main problem associated with solid formulation (European Medicines Agency 2006). The age at which children can swallow solid oral dosage forms is highly dependent on the individual. However, six years of age is typically considered the age when conventional solid formulations are a suitable choice (Liu et al. 2014).

Oral liquid dosage forms, such as solutions, syrups and suspensions, are usually considered the most suitable formulation for children – especially for paediatric patients who cannot swallow capsules or tablets (European Medicines Agency 2006; Liu et al. 2014). However, those have issues such as taste, portability, stability and the inclusion of inappropriate excipients for paediatric patients (Liu et al. 2014). For instance, preservatives are required in liquid preparations, but they are associated with a bitter taste.

Moreover, the safety and toxicity of the preservatives should be considered, especially when these liquids are used in neonates. With oral liquid formulations, taste masking is essential.

One dose from a liquid formulation can be large in volume, which may be inconvenient for both patient and carer; although the more palatable the formulation, the higher is the accepted dose volume (European Medicines Agency 2006). To overcome problems associated with liquid formulations, dispersible tablets and effervescent formulations have been developed (Liu et al. 2014). Dispersible tablets disintegrate in the mouth due to saliva, and they can also be dissolved into a small amount of liquid. Effervescent formulations usually require a large volume of water to which they are dissolved. However, some patients, especially in paediatric or geriatric populations, can have difficulties taking a large volume of liquids. Aspiration of thin liquid is another concern when used effervescent tablets. Moreover, the possibility of tooth erosion due to the long term use of effervescent formulations must be taken into account.

2.2 Geriatric patient

In elderly patients, poor dentition and reduced masticatory strength are reasons behind the increased oral-phase duration and the amount of oral residue during swallowing (Liu et al. 2014). Dysphagia that is difficulty in swallowing is particularly common in patient with age-related diseases such as Parkinson’s disease, Alzheimer’s disease and acute stroke. Besides taste, other characteristics affecting swallowability are size, shape, density, and surface characteristics of tablets and capsules (European Medicines Agency 2006).

3 MINI-TABLETS

European Medicines Agency's Committee for Medicinal Products for Human Use (2006) recommends formulating tablets and capsules to be as small as possible to enhance acceptability in paediatric use. Also, they suggest that dosing multiple mini-tablets instead of a single larger tablet may be beneficial and allow dosing flexibility. Other solutions to overcome problems associated with liquid dosage forms besides mini-tablets are other multiparticulate formulations such as beads and granules. Multiparticulates are also an appropriate formulation for geriatric patients (Liu et al. 2014).

3.1 Dosing

Multiparticulate formulations like mini-tablets could be provided, for example, in single-dose sachets or in capsules that can be opened (European Medicines Agency 2006). The required dose can be administered directly into the mouth or mixed with a small amount of soft food or drink before administration to aid the acceptance. The age of six months is usually considered an appropriate age to begin using multiparticulates because infants older than this can swallow thick, semi-solid food to which multiparticulates can be mixed (Liu et al. 2014). The advantage of mixing multiparticulates with semi-solid food is decreased aspiration risk compared to thin liquids. The downsides of multiparticulates are grittiness and poor mouthfeel. Because multiparticulates can be required to be mixed with food or drink before swallowing, these formulations are sometimes considered more time-consuming and more challenging to take compared to liquid formulations or chewable tablets amongst carers and patients. This can pose problems to adherence.

3.2 Benefits of mini-tablets

Solid oral dosage forms such as tablets and capsules have benefits like greater stability, the accuracy of dosing, and improved portability compared to liquid formulations (European Medicines Agency 2006). With solid dosage forms, the product's palatability can be improved by using film coating and therefore taste rarely is an issue, unlike with liquids. Solid dosage forms also permit the development of modified-release formulations, which have benefits such as wider dosing intervals (Liu et al. 2014). However, as previously mentioned, problems with tablets' and capsules' swallowability also apply to modified-release formulations. Therefore, crushing modified-release tablets to aid the ingestion can occur before administration. This can lead to an increased risk of toxicity because a high level of active substance content is released in a shorter time interval than intended. One solution to overcome these problems is developing modified-release multiparticulate systems such as granules, mini-tablets, pellets and microcapsules, which can be easier to administer to paediatric and geriatric patients. These multiparticulate modified-release systems can be administered in capsules or sachets or further compressed into orally disintegrating tablets.

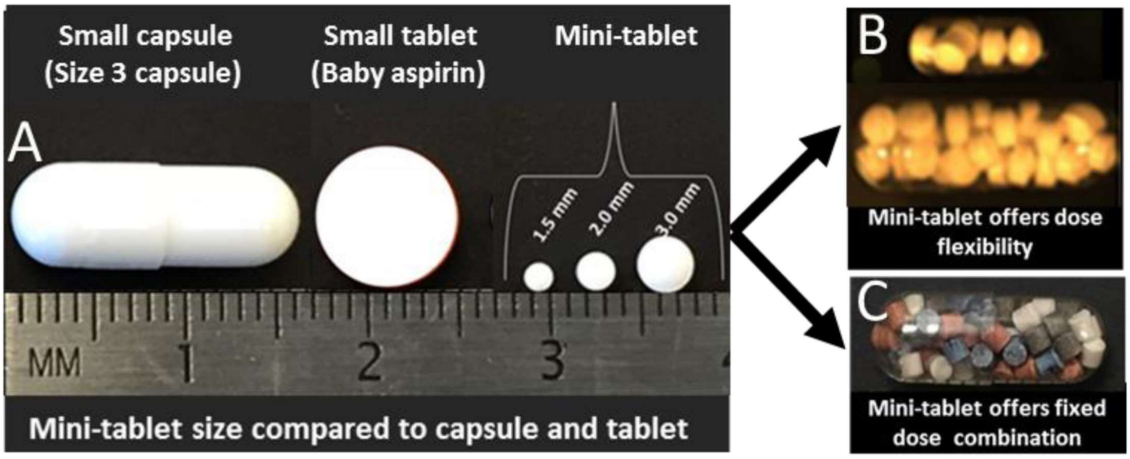


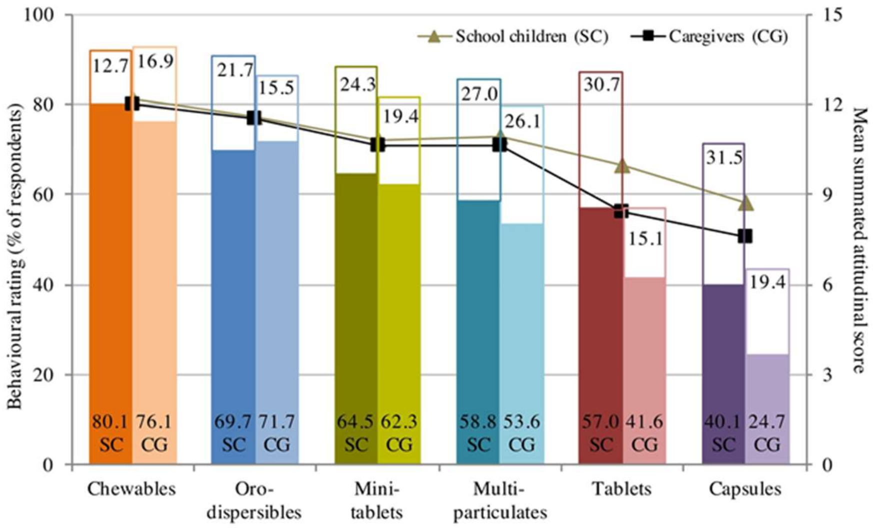
Figure 1. Mini-tablets offer dose flexibility as the dose is determined by the number of mini-tablets packed, e.g. in a capsule (Mitra et al. 2017). They also offer a possibility for easier combination therapy if multiple different mini-tablets are packed in a capsule. As a single-dose unit, small mini-tablets are easier to swallow compared to conventional sized tablets and capsules.

Mini-tablets can be used as a single tablet (Mitra et al. 2017). Mini-tablets can offer flexibility to combination therapy as multiple different mini-tablets containing different active substances can be packed into, e.g. capsules or sachets to be administered as a single dosage (Figure 1). Mini-tablets also enable release profile alteration as mini-tablets can be uncoated, coated or matrix mini-tablets. A very wide release profile can be achieved when combining mini-tablets of different release profile.

3.3 Mini-tablet acceptability

Ranmal et al. (2016) described mini-tablets as 2-3 mm tablets, and one dose consisted of several mini-tablets instead of one bigger tablet. Multiparticulates, on the other hand, are described as small sprinkles or granules mixed with a spoonful of soft food before swallowing. As the researchers state in the article, both dosage forms can be administered either way, but this differentiation was done to ensure clarity in the study. They studied the overall attitudes towards different formulations, and mini-tablets were relatively well accepted both in school children and in adolescence. However, multiparticulates became less favourable with increasing age, as seen in Figure 2. The lines in the figure indicate the mean summated attitudinal scores, and the bar graphs indicate the percentage of school children and adolescents willing to take the formulation. In addition, bar graphs indicate the willingness of carers to purchase the formulation as an over-the-counter paediatric medicine. The coloured proportion of the bars indicates the positive attitudes towards the formulation, and the clear part represents neutral attitudes.

(a) School children



(b) Adolescents

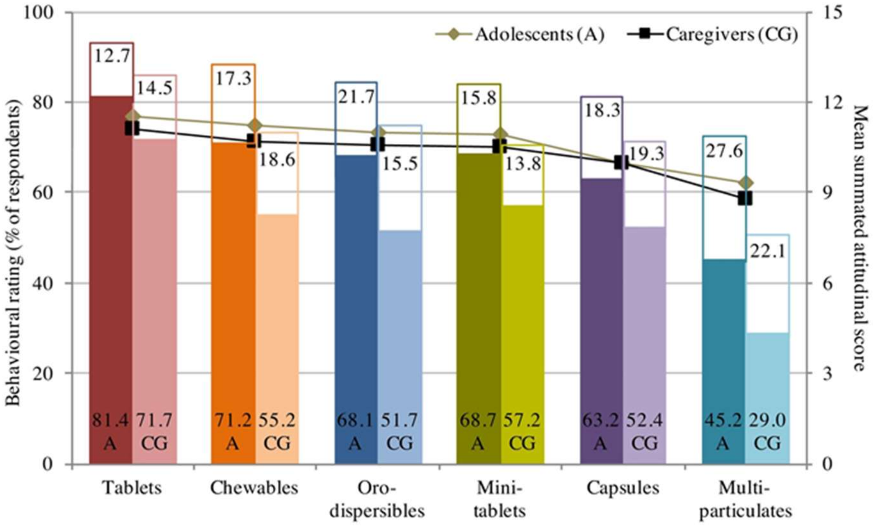


Figure 2. Attitudes towards different formulation in (a) school children (6-11 years of age) and their caregivers and (b) adolescents (11-17 years of age) and their caregivers (Ranmal et al. 2016).

In the study, Ranmal et al. (2016) identified potential reasons why the mini-tablet formulation acceptability decreased with age. These reasons were, for instance, that older children viewed multiparticulates as infantile. Children also had reservations about administering medicines with food, especially about the adverse effect the medicine might have on the taste of the food. Furthermore, other concerns towards mini-tablets such as handling difficulties, risk of aspiration or choking, and concern that mini-tablets would attach in teeth or tonsils were identified in the study. However, one limitation of the study is that because participants were not required to swallow the studied formulations, the actual ability to use these formulations was not captured. In addition, the attitudes towards different formulations were significantly affected by age and prior use of dosage forms. However, prior use of mini-tablets was not detected amongst participants because of the lack of commercially available products.

Thomson et al. (2009) investigated the ability and willingness of children of two to six years of age to swallow mini-tablets. Mini-tablets used in the study were uncoated, round, and 3 mm in diameter. The ability and willingness to swallow the mini-tablets increased with age, and concurrently the number of children who chewed the mini-tablet before swallowing decreased with age (Figure 3). A total of 76 % of 4-year-old children and 87 % of 5-year-old children were able and willing to swallow the mini-tablets. Chewing did not negatively impact swallowing. Researchers speculate, however, that chewing might become an issue if the mini-tablet contained a bitter active substance. The bad taste might lead to problems with administering subsequent doses to the child and affect adherence to the treatment. In the study, no children choked or aspirated the mini-tablet during swallowing. Nonetheless, one limitation of this study is that they asked children to swallow only one mini-tablet and not multiple mini-tablets simultaneously. Hence, the study does not provide information on multiple dosing of mini-tablets.

