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Research paper

Orally disintegrating mini-tablets (ODMTs) – A novel solid oral dosage form for paediatric use

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ABSTRACT

The new European regulations on paediatric medicines and recent WHO recommendations have induced an increased need for research into novel child-appropriate dosage forms. The aim of this study was the development of orally disintegrating mini-tablets (ODMTs) as a suitable dosage form for paediatric patients. The suitability of five commercially available ready-to-use tableting excipients, Ludiflash®, Parteck® ODT, Pearlitol® Flash, Pharmaburst® 500 and Prosolv® ODT, to be directly compressed into mini-tablets, with 2 mm in diameter, was examined. All of the excipients are based on co-processed mannitol. Drug-free ODMTs and ODMTs with a child-appropriate dose of hydrochlorothiazide were investigated.

ODMTs could be produced with all investigated excipients. ODMTs with a sufficient crushing strength >7 N and a low friability <1% could be obtained, as well as ODMTs with a short simulated wetting test-time <5 s. ODMTs made of Ludiflash® showed the best results with crushing strengths from 7.8 N up to 11.8 N and excellent simulated wetting test-times from 3.1 s to 5.0 s. For each excipient, ODMTs with accordance to the pharmacopoeial specification content uniformity could be obtained. The promising results indicate that orally disintegrating mini-tablets may serve as a novel platform technology for paediatrics in future.

1. Introduction

In 2008, a WHO expert forum proposed a shift of paradigm towards solid oral dosage forms for paediatric medicines [1]. Previous opinions, such as of the EMA, represented in the "Reflection Paper: formulations of choice for the paediatric population", characterized liquid formulations as mostly appropriate for younger children (⩽8 years) [2]. Powders, multiparticulates and orodispersible dosage forms were discussed to be appropriate at the age of ⩾2 years. To include medication for developing countries, the recommendations would have to consider the requirements for different climate zones. High temperatures often cause stability problems for liquid formulations. Further, high costs for transportation and storage have to be taken into account. Therefore, liquids should be avoided whenever possible and solid dosage forms, which fulfil desired properties for paediatric use, are highly recommended for global use [1]. Child-appropriateness of a dosage form is indicated by easy administration, palatability, the possibility for weight-based dosing and dose titration, as well as the use of safe, well-established and stable excipients. Therefore, a new versatile solid platform technology is required [1,3].

One approach is the use of mini-tablets as an applicable dosage form for young children. Mini-tablets are defined as tablets with a diameter of 3 mm or less [4]. They can be produced by conventional tablet presses, using a multiple tool. The applicability of mini-tablets has been recently proposed particularly for young children [5]. A preferred applicability of mini-tablets in preschool children (2–5 years) and even probably in infants and toddlers (1 month to 2 years) was recommended, depending on the tablets properties. Thomson et al. recently investigated the acceptability of placebo mini-tablets in 100 preschool children. Forty-six per cent of the children at the age of two years and up to 86% of the 5-year-old children swallowed the mini-tablet. None of the children choked or aspirated the mini-tablet [6]. Therefore, the use of mini-tablets in children between 2 and 6 years should be safe. Furthermore, mini-tablets enable the flexible dosing and administration. For an improved acceptability by parents, suitable dosing devices that count automatically a variable number or electronic dispensers would be desirable [7].

With regard to the appropriateness of a solid oral dosage form, age-dependency of swallowability has to be taken into account. Before 5 month of age, an extrusion reflex enables the infants to swallow only liquids. However, at the age of 6 month, they can physiologically and anatomically swallow multiparticulates in soft food or beverages, depending on size, shape and hardness of the particles [8]. Hence, a dosage form, which disintegrates rapidly and smoothly in the oral cavity within a small amount of saliva, might be a suitable dosage form even for infants and toddlers.

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This led to the second approach for paediatric solid dosage forms: orally disintegrating tablets (ODTs). These tablets disintegrate in the mouth into small particles in a few seconds [9]. With a disintegration time of less than 60 s, they belong to fast-dissolving drug formulations, like oral lyophilisates and wafers. These formulations should be preferred applicable for infants and toddlers [5]. Further, applicability for term newborn infants (0–28 days) was taken into consideration. Rancé et al. investigated the acceptability of commercially available orodispersible tablets made from mannitol, Eudragit® NE 30 D, colloidale silicon dioxide, crospovidone, aspartame and magnesium stearate, containing 20 mg prednisolone in 56 two- to 12-year-old children with ear, nose and throat disorders [10]. A good acceptance for 96% of the patients was shown.

ODTs can be manufactured by different processes like lyophilisation, moulding and sublimation, using a sugar-floss system or direct compression [11]. The process of direct compression is convenient and cost-effective, but is highly influenced by the characteristics of the active pharmaceutical ingredient (API) as well as the used excipients, like flowability, compressibility and compactability [12]. Therefore, excipients that offer excellent compaction properties should be preferably used.

