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Review article

The revival of the mini-tablets: Recent advancements, classifications and expectations for the future

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ABSTRACT

Mini-tablets have recently raised huge interest in pharmaceutical industry. The present review aims to identify the rational, the opportunities and challenges of this emerging small solid drug dosage form by a structured literature review following the PRISMA algorithm. In total, more than 5,000 literature and patent sources have been found starting with the very first in the 60s of the past century, followed by the first multiparticular products using mini-tablets with pancreatin (Panzytrat® by the former BASF subsidiary Knoll/Nordmark) authorized in 1985. There seems to be a second boost of common interest in the 2000s when clinical studies demonstrated that one or more mini-tablets could enable superior drug administration even in very young patients including neonates over the former gold standard, a liquid drug preparation. Several pharmaceutical companies immediately started clinical development programs using the mini-tablet concept and the first products have been recently authorized by the competent authorities. Superiority was given as the mini-tablets ease the swallowing procedure compared to conventional tablets, enable various modified drug release opportunities including taste-masking by film-coating technology and provide excellent drug stability compared to liquid oral dosage forms. Due to these product attributes they are particularly beneficial to children and their caregivers. Furthermore, there is potential for precise individual drug dosing by counting adequate amounts of the multiple drug carriers. Most recently, two novel products with different concepts were authorized by the EMA and entered the market which are highlighted in this review: the first orodispersible mini-tablet with enalapril maleate for congenital heart failure (Aqumeldi® from Proveca Pharma) and the first single unit mini-tablet with matrix-type controlled melatonin release for insomnia (Slenyto® from Neurim Pharmaceuticals).

Our review reveals, that the majority of the published scientific papers use co-processed, ready-to-use excipients for the orodispersible mini-tablet formulations. However, traditional fillers such as microcrystalline cellulose or lactose have also been used for immediate release mini-tablets after adding a (super)disintegrant and a lubricant. The manufacturing of mini-tablets is conducted on conventional rotary tablet presses, predominantly equipped with multi-tip toolings to improve the yield or production speed. Scaling-up has been successfully realized from compaction simulators to pilot and production scale. Film-coatings enabling gastric resistance, taste masking or sustained-release properties have been realized in both fluid-bed and drum coaters using the same polymers as for conventional tablets. There is still a significant lack in regulatory guidance despite the recent success of the mini-tablet concept, starting from suitable characterization methods in the pharmacopoeias up to the design and conduct of clinical studies on mini-tablets.

1. Introduction

Solid drug dosage forms are globally being used to enable the handling and dosing of a defined amount of active pharmaceutical ingredient (API) for medical treatment of patients, to increase convenience and safety of the drug administration and to adequately provide the required drug concentrations at the targeted site of action.

Tablets with small dimensions were mentioned for the first time in the year 1963 by Tamura et al. [1], who introduced the term “micro tablets” for infrared spectrophotometry. In 1998, Lennartz and Mielck

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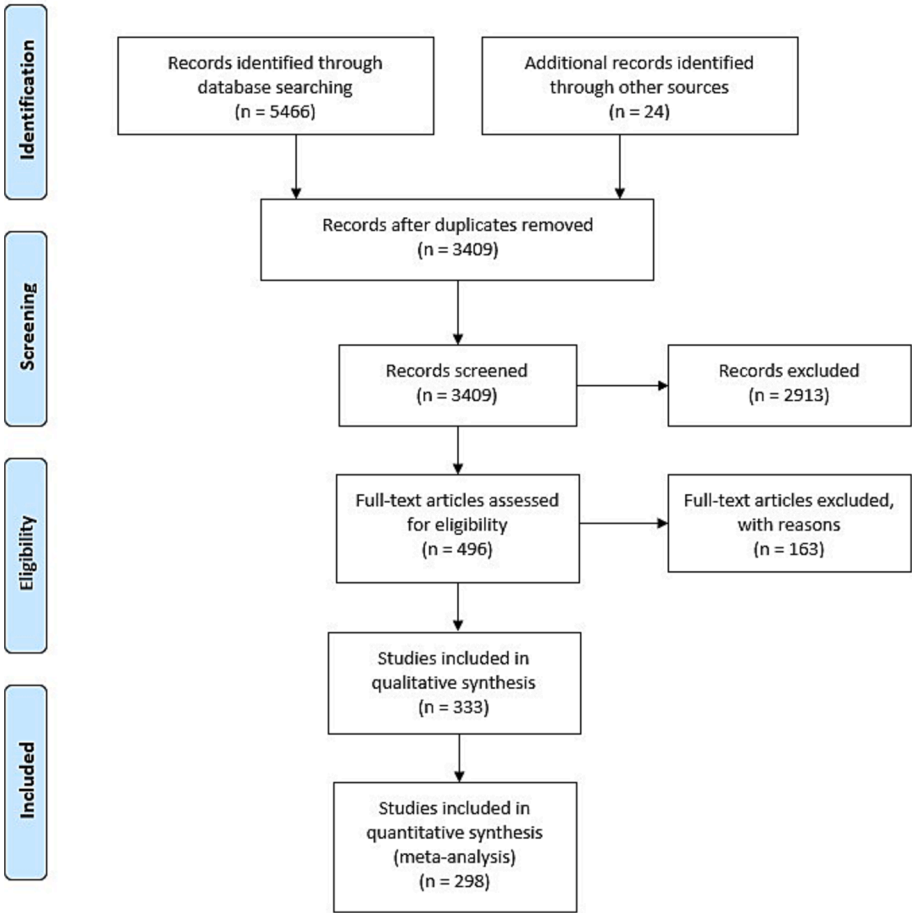

