Research paper

Evaluation of dissolution techniques for orally disintegrating mini-tablets

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ABSTRACT

Mini-tablets are suitable for paediatric as well as geriatric use since they may provide flexible and accurate dosing and administration. Due to the minute tablet size, there is a need for new standardized quality evaluation procedures and conventional techniques may have to be adopted. The main objective of the study was to evaluate different dissolution techniques for orally disintegrating mini-tablets. Dissolution tests using mini-paddle apparatus were compared with standard size paddle apparatus, and the effect of paddle rotation speed was evaluated. Also, the filter choice, and its impact on dissolution, was considered. Sodium salicylate was used as a model drug substance and was mixed with different size fractions of mannitol. The powder mixtures were compacted into 2 mm flat faced tablets. The mini-tablets were characterized regarding weight and content uniformity, tensile strength, friability, disintegration and dissolution. Similar dissolution profiles were obtained with both mini and standard equipment. The paddle rotation speed affected the dissolution profiles; a low paddle speed resulted in a slower dissolution. Furthermore, choosing a chemically inert filter will increase the likelihood of obtaining reliable and accurate results. An appropriately designed dissolution test using mini-paddle apparatus is required prior to further implementation in quality control procedures.

1. Introduction

There has been an increasing demand for research and development of age-appropriate dosage forms in order to improve drug treatment of children. Mini-tablets are suitable for paediatric as well as geriatric use since they provide flexible and accurate dosing and administration [1–3 [49]]. Mini-tablets typically have a diameter of ≤3 mm and can be manufactured using a conventional tablet machine, fitted with single-tip or multiple-tip punches. Different types of mini-tablets can be produced, e.g. extended release formulations or orally disintegrating mini-tablets (ODMT). Mini-tablets can either be administered individually or filled in capsules or compacted into larger tablets. Previous studies have shown that mini-tablets are well accepted by children of different ages, and children as young as six months demonstrated high swallowability of mini-tablets [3–10]. In a cross-over study Spoomer et al. [8], also showed that mini-tablets were highly accepted in children 6–12 months of age, and comparable with a sweet liquid formulation [3]. Stoltenberg and Breitkreutz have shown that orally disintegrating mini-tablets could be a suitable dosage form for children [3]. Mini-tablets can thus be regarded as a suitable dosage form for young children and used as an alternative to liquid formulations.

An appropriate dosage form for paediatric use should ideally possess convenient administration (including palatability and minimal manipulation pre-administration), flexibility in dosing and safety. Being a solid dosage form, mini-tablets have several advantages over liquid formulations, for example stability and taste masking. They also offer a high degree of dose flexibility, and may provide a more accurate dosing for paediatrics, compared to splitting of tablets initially intended for adults [11]. Mini-tablets also have some limitations and challenges; they can be difficult to handle due to the small size and it may be difficult to obtain an acceptable dose homogeneity in a single unit.

When manufacturing mini-tablets, a good powder flowability is essential to obtain a uniform die filling, and to fulfil weight and dose uniformity requirements. There is also a particle size limitation, since the die diameter is narrow, to avoid die blocking. The die diameter and length affect the powder flow rate, where a smaller opening lowers the flow rate [12]. Direct compression is the preferred manufacturing technique for mini-tablets, provided that the powder mixture has sufficient flow properties [13,14]. Multiple-tip tools are generally used since this increases the output. However, care must be taken regarding mechanical stability and precision of the tools, since a high die wall friction can lead to abrasion and tool damage [15].

Mini-tablets are especially suitable for administration of low doses of potent drugs, in order to make the number of mini-tablets in one dose as

small as possible. Dose homogeneity is thus an important characteristic of mini-tablets to ensure that each individual unit contains the correct amount of drug. Interactive mixtures, where micronized cohesive drug particles are mixed with free flowing coarse carrier particles, have been shown to possess high dose homogeneity even with low drug concentrations [16]. In interactive (also called adhesive or ordered) mixtures, the finer drug particles are adhered to the surface of the coarser carrier particles by adhesion forces ([48] [17]. Initially during mixing, electrostatic forces are also promoting adhesion of the small particles onto the carrier particles [18]. Interactive mixtures can be used as an approach to facilitate homogeneity and minimize segregation [20]. Overall, the result of interactive mixing is a uniform mixture with good flow properties, due to cohesive and adhesive forces that are stronger than gravitational forces. A previous study showed that by using interactive mixtures, mini-tablets with high dose homogeneity could be obtained and that free-flowing carrier particles around 200 μm were most suitable with respect to degree of homogeneity [21]. However, carrier particles sizes down to 20–30 μm have also been reported for interactive mixtures [17,22]. In general, homogeneity of an interactive mixture is affected by particle properties such as particle size, size distribution and surface roughness, as well as mixing equipment and mixing process [23, 24].

Dissolution testing is mandatory during pharmaceutical quality control of solid oral dosage forms, to ensure that compounded drugs are released in a defined and predictable manner. There is a need for new standardized quality evaluation procedures as a consequence of the small sized mini-tablets. Conventional dissolution techniques may have to be adopted without compromising the reliability and predictability to fit mini-tablets. Different setups of dissolution equipment for mini-tablets (basket and paddle method, amount of dissolution medium and paddle rotation speed) can be found in the literature [25–31]. Standard paddle experiments require both large volumes of test media which, particularly when using biorelevant media, can be cost intensive, and large sample sizes that are typically not available in the early stage development when the main objective is to characterize the physico-chemical properties of the active ingredient and the final formulation has not yet been established. It may thus be helpful to use a test system that requires smaller sample sizes and smaller volumes of media but has the same reliability and predictivity as the standard test apparatus.