Excipients for ODTs have to be selected based on material characteristics (plastic, elastic or brittle material) and desired functionalities like defined particle size distribution, good flowability, enhanced compactability or fast disintegration. Mannitol represents an often used excipient for fast-dissolving drug formulations. However, when used as untreated powder, the poor flowability, insufficient binding properties and compactability are limiting factors [13]. Hence, co-processed excipients with mannitol are an option. Co-processing means the interacting of two or more excipients at the subparticle level, due to co-spray-drying, co-spray-agglomerating or co-granulating, which led to an improved functionality [14–16]. Various co-processed ready-to-use excipients for direct compression of ODTs are commercially available, which allows the use without restrictions or requirements for royalty payments for ODT technologies protected by patents. Co-processed mannitol could be a useful tableting excipient for ODTs. Its low hygroscopicity enables stability comparable with conventional tablets without the need of highly sophisticated primary packaging. Furthermore, the disintegration properties of the obtained tablets are better compared to other polyols like isomalt [17]. Mannitol has a sweet taste. However, additional taste masking like coating of bitter drug substances may be required, especially for high soluble drugs, which may dissolve rapidly in the mouth [18].

The purpose of this study was to combine the mini-tablet and the fast-dissolving dosage form approaches to prepare orally disintegrating mini-tablets (ODMTs) as a novel solid oral dosage form with co-processed ready-to use excipients, which could be probably used for infants and toddlers (<2 years of age).

Until today, the manufacturing of mini-tablets with these excipients has not been described in literature. Five commercially available excipients with mannitol as the main component, intended to be used for direct compression of orally disintegrating tablets, were investigated with regard to their child-appropriateness and suitability for manufacturing. All investigated ready-to-use tableting excipients consist of ingredients which comply with leading pharmacopoeial monographs (Table 1). However, the number of ingredients should be kept as small as possible and the toxicological risk for paediatric subpopulations should be considered [19]. Further, we examined the preparation of ODMTs with hydrochlorothiazide as a novel paediatric medicine. Hydrochlorothiazide is a diuretic drug which is used in various indications and conditions in children, like bronchopulmonary dysplasia, pulmonary hypertension and diabetes insipidus renalis [20]. It is listed on the WHO Model List of Essential Medicines for Children, which represents essential medicines for basic health care of children [21]. Furthermore, a study about prescriptions of compounded drugs for paediatric patients, performed in Germany in 2006, indicated that in 75% of the examined German hospitals, paediatric doses of hydrochlorothiazide were needed, but no appropriate formulation was available [20]. The study demonstrated that for infants and toddlers, single dosages between 1 mg and 5 mg were mostly needed. Only for elderly patients, medications with hydrochlorothiazide are approved. Tablets and capsules with a minimum dose of 12.5 mg, which needs to be splitted, are available on the German market. Therefore, paediatricians prescribe, for example, low-dose compounded formulations with hydrochlorothiazide for unlicensed use. Further, in child-appropriate solutions or suspensions, problems with stability and dosage errors could be demonstrated [22]. Moreover, a more stable suspension, containing 1 mg HCT per ml, was developed [20]. The investigated small dose of 1 mg per ODMT enables to cover a broad weight range by simply counting mini-tablets without any tablet-splitting.

2. Materials and methods

2.1. Materials

The ready-to-use tableting excipients Ludiflash® (BASF, Ludwigshafen, Germany), Parteck® ODT (Merck, Darmstadt, Germany), Pearlitol® Flash (Roquette, Lestrem, France), Pharmaburst® 500 (SPI Pharma, New Castle, USA) and Prosolv® ODT (JRS Pharma, Rosenberg, Germany) were used as received. The single components of the investigated excipients are presented in Table 1 [23–27]. Sodium stearyl fumarate (SSF, Pruv®, JRS Pharma) and magnesium stearate (Bärlocher, Unterschleissheim, Germany) were used as lubricant. Hydrochlorothiazide (HCT) was obtained from Unichem (Mumbai, India).

2.2. Determination of the particle size distribution

For the determination of the particle size distribution, the co-processed excipients and the hydrochlorothiazide powder were investigated by laser light diffraction (Helos H1402/KF-Magic, Sympatec, Clausthal-Zellerfeld, Germany). The powder samples were dry dispersed with a pressure of 1.0 bar and a feed rate of 80% (Vibri, Rhodos T4.1, Sympatec, Clausthal-Zellerfeld, Germany). The measurements were conducted in triplicate per batch.

2.3. Determination of the specific surface area

The specific surface area of the co-processed excipients was measured by nitrogen adsorption. About 2 g of each excipient was weighed in a sample tube and was then degassed (SmartPrep, Micromeritrics, Norcross, USA) for 1 h at a temperature of 60 °C using nitrogen as purge gas and further 24 h under vacuum at room temperature. Evaluation of the specific surface was made in an adsorbing device (Tristar 3000, Micromeritrics, Norcross, USA), where a mixture of nitrogen and helium flowed over the powder. The adsorbed amount of nitrogen was calculated, using the equation according to Brunauer, Emmet and Teller, to determine the specific surface. The measurements were performed in triplicate per batch.

2.4. Lubrication

For preparation of ODMTs with the ready-to-use excipients, the addition of a lubricant was mandatory. However, it may reduce the tablet strength and has a negative effect on the wettability of

Table 1
Compositions and properties of the co-processed excipients and hydrochlorothiazide, mean ± standard deviation (n = 3).