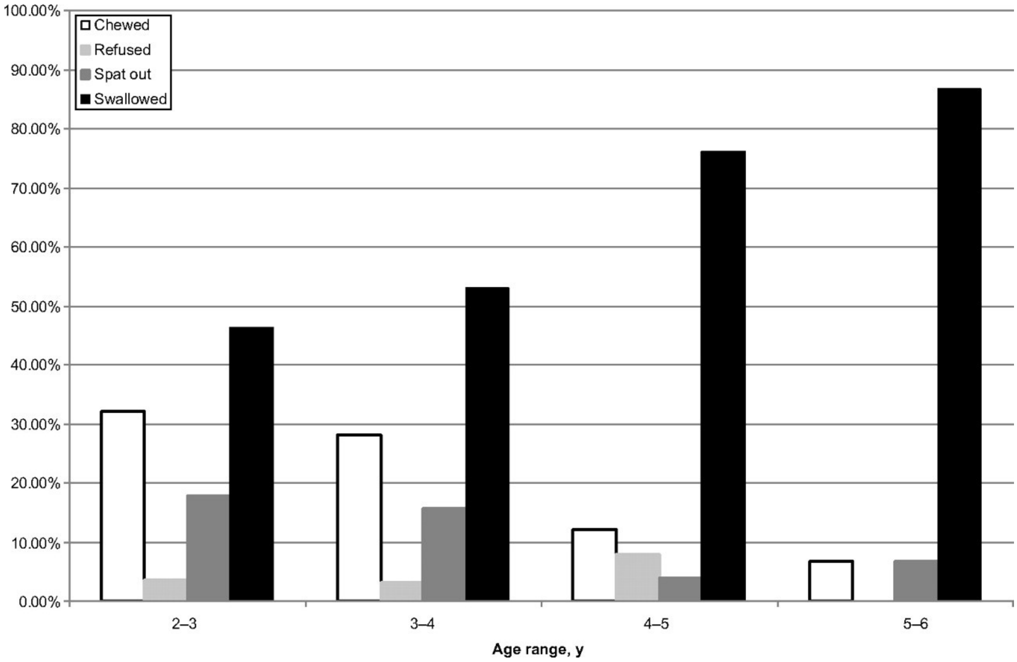


Figure 3. The ability to swallow mini-tablet indicated as a percentage per age group (Thomson et al. 2009).

Klingmann et al. (2018) studied the acceptability of 25-400 uncoated placebo mini-tablets of 2 mm in diameter compared to 5-10 ml of glucose syrup, offering insight into the acceptability of multiple mini-tablets in one dose. The first age group included infants 6-23 months of age, and the second included children 2-5 years of age. A minimum of 25 and a maximum of 100 mini-tablets and 5 ml syrup were administered to the infants. To children 2-5 years of age, the minimum was 100 minitablets, the maximum 400 mini-tablets and 10 ml syrup. The mini-tablets were administered with soft food or drink. In the age group 6-23 months of age, the acceptability of 25 and 100 mini-tablets were significantly greater than the 5 ml of syrup. In comparison, in the age group 2-5 years of age, the acceptability of 100 mini-tablets was smaller than the acceptability of the syrup. However, the acceptability of 400 mini-tablets was non-inferior compared to the 10 ml of syrup, but no superiority was distinguished.

When administering 25 mini-tablets, only 6 % of the children 6-23 months of age chewed or left some of the mini-tablets unswallowed (Klingmann et al. 2018). When 100 mini-tablets were administered, 21 % chewed or left some of the mini-tablets unswallowed.

Moreover, in this age group, the leftover syrup was detected in 44 %. In comparison, in the age group of 2-5 years of age, 42 % chewed or left some mini-tablets unswallowed when 100 mini-tablets were administered. When administering 400 mini-tablets, 69 % chewed or left mini-tablets unswallowed. In this age group, however, the leftover syrup was detected in 52 % of the children. Most of the children in this age group ultimately ingested the total dose, but when administering 400 mini-tablets, 30 % of patients could not take ≥50 % of the mini-tablets. No adverse events were detected when swallowing the uncoated mini-tablets.

4 MANUFACTURING

Direct compression refers to the tabletting process where tablets are compressed directly from a powder mixture containing active substance and excipients, wet or dry granulation is not involved (Gohel and Jogani 2005). As a result, direct compression is a straightforward process with fewer unit operations, leading to shorter processing time and lower energy consumption than granulation processes (Gohel and Jogani 2005; Jivraj et al. 2000). Fewer unit operations also enable reduced contamination risk; thus, the validation and documentation requirements are reduced (Gohel and Jogani 2005). Since there are no wetting or drying steps in direct compression, it is suitable for moisture and heat sensitive active substances. Furthermore, the chance for microbial growth is reduced because no water is needed during the process.

Granulation is a process where fine particles agglomerate into larger particles with controlled properties like strength, porosity, flowability, compressibility, bulk density, and particle size distribution (Suresh et al. 2017). Granulation enables easier material handling by reducing dustiness and minimising segregation, and it also allows better control of the disintegration and dissolution characteristics and active substance content uniformity of tablets − especially at low drug concentrations (Suresh et al. 2017; Thapa et al. 2019).

4.1 Direct compression

For successful direct compression, the powder formulation must have good flowability, compression properties, and high bulk density (Gohel and Jogani 2005; Jivraj et al. 2000). Other factors playing a role are similar particle size distribution and density, which reduces the possibility of segregation during the process. Segregation of powder may cause problems such as weight variation and problems in content uniformity of tablets.

Different stages of the compaction process can be differentiated in the direct compression process (Jivraj et al. 2000). First, particles move to occupy void spaces within the die cavity in the rearrangement phase. This stage is followed by the deformation phase, where the material starts to deform elastically after the particles can no longer rearrange in the die cavity. After the elastic limit of the material is exceeded, the compaction stage starts. Compaction means that the material deforms either plastically or destructively. The mechanism in which the material is compacted is determined by the characteristics of the material, compaction speed, compaction pressure and particle size. When the compression process ends, begins the relaxation stage. If elastic forces exceed the tensile strength of the compressed tablet, the tablet integrity will fail. The key to manufacturing good tablets is the right balance of brittle fracture and plastic behaviour.

Direct compression does not require as high compaction pressure as the production of tablets by slugging or roller compaction (Gohel and Jogani 2005). Therefore, punches and dies exhibit less wearing. Also, directly compressed tablets exhibit fewer dissolution profile changes during storage than tablets made from granules. Other benefits of direct compression are disintegration directly into particles of active substance and excipients instead of granules, leading to faster dissolution. The disadvantage of direct compression is that the formulation should not, in general, contain more than approximately 30 % of the active substance (Jivraj et al. 2000). In addition, a directly compressible excipient should have high dilution potential because that enables very light tablets; that is, the higher the dilution potential, the more active substance it can be mixed with (Gohel and

Jogani 2005). The directly compressible formulation may be achieved with fewer excipients, but it may require special excipients, which are more expensive than the original raw materials (Gohel and Jogani 2005; Jivraj et al. 2000).

4.2 Mixing

Mixing equipment can be categorised according to their mixing mechanism; the four main types are tumbler, convective, hopper and fluidised mixer (Fan et al. 1990). The tumble mixer is an enclosed vessel rotating about an axis which makes the particles tumble over each other in the mixer. The tumble mixers can be further categorised based on the vessel shapes. In most of the convective mixers, an impeller moves particles around within the powder mixture. Hopper mixer performance is based on a gravity flow which induces the particle flow. The mixing performance in a fluidised bed mixer is based on both convective and gravity effects because a gas stream makes the powder flow upwards against the gravity, and the weight of the particles is counterbalanced. This increases the individual particle mobility substantially.

4.2.1 Factors affecting the mixing process

The mixing process is affected by mixer geometry, flow rate and other material properties like bulk density and cohesion (Vanarase et al. 2013). In shear mixers, the impeller rate also influences the mixing efficiency. In general, in a free-flowing powder mixture, individual particles can move independently, whereas, in a cohesive mixture, particles face some inter-particulate bonding, allowing particles to move only in association with other particles (Fan et al. 1990). The cohesive materials require more energy to generate the inter-particulate motion; therefore, the mixing process of the cohesive material reaches an equilibrium state relatively slowly compared to the free-flowing mixing system (Chang et al. 1995). However, the free-flowing material tends to unmix. Thus, the cohesive mixture has a better quality of mix in the equilibrium state than the free-flowing systems in terms of scale and intensity of segregation.

4.2.2 V- and bin-blender

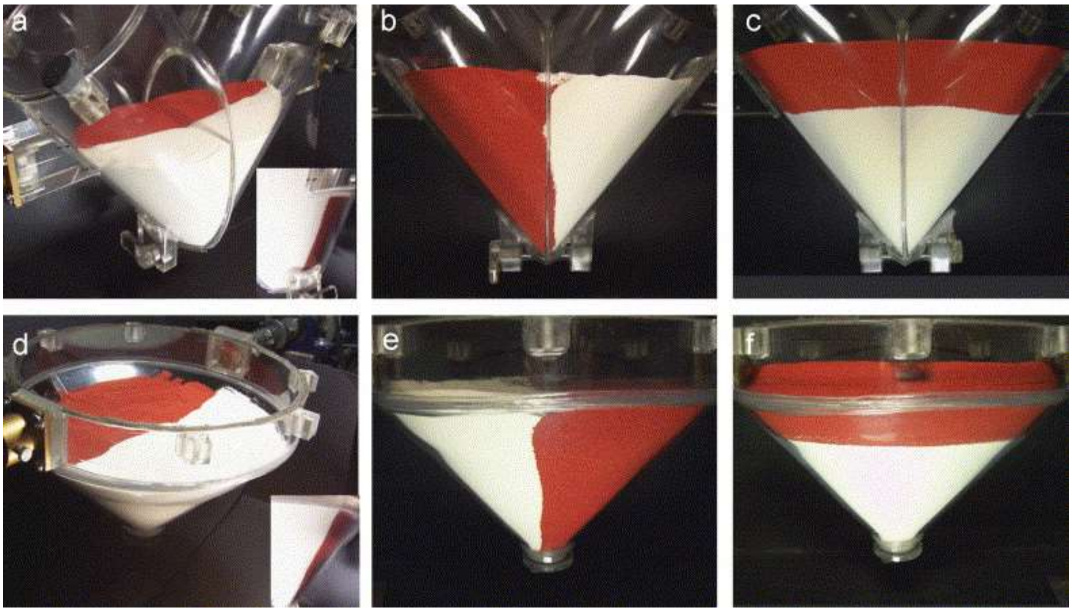


Figure 9. Different loading profiles in a V- and bin-blender (Lemieux et al. 2007). Pictures (a), (b) and (c) are from the V-blender whereas (d), (e) and (f) are from the bin-blender. Pictures (a) and (d) show front-back (FB), pictures (b) and (e) right-left (RL), and (c) and (f) top-bottom (TB) loading profile.

The mixing process in a V-blender and a bin-blender is affected by the loading profile, fill level and rotational speed (Lemieux et al. 2007). There are three different loading profiles: a front-back (FB), a right-left (RL) and a top-bottom (TB), from which the top-bottom is most used. Figure 9 illustrates the different loading profiles. In their study, blend uniformity was reached for the front-back and top-bottom loading profiles. It was seen that for both blenders and loading profiles, the mixing time decreased when the fill level or the rotational speed decreased. However, the fill level was a more influential factor. The effect of rotational speed on the blend uniformity is more important for the V-blender than it is for the bin-blender. However, contrary to the front-back and top-bottom loading profiles, the right-left loading profile mixing performance was improved by increasing the rotational speed in both blenders. Both blender types performed poorly when using the right-left loading profile. However, the V-blender performed better.

4.3 Granulation

Dry granulation is a relatively simple and cost-effective method of granulation where the powder is compacted and then milled (Suresh et al. 2017). One of the main benefits of dry granulation over wet granulation is the absence of water and organic solvents (Kleinebudde 2004). Therefore, dry granulation is a suitable process for heat and moisture sensitive drugs. A negative aspect of dry granulation is dust production and the production of fines that can impair the compaction attributes of the granules (Suresh et al. 2017).