The main objective of this study was to evaluate dissolution techniques for orally disintegrating mini-tablets. At present, rather limited information can be found in the scientific community, and there are no international pharmacopoeial guidelines, for dissolution testing of mini-tablets. Dissolution tests using mini-paddle apparatus were therefore compared with standard size paddle apparatus, and the effect of paddle rotation speed was evaluated. Also, the filter choice, and its impact on post-drug dissolution, was considered. Any surface that meets the sample has potential to either add extractable impurities to, or bind drug component(s) from, the aspirated samples. Different filter membrane types were investigated. Furthermore, the effect of particle size of the filler on mixture homogeneity and tablet properties was evaluated.

2. Materials and methods

2.1. Materials

Sodium salicylate (Sigma-Aldrich, Merck KGaA, Darmstadt, Germany) was used as model drug and Parteck® ODT was used as filler (Merck Life Science, Merck KGaA, Darmstadt, Germany). Parteck® ODT (hereafter referred to as mannitol) is a directly compressible excipient for orally disintegrating tablets containing mannitol (90–95%) and croscarmellose-sodium (3–7%). Magnesium stearate was used as a lubricant (Sigma-Aldrich, Merck KGaA, Darmstadt, Germany). The materials were stored at ambient conditions for at least 24 h prior to further characterization and handling (21.6 ± 0.4 °C and 21.8 ± 6.3% relative humidity (RH)).

Sodium salicylate was milled by hand using a mortar and pestle and then passed through a 45 μm sieve (Retsch, Germany). Mannitol was fractionated into sieving ranges of 90–125 μm, 125–180 μm and 180–250 μm, respectively (Retsch, Germany). The resulting materials were characterized with low-vacuum scanning electron microscopy (SEM) (Carl Zeiss EVO GmbH, Germany) using variable-pressure secondary electron detector (VPSE) or backscattered electron detector (HDBSD) at accelerating voltage of 15.00 kV and probe current of 300 pA. The dry powdered samples were dispersed on an adhesive carbon tape mounted on an aluminum stub before examination in the microscope.

2.2. Evaluation of membrane filters

Three different syringe 0.45 μm membrane filters were evaluated (*Nylon*-Millex®-HN, *Polytetrafluoroethylene (PTFE)*-Millex®-HV and *Polyvinylidene fluoride (PVDF)*-Millex®-LH) (Merck Life Science, Merck KGaA, Darmstadt, Germany) for their filtering ability of sodium salicylate samples prior to spectrophotometric analysis. A stock solution containing 0.015 mg/mL of sodium salicylate was prepared in freshly tapped Milli-Q water (Direct-Q UV system, Merck Life Science, Merck KGaA, Darmstadt, Germany). Sample aliquots (3 mL) were withdrawn from the stock solution and filtered prior to spectrophotometric analysis at 295 nm (CE 3041, Cecil Instruments, United Kingdom). 5 mL sample aliquots were also aspirated and filtered with the same three filter types in a consecutive experiment. The first 2 mL of the filtered solution was however discarded prior to the spectrophotometric analysis. Triplicate measurements (n = 3) were performed for each datapoint and filter type. A new filter was used for each filtration.

The tendency for the model drug to be adsorbed to the membrane filter was evaluated using the following equation [32].

$$\text{Recovery}(\%) = \frac{A_{filtrate} - A_{blank}}{A_{reference}}$$

$A_{filtrate}$ corresponds to the absorbance of filtered sample solution, A_{blank} corresponds to the absorbance of filtered Milli-Q water and $A_{reference}$ corresponds to the absorbance of the unfiltered solution. Filter recoveries >95% were regarded as acceptable [32].

2.3. Preparation of interactive mixtures

Interactive mixtures (25 g) were prepared by mixing sodium salicylate (5% w/w) and mannitol for 24 h at 72 rpm using a Turbula mixer (Willy A. Bachofen AG, Switzerland). Magnesium stearate (2.5% w/w) was added and mixed for one additional minute. A relatively high friction has previously been reported during compaction of mannitol and therefore 2.5% w/w magnesium stearate was considered suitable [33]. Three different interactive mixtures were prepared, with different size fractions of mannitol, 90–125 μm, 125–180 μm and 180–250 μm, respectively.

2.4. Determination of mixture homogeneity

The interactive mixture homogeneities were determined by withdrawing 30 samples (approximately 10 mg each) from each mixture with a powder thief. Samples were taken within three days after mixing. Samples were taken from different positions in the powder mixtures and weighed. Each powder sample was dissolved in 50 mL of Milli-Q water, followed by filtration through 0.45 μm Millex®-HV PVDF filter prior to UV spectrophotometric analysis (CE 3041, Cecil Instruments, United Kingdom) at 295 nm. Each datapoint was measured in triplicate (n = 3), using a new filter for every sample. The degree of mixture homogeneity was expressed as relative standard deviation (RSD) of normalized values, i.e. the ratio between measured content and theoretical content with respect to sample weight.

2.5. Compaction of tablets

Mini-tablets were compacted using a single-punch tablet machine (Korsch XP1, Korsch, Germany). Compaction was performed within one week after mixing. Nine flat-faced mini-tablets (each weighing approximately 10 mg) with a diameter of 2 mm were produced during each compaction. The powder mixtures were manually filled into the hopper shoe for automatic filling into the die. The compaction pressure was set to 150 MPa by adjusting the position of the upper punch and the compaction speed was 20 strokes per minute (Table 1). Batch 1–3 had the same content, except for the particle size of the filler (batch 1: 180–250 μm, batch 2: 125–180 μm and batch 3: 90–125 μm). Approximately 600 tablets were compacted for each batch. The resulting mini-tablets were stored at ambient conditions for at least 24 h prior to characterization (21.6 ± 0.4 °C and 21.8 ± 6.3% RH).