Trademark	Pearlitol® Flash	Parteck® ODT	Ludiflash®	Pharmaburst® 500	Prosolv® ODT	Hydrochlorothiazide
Batch No.	849821	F1562390926	16700909T0	09F064	Q1X090622	R0HCT/907222
Components	Mannitol Maize starch	Mannitol Croscarmellose sodium	Mannitol Crospovidone Polyvinyl acetate dispersion	Mannitol Crospovidone Sorbitol Precipitated silicon dioxide	Mannitol Crospovidone Microcrystalline cellulose Colloidale silicon dioxide Fructose	
Particle sizes						
D_{10} (μm)	13.82 ± 0.05	24.59 ± 0.42	26.54 ± 0.37	28.46 ± 0.93	23.04 ± 0.20	13.16 ± 0.04
D_{50} (μm)	71.74 ± 2.19	103.18 ± 2.15	87.94 ± 1.02	106.87 ± 2.58	85.52 ± 1.64	39.91 ± 0.15
D_{90} (μm)	269.05 ± 13.20	349.99 ± 32.81	308.17 ± 9.93	206.17 ± 0.70	344.48 ± 3.78	93.18 ± 1.03
Specific surface area (m^2/g)	0.48 ± 0.01	3.46 ± 0.06	0.41 ± 0.01	3.28 ± 0.07	1.92 ± 0.05	

the tablet, which could prolong the disintegration time [12]. Preliminary experiments with powder blends containing Ludiflash® were performed to determine a suitable lubricant and a suitable amount of lubricant. The comparative study between ODMTs, containing various concentrations (between 2% and 5%) of magnesium stearate and sodium stearyl fumarate (Pruv®), respectively, verified the benefit of sodium stearyl fumarate. Even in higher concentrations, sodium stearyl fumarate was superior compared to low concentrations of magnesium stearate relating to SWT time and crushing strength. Hence, a medium concentration (3.5% w/w) of sodium stearyl fumarate was used as lubricant for the investigated formulations to balance lubrication and disintegration properties.

2.5. Powder mixing

Compositions of the prepared powder mixtures are shown in Table 2. Before compression, each excipient was blended with the lubricant (3.5% (w/w) SSF) and for drug-loaded formulations with HCT (15.4% w/w). Preliminary experiments revealed that the time-point of adding the lubricant did not significantly alter the results (crushing strength and simulated wetting test-time) within the time-frame of 10 min. Therefore, all components at once, a total of 200 g powder, were blended in a 1000-ml vessel with a Turbula mixer (T2F, W. A. Bachofen AG, Basel, Switzerland) for 10 min. The speed of rotation was 49 rpm.

2.6. Flow properties of HCT powder and of the powder blends

For direct compression, the flowability of the powder blends is very important. Therefore, two methods were used for powder flowability measurement. At first, bulk density and tapped density of the powder blends (Table 2) were determined according to Ph. Eur. 2.9.36 in order to calculate Hausner ratio and Carr's index [28]. Additionally, it was performed for HCT without the excipients. The lower the Hausner ratio and the Carr's index, respectively, the better is the powder flowability. The procedure was repeated three times per batch.

The second method for flowability characterisation was the ring shear cell test. A ring shear tester RST-01.pc (Dr. Dietmar Schulze, Schüttgutmesstechnik, Germany) was used. The ratio ff_c of consolidation stress to unconfined yield strength was used to characterise flowability. A classification of powder flow behaviour has been defined by Jenike [29] according to the ff_c value: from $ff_c < 1$ (complies not flowing) to $ff_c > 10$ (free-flowing behaviour). Pre-shear normal stress was kept constant at about 5000 Pa. The measurement was performed in triplicate per blend.

2.7. Preparation of ODMTs

The powder mixtures (Table 2) were compressed into biconvex mini-tablets of 2 mm diameter and a mass of approximately 6.5 mg. Compression forces (maximum upper punch forces) of 3 kN, 5.5 kN and 8 kN were applied for all of the ODMT formulations without API, additionally a compression force of 10 kN was used for Pearlitol® Flash. For the formulations with HCT, compression forces of 5.5 kN and 8 kN (respectively, 8 kN and 10 kN for Pearlitol® Flash) were used. The ODMTs were compressed on an instrumented rotary tablet press (Pressima, MX-EU-B/D, IMA Kilian, Cologne, Germany) equipped with a power feeder (speed of rotation of 10 rpm) and one Euro-B 19-tip mini-tableting tool (Ritter, Stapelfeld, Germany). The speed of rotation was 10 rpm. The check of calibration of the maximum upper punch forces showed a maximum deviation $\leqslant$0.13 kN in the range of 0.5–20 kN. The time of filling of the multiple die was 2 s. The obtained ODMTs were dedusted for 1 min using an air jet sieve (Hosokawa Alpine, Augsburg, Germany) with a nominal mesh size of 125 μm and a pressure of 600 Pa. The tableting process, as well as afterwards storage of the ODMTs, took place in a conditioned room at 21 °C and 45% RH.

Table 2
Varied formulations of orally disintegrating mini-tablets with and without active pharmaceutical ingredient (% (w/w)), sodium stearyl fumarate (SSF), hydrochlorothiazide (HCT).