Wet granulation is a process where a liquid solution is added into an agitated powder blend (Suresh et al. 2017). The granules are formed due to the adhesive forces between the binder and the solid surface of the original material, together with the capillary and viscous action of the binder. The use of a liquid binder enhances compaction characteristics and improves the homogeneity of content in granules. The granules are then dried and further processed. In wet granulation, process control, kinetics and scale-up of the process is complicated. The downsides of wet granulation are high equipment costs and the need for efficient process control. Also, if not controlled effectively, moisture content can have undesirable effects on active substances. However, wet granulation has benefits over other granulation methods such as better drug uniformity, improved flowability, increased bulk density and porosity (Thapa et al. 2019). Wet granulation can also be used to achieve a high drug load.

Granule attributes affecting the end-product quality are, for example, granule size distribution, porosity, density, flow properties, compressibility, shape, morphology and mechanical strength (Thapa et al. 2019). Control of these attributes is essential to achieve products of desired quality.

4.4 Roller compaction

In the past, dry granulation has been done by slugging, but nowadays, roller compaction is a more common process (Sun and Kleinebudde 2016). In roller compaction, powders are passed between two counter-rotating rollers, and the powder forms a compact due to the large pressure in the roller gap (Kleinebudde 2004). The formed compact is then milled into granules of the wanted size. The benefits of roller compaction over slugging are greater production capacity, more easily controllable operating parameters and dwell time and smaller consumption of powder lubricant. Other advantages of roller compaction are that it is a continuous process, the process is easy to automate, and it is easily scalable, enabling low operational costs.

In dry granulation, the amount of lubricant and the addition method, external or internal lubrication, are significant factors since they can lead to very different granule properties (Sun and Kleinebudde 2016). In external lubrication, tool surfaces are covered with lubricant, whereas in internal lubrication, lubricant is mixed with the powder before granulation. In general, internal lubrication tends to have a more detrimental effect on tablettability compared to external lubrication. The tensile strength of tablets can be significantly affected by the lubricant. However, this is also dependent on the other materials used.

4.4.1 Roller compaction process

The compact shape depends on the rollers used in the roller compaction process; smooth, fluted or knurled rollers form dense ribbons, whereas briquettes are formed when pocket rollers are used (Kleinebudde 2004). The space between the rollers can be divided into three zones: a feeding zone, a compaction zone, and an extrusion zone (Figure 4). In the feeding zone, the stresses are small, and the densification of the material happens due to rearrangements of particles. When pressing forces becomes active in the compaction zone, particles deform plastically or break. A nip or gripping angle is the transition between the feeding zone and the compaction zone. For successful roller compaction, adequate powder supply to the nip angle is required, and the powder coming to the nip angle must be carried entirely into the narrowest part of the roller gap. Compaction pressure must be uniformly distributed over the entire roller. The main variables affecting the roller compaction process are compaction pressure, rate of a feeding system, and roller speed.

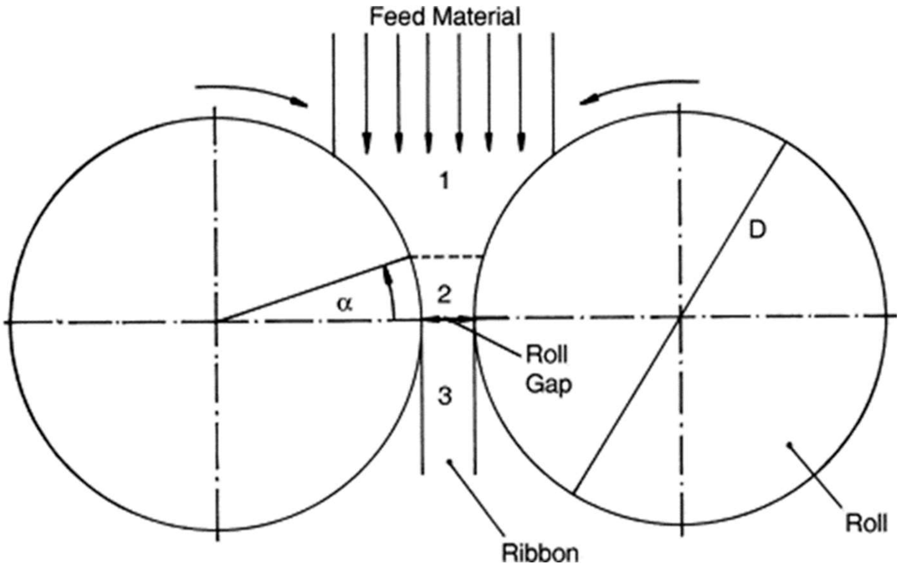


Figure 4. A schematic diagram of roller compactor where 1 is the feeding zone, 2 is the compaction zone, and 3 is the extrusion zone (Kleinebudde 2004).

Roller compaction has some problems such as homogeneity of the compact, high amount of leakage of uncompacted material, and loss in compactibility (Kleinebudde 2004). Uncompacted material results from leakage between roller side seals. However, this can be avoided using concave rollers for sealing. The uncompacted material can also be recycled; on the other hand, this might result in inhomogeneity of the final product if the composition of uncompacted material differs from the original powder. Multiple compactions of the material can also affect compactibility negatively. Although, the flowability of granules might be enhanced if the material is passed several times through a roller compactor. Vacuum deaeration can also be used to overcome leakage of uncompacted material. It also enables avoidance of compressed air inside the compact and a disturbance of the feeding by upwards airflow. If vacuum deaeration is used, it must be uniformly distributed before the nip angle.

4.4.2 Loss of tablettability and ribbon porosity

The dry granulation process has been associated with a negative phenomenon – loss of tablettability or reworkability of granules (Sun and Kleinebudde 2016). The applied force influences the degree of loss of tablettability during roller compaction. In general, higher applied forces cause a more significant loss of tablettability. This is likely due to more porous granules obtained under a lower roll pressure, as the porous granules can deform or fracture more easily during tabletting. Hence, avoiding over-compression is of importance. Loss of tablettability affects more often plastically deforming materials, but it can also affect brittle and fragmenting materials (Kleinebudde 2004). Deformation behaviour of the material and thus loss of tablettability can also be influenced by the moisture content (Sun and Kleinebudde 2016). Overcompaction can also yield discoloured, hot and severely cracked or plasticised ribbons; also, splitting of the ribbons can occur (Kleinebudde 2004).

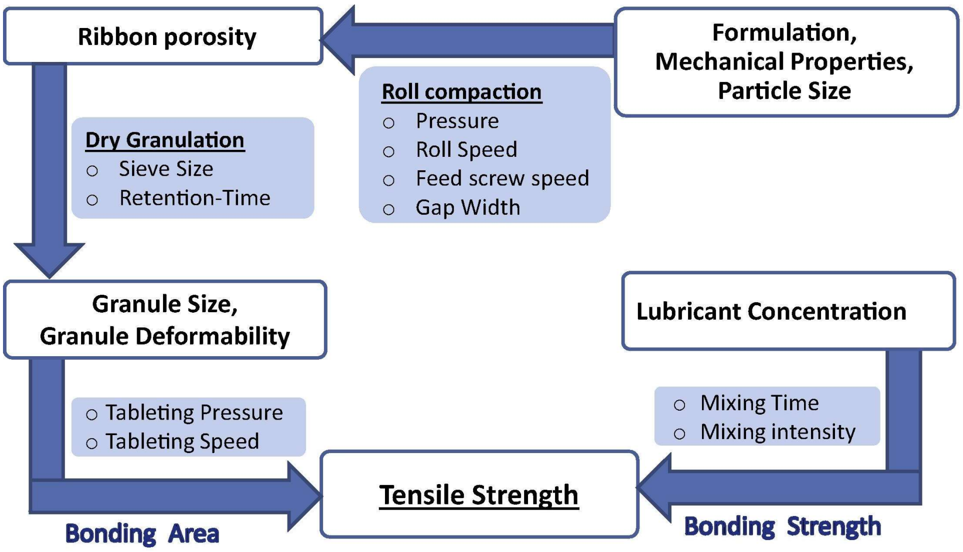


Figure 5. Different factors impacting the tablettability of dry granulated powders (Sun and Kleinebudde 2016). Coloured boxes represent important process variables, and non-coloured boxes represent material properties.

In addition to the control of loss of tablettability, control of ribbon porosity is important (Sun and Kleinebudde 2016). Ribbon porosity is affected by formulation, compaction force, gap width, and powder feed rate, as illustrated in Figure 5. Using small particles for starting materials is beneficial as the particle size affects the final tensile strength of tablets after dry granulation. In general, smaller binder particles of the same material have higher tablettability. However, particle size should not be that small that it hinders powder flowability because consistent powder feeding is necessary for a successful roller compaction process. Chemically identical material can behave differently in roller compaction and exhibit different tablettability due to possible differences in physical forms like polymorphism, solvates or amorphous forms. Materials, which have the same solid phase, can also exhibit batch-to-batch differences in particle size, morphology, shape, or surface roughness.

4.5 High-shear wet granulation

Shear granulators can be divided into low-shear and high-shear wet granulators (Suresh et al. 2017). The impeller rate in the low-shear wet granulators is typically less than 150 rpm and in the high-shear wet granulators more than 200 rpm. The basic principle in the high-shear wet granulation is that the impeller rotates at high speed, keeping the powder in agitation in a closed vessel when a binder liquid is added into the process. Figure 6 shows a schematic view of the high-shear granulator. In the pharmaceutical industry, high-shear wet granulation is one of the most used wet granulation techniques (Thapa et al. 2019).

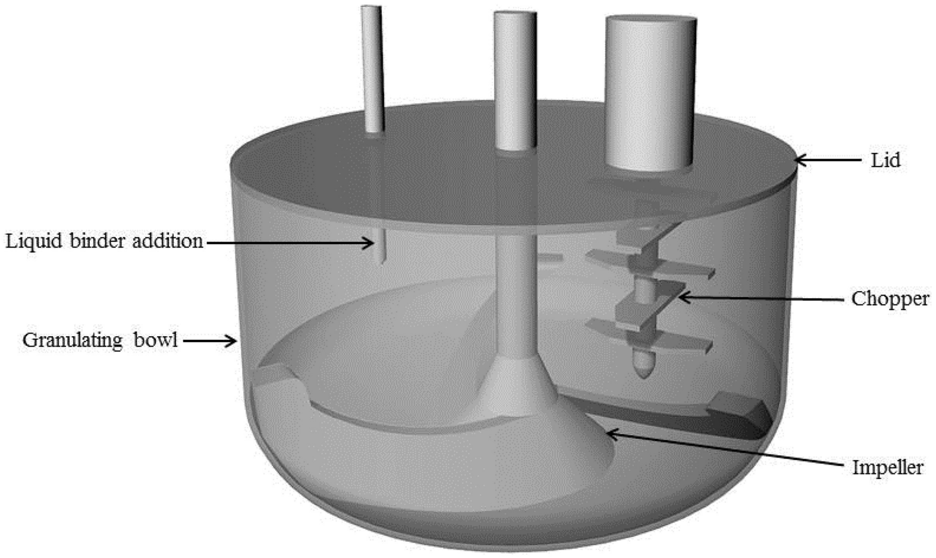


Figure 6. A high-shear wet granulation vessel (Thapa et al. 2019).

The high-shear wet granulation has benefits such as shorter processing time, more significant densification of granules, a narrow range of operating conditions, lower granulating fluid requirement, better predictability of the granulation endpoint, better reproducibility, and improved granule hardness (Thapa et al. 2019). In addition to these, the high-shear wet granulation can be used to achieve high drug load, better drug distribution in the final product, and improved dissolution properties of the final product (Suresh et al. 2017). The high-shear wet granulation has some disadvantages such as lump formation due to over wetting, mechanical degradation of fragile particles and chemical degradation of thermally sensitive materials at high temperatures. The physical and mechanical properties of the granules produced in high-shear wet granulation are affected by the shape, size and speed of the impeller, and the geometry of the granulator bowl, fill ratio and bowl material, amongst other factors.

4.5.1 The high-shear wet granulation process

In general, first, in high-shear wet granulation, the dry powders are mixed at a low impeller rate to ensure uniform distribution of active substances and excipients (Thapa et al. 2019). After the mixing, a binder is added at a high impeller rate. Pouring and spaying are the most common methods to add the binder, and the main difference between them is the droplet size. In general, the binder droplet size is small when the binder is sprayed, and it is also uniformly distributed onto the powder bed. Hence granules of narrow size distributions are achieved. In the pouring method, the uniform distribution of the binder relies heavily on the impeller rotation. Compared to the pouring, the spray method produces more spherical granules and improves flowability.