2.6. Characterization of mini-tablets

2.6.1. Uniformity of mass

Uniformity of mass of the mini-tablets was determined according to European Pharmacopoeia (Ph.Eur.) 2.9.5. *Uniformity of mass of single dose preparations* [34]. 20 mini-tablets were randomly sampled, each separately weighed and compared with the average mass.

2.6.2. Uniformity of content

Uniformity of content was tested on single tablet units according to Ph.Eur. 2.9.6. *Uniformity of content of single dose preparations* and on multiple units according to Ph.Eur. 2.9.40 *Uniformity of dosage units* [34]. Ten randomly sampled single units or multiple units (consisting of ten tablets) were weighed and then dissolved in 50 mL and 500 mL Milli-Q water, respectively. Each sample was then filtered through PVDF filters and the amount of sodium salicylate was analysed in triplicate (n = 3) with UV-spectrophotometry (CE 3041, Cecil Instruments, United Kingdom) at 295 nm. A new filter was used for every sample. According to Ph.Eur., a tablet batch passes the test for single units if none of the individual units deviate more than 15% from the average content and for multiple units if the acceptance value (AV) is below 15 [34].

2.6.3. Radial tensile strength

The tensile strength of the mini-tablets were determined using a diametral compression test (PTB 311E, Pharmatest, Germany) (n = 10), and was calculated according to Fell and Newton using the fracture force and the height and diameter of the tablet [35].

2.6.4. Friability

The friability of the mini-tablets was determined according to Ph. Eur. 2.9.7. *Friability of uncoated tablets* (PTF 10 E, Pharmatest, Germany) [34]. The procedure was slightly modified according to Mortazavi et al. [36]. Twenty tablets were deducted and weighed before and after the test. For tablets with a unit mass of less than 650 mg, the recommended total weight of the tablets is 6.5 g. In order to decrease the number of mini-tablets in the test, 6.3 g of glass beads with a diameter of 2 mm were used together with twenty mini-tablets (approximately 10 mg each). The test continued for 100 rotations at 25 rpm, and the friability was calculated. According to Ph.Eur., a friability of ≤1% is considered acceptable [34].

2.6.5. Disintegration

Disintegration of the mini-tablets was performed according to Hagen et al. [21]. Ten randomly selected mini-tablets were placed one by one in a petri-dish filled with 40 mL 0.05 M phosphate saline buffer (pH 6.8, 37 °C). According to Ph.Eur., disintegration of orally disintegrating tablets should occur within 3 min [34]. The disintegration was considered to be complete when the remainder of the tablet was a soft mass without rigid structures as specified in Ph.Eur. 2.9.1. *Disintegration of tablets and capsules* [34].

2.6.6. Dissolution testing

Sodium salicylate dissolution was measured in Milli-Q water, using a 6-station tablet dissolution testing instrument (PTWS 120 D, PharmaTest, Germany) at 37 °C, applying three different rotation speeds (50, 75 and 100 rpm). Water was used as the dissolution media as described in the United States Pharmacopoeia (USP) monograph on sodium salicylate tablets [50]. The dissolution tests were conducted as described in Ph.Eur. 2.9.3. *Dissolution test for solid dosage forms* (Apparatus 2) [34], with a few exceptions regarding equipment and the volume of dissolution media. The dissolution experiments were performed in mini-vessels (250 mL) and standard-sized vessels (900 mL) under sink conditions. The mini-vessel is a scaled down version of the standard size vessel with 1/3 of the dimensions of the standard equipment regarding the vessel and paddle. Six mini-tablets were used in each mini-vessel and 21–23 tablets (depending on batch) in the standard size vessels, giving the same maximum theoretical concentration of sodium salicylate (0.012 mg/mL) in both vessel sizes. All mini-tablets were weighed individually before determining the exact number of tablets corresponding to the desired amount of drug. Sample volumes of 3 mL were withdrawn at specific time points (0.5, 1, 1.5, 5, 10 and 20 min) and immediately filtered using PVDF filters. A new filter was used for every sample. The amount of sodium salicylate in each sample was measured in triplicate (n = 3) with UV-spectrophotometry (CE 3041, Cecil Instruments, United Kingdom) at 295 nm. When calculating the fraction of drug released, the decrease in volume for each sampling point was taken into consideration and correlated. The sampling zone was defined as half the distance from the surface of the dissolution media and the highest position of the paddle blade [34].

2.7. Statistical analysis

Mean values ± standard deviations (SD) and 95% confidence intervals were used for the analyses. *P*-values were calculated using student's t-test (two-tailed), a p-value <0.05 was considered statistically significant. The analyses were performed using Microsoft Excel (Office 365, version 1911).