	Pea	Pea_HCT	Par	Par_HCT	Lud	Lud_HCT	Pha	Pha_HCT	Pro	Pro_HCT
Pearlitol® Flash	96.5	81.1	–	–	–	–	–	–	–	–
Parteck® ODT	–	–	96.5	81.1	–	–	–	–	–	–
Ludiflash®	–	–	–	–	96.5	81.1	–	–	–	–
Pharmaburst® 500	–	–	–	–	–	–	96.5	81.1	–	–
Prosolv® ODT	–	–	–	–	–	–	–	–	96.5	81.1
SSF	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
HCT	–	15.4	–	15.4	–	15.4	–	15.4	–	15.4

2.8. Crushing strength

Since mini-tableting tools are very fragile, good compactability properties of the powder mixtures are required. Moreover, a sufficient mechanical stability is advantageous for further processing like packaging and practical handling. The sensitivity of the common hardness tester is not sufficient to distinguish between the formulations, in this particular case. Therefore, the radial crushing strength of the produced ODMTs was determined using a texture analyzer (TA-XT2i, Stable Micro Systems, Godalming, UK).

The ODMTs were deformed in a defined way by a punch over a constant distance of 1 mm using a speed of 0.1 mm/s. A force–distance diagram was recorded and the maximal force was determined for 20 ODMTs per batch [30].

2.9. Friability

Due to the low mass and dimension of the ODMTs, they are more comparable to multiparticulates like pellets than to conventional tablets. To analyse the abrasion resistance, friability was tested based on a method for friability of granules and spheroids described by Sucker et al. [31]. To simulate realistic conditions in a multi-dose container, the proposed method was adapted for ODMTs. Approximately 1 g of ODMTs was filled into a snap-cap vial and placed on a mechanical shaker (Universal shaker SM 25, Edmund Bühler, Hechingen, Germany) for 1 h, with a shaking frequency of 200 vibrations/ min. Subsequently, the samples were dedusted for 1 min using an air jet sieve (Hosokawa Alpine, Augsburg, Germany) with a nominal mesh size of 125 μm and a pressure of 600 Pa. The samples were weighed before and after the treatment. The test was conducted in triplicate.

2.10. Simulated wetting test

The simulated wetting test-time (SWT time) of the ODMTs was evaluated according to Park et al. [32]. The method is a further development of the already established Wetting Time [33]. It is a simple method which simulates the physiological conditions on a wet tongue surface, with the major restriction that the influence of the mechanical stress, induced by human tongue remains disregarded. The method takes tablet sizes into consideration; therefore, it was modified with regard to the small size of the ODMTs. For evaluation, one Whatman filter paper disc (5 mm in diameter) was placed in each well of a 96-well plate and 20 μl of a 0.1% (w/w) Brilliant Blue 85 E 133 solution (BASF, Ludwigshafen, Germany) was added. The blue dye solution was used to enable suitable visual end-point detection. A single ODMT was placed on the surface of the wet paper disc into the dye solution, using a pair of forceps. The volume of the solution covered only the bottom of the tablet. The time required for the blue dye solution to wet the tablet completely is defined as the SWT time. The SWT time of ten ODMTs per batch was determined.

2.11. Mass variation and content uniformity

Twenty ODMTs were weighed on an analytical balance (Sartorius MC 210 P, Sartorius, Göttingen, Germany) to determine mass variations. Further content uniformity according to Ph. Eur. 2.9.40 was carried out [28]. To determine the acceptance values (AVs), the content of the ODMTs was evaluated by using a high-performance liquid chromatography (HPLC) method [20]. The HPLC system (Hewlett-Packard 1090, Agilent, Boeblingen, Germany) was equipped with a LiChroCART® 250-4 Purospher® RP-18 (5 μm) and a precolumn LiChroCART® 4-4 Purospher® RP-18 (5 μm) (both Merck, Darmstadt, Germany) using a mobile phase of 70:30 (V/V) of methanol and distilled water. The mobile phase eluted at a flow rate of 0.4 ml/min. Each of ten ODMTs per batch was dispersed in 10.0 ml methanol. The received samples were filtered with a filter made of polypropylene with a pore size of 0.45 μm before injecting. Fifteen microlitres of the filtrate was injected three times, using an auto injector system. The column temperature was kept at 40 °C. A wavelength of 269 nm was used to measure absorption.

3. Results and discussion

3.1. Flow properties of HCT powder and of the powder blends

Useful excipients for direct compression should possess good flow and compression properties.

The Hausner ratio and the Carr's index refer to the packing characteristics of the materials and might be used as an indication for flowability of the powder mixtures. From the results, presented in Table 3, the powder blends containing HCT could be categorised into three groups: Pearlitol® Flash (Pea_HCT) and Pharmaburst® 500 (Pha_HCT) showed a fair flowability which could be due to their narrow particle size distribution. Additionally, Pharmaburst® 500 contains precipitated silicon dioxide for flowability improvement (Table 1). Another influencing factor could be the particle shape. The values for Parteck® ODT (Par_HCT) and Ludiflash® (Lud_HCT) indicated a passable flowability and the values for Prosolv® ODT (Pro_HCT) a poor flowability (Table 3) although colloidale silicon dioxide was integrated in the excipient to compensate the poor flowability of also the integrated microcrystalline cellulose (Table 1). The powder blends could be ranked, starting with the lowest value, as follows, Pea_HCT < Pha_HCT < Par_HCT < Lud_HCT < Pro_HCT. However, all of the excipients improved the very, very poor flowability of HCT (Table 3).