There are two methods to add the binder – wet binder-addition and dry binder-addition (Thapa et al. 2019). The binder polymer is dissolved into the solvent in the wet binder-addition method, and then this liquid binder is added onto the powder bed. In the dry binder-addition method, the dry binder polymer is first mixed with the powder mixture, and then the solvent is added onto the powder bed at a high impeller rate. The dry addition method produces larger granules compared to the wet addition method. The binder and powder bed together form a wet mass of granules of desired particle size (Suresh et al. 2017).

The viscosity of the binder affects the granule properties significantly (Suresh et al. 2017). Using high viscosity binder, the granule size increases, and the strength decreases with impeller rate. Moreover, it is important to control the initial moisture content of the powder as it can have a positive effect on the coalescence process as a result of increased saturation. This can cause increased porosity and increased granule size, which results in increased flowability and blend density. The initial moisture content can, however, cause poor tablettability. The process is stopped at the phase inversion point because after the phase inversion, the growth of granules would be uncontrollable (Suresh et al., 2017). Then the granules are dried either in the same vessel or in a separate dryer.

4.5.2 Granule formation in high-shear wet granulation

Wet granulation has three rate processes: wetting and nucleation, consolidation and growth, and attrition and breakage, as seen in Figure 7 (Suresh et al. 2017). When the liquid binder is brought in contact with the dry powder bed and distributed throughout it, the liquid forms bridges between the particles. This is called wetting. During nucleation, the initial nuclei of granules are formed when the sticky surfaces of particles collide and coalesce. When a collision between granules, granules and powder, or granules and equipment continues, the granules compact and grow. This is called the consolidation and growth rate process. In the attrition and breakage rate process, wet or dried granules break into smaller granules due to impact, wear or compaction. This can happen in the granulator or during subsequent handling of the granules. In wet granulation, one other important term to understand is wet massing, which means consolidation and growth of granules due to the movement of particles and the presence of sticky surfaces. In wet granulation, binder introduction and wet massing cannot be separated unless carried out in different vessels.

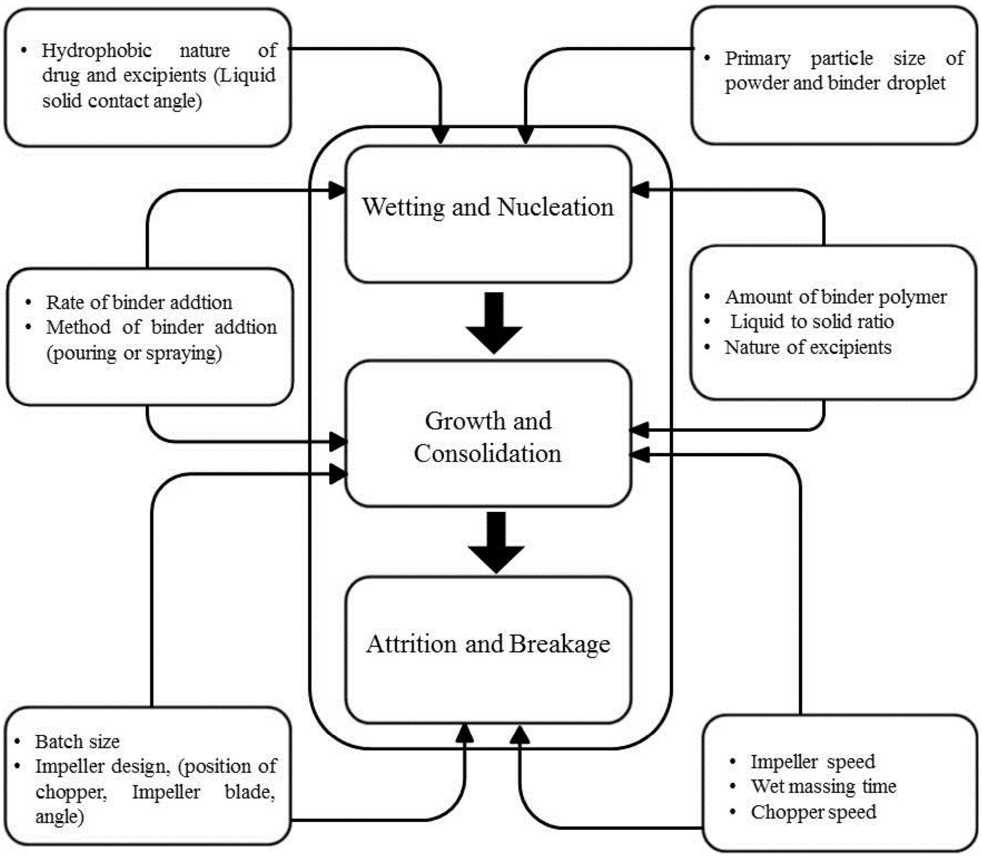


Figure 7. Different stages of high shear granulation and the variables influencing the process (Thapa et al. 2019).

4.5.3 Process parameters affecting high-shear wet granulation

Wetting and nucleation, and therefore the granule attributes, are influenced by the amount of liquid binder and its properties such as viscosity, density, wettability, solid-liquid contact angle, and liquid droplet size alongside the spray rate (Suresh et al. 2017). The granule attributes are also dependent on the formulation of the powder, the process factors such as equipment and operating parameters alongside these rate processes. The extent of pore saturation with the binder is dependent on the process, and formulation conditions and the pore saturation strongly influences the granule growth. The porosity is influenced by the growth and consolidation of the granules. The porosity affects the quality of the granules, such as strength, hardness and dissolution characteristics.

During the high-shear wet granulation, the high impeller rate aids the uniform distribution of the binder onto the powder bed and this initiate wetting and nucleation (Thapa et al. 2019). The high impeller rate also prevents large granules from forming due to the generation of high agitation force, which causes the large granules to break into small uniform granules when they cannot resist high-shear forces. On the other hand, high agitation forces the liquid binder to squeeze into the granules' outer surface, improving granule growth. Also, the use of higher speed results in denser granules (Suresh et al. 2017).

The amount of liquid is a critical process variable in the high-shear wet granulation as it governs the granule growth (Thapa et al. 2019). An inadequate amount of the binder may cause a high proportion of fine particles with weak and porous granules, whereas over-granulation may occur if there is an excessive amount of the binder. The over-granulation can cause uncontrolled granule growth or slurry formation. A uniform binder distribution and a narrow granule size distribution is achieved at a slow binder addition rate. However, an increase in the overall granulation time can occur if the binder addition rate is further reduced as it decreases the granule growth rate. If the binder addition rate is too fast, the binder may not distribute uniformly onto the powder bed, and this can lead to lump formation and wide granule size distribution – this may be further enhanced at low impeller rates.

The mechanical strength of granules increases when the fill level increases because the number and intensity of collisions between particles increase (Thapa et al. 2019). However, the uniform distribution of the binder may be harder to achieve as the fill level increases and hence, overfill of the vessel should be avoided. A fill ratio of 50-70 % is commonly used (Suresh et al. 2017). Overfill can also cause inadequate mixing and production of more fines. However, underloading should also be avoided because it can cause poor granulation due to the dissipation of mechanical energy supplied to the powder bed.

Wet massing time can have a significant effect on the granule properties (Thapa et al. 2019). Long wet massing time can favour monomodal granule size distribution, whereas short massing time may lead to bimodal granule size distribution. The wet massing is vital to the uniform distribution of the binder, it consolidates granules and improves their strength, and it is also important to reproducible granule size distribution. For example, porous and fragile granules are formed when wet massing is insufficient. On the other hand, very hard and dense granules are formed if the wet massing is excessive. The porous and fragile granules are hard to handle in downstream processes. However, the compactibility of hard and dense granules is reduced, and those can also have worse disintegration and dissolution rate.

4.6 Twin-screw granulation

Twin-screw granulation is an alternative wet granulation method to high-shear wet granulation, and it offers fewer or no scale-up steps allowing continuous granulation (Thapa et al. 2019). The twin-screw granulation also has other advantages, such as simple maintenance, high product quality and easy integration with drying, milling and tabletting operations (Suresh et al. 2017). In twin-screw granulation, the powder material is fed into a chamber housing two parallel co-rotating screws, and then a binder is added at specific locations to form granules, as seen in Figure 8.

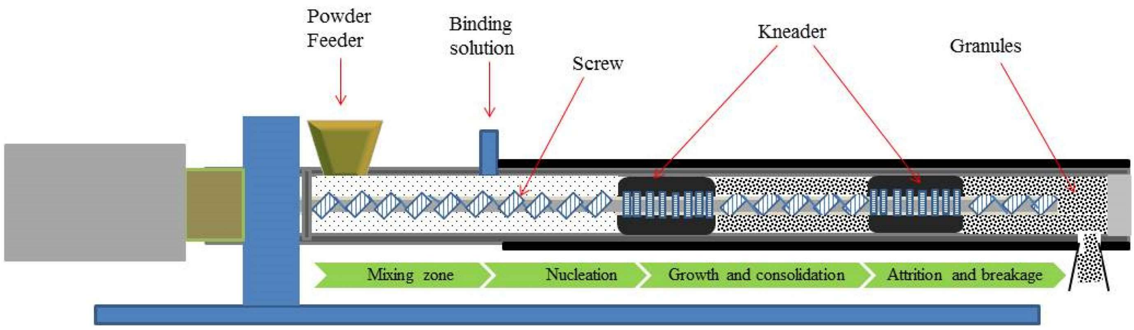


Figure 8. A schematic view of a twin-screw granulator (Thapa et al. 2019). First materials are fed in a powder feeder where the screw conveys the materials to a liquid feeding zone. A binder is introduced in the liquid feeding zone, and the materials get wet, forming agglomerates. Kneading aids the coalescence and consolidation of the agglomerates.

A screw block chamber can be divided into three elements: a conveying element, a kneading block and a comb mixer element (Suresh et al. 2017). The conveying element transports material to the mixing zone with low shear. The kneading block is a primary mixing zone where the kneading blocks use high shear, energy and compaction to form dense and large granules. The comb mixer is the secondary mixing zone, generating forward or revers flow to better mix and moderate granule density.

Parameters influencing the granule properties in the twin-screw granulation are, for example, kneading block and angle, and screw length, configuration geometry and speed (Suresh et al. 2017; Thapa et al. 2019). Moreover, the cross-sectional area, material feed rate, barrel temperature, fill level, and binder introduction affect the granule properties. The screw speed affects the granule size distribution and porosity and the mean residence time of the materials (Thapa et al. 2019). For instance, a low screw speed results in longer residence time and dense and hard granules.

4.7 Drying

After the wet granulation, a drying process is needed to achieve a suitable moisture content of the granules for further processing (Giry et al. 2006). Although, it is important to retain an adequate amount of moisture in the granules to preserve cohesion and reduce static electric charges on the particles. Heat transfer, mechanical stress, and intra-granular and inter-granular solute migration differ depending on the drying equipment. Likewise, granule size distribution, density, porosity, and homogeneity can differ depending on the drying method and process parameters.

The drying process can be divided into three phases (Giry et al. 2006). The first phase is heating, where the heat is usually transferred to the granule by convection or conduction. The second phase is the constant evaporation rate phase, where an equilibrium between evaporation and migration is reached at a constant temperature as the water is drawn to the surface by capillary forces. Factors like crystal packing, moisture content, temperature, hydrogen bonding, and porosity affect dehydration reactions. During drying, the liquid bridges in the wet granules are transformed into dry bonds. The third phase is the falling rate of the evaporation, where the temperature increases because the heat transferred to the granules is no longer used to evaporate water.

Factors affecting the drying process are formulation, drying equipment, type of solvent, drying time, evaporation surface, temperature, relative humidity, and pressure (Giry et al. 2006). The drying time can be decreased by increasing the evaporation surface, mixing the granules while drying or increasing the temperature. It can also be done by decreasing relative humidity or decreasing pressure. It should be noted that granule breakage can occur when drying takes place under stress conditions like in high shearing speed.