3. Results and discussion

3.1. Characterization of the mixtures

Sodium salicylate was chosen as a model drug since it is easily quantified with UV-spectroscopy and it is a well-documented substance in e.g. interactive mixtures [16,21]. Mannitol was chosen as the filler since it is a common and suitable excipient in e.g. ODMT due to its sweet taste [3]. The model drug and the fillers were characterized with scanning electron microscopy. The SEM pictures confirmed that the particle size of sodium salicylate was substantially smaller than the particle size of the fillers, which was expected considering the performed sieving of the materials. Furthermore, the drug particles varied in size and had a somewhat flaky appearance (Fig. 1). The SEM analysis confirmed the difference in particle size between the carriers due to sieving. These images illustrate that the smaller drug particles have been attached to the surface of the larger filler particles indicating interactive mixing, at
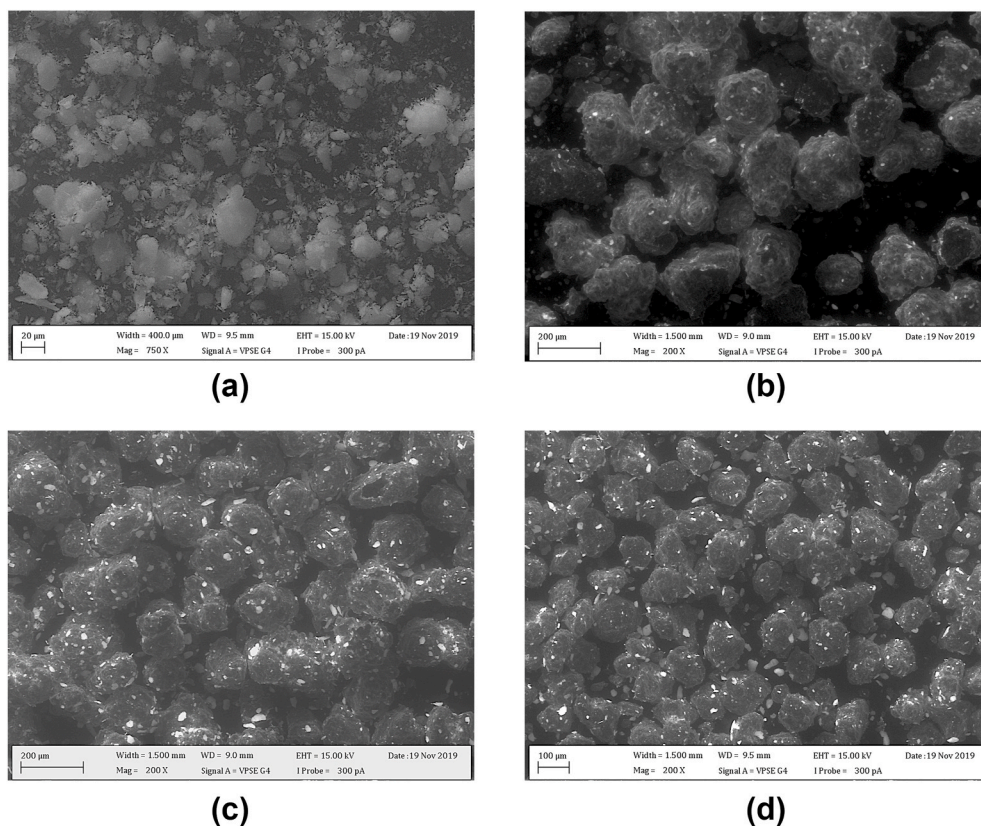
Table 1
The tablet machine settings and measured compaction pressure (mean value ± standard deviation (SD)) for each batch.

Batch	Particle size of filler (μm)	Compaction pressure (MPa)	Compaction speed (strokes/min)	Measured compaction pressure (MPa)
1	180–250	150	20	158 ± 5.4
2	125–180	150	20	153 ± 8.9
3	90–125	150	20	149 ± 6.2

Fig. 1. SEM pictures of sodium salicylate and three different powder mixtures containing 5% w/w sodium salicylate and different particle sizes of mannitol. The brighter areas in 1B-1D display particles of sodium salicylate. **A:** Sodium salicylate (after ≤45 μm sieving) at 750× magnification. **B:** Powder mixture 1 (filler sieve range 180–250 μm) at 200× magnification. **C:** Powder mixture 2 (filler sieve range 125–180 μm) at 200× magnification. **D:** Powder mixture 3 (filler sieve range 90–125 μm) at 200× magnification.

least to some degree. The mixtures were mixed for 24 h. The suitable mixing time for interactive mixtures can be affected by particle properties of drug and excipient as well as by mixing equipment and scale. Generally, relative long mixing times are required in order to achieve interactive mixtures on a small scale. In literature, mixing times between 10 and 72 h have been reported for interactive mixture [16,21,22,37]. However, mixing time has been shown to decrease when mixing is conducted on a larger scale [38].

The results from this study regarding mixture homogeneity showed that batch 1, containing mannitol with the largest particle size, had the highest degree of homogeneity, i.e. lowest RSD (Table 2).

In practice, an RSD < 5% for interactive (ordered) mixtures confirms a good homogeneity with a low degree of segregation [20]. Only batch 1 had an RSD below 5%, indicating that the homogeneity was inadequate in batches 2 and 3. This could be due to the flaky appearance and the varied particle size of the drug particles as verified by the SEM photographs. The acquired results show that the carrier particle size is important for the homogeneity of the interactive mixture, which is in agreement with a previous study where different particle sizes of granulated or spray-dried mannitol were mixed with sodium salicylate. The best homogeneity after mixing for 24 h was obtained with intermediate particle sizes (180–250 μm and 250–355 μm) of mannitol [21]. In addition, another study also showed that a higher degree of homogeneity was obtained in interactive mixtures containing sodium salicylate

and mannitol (180–250 μm) compared to larger particle size fractions of mannitol [39]. It may be hypothesized that the carrier particles should be sufficiently large in order to facilitate the deagglomeration of the smaller drug particles and sufficiently small in order to promote strong adhesion forces. An increased amount of small carrier particles has previously been shown to increase the adhesion forces in interactive mixture [17]. Effective deagglomeration during mixing will result in a more even distribution of the drug particles onto the carrier particles and together with adhesion forces lead to a high degree of homogeneity. However, the effect of carrier particle size on degree of homogeneity needs to be investigated further. Furthermore, surface roughness of the carrier particles may influence the homogeneity of the mixture where a higher surface roughness has been shown to promote a higher degree of homogeneity [23].