Results of the ring shear cell measurements provide differing results (Table 3). Therefore, most of the blends could be considered as free-flowing powders (ff_c > 10) and Par_HCT as almost free-flowing (ff_c = 9.7). Following ranking could be made: Pea_HCT < Pha_HCT < Lud_HCT < Pro_HCT < Par_HCT. The range was similar to the results of the determination of the Hausner ratio and Carr's index, except for the results of Par_HCT. However, the cohesive flow properties of HCT were also shown (ff_c = 4). The derived values

Table 3
Flow properties of the powder blends with 15.4% (w/w) hydrochlorothiazide and 3.5% (w/w) sodium stearyl fumarate (with Parteck® ODT (Par_HCT), with Pharmaburst® 500 (Pha_HCT), with Ludiflash® (Lud_HCT), with Prosolv® ODT (Pro_HCT) and with Pearlitol® Flash (Pea_HCT)) and of hydrochlorothiazide powder (HCT): Bulk and tapped density, Hausner ratio, Carr's index, ff_c value and flowability, mean ± standard deviation (n = 3).

	Density (g/ml)		Flow properties				
	Bulk	Tapped	Hausner ratio	Carr's index	According to Ph. Eur. 2.9.36	ff_c value	According to Jenike
Pea_HCT	0.61 ± 0.01	0.75 ± 0.00	1.22 ± 0.01	17.70 ± 0.95	*Fair*	16.4 ± 2.6	*Free-flowing*
Par_HCT	0.61 ± 0.01	0.77 ± 0.01	1.26 ± 0.02	20.51 ± 1.19	*Passable*	9.7 ± 1.3	*Easy-flowing*
Lud_HCT	0.57 ± 0.00	0.73 ± 0.00	1.27 ± 0.00	21.43 ± 0.09	*Passable*	12.2 ± 1.0	*Free-flowing*
Pha_HCT	0.47 ± 0.00	0.59 ± 0.00	1.24 ± 0.00	19.06 ± 0.30	*Fair*	13.1 ± 1.9	*Free-flowing*
Pro_HCT	0.58 ± 0.01	0.80 ± 0.00	1.36 ± 0.02	26.61 ± 0.94	*Poor*	10.2 ± 0.4	*Free-flowing*
HCT	0.51 ± 0.01	0.83 ± 0.01	1.61 ± 0.01	37.69 ± 0.51	*Very, very poor*	4 .0 ± 0.1	*Cohesive*

for the flow properties differ widely. This could be due to the effect that the ring shear tester was more appropriate for discriminating of more cohesive powders. It could hardly distinguish between ff_c values above 10. All of the blends showed a sufficient flowability for direct compression and each excipient should be applicable for manufacturing of ODMTs.

3.2. Formulation and preparation of ODMTs

All formulations without API could be compressed into mini-tablets with a crushing strength >7 N, by using a maximum compression force of 8 kN, except for formulations containing Pearlitol® Flash. The additionally applied compression force of 10 kN onto formulations with Pearlitol® Flash led to ODMTs with a crushing strength of almost 7 N. Further, the manufacturing feasibility of ODMTs containing 1 mg HCT could be verified with all investigated excipients. In this case, only compression forces $\geqslant$5.5 kN were used to achieve a sufficient mechanical stability. For Pearlitol® Flash, higher compression forces (8 kN, 10 kN) were employed to achieve mechanically stable ODMTs. Exemplarily, in Fig. 1, five ODMTs with 1 mg HCT, a single dose for an infant weighing 5 kg, in comparison with a dosing spoon with 5 ml of a Brilliant Blue solution to simulate the required amount of hydrochlorothiazide (HCT) solution (1 mg/kg body weight), are depicted.

3.3. Crushing strength and compactability

Values for crushing strength of the ODMTs without API are plotted in Fig. 2. The highest forces (25.2 N) were measured for the formulation containing Parteck® ODT, compressed at 8 kN. The lowest forces (1.2 N) were measured for the formulation containing Pearlitol® Flash, compressed at 3 kN. The formulations without API, compressed at various forces with a crushing strength above 7 N, could be ranked from the highest to the lowest crushing strength as follows: Par_8 kN > Pha_8 kN > Par_5.5 kN > Lud_8 kN > Pha_5.5 kN > Pro_8 kN > Lud_5.5 kN > Par_3 kN. HCT showed a decreasing effect on the crushing strength for all formulations. Nevertheless, sufficient values could be achieved with several excipients (Table 4). Four different formulations with HCT accomplished a sufficient crushing strength above 7 N, Par_HCT_8 kN > Lud_HCT_8 kN > Pha_HCT_8 kN > Par_HCT_5.5 kN. With Pearlitol® Flash, ODMTs neither with HCT nor without HCT could achieve a crushing strength of $\geqslant$7 N. For Prosolv® ODT, only one formulation (Pro_8 kN) obtained a sufficient crushing strength, although microcrystalline cellulose was used for its composition.