4.7.1 A multiphase and a single pot drying process

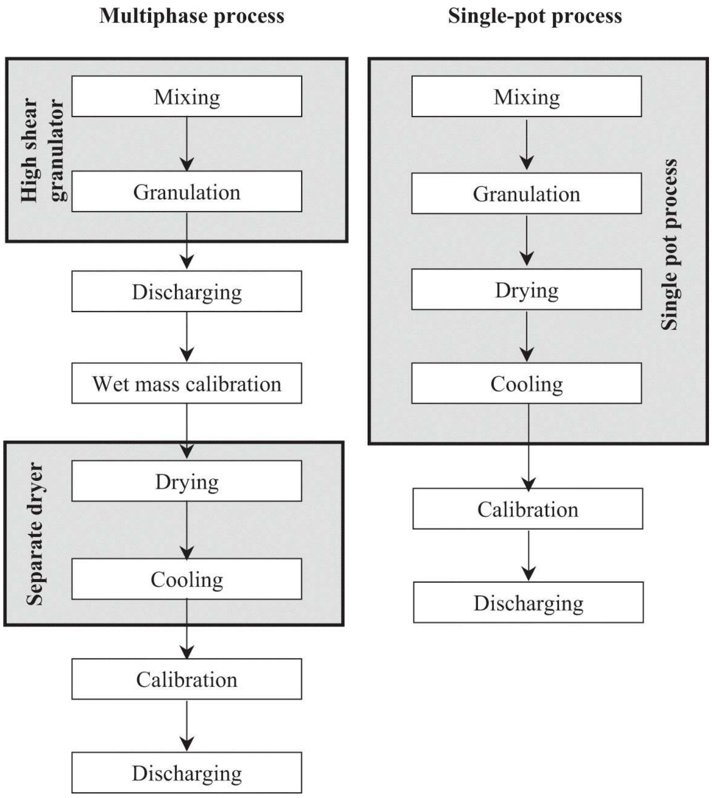


Figure 10. A multiphase granulation and a single pot process illustrated in a schematic view (Giry et al. 2006).

Drying can be a multiphase or a single pot process, as seen in Figure 10 (Giry et al. 2006). The drying process takes place in a separate device like a tray dryer or a fluid bed dryer in the multiphase drying process. The single pot process allows mixing, granulating, and drying in the same apparatus, thus improving handling and decreasing the risk of cross-contamination. However, in the single pot process, lump formation can occur without wet milling before drying. Other disadvantages of the single pot process are longer drying time than the fluid bed drying, although solutions to reduce the drying time, such as the spherical chamber, tilting bowl, microwaves, and gas stripping, have been developed.

4.7.2 Tray and fluid bed drying

In the tray dryer, the wet granules are spread on top of large sheets of paper on shallow wire trays (Giry et al. 2006). The trays are then placed in a drying oven with a circulating air current and thermostatic heat control. The disadvantages of tray drying are relatively long drying time and difficulty to control the process. Liquid evaporation in the tray dryer is very slow, and thus less porous granules are produced.

In the fluid bed dryer, a rising air stream suspends particles in a vertical column (Giry et al. 2006). The airflow rate needs to be optimised to ensure efficient fluidisation of the granule bed. During the fluid bed drying, the water evaporation rate can be improved by increasing the inlet air temperature and the process air flow rate. However, when increasing the temperature, degradation of the drug can occur. Also, the turbulent motion of the powder bed in the fluid bed dryer leads to rapid evaporation of water from the granules and limit the shrinkage. Thus, granules of large mean diameter and high porosity are produced. Heat transfer in a fluid bed dryer is due to convection, and compared to tray drying, the fluidised bed process is much faster.

4.8 Milling

Granules must be of a specific size to pass a screen and leave a conical mill screen during the milling process (Verheezen et al. 2004). Thus, the screen size determines the maximum particle size of the milled granules. The most important parameter influencing the granule size is the bore size in the screens – when the sieve bore size decrease, increases the degree of size reduction. When the bore size is small, it is difficult for the granules to leave the screen even after the granules have reached the size that enables transportation through the screen. This results in more impacts on the granules, thus increasing the degree of size reduction. The screen type has more influence on the coarser feed material. Besides formulation, the screen type also affects the residence time of the granulate in the mill.

The formulation affects the final particle size achieved in the conical screen mill (Figure 11) (Verheezen et al. 2004). For instance, Verheezen et al. (2004) detected that the size reduction ratio decreased when the amount of hydroxypropyl cellulose (HPC) increased in the formulation under similar milling conditions. The degree of size reduction was directly correlated with the strengths of the granules as the degree of size reduction of weak granules was larger than the size reduction required for granules to leave the screen. Impeller rate also affected the size reduction of the granules in the milling process, and change in the impeller rate was more important when the feed material was coarser. In addition, when the feed material was coarser, mill settings became more critical and the milling process less controllable.

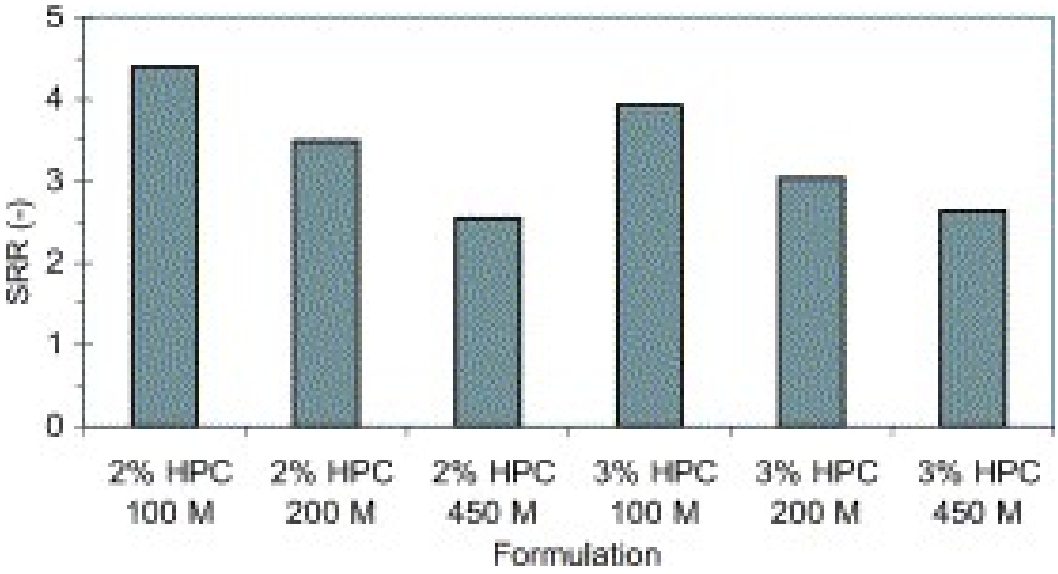


Figure 11. The size reduction ratio (SRR) of different formulations in a conical mill using equal process conditions (impeller rate 3000 rpm and a 0.61 mm screen with spherical bores) (Verheezen et al. 2004).

4.8.1 Residence time in the mill

In the continuous conical milling process, the residence time in the mill determines the physical properties like particle size distribution of the milled material (Barrasso et al. 2013). Moreover, for a given material feed rate, the residence time is affected by the density of the granules, screen size, and impeller rate. The residence time can be decreased by increasing the impeller rate. The residence time also determines the number of impeller passes, that is to say, the amount of shear material experiences in the milling chamber. Barrasso et al. (2013) study determined how by increasing the impeller rate, the number of impeller passes decreases in the case of low-density ribbons, and an opposite reaction was observed for high-density ribbons. This is because the high-density ribbons require more energy for breakage, and thus the residence time of the material is longer before they exit the mill. The particle size of the milled material decreases when the number of impeller passes increase.

4.8.2 Formation of fines during milling

The formation of fines is related to the formulation (Figure 12) and the total degree of size reduction (Verheezen et al. 2004). It is impossible to only control the formation of fines by modifying parameters such as screen size, screen type, impeller rate or particle size of the feed material. The disadvantages of the fines in the downstream processes are the impact on the flowability of granules, and fines can also cause segregation. If a high size reduction of the granules is required together with the limited formation of fines, a multiple-step milling process with decreasing screen bore sizes and separation of in-size particles is one method to be considered. Also, a sieving process to separate the fines from the desired sized particles may be suitable.

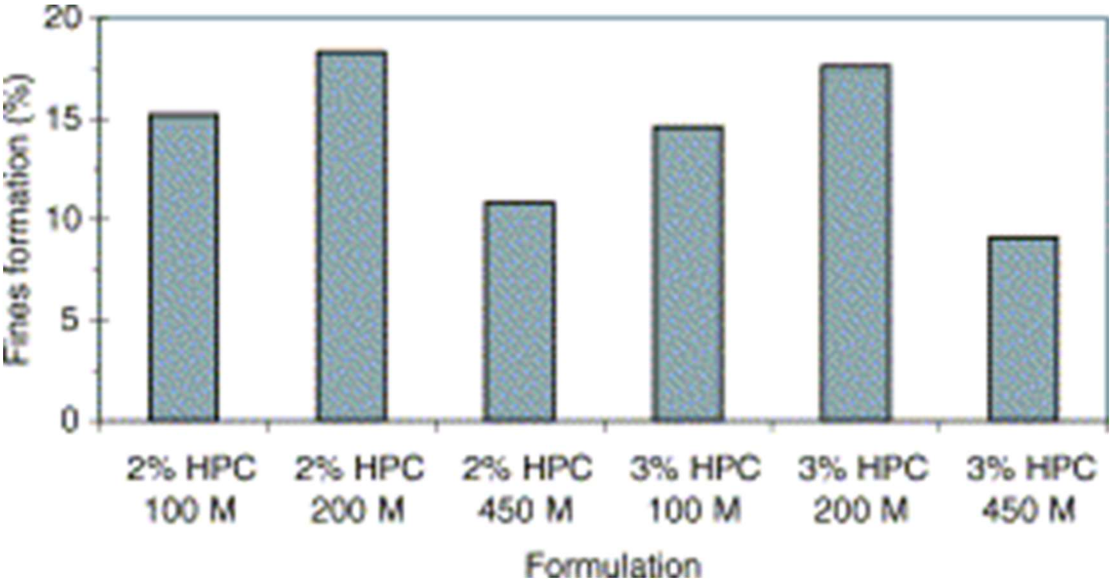


Figure 12. The effect of formulation on the formation of fine particles (<100 µm) under equal conditions (impeller rate 3000 rpm and a 0.61 mm screen with spherical bores) (Verheezen et al. 2004).

5 TABLETTING OF MINI-TABLETS

In the rotary tablet press, the lower punch is moved down by the fill cam under the feed frame (Schomberg et al. 2020). As seen in Figure 13, the feed wheel brings the granules to the die, and the granules enter into the die under the influence of the feed wheel and the suction and gravity fill (Goh et al. 2019; Schomberg et al. 2020). The punch moves until the fill depth is reached. If the fill depth needs to be altered, another fill cam must be installed (Figure 14 and 15). Initially, the die cavity is overfilled, and to achieve dosing depth, a weight adjustment mechanism raises the lower punch position to the desired fill depth. The excess powder is then scraped off at the end of the feed frame by a metering wheel. After reaching the dosing depth, the remaining powder in the die is compacted (Schomberg et al. 2020).

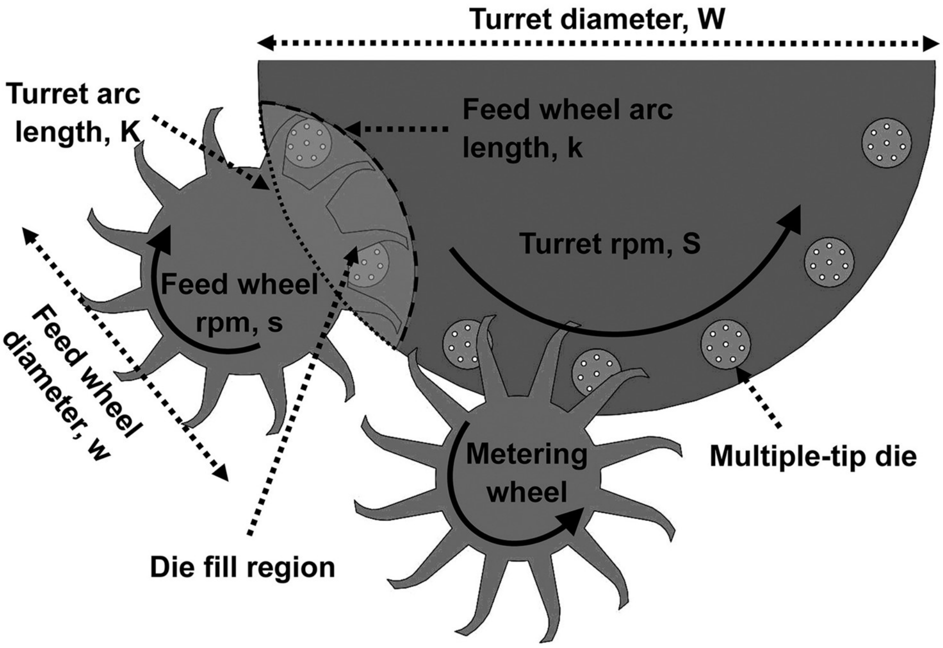


Figure 13. Schematic picture showing the turret, feed wheel and metering wheel on the rotary press (Goh et al. 2019).