3.2. Evaluation of the membrane filters

Fig. 2 shows the filtration recovery of sodium salicylate when evaluating three different membrane types. A recovery >95% is considered acceptable [32]. For experiments without any discarded volume, the highest filtration recovery was obtained with the PTFE and PVDF membranes, whereas the nylon filter provided a significantly lower recovery (nylon vs PTFE p = 0.003; nylon vs PVDF p = 0.001). There was no statistically significant difference between the PTFE and PVDF filters (p > 0.05). However, in experiments when discarding the first 2 mL of the filtered solution, the nylon filter also resulted in an acceptable recovery, with a filtration recovery similar to the other two membrane types (p > 0.05). A nylon material is not inert, but has a rather chemically active surface, and can interact with both basic and acidic compounds through the formation of strong hydrogen bonds with substance(s) being filtered. Thus, to obtain a higher recovery with a nylon membrane filter, typically the filter should be flushed with an adequate sample volume (to saturate the filter) prior to analysis; in this study 2 mL was sufficient. PVDF and PTFE membrane filters can be considered more
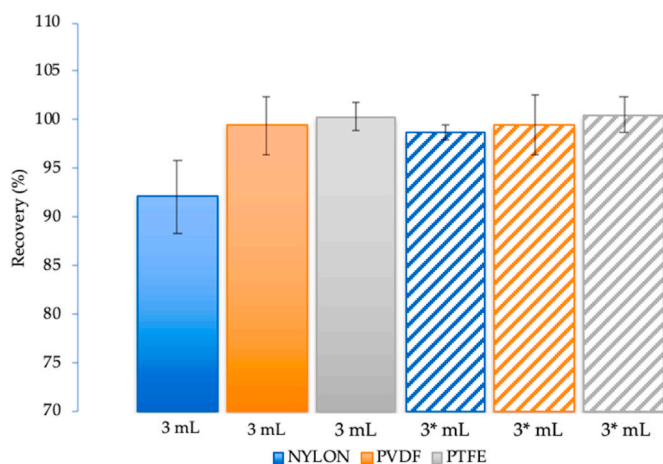
Table 2
The content of sodium salicylate in the samples of the three different powder mixtures (mean value and the relative standard deviation (RSD) of each batch (n = 30)).

Batch	Particle size of filler (μm)	Mean content of drug (%)	RSD (%)
1	180–250	97.8	4.6
2	125–180	101.4	15.4
3	90–125	102.1	11.0

Fig. 2. Recovery of sodium salicylate during the filtration step. The error bars represent 95% confidence intervals for triplicate analyses (n = 3). Columns marked with 3 mL correspond to the total volume of filtrated sodium salicylate samples for each experiment. Columns marked 3* mL correspond to experiments where the first 2 mL, of the initial sample volume of 5 mL, were discarded prior to spectrophotometric analysis.

inert surfaces, and do not require a pre-flush with sample, and are thus preferable for filtering samples in dissolution testing. These results are in agreement with a previous study by Kiehm and Dressman [32]. The PTFE membrane filter appears to have a tendency to overestimate the recovery (i.e. a recovery >100% was observed) and therefore, PVDF membrane filters were selected and used in the subsequent dose homogeneity and dissolution tests.

3.3. Characterization of the mini-tablets

All tablet batches complied with the uniformity of mass and uniformity of content tests according to the corresponding chapters in the European Pharmacopoeia (Ph.Eur. 2.9.5 and Ph.Eur. 2.9.6) [34] (Table 3). The uniformity of content was acceptable both when measured on single as well as multiple units. For single units, the deviation from the average content was less than 15% according to the guidelines in the pharmacopoeia [34]. For multiple units, all batches exhibited an AV-value below 15. Although dose homogeneity was lower in the powder mixtures of batch 2 and 3 (expressed through relatively high RSD values (Table 2)) compared to batch 1, uniformity of content of all mini-tablet batches was within acceptable limits. The drug content of the mini-tablets was somewhat lower compared to the corresponding powder mixtures, especially for batch 2 and 3 (Tables 2 and 3). Drug content was calculated based on the theoretical content in the samples (powder and tablet), i.e. 5 % w/w sodium salicylate. Some loss of drug cannot be excluded during the handling of the mixtures; thus, the content may be lower in the tablets compared with the powder mixtures when comparing with the theoretical amount. The sample size was approximately the same when measuring the homogeneity of mixtures

and tablets (approximately 10 mg). Sample size has otherwise been shown to affect the results [21]. Another aspect could be the difficulty to obtain reproducible and representative samples for the mixtures which may have influenced the results.

The filler particle size is a critical parameter in the manufacturing process of mini-tablets. Too large particles may block the die [13,14]. In this study, batch 1 consisted of filler particles up to 250 μm, corresponding to 1/8 of the die diameter (2 mm). The powder mixtures were easily filled, in an automatic process, from the hopper shoe into the dies, and the smooth die filling resulted in acceptable tablet weight uniformity values.