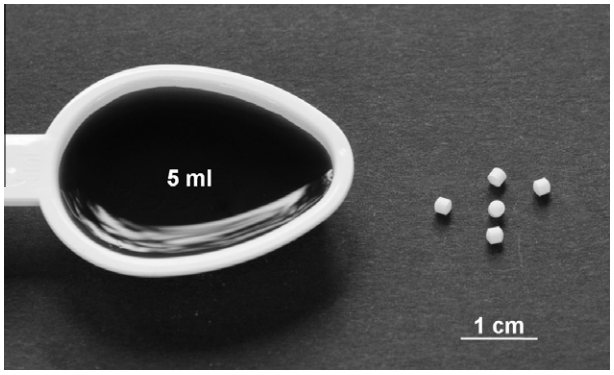

Fig. 1. Left: dosing spoon with 5 ml of a Brilliant Blue solution to simulate the required amount of hydrochlorothiazide (HCT) solution for a child weighing 5 kg (1 mg HCT/kg); right: five orally disintegrating mini-tablets (ODMT) with 1 mg hydrochlorothiazide per mini-tablet.

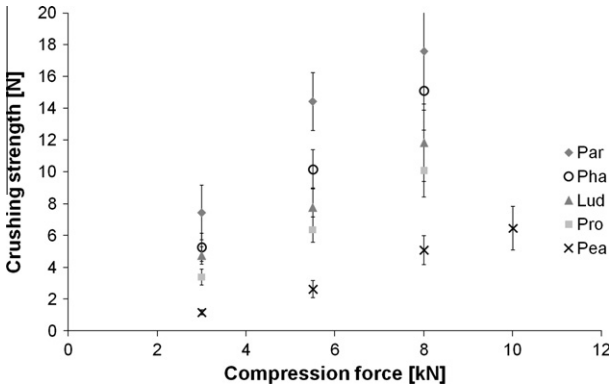

Fig. 2. Effect of compression force on crushing strength of mixtures of co-processed excipients, containing 3.5% (w/w) of sodium stearyl fumarate as lubricant; Parteck® ODT (Par), Pharmaburst® 500 (Phar), Ludiflash® (Lud), Prosolv® ODT (Pro), Pearlitol® Flash (Pea); mean ± standard deviation; $n = 20$.

Microcrystalline cellulose shows mainly plastic deformation properties and therefore an excellent compactability (Table 1).

With regard to the compactability, meaning the relation of the applied compression force to the achieved crushing strength, the excipients could be well distinguished. Parteck® ODT revealed the best compactability by high crushing strengths at low compression forces. Parteck® ODT shows a large specific surface area (3.46 m^2/g), which could have a major influence on the compactability [34], as well as the type of co-processing (Table 1). Ludiflash® contained polyvinyl acetate dispersion, which could improve binding properties. Pharmaburst® 500 showed also a good compactability, influenced by the included plastically deforming sorbitol, which obtains good binding properties (Table 1). Pearlitol® Flash would need much higher compression forces to achieve an acceptable crushing strength (Fig. 2). This could be disadvantageous for the sensitive multiple tableting tools, causing increased abrasion or even damage. The moderate compactability was due to the distinctive elastically deformation during compression and soft mechanical properties of the used maize starch. Superdisintegrants like crospovidone and croscarmellose sodium, which were used for the remaining excipients, presented in Table 1, have only minor impact on the compactability [12].

3.4. Friability

To simulate the mechanical stress applied to ODMTs in multi-dose containers, a newly developed method was used to determine the friability. The method was suitable to detect ODMTs with inadequate friability.

Most evaluated ODMTs were slightly friable, except for the formulations Pea_3 kN (approximately 30% friability) and Pro_3 kN (approximately 5% friability). With regard to the results for crushing strength, the Pearlitol® Flash formulation compressed at 3 kN showed the lowest values (Fig. 2). But friability does not always correlate with the crushing strength. The Prosolv® ODT formulation compressed at 3 kN revealed higher crushing strength values than the Pearlitol® Flash formulation compressed at 5.5 kN which showed in contrast a sufficient friability. The obtained friable ODMTs would not sufficiently resist mechanical stress, which may occur during usual handling. This was a further indication for the exclusive application of compression forces $\geqslant$5.5 kN for the formulations containing HCT.

All ODMTs containing HCT compressed at 5.5 kN and 8 kN (or 8 kN and 10 kN, respectively, in cases of ODMTs containing Pearlitol® Flash) showed a low friability <1%, which refers to an adequate resistance against abrasion (Table 4).

Table 4
Technological parameters and properties of orally disintegrating mini-tablets composed of the co-processed excipients: Parteck® ODT (Par), Pharmaburst® 500 (Pha), Ludiflash® (Lud), Prosolv® ODT (Pro), Pearlitol® Flash (Pea) with 3.5% (w/w) sodium stearyl fumarate, 1 mg hydrochlorothiazide (X_HCT) or without hydrochlorothiazide, mean ± standard deviation.