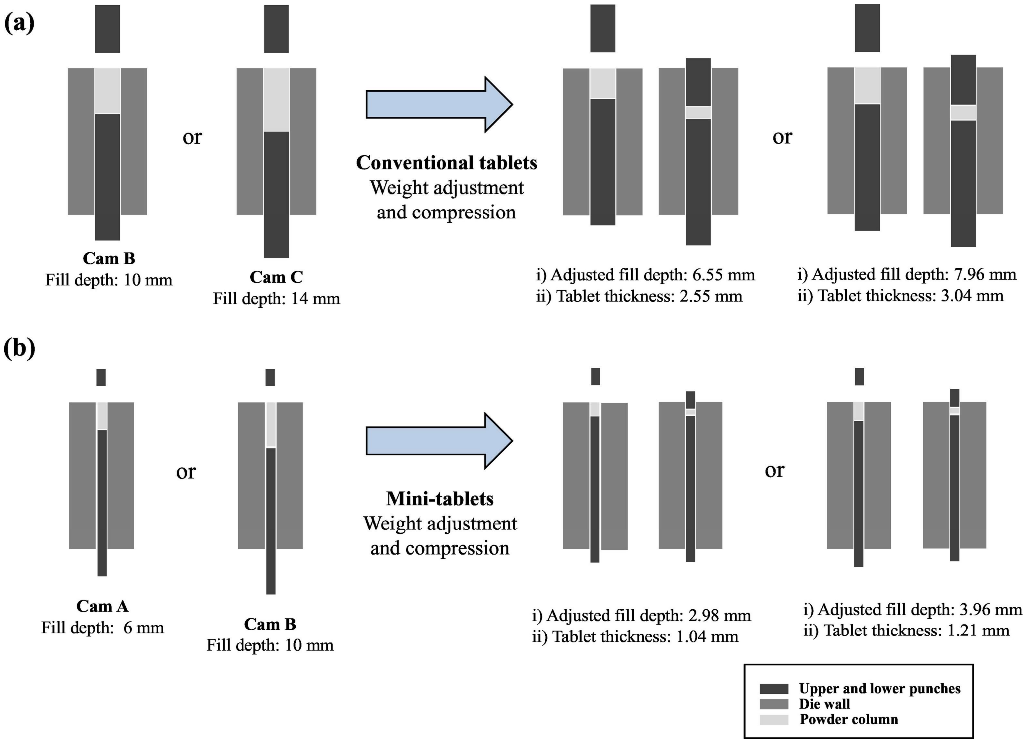


Figure 14. The effect of different fill cams on the tablet thickness in mini-tablet (2 mm) and conventional tablet (5.5 mm) process (Cho et al. 2020).

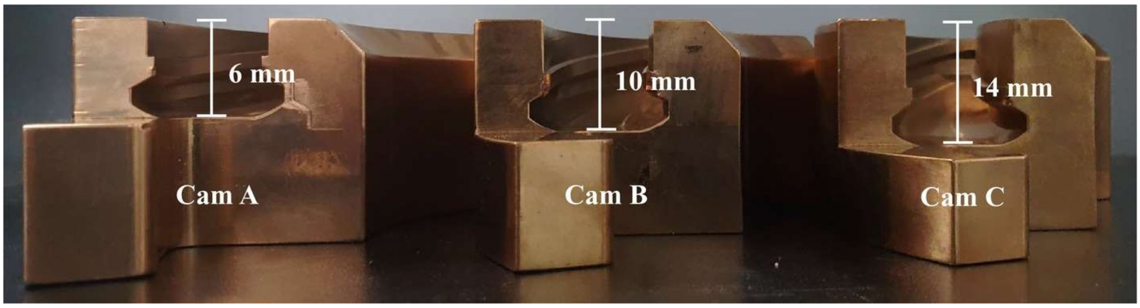


Figure 15. Different fill cams; maximum fill depth 6 mm, 10 mm, and 14 mm (Cho et al. 2020).

There are two kinds of rotary tablet presses; the one with a "floating" compression roller which is held down by a piston that allows the roller to move up vertically by an air compensator mechanism, and the one with a fixed roller where the compression force applied is determined by the tablet weight (Goh et al. 2019). The benefit of a "floating" compression roller is that if the compression force goes beyond a set value, the roller can move up. This allows control of the peak compression force applied during the process regardless of the tablet weight.

5.1 Gravity fill

During gravity fill, nose flow and bulk flow can be observed, as seen in Figure 16 (Mills and Sinka, 2013). Nose flow refers to a situation where the acceleration of the shoe forces the powder toward the back of the shoe, forming a nose-shaped profile. When the shoe is then moved over the die opening, the powder starts to fall into the die. This is the so-called nose flow. Small powder height in the shoe facilitates better nose flow into the die because air can more readily escape from the die allowing the powder at the tip of the nose to enter the die without covering it. This increases the die fill ratio.

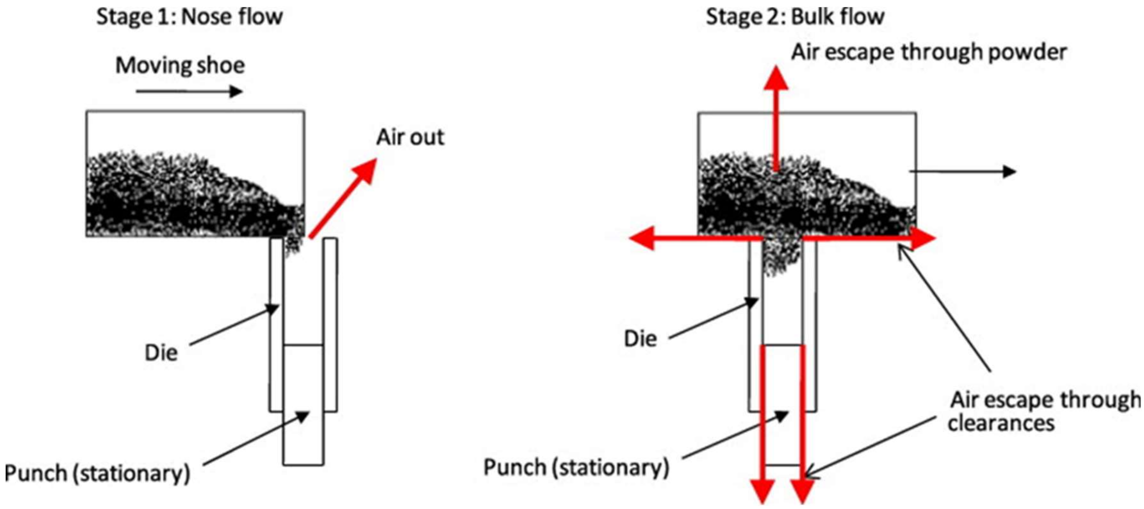


Figure 16. Movement of the shoe and airflow during gravity fill (Mills and Sinka 2013).

Nose flow changes to bulk flow when the shoe completely covers the die and the material continues to fall into the die (Mills and Sinka 2013). During bulk flow, the air escapes through the clearances between the shoe, die and bottom punch as well through the powder in the shoe. For poorly flowing powders, intermittent flow is observed. In intermittent flow, blocks of powder detach from the shoe and fall into the die, and thus the flow is not a continuous stream like with free-flowing powders.

When the mass delivery into the die starts during gravity fill, the pressure in the die starts to increase (Baserinia and Sinka, 2019). The increase in the air pressure results from the powder flow into the die, which decreases the die volume air can occupy. This pressure gradient is in the opposite direction of flow and thus inhibits further powder discharge into the die. The air pressure can dissipate through the powder bed and the clearances in the system. This, however, is dependent on the powder properties, such as permeability. When the permeability is low, it is more difficult for air to escape through the powder bed. In such a case, the pressure is mainly dissipated through the clearances.

During conventional tablet production with a large die diameter, the die cavity can be efficiently filled by the spontaneous flow of granules even at lower rotational speed (Cho et al. 2020). Hence, a shallow fill cam and adequate rotational speed are suitable for an efficient and reproducible tabletting process. However, during mini-tablet production, flow problems such as arch formation inside the die cavity might occur more frequently due to a thin and long shaped die cavity. Hence, the die fill efficiency by the gravity fill is relatively lower.

5.2 Suction fill

The die fill is dependent on the retention time, which is the time the die spends in the die fill region (Cho et al. 2020; Goh et al. 2019). With increasing rotational speed, the retention time decreases, thus reducing the efficiency of gravity fill (Cho et al. 2020). However, increasing rotational speed increases the downward velocity of the lower punch, which creates a pressure gradient towards the direction of flow (Baserinia and Sinka 2019; Cho et al. 2020). This pressure gradient enhances the die fill by “sucking” more powder into the die, hence the name suction effect. The suction effect increases the amount of powder entering the die cavity despite the decreased retention time. The suction effect is illustrated in Figure 17. In addition, an external force like a suction effect can break localised arches inside the die cavity, enabling the powder to deposit deeper into the die cavity (Cho et al. 2020). As flow problems such as arch formation might occur more frequently during mini-tablet production due to a thin and long shaped die cavity, the suction effect is the main parameter affecting die fill behaviour during the mini-tablet production.

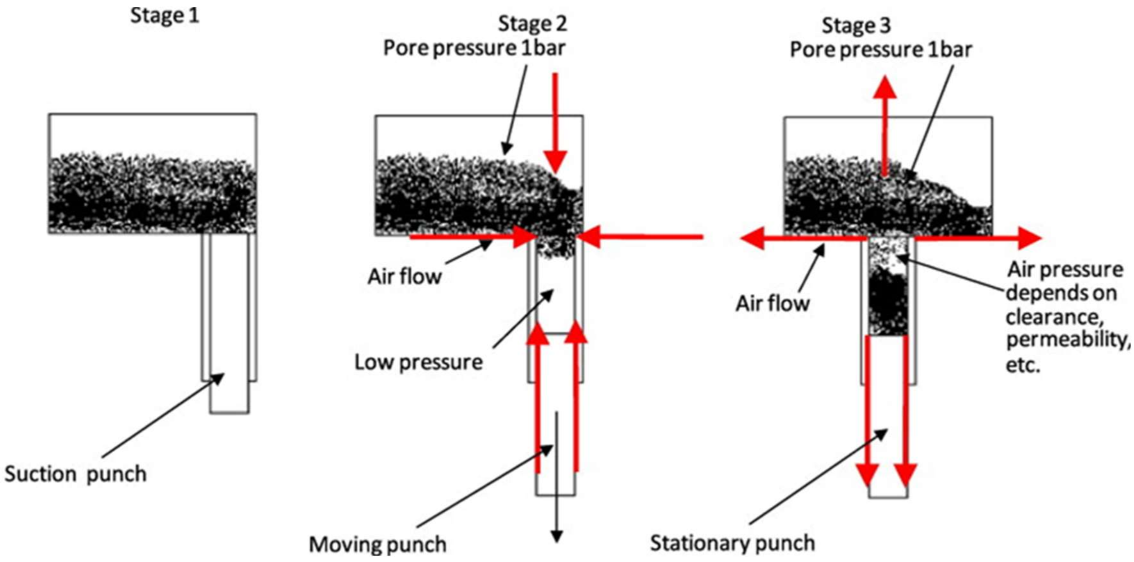


Figure 17. Punch movement and airflow during suction fill (Mills and Sinka, 2013).

When the powder flows into the die, the air has no way out because of the clearances in the system that are compressed between the particles and the punch (Baserinia and Sinka 2019). Thus, the pressure starts to build in the die towards the end of the suction period. The pressure increase continues, and eventually, the suction fill changes to gravity fill. The differential pressure created between the die and the open atmosphere determines the amount of powder introduced into the die. For powders with higher permeability and large particle size, it is easier for air to permeate into the die during suction fill resulting in a smaller negative pressure gradient in the die and reduced suction effect. Other parameters influencing the pressure difference are powder discharge into the die, the shoe and punch motion, and the system’s clearances.

5.3 Parameters influencing the mini-tablet tabletting process

The suction effect can be increased using a deeper fill cam and higher rotational speed, which diminishes the influence of the gravity fill, thus reducing the tablet weight deviation (Cho et al. 2020). However, Cho et al. (2020) postulated that the thin and long shape of the die cavity could lead to a less suitable condition for the suction effect to fully exhibit its effect on die fill. To achieve adequate die fill, consideration of adjusting other parameters, such as fill depth, the geometry of die and lower punch, friction between granules and die wall, and shape and size distribution of granules, should also be given.