The manufactured mini-tablets had a sufficient mechanical strength, illustrated by their radial tensile strength and friability (Table 3). The tensile strength was in the same order of magnitude as previously reported results for 2 mm mini-tablets [31,40]. Batch 1 tablets demonstrated significantly higher tensile strength when compared with tablets from the other batches (p < 0.05). This may be attributed to the slightly higher compaction pressure during manufacturing, and/or the larger carrier particle size. The Ph.Eur. monograph on friability is, however, not designed for the low mass and the small dimensions of mini-tablets and therefore, the relevance and applicability of the Ph.Eur. monograph can be questioned. In the literature, the test in the Ph.Eur. monograph has been replaced by friability tests for granules and spheroids [3,41]. In the present study, the friability test was adapted using glass beads due to the low weight of the mini-tablets [36]. The disintegration time was around 20 s for all batches and there were no significant differences (p > 0.05). The disintegration test was performed under static conditions, and the disintegration time was well below the limit of 3 min, suggesting that the tablets are suitable as orally disintegrating tablets. The small size of the mini-tablets makes them unsuitable for testing according to the standard technique described in the pharmacopoeia. A dynamic test would probably be more accurate in order to mimic the effect of movements of a human tongue. To conclude, the mini-tablets produced showed suitable properties regarding weight and dose homogeneity, disintegration, tensile strength and friability irrespective of the particle size of the filler.

During compaction, some friction build-up was experienced, despite the use of 2.5% of magnesium stearate, and that could cause problems in large scale tablet-production. The friction could be a consequence of die wall abrasion from the use of small sized punches or simply that an insufficient amount of lubricant was used, which prevented the newly manufactured tablets to eject properly from the press. The amount of magnesium stearate did not appear to have had any decisive negative effect on tablet strength and disintegration, even though some mini-tablets were floating on the surface for a few seconds during the disintegration test, probably due to the hydrophobic effect of the lubricant. A high amount of lubricant can otherwise affect the properties of ODMTs e.g. tablet strength and disintegration negatively [3], and this has to be taken into consideration when choosing the appropriate amount of lubricant.

Table 3
Characterization of mini-tablets.

Batch	Weight (mg) n = 20	Uniformity of content (min-max) (%)*n = 10	Uniformity of dosage units (AV) **n = 10 × 10	Radial tensile strength (MPa) n = 10	Friability (%) ***n = 20	Disintegration time (s) ****n = 10
1	10.43 ± 0.18	92.9–101.0	11.0	3.2 ± 0.3	0.49	23.3 ± 5.8
2	10.00 ± 0.27	87.4–96.1	11.8	2.0 ± 0.2	0.38	20.7 ± 6.8
3	9.42 ± 0.44	88.1–93.3	12.3	2.2 ± 0.4	0.56	19.0 ± 5.4

*According to Ph.Eur. 2.9.6: individual content should be between 85 and 115% of average content [34].
**According to Ph.Eur. 2.9.40: acceptance value (AV) should be below 15 [34].
***According to Ph.Eur. 2.9.7: friability ≤1% is acceptable [34].
****According to Ph.Eur. disintegration should occur within 3 min for orodispersible tablets [34].

3.4. Dissolution testing of mini-tablets

The dissolution tests using both the mini-paddle and standard size paddle equipment showed that sodium salicylate was rapidly dissolved due to its high solubility in water. The use of an orally disintegrating filler facilitated rapid tablet disintegration. For all batches, most of the sodium salicylate was released within the first 5 min and the dissolution profiles did not differ between the batches. Consequently, no effect of the particle size of the filler was observed, which is probably due to the high-water solubility of both the drug substance and the filler resulting in a rapid dissolution. Dissolution profiles for batch 1 are shown in Fig. 3 (data for batch 2 and 3 are not shown because of the aforementioned similarities in dissolution profiles between the batches). The number of tablets was chosen based on a theoretical maximum concentration of
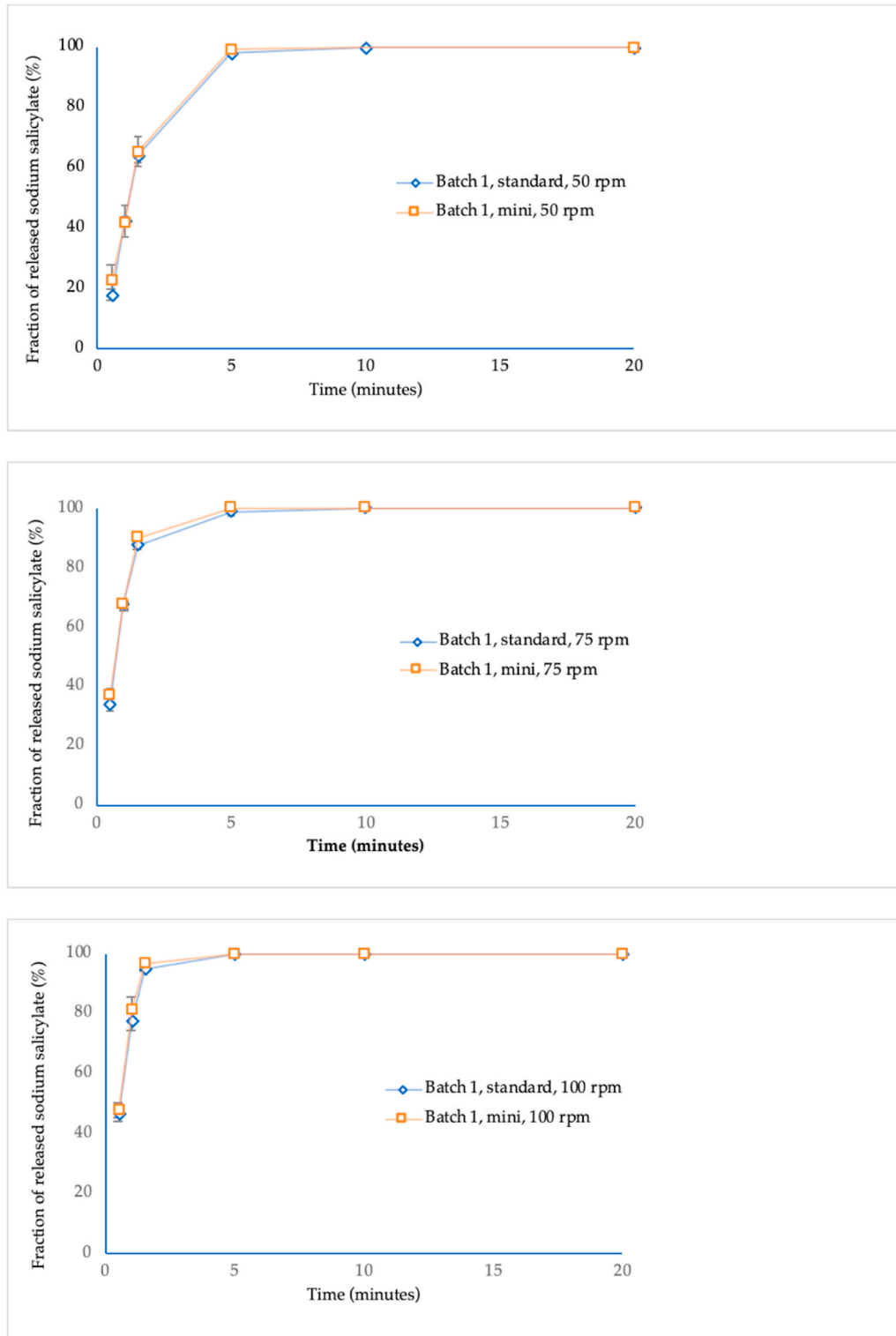