	Compression force (kN)	Crushing strength (N) (n = 20)	SWT time (s) (n = 10)	Friability (%) (n = 3)
Pea	8	5.1 ± 0.9	4.1 ± 0.4	<1
	10	6.5 ± 1.4	5.0 ± 0.4	<1
Pea_HCT	8	4.5 ± 0.8	4.6 ± 0.6	<1
	10	5.6 ± 1.1	5.7 ± 0.7	<1
Par	5.5	14.4 ± 1.8	18.8 ± 1.7	<1
	8	17.6 ± 3.7	25.2 ± 3.5	<1
Par_HCT	5.5	7.4 ± 1.7	14.0 ± 1.4	<1
	8	11.8 ± 2.2	21.3 ± 2.8	<1
Lud	5.5	7.8 ± 1.2	3.1 ± 0.3	<1
	8	11.8 ± 2.5	5.0 ± 0.6	<1
Lud_HCT	5.5	5.7 ± 0.5	3.0 ± 0.2	<1
	8	8.1 ± 1.4	4.9 ± 0.4	<1
Pha	5.5	10.2 ± 1.2	6.1 ± 0.3	<1
	8	15.1 ± 2.5	9.2 ± 0.8	<1
Pha_HCT	5.5	5.7 ± 0.9	4.2 ± 0.4	<1
	8	8.0 ± 1.6	6.6 ± 0.6	<1
Pro	5.5	6.4 ± 0.8	8.0 ± 2.2	<1
	8	10.1 ± 1.7	23.1 ± 10.5	<1
Pro_HCT	5.5	4.4 ± 0.9	5.0 ± 1.6	<1
	8	6.6 ± 0.7	14.8 ± 5.6	<1

3.5. Simulated wetting test-time

The values for SWT time of the drug-free ODMTs are described in Fig. 3. At very low compression forces (3 kN), all formulations except for formulations with Parteck® ODT showed short SWT times of ⩽5 s. Additionally, the formulations containing Ludiflash® or Pearlitol® Flash, respectively, compressed with higher forces, obtained sufficient SWT times as well. The nine formulations with an excellent SWT time <5 s can be ranked, beginning with the shortest SWT time, as follows: Lud_3 kN < Pro_3 kN < Pea_3 kN < Lud_5.5 kN < Pea_5.5 kN < Pha_3 kN < Pea_8 kN < Lud_8 kN < Pea_10 kN. Increasing compression forces did influence the SWT times of formulations with Ludiflash® and Pearlitol® Flash only slightly. Therefore, short SWT times could be achieved in spite of the applied high compression forces. In case of Parteck® ODT, even with very low compression forces (3 kN), no suitable SWT times were attainable. With increasing compression forces, the SWT times increased from 10.8 to 25.2 s (Fig. 3). The use of the superdisintegrant crospovidone and maize starch showed a positive influence on the SWT times in most cases, whereas Parteck® ODT, which included another superdisintegrant, croscarmellose sodium, did not achieve satisfactory results. Therefore, the type of co-processing could have a major influence. The complex composition of Prosolv® ODT, containing crospovidone, as well as microcrystalline cellulose and fructose, showed SWT times strongly dependent on the applied compression forces (Table 1).

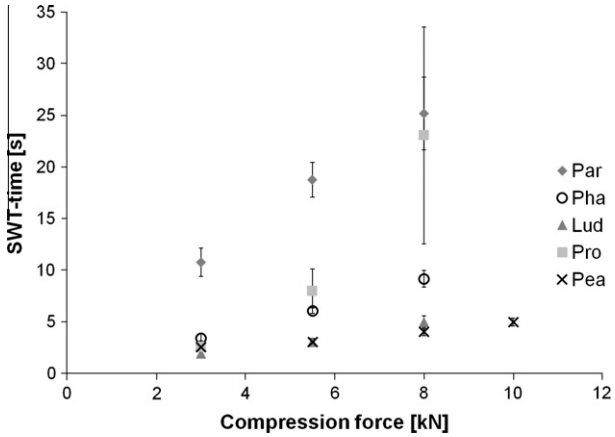

Fig. 3. Effect of compression force on simulated wetting test-time of mixtures of co-processed excipients, containing 3.5% (w/w) of sodium stearyl fumarate as lubricant; Parteck® ODT (Par), Pharmaburst® 500 (Phar), Ludiflash® (Lud), Prosolv® ODT (Pro), Pearlitol® Flash (Pea); mean ± standard deviation; n = 10.

The comparison of ODMT properties with and without HCT showed hardly any impact of HCT on the SWT time, in cases of Ludiflash® and Pearlitol® Flash. But for Pharmaburst® 500, Prosolv® ODT and Parteck® ODT, the SWT time decreased (Table 3). The ODMTs containing HCT with a suitable SWT time <5 s could be ordered starting with the lowest SWT time as follows: Lud_HCT_5.5 kN < Pha_HCT_5.5 kN < Pea_HCT_8 kN < Lud_HCT_8 kN < Pro_HCT_5.5 kN. Ludiflash® and Pearlitol® Flash performed the best, regarding the SWT time. They created five different ODMT formulations with and without API with various applied compression forces and excellent SWT times.