5.3.1 The height of the powder bed in the shoe

The powder bed height in the shoe is an important process parameter for die fill because the height of powder exerts pressure on the powder at the die opening (Mills and Sinka 2013). This is a driving force for die fill, but it can also cause local densification and particle interlocking, hindering flow. Besides, the densification of the powder bed can also reduce the escape of air from the die by making the powder bed less permeable for air. This reduces the die fill ratio during gravity fill. However, during suction fill, larger powder height means more mass available to be sucked into the die (Baserinia and Sinka 2019).

The more freely the air can escape from the die, the smaller is the air pressure gradient formed which inhibits the powder flow under gravity fill (Baserinia and Sinka 2019). Thus, a smaller air pressure build-up increases the mass of the powder delivered into the die. Powders with larger particle size and smaller bulk density, that is larger porosity, have greater permeability compared to powders with smaller particle size and higher bulk density. When the permeability is smaller, the differential pressures recorded in the die are larger. The higher the permeability, the more efficacious gravity fill is. However, larger permeability results in reduced suction fill efficiency because then the pressure gradient to the same direction as flow is smaller.

5.3.2 Suction and shoe velocities

In suction fill, powder flow is dependent on both suction and shoe velocities (Baserinia and Sinka 2019). When shoe velocity is sufficiently large, increasing suction velocity results in increased mass discharge into the die (Baserinia and Sinka 2019). This means that for a given shoe velocity, there exists an optimum suction velocity at which the mass of the powder introduced into the die is the largest. At suction velocities above the optimum value, the mass delivered into the die is reduced due to the reduced powder mass available at the vicinity of the die opening.

The die is filled when the shoe passes over the die opening if the shoe velocity is sufficiently low (Mills and Sinka 2013). There is a critical velocity after which the die remains incompletely filled if the shoe velocity is increased above this threshold. In other words, the critical velocity is the maximum velocity of the shoe that fills a die after one pass. The critical velocity correlates with the particle size of the powder. Furthermore, the larger the particle size, the higher the critical velocity. The critical velocity of the shoe increases significantly when suction fill is used compared to the critical velocity of gravity fill. In other words, under gravity fill, increasing the shoe velocity results in a significant reduction of the powder mass introduced into the die (Baserinia and Sinka 2019).

5.3.3 Mini-tablet punches and the fill depth

Conventional tablets can be made using tablet punches with one die hole and a single-tip (Cho et al. 2020). Mini-tablets, however, can be produced using multi-tip punches, as seen in Figure 18. Mitra et al. (2020) remark that compared to the manufacturing of conventional tablets, the small size of mini-tablets allows the manufacture of a significantly larger number of mini-tablets. More than 0.8 million mini-tablets of 1.2 mm in diameter were manufactured from one kilogram of the formulation in their study. If a rotary tablet press with 24 stations is equipped with 18-tip punches and run at 60 rpm turret speed, the production rate is 1.5 million mini-tablets per hour. In comparison, when manufacturing conventional 100 mg tablets, around 18 times longer run and approximately 80 times larger batch size is required to get the same number of tablets. When considering the final formulation, if these mini-tablets were to be used as a multiparticulate formulation of five mini-tablets filled into a capsule, more than 150 thousand final dosage units could be from one kilogram of the formulation manufactured. In comparison, from the same amount of formulation, only 10 thousand of 100 mg size tablets could be manufactured. Of course, it should be noted that mini-tablet manufacture needs special equipment like sensitive characterisation tools and modification to the tablet press. In addition, filling the mini-tablets into a capsule would be an additional unit operation.

Figure 18. Punches and die for a conventional tablet of 5.5 mm in diameter (a) and multi-tip punches and die used for producing mini-tablets of 2 mm in diameter (b) (Cho et al. 2020). Photo (c) illustrates tablets produced beside a Korean coin (diameter of 24 mm).

5.3.4 Turret and paddle speed

Higher fill depth and higher dosing depth increase the difficulty of obtaining complete die fill by gravity fill alone (Schomberg et al. 2020). Also, with higher fill depth, densification of the powder can be observed. Two mechanisms influence the densification during die fill; the paddle speed and the dosing depth. Especially at low turret speeds and low dosing depth, increasing paddle speed, the powder in front of the paddles and inside the die can be densified.

In the rotary tablet press, the production rate can be increased by increasing turret speed (Schomberg et al. 2020). When the turret speed increases, the time for die fill is decreased (Goh et al. 2019). Conversely, increased turret speed creates a stronger suction effect as the lower punch is retracted more quickly. However, there is a critical velocity after which the dies can no longer be filled completely because the suction effect cannot compensate for the reduced retention time (Cho et al. 2020; Schomberg et al. 2020). The critical velocity is dependent on the applied paddle speed and the material properties, such as flowability. Lower paddle speed is required when the flowability is suitable to achieve adequate die fill at a certain turret speed.

Paddle speed affects the mini-tablet tensile strength, which is an important quality attributed as it indicates the tablet’s robustness in downstream processing (Goh et al. 2019). In the study conducted by Goh et al. (2019), the tensile strength decreased with increased paddle speed for mini-tablets 1.8 and 3 mm in diameter. In their study, the turret speed did not appear to have a clear effect on tensile strength. They hypothesise that because the volume of the die is small for both 1.8 and 3 mm mini-tablets, these opposing effects, that is, decreased die fill time and increased suction effect, could have masked the effect of the turret speed on mini-tablet weight and weight variation. The turret speed also affects the mechanical strength of the tablets. When the turret speed increases, the compression profile narrows, the strain rate increases and dwell time decreases.

5.3.5 Paddle angle

Goh et al. (2019) expected that during tabletting, a flat paddle (90° angle) would produce lower die fill densities because it sweeps feed material horizontally across the die. Thus, the flat paddle would cause fluidisation while exerting little downward force. They expected that using an angled paddle (45°) could result in a greater forced feeding effect because some of the force would be directed downward towards the die orifice as it passes under the feed frame. However, the results of the study showed that mini-tablets produced with the flat paddle were heavier. They discussed that one possible explanation for this could be that an angled paddle compresses powder inside the feed frame, thus hindering the free-flowing behaviour of the powder. The compression effect is also emphasised by the region of high-shear conditions, which the gap between the die table and the paddles creates. On the contrary, the force exerted by the flat paddle on the particles created greater fluidisation of powder and maintained powder aeration to facilitate die fill.

Another possible explanation for the reduced die fill density with the angled paddle could be its greater surface contact area with the granules than the flat paddle (Goh et al. 2019). The greater surface area could distribute the force from the angled paddle across many particles, reducing the overall forced feeding effect despite more force being directed downward. On tensile strength for the 1.8 mm mini-tablets, the paddle angle did not have an apparent effect. However, higher tensile strength was detected for 3 mm mini-tablets produced with the angled paddle, especially at lower paddle speeds than the flat paddle. The researchers discuss that for 3 mm mini-tablets, the flat paddle could have increased granule over-lubrication due to the fluidisation effect, resulting in smaller tensile strength. The over-lubrication leads to poor interparticle bond formation during compaction and thus poorer mechanical strength of tablets.

5.3.6 The compression roller displacement values and compaction force

Variation in the compression roller displacement values across the cycles was comparable between the 3 and 1.8 mm mini-tablets (Goh et al. 2017). However, variations in the compression roller displacement values within the cycles were higher when producing the 1.8 mm mini-tablets than the 3 mm mini-tablets. This was suggested to be due to the narrow orifices of the 1.8 mm mini-tablet dies, which were more challenging to fill uniformly compared to the 3 mm dies. When producing mini-tablets of 1.8 mm in diameter, the gravity fill may be less dominant than the suction fill. This may be because residual air trapped inside the die has less effective evacuation possibilities. Thus more significant back pressure is created, which prevents the granules from entering the orifice by the gravity fill alone. More cohesive granules can also form stable arches over the small orifice and hinder die fill.

Compared to conventional tablets, mini-tablets require much lower compaction force to get similar compaction pressures (Goh et al. 2017). This is due to the smaller surface area of mini-tablets of the force application. During the mini-tablet production to detect weight variation, variation in the compaction force might not be a sensitive enough parameter.

This is because the compaction force and tablet weight have a non-linear relationship, and it also becomes less sensitive at low compaction forces.

5.4 Particle size

Particle size distribution and flow properties are critical parameters contributing to successful mini-tablet production (Zhao et al. 2018). Inconsistent die filling may result from using a fine blend with a small particle size distribution and poor flowability. In other words, cohesive flow during die fill is presented with powders with smaller particle size (Mills and Sinka, 2013). Cohesive powders also exhibit intermittent flow during die fill, whereas large particle size promotes the free-flowing behaviour of powders. In gravity fill, particle size and flowability have a consistent relationship.

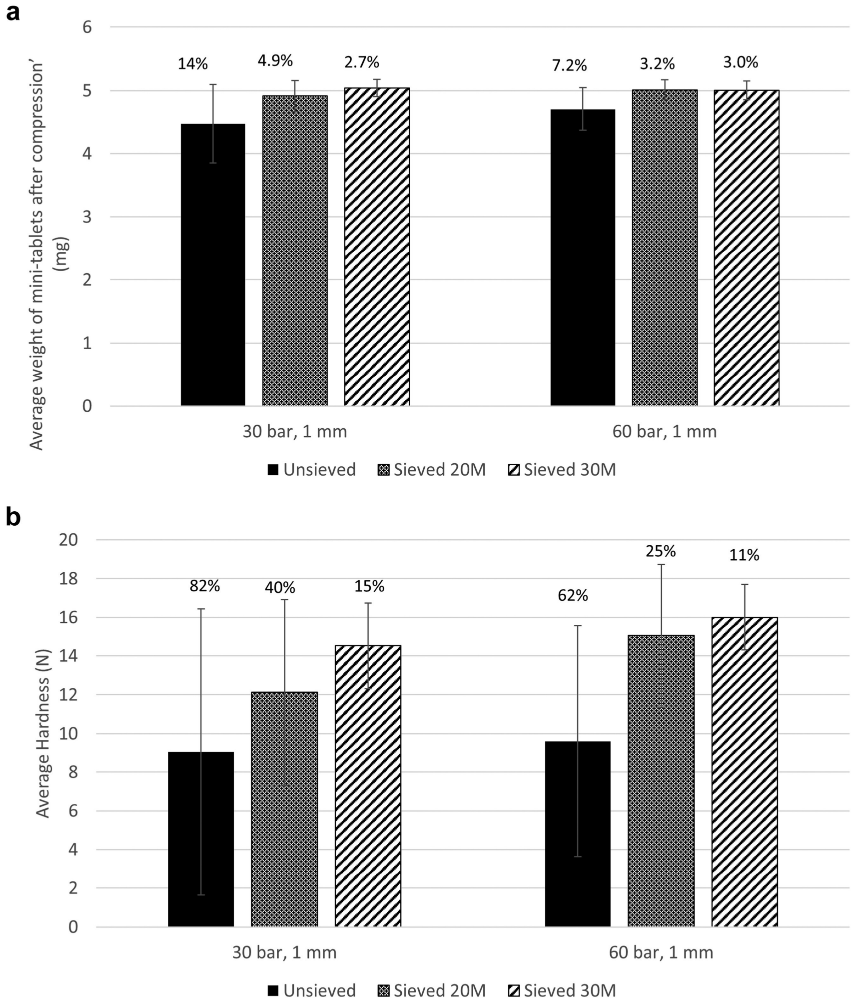


Figure 19. The average weight (a) and hardness (b) of compressed mini-tablets (Zhao et al. 2018). The error bars indicate the relative standard deviation values. The unsieved granule formulation had a significant portion of particles above 841 µm. To remove the large particles above 840 and 595 µm, 20 mesh and 30 mesh screens were used.

Zhao et al. (2018) studied the impact of granule size on successful mini-tablet production. Unsieved granules had a significant portion of particles above 841 µm, and the granule blend was screened to remove the particles above 840 and 595 µm. These three granule formulations were then further processed into mini-tablets of 1.7 mm in diameter. As seen in Figure 19, after removing particles above 595 µm, the average tablet hardness increased, and the variability decreased. The high tablet weight and hardness variation of the unsieved granule blend were not due to poor flow. Hence they postulated that large granules with wide particle size distribution caused inadequate die filling. These results support the experimental findings of Flemming and Mielck (1995), who suggested that in mini-tablet production, the particle size should not exceed 1/3 of die diameter. Zhao et al. (2018) propose that particle size distribution should be controlled independently of its impact on flowability.