Fig. 3. Dissolution profile of batch 1 when comparing standard size paddle equipment and mini-paddle equipment at 50, 75 and 100 rpm. The error bars represent 95% confidence intervals (n = 3).

sodium salicylate. This theoretical concentration was chosen to be able to quantify the amount of dissolved sodium salicylate using UV-spectroscopy and to maintain sink conditions throughout the experiments. Due to the low amount of drug in each mini-tablet, it was not possible to measure dissolution on a single unit using UV-spectroscopy. However, a dose of mini-tablets can consist of several units, and therefore measurements on multiple units are still relevant.

Depending on the rotation speed, different dissolution profiles were obtained due to differences in hydrodynamic conditions. Similar results have been seen in previous studies for standard size tablets [42]. Initial sampling points (0.5–1.5 min) from batch 1 showed that the amount of released sodium salicylate increased with increased rotation speed (p < 0.05 when comparing the different speeds) (Fig. 4). This observation was confirmed with both the mini-paddle and the standard sized paddle apparatus. At the later sampling points (5–20 min), the dissolution profiles reached a plateau where all sodium salicylate had been released, and consequently the effect of rotation speed was no longer seen. Furthermore, coning tendencies, i.e. where undissolved material accumulates in the "dead zone" under the paddle in the vessel, were visually observed at a paddle rotation speed of 50 rpm. At higher paddle rotation speeds, this was not observed. Higher paddle rotation speed may alleviate the coning effect and is thus preferred to obtain reliable dissolution results, especially for poorly soluble drugs [42]. Due to the high water solubility of the drug and excipient used in the present study, the effect of coning was limited and besides the visual observation mentioned above, the dissolution profiles showed no indications of a coning effect.

Data retrieved from batch 2 and 3 confirmed the results with batch 1 tablets.