3.6. Mass variation and content uniformity

Mass variation and content uniformity are important quality attributes for low-dose dosage forms. The results of the analysis of mass variation are demonstrated in Table 5. The determined mean values of the produced ODMTs vary between 6.41 mg and 6.61 mg. However, the mass variation within one batch was negligible in all cases, which indicates an acceptable process and a good quality of the ODMTs.

With a drug content of only 1 mg HCT, the investigated mini-tablets belong to low-dose dosage forms. Direct compression of the low-dose powder blends including an API with cohesive flowing properties (Table 3) might be critical for the uniformity of dosing. The AV of one formulation for each excipient is presented in Table 5. All examined batches complied with the requirements of the Ph. Eur. (AV < 15), but showed relatively high AVs between 10.69 and 14.17, independent from the determined mass variation.

Table 5
Mass variation and content uniformity of orally disintegrating mini-tablets containing 1 mg hydrochlorothiazide (formulations with Parteck® ODT (Par_HCT), with Pharmaburst® 500 (Pha_HCT), with Ludiflash® (Lud_HCT), with Prosolv® ODT (Pro_HCT) and with Pearlitol® Flash (Pea_HCT)), mean ± standard deviation.

	Compression force (kN)	Mass (mg) (n = 20)	Drug content (mg) (n = 10)	Acceptance value
Pea_HCT	8	6.61 ± 0.09		
	10	6.51 ± 0.10	0.99 ± 0.05	11.35
Par_HCT	5.5	6.41 ± 0.09		
	8	6.47 ± 0.09	0.99 ± 0.05	11.70
Lud_HCT	5.5	6.55 ± 0.10		
	8	6.48 ± 0.08	0.98 ± 0.06	14.17
Pha_HCT	5.5	6.52 ± 0.07		
	8	6.58 ± 0.10	0.98 ± 0.05	12.78
Pro_HCT	5.5	6.54 ± 0.10		
	8	6.58 ± 0.13	0.97 ± 0.04	10.69

An influence of the flow properties of the blends on the content uniformity was not recognisable (Tables 3 and 5). The variation between the particle sizes of the co-processed excipients and the hydrochlorothiazide powder could led to a slight segregation of the powder mixtures (Table 1). However, the results are nearly comparable with AVs for extemporaneous preparations for children containing HCT, described in literature [20]. However, the mean values for drug content related to the nominal content were much higher in the present study. Therefore, the ODMTs offer an advantage over previously introduced formulations.

3.7. Suitability for preparation of ODMTs

Requirements for a suitable tableting excipient for direct compression of ODMTs are diverse. First of all, the excipient should obtain good flow properties to achieve an acceptable tableting process, as well as to produce ODMTs with sufficient content uniformity. All of the excipients obtained a suitable flowability, whereby Pearlitol® Flash showed the best results (Table 3). Further, tableting excipients should show a good compactability. This enables the use of low compression forces as possible as to produce ODMTs with high crushing strengths and low friability. Parteck® ODT fulfilled these demands best (Fig. 2, Table 4).

Another aspect is the desired short SWT time as an indicator for fast disintegration on the tongue and particular appropriateness for paediatric use. Ludiflash® and Pearlitol® Flash fulfilled these recommendations best (Fig. 3, Table 4).

The combination of high crushing strength and low SWT time in one formulation would be most desirable. Ludiflash® performed the best for formulations with and without API. For formulations compressed at 8 kN, a high crushing strength of 11.8 N and a low SWT time of 5.0 s were achieved (Figs. 2 and 3). For formulations with HCT, Ludiflash® results in a sufficient crushing strength of 8.1 N and a low SWT time of 4.9 s for the formulation compressed at 8 kN (Table 3). Therefore, Ludiflash® was the ready-to-use tableting excipient of choice for ODMTs in our study.

4. Conclusion

With orally disintegrating mini-tablets, a novel solid oral dosage form was developed, fulfilling all current demands for child-appropriate dosage forms such as easy administration, flexible dose titration and safe excipients. ODMTs combine the advantages of liquids, like ease of application and individual dose adaption, with the advantages of solids such as good stability and low transport and storage costs. The investigated ready-to-use excipients based on mannitol are appropriate for direct compression on conventional tableting machines. The employed analytical technologies enable the evaluation of the properties of ODMTs. A differentiation of the evaluated excipients could be made, with regard to compactability, friability and simulated wetting test-time. Formulations containing Ludiflash® obtained ODMTs with a high compactability, a low friability, as well as a short SWT time. ODMTs, containing 1 mg HCT, showed low mass variations and a sufficient content uniformity for all excipients. However, the feasibility with further APIs, with other properties regarding flowability and solubility, has still to be proven. The gap of a suitable option to administer an adequate dose of HCT to very young children could be filled. Further investigations, with regard to taste masking, dissolution and advanced suitable dosing systems, have still to be performed. The described solid dosage form may serve as a novel platform technology for paediatrics. However, the suitability for paediatric use has to be demonstrated in acceptability studies. ODMTs are supposed to be a very promising oral solid dosage form for paediatric use in the future.

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