5.5 Flowability

The Hausner ratio, basic flow energy and specific energy reflect inter-particulate friction under dynamic conditions, whereas the angle of internal friction under static conditions (Goh et al. 2017). The high Hausner ratio, basic flow energy and specific energy values indicate poorer flowability and greater extent of the inter-particulate friction.

More significant variation in the compression roller displacement values across the compaction cycles indicated higher variation in mini-tablet weights (Goh et al. 2017). These mini-tablets were generally produced from granules with a higher Hausner ratio, basic flow energy and specific energy values but a lower angle of internal friction. The Hausner ratio and specific energy only affected the compression roller displacement values across the cycles when producing 1.8 mm mini-tablets. When considering the weight variation across the cycles, the importance of dynamic flow and mixing inside the feed frame must be considered.

A higher angle of internal friction value indicates greater static inter-particulate friction, which could be important during suction fill of the granules (Goh et al. 2017). The granules with a larger angle of internal friction might attach more closely during the suction fill. This could improve the reproducibility of die fill across compaction cycles and explain why the angle of internal friction was negatively associated with the compression roller displacement values across the compaction cycles of the 1.8 and 3 mm mini-tablet production. When producing the 1.8 mm mini-tablets, the angle of internal friction had a significant effect on the compression roller displacement values within and across the cycles. This shows the importance of the static inter-particulate friction and suction fill for the 1.8 mm mini-tablet production.

During tabletting, the rotating paddles in the feed frame fluidise the granule bed (Goh et al. 2017). Efficient fluidisation is required at each compaction cycle to ensure consistency in the amount of granules passed over the die orifice. High dynamic inter-particulate friction of the granules, that is, granules with high Hausner ratio, basic flow energy and specific energy values, hinder efficient fluidisation. This leads to higher variation in the amount of granules distributed into the die orifices with each pass under the feed frame.

5.6 Tensile strength, weight variability and content uniformity

Mitra et al. (2020) successfully manufactured mini-tablets of 1.2, 1.5, 2, and 2.5 mm in diameter using a direct compression process. The mini-tablets produced had acceptable weight variability, tensile strength, friability, disintegration time and dissolution properties. However, the smallest mini-tablet of 1.2 mm in diameter and 1.2 mg in weight had slightly larger weight variability compared to the largest mini-tablet of 2.5 mm in diameter and 10 mg in weight. They speculate that one factor contributing to the weight variability for a given blend and compression conditions could be increased difficulty to uniformly fill the die with the powder blend as the mini-tablet size decreases.

Mitra et al. (2020) did not observe a specific trend of the impacts of the formulation variables like ibuprofen particle size on the mini-tablet tensile strength or friability. However, in general, a higher solid fraction of mini-tablets were associated with higher tensile strength and lower friability. Drug particle size, drug loading, tablet size, or other formulation variables had no significant impact on the mini-tablet disintegration time. In general, a faster drug release rate was achieved by decreasing ibuprofen particle size, decreasing ibuprofen concentration in the formulation, and decreasing mini-tablet size. The results suggest that the mini-tablets would sustain the mechanical stresses of downstream processing like coating and packaging. However, researchers note that product-specific acceptance criteria of the mini-tablet tensile strength and friability are yet to be developed.

From the different formulation variables evaluated, mini-tablet size and drug loading (3–25 %) had a statistically significant impact on individual mini-tablet content uniformity (Mitra et al. 2020). Further, improved content uniformity variability was achieved with a larger mini-tablet size and higher ibuprofen loading, as illustrated in Figure 20. The effect of ibuprofen particle size of 60–100 µm was also studied, but it did not significantly impact mini-tablet content uniformity.

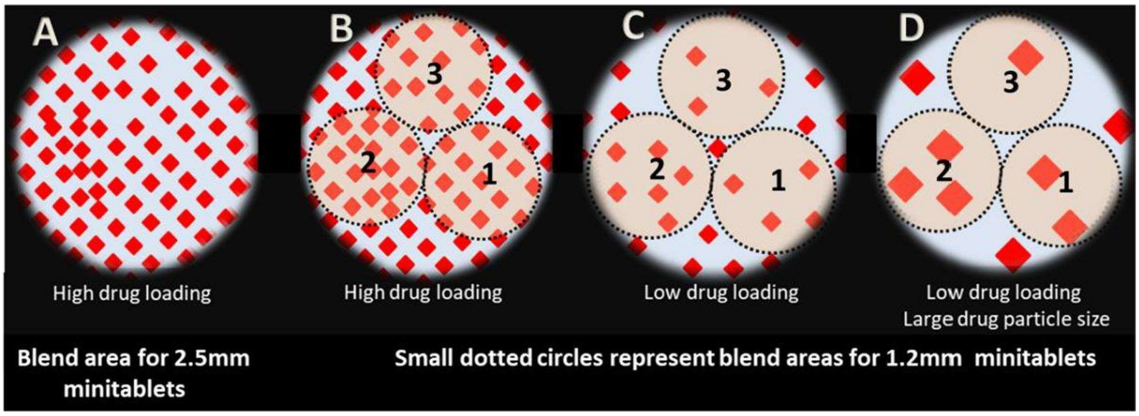


Figure 20. A schematic view describing increased content uniformity variability with decreasing mini-tablet size, decreasing drug loading, and increasing drug particle size (Mitra et al. 2020).

Higher content uniformity variability was detected from smaller mini-tablets made using larger ibuprofen particle size and with lower ibuprofen loading compared to the larger mini-tablets with higher ibuprofen loading and smaller ibuprofen particle size (Mitra et al. 2020). In simple terms, when mini-tablet size decreases, the content uniformity variability increases despite the homogeneity of the bulk powder blend. Based on the results, Mitra and colleagues suggest that with improved weight control, all the mini-tablet batches could have acceptable content uniformity. Furthermore, smaller drug particle size, more efficient mixing or granulation could further improve the content uniformity of mini-tablets.

Moreover, Gupta et al. (2020) detected that by increasing the ibuprofen loading from 0.67 % to 16.67 %, the content uniformity standard deviation of mini-tablets of 1.2 mm in diameter decreased. However, a similar effect was not detected when the ibuprofen loading of mini-tablets of 2 mm in diameter was increased as it had little to no impact on the content uniformity variability. In general, lower ibuprofen loading and coarser ibuprofen particle size caused higher content uniformity variability of mini-tablets compared to higher ibuprofen loading and smaller ibuprofen particle size. Gupta et al. (2020) proved that with the application of appropriate weight control strategies, it is possible to manufacture mini-tablets of 1.2 and 2.0 mm in diameter with acceptable content uniformity of a single mini-tablet. However, consideration to the active substance particle size and loading needs to be given.

5.7 Allowable counting error

If mini-tablets do not meet the content uniformity criteria as single unit dosage forms, the number of mini-tablets in one dosage unit can be increased (Mitra et al. 2020). In other words, weight variability decreases as the number of mini-tablets in one dosage unit increases. For example, the individual mini-tablets of 1.2 mm in size (100 µm ibuprofen particle size, 3 % loading) did not meet the content uniformity acceptance criteria as a single unit dosage form, as a multiple unit dosage forms (5, 10, 15, and 20 mini-tablets per unit) the dosage form was inside the ±25 % acceptance range. In fact, most of the dosage forms were inside the ±15 % range. However, another aspect to consider, besides the content uniformity of multiple unit dosage forms, is the allowable counting error. It must be ensured that the dosage strength is within an acceptable range, and variability in the number of mini-tablets in one multiple unit dosage forms can have a significant impact.

For example, a total of 28, 21, 17, 12, 8 and 5 mini-tablets of 3 mm in diameter can be filled into capsule size 0, 1, 2, 3, 4 and 5, respectively (Mitra, et al. 2017). In comparison, around 100, 140, 200, 250, and 350 mini-tablets of 1.2 mm in diameter can be filled in capsule shell sizes 4, 3, 2, 1, and 0, respectively (Mitra, et al. 2020). If a hypothetical limit of ± 10 % is used, the allowable counting error for mini-tablets of 1.2 mm in diameter filled in capsule shell sizes 4, 3, 2, 1, and 0 are ± 10, ± 14, ± 20, ± 25 and ± 35, respectively. In comparison, the allowable counting error of mini-tablets of 3 mm in diameter filled in size 0 capsules is only ± 2 mini-tablets (Mitra, et al. 2017).

The most dosing flexibility would be achieved by the ability to count and deliver single mini-tablets or other exact numbers of mini-tablets (Mitra, et al. 2020). To date, although the counting technology has advanced in recent years, it still mainly focuses on delivering tens of relatively large mini-tablets of 2 mm or larger in diameter into a one dose unit. In the future, accurate dispensing technology which allows dispensation of even one small mini-tablet should be developed and approved by regulatory bodies (Mitra, et al. 2017). The accurate and reproducible counting technology would allow dispensation of even one mini-tablet into e.g. a multiparticulate formulation used in combination or individualised drug therapy, thus enabling the use of the full potential of mini-tablets.

5.8 Reducing mini-tablet size

It is more difficult to achieve adequate weight control and content uniformity of smaller size mini-tablets compared to larger mini-tablets (Mitra, et al. 2020). In general, weight variation increases when mini-tablet size decreases because small absolute weight variation results in a large relative variation (Mitra, et al. 2017). However, in the literature mini-tablets as small as 1.2 mm in diameter have been successfully manufactured with acceptable weight variability, tensile strength, disintegration time and dissolution properties using a direct compression process (Mitra, et al. 2020). In addition, Tissen et al. (2011) successfully manufactured mini-tablets of 1 mm and 2 mm in diameter using direct compression and drug load up to 90 %. However, 25 % of 1 mm mini-tablets were bisected by the scraper, suggesting that scraper modification is needed to manufacture mini-tablets of 1 mm in diameter successfully.

Despite the challenges of achieving adequate weight control and content uniformity of smaller size mini-tablets as a single unit dosage form, the small mini-tablet size allows better weight control of multiparticulate formulation than larger mini-tablets (Mitra, et al. 2020). For example, in a volumetric filling operation to have 120 mg by filling mini-tablets of 1.2 mm (mini-tablet weight 1.2 mg) and 3 mm (mini-tablet weight 15 mg) in diameter into a size 4 capsule, exclusion or inclusion of only one mini-tablet can cause approximately 1 % and 13 % drift in weight, respectively (Mitra, et al. 2017; Mitra, et al. 2020). Moreover, the smaller size of mini-tablets also allows dose titration in small increments (Mitra, et al. 2020). For example, exclusion or inclusion of one mini-tablet of 1.2 mm in diameter and 1.2 mg in weight with a hypothetical 90 % drug loading would cause a 1.08 mg change in the drug content of the multiparticulate formulation.

Mitra et al. (2020) remark that the excipient burden for paediatric patients needs to be considered when designing paediatric formulation. High drug load enables the manufacture of smaller mini-tablets, which in addition reduces the excipient burden. For example, if the drug load is 90 %, to have 1 mg of the active substance in a mini-tablet, a total of 1.11 mg of the formulation is needed. In comparison, if the drug load is 25 %, 4 mg of the formulation is needed. A high drug load also enables the administration of fewer mini-tablet in one multiparticulate dose, which is especially advantageous with paediatric formulations as this might aid the swallowability and administration of the multiparticulate formulation. For example, if using paracetamol mini-tablets of 3 mm in diameter, 16 mg in weight and 25 % drug load, 31 mini-tablets are needed to have 124 mg of paracetamol. These cannot be filled in the largest capsule of size 0 (Mitra et al., 2017). When using a 90 % drug load, only around nine mini-tablets of the same size are needed to have 130 mg of paracetamol, which can be filled into capsule size 4 (Mitra et al., 2017). It is likely that in commercial use, a multiparticulate formulation containing nine mini-tablets would be much more preferred compared to a multiparticulate formulation containing 31 mini-tablets.

Handling a mini-tablet of 3 mm in diameter might be considered problematic by carers and patients, let alone even smaller mini-tablets. As a result, in commercial use, it may not be feasible to pack individual mini-tablets into a blister package or a bottle as it is challenging to handle the very small mini-tablets. Thus, new innovative solutions to administer the single small mini-tablets are needed. It is good to recognise that even with innovations, the best potential of these very small mini-tablets as small as 1 mm in diameter might be in the individualised and combination therapy, where multiple different mini-tablets of the exact desired number are packed into a capsule or a sachet.

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