During sampling, the same total volume of dissolution media was removed (i.e. 3 mL) in experiments with both the mini-paddle apparatus and the standard size apparatus. It would probably have been more appropriate to remove an equal volume of dissolution medium corresponding to the start volume, which is 1/3 of the medium volume from the mini-paddle equipment compared to standard size paddle equipment, as previously shown by Klein and Shah [42]. An alternative procedure is to maintain a constant volume throughout the experiment, and to replace the sampled dissolution media volume. However, this did not affect the analysed amount of released drug in any way (data not shown). Performing dissolution tests in a large volume of dissolution media can result in analytical detection problems when the amount of drug is limited, e.g. in mini-tablets, but also during early stage development of formulations. However, this may be alleviated through a change in analytical detection technique. Using a scaled down version of the standard equipment, reduced amount of drug and reduced volume of dissolution media are required. The incentives of scaling down the experiments may be both economic and environmental. However, care has to be taken in order to secure that the experiments are performed under sink conditions. In the present study, a drug with high solubility in water was used. Drugs with poor solubility in the dissolution media may require larger media volumes, which may affect the quantitative precision due to lower drug concentrations. Drug substances with different physiochemical properties should be included in future studies in order
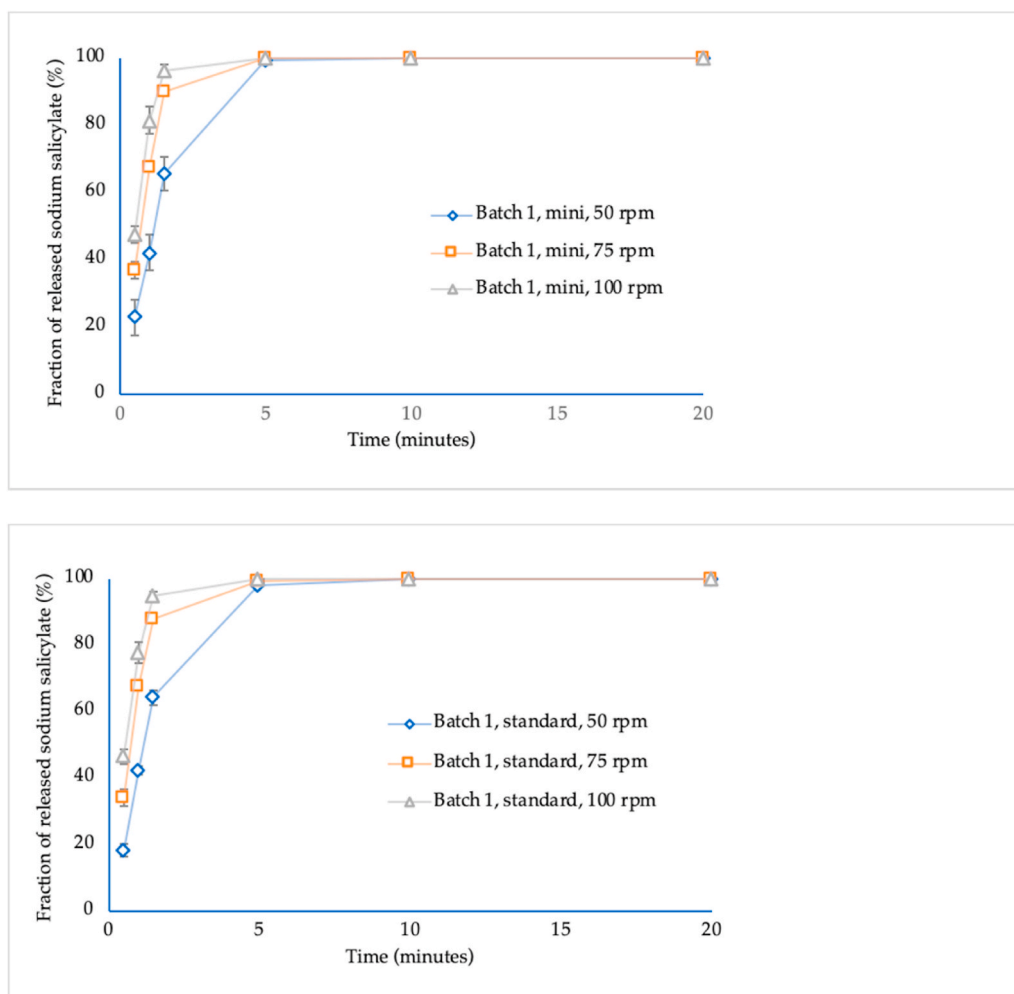

Fig. 4. Dissolution profile of batch 1 when comparing different paddle rotation speeds using mini-paddle and standard equipment at paddle rotation speed 50, 75 and 100 rpm. The error bars represent 95% confidence intervals (n = 3).

to further evaluate dissolution techniques for ODMT:s. Furthermore, different composition and manufacturing parameters should be further investigated in order to optimise the formulation of mini-tablets containing drug substances with different physio-chemical properties. During further development of an appropriate dissolution technique for mini-tablets, more frequent sampling at the beginning of the dissolution experiments (especially for highly water-soluble drugs), suitable paddle rotation speed and choice of different dissolution media and volumes should be considered.

The results of this study indicate that there are similarities in hydrodynamic conditions between the two dissolution testing apparatuses used and confirm the hypothesis that dissolution tests can be performed under scaled down conditions [42]. Other commercially available miniaturized dissolution testing equipment does not have dimensions equivalent to the standard paddle equipment and, thus differ in hydrodynamic conditions [42,43]. In a previous study, different speed factors were proposed when using small volume dissolution equipment in order to mimic the conditions in the standard volume dissolution equipment [43]. Alteration of the experimental conditions when performing standard paddle apparatus dissolution tests, using tilted vessels, confirmed the presence of coning. This particular hydrodynamic condition is especially pronounced when using high concentrations of insoluble excipients or poorly soluble drug substances and low rotation speed [42, 44]. The coning phenomenon is complex and may also be affected by other parameters such as fluid density, fluid viscosity, the particle density and the diameter of the particles. By applying the Zweitering equation, the minimum stirring speed to avoid coning can be calculated. The equation may be applicable even for non-spherical, porous and swellable particles [,45[46]]. Other types of equipment, flat-bottom vessels and Peak™ (convex bottom) have also been evaluated to improve the hydrodynamic conditions and avoid coning [44].

4. Conclusions

The mini-paddle apparatus proved useful for dissolution testing of mini-tablets. Similar dissolution profiles were obtained with both the mini-paddle and standard size paddle equipment and the results showed that the standard paddle experiments could be scaled down without losing the reliability and the predictability of the standard method. The paddle rotation speed affected the drug dissolution profiles in both equipment types. At low paddle speed, coning was visually observed. Coning can affect the release profile, especially for poorly soluble drugs, and a suitable paddle speed should be chosen carefully to avoid coning. The effect of rotation speed has to be investigated further for more precise recommendations. Choosing an appropriate inert filter membrane can have a significant effect on the dissolution results. The mini-tablets produced in this study showed suitable properties regarding weight and dose homogeneity, disintegration, tensile strength and friability irrespective of the particle size of the filler. In addition, the particle size of the filler did not affect the dissolution profile. An appropriately designed dissolution test using mini-paddle apparatus is required prior to further implementation in quality control procedures.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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CRediT authorship contribution statement

Emma Hellberg: Formal analysis, Investigation, Visualization, Writing - original draft, Writing - review & editing. **Annica Westberg:** Formal analysis, Investigation, Visualization, Writing - review & editing. **Patrik Appelblad:** Conceptualization, Methodology, Resources, Validation, Writing - review & editing. **Sofia Mattsson:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing, All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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