Fig. 1. PRISMA flow diagram with the number of identified, included or excluded literature sources, modified from [17].

defined "mini-tablets" for pharmaceutical use as tablets of 2 to 3 mm in diameter and height [2]. Until today, there is neither a commonly accepted definition nor a pharmacopoeial monograph or a standard term being specified. However, compendial quality control methods for tablets often fail for the characterization of mini-tablets, e.g. disintegration testing as these small-sized drug carriers immediately pass the end-point determining mesh of the pharmacopoeial apparatus [3], can hardly be accurately weighed individually for testing mass variation or friability, often fail in breaking strength testing by the conventional hardness testers and many more.

The first industrial scale production of mini-tablets has been established by Nordmark Arzneimittel in Uetersen, Germany, for the commercial product Panzytrat® which was launched in 1985 by the former BASF subsidiary Knoll, nowadays marketed by Allergan Pharmaceuticals. Panzytrat® contains hard capsules with enteric-coated mini-tablets of pancreatin for the treatment of pancreas insufficiency. Hence, it offers the nature of a solid multiple-unit dosage form containing the total API amount of a single dose divided into uniform small subunits with specific gastric-resistant drug release profile. The risk of dose dumping, the unintended premature drug release in the gastrointestinal tract, is diminished by the multiple-unit approach. Multiple-unit dosage forms may consist of various solid drug carriers such as granules, pellets or mini-tablets. The small sized drug carriers can be processed by filling into a sachet or capsule, or by compacting them to a larger tablet. Withdrawal from a multi-dose container can be performed by determining the required number of units using an appropriate medical device.

Mini-tablets hold some advantages over pellets or granules due to relatively easy and cheap manufacturing technique, their extraordinary uniformity of shape and mass, low porosity, smooth regular surface, attainable high strength, low coating material requirements for modified-release dosage forms and feasibility for continuous mass production [2,4]. In addition to the usage of mini-tablets as a subunit of the multi-unit dosage form, mini-tablets have been suggested as an ideal monolithic drug dosage form for oral administration for children due to their small dimension, high stability even at accelerated climate conditions and their relatively narrow content uniformity [5]. In 2009, an expert panel of the World Health Organisation (WHO) recommended the preferred use of "multiparticulates such as pellets or mini-tablets" for children instead of the commonly accepted liquid formulations [6]. The European Medicines Agency (EMA) included mini-tablets in their "Guideline on pharmaceutical development of medicines for paediatric use" in 2013 [7]. The mini-tablet concept was later enlarged for geriatric patients who may also need fine adjustments to the administered doses [8]. The use of a mini-tablet as monolithic solid drug carrier has been realized for the first time in the year 2020, when Slenyto® for the treatment of insomnia in paediatric patients was authorized by a Paediatric Use Marketing Authorisation (PUMA) and introduced by Neurim Pharmaceuticals in two drug strengths, 1 mg resp. 5 mg melatonin.

Changing the nature and application sites of the mini-tablet, e.g. by accelerating the disintegration by orodispersible properties [9] or by adding mucoadhesive excipients for nasal [10] or ocular [11,12] mucosal administration, show promising future treatment opportunities. Most recently, the product Aqumeldi® by Proveca Pharma, containing 0.25 mg enalapril maleate in an orodispersible mini-tablet, received a PUMA approval. The product is intended for the treatment of heart failure in children from birth to less than 18 years [13].

The authors are aware that numerous review papers on mini-tablets have been published in the past years, and some are highly recommended to the readers [14,15], but believe that the time has come to

Table 1
Search terms for the structured literature research.

Search terms	
mini tablet(s)	minitablet(s)
micro tablet(s)	microtablet(s)
mini compact(s)	minicompact(s)
small tablet(s)	smalltablet(s)
mini matrix tablet(s)	matrix mini tablet(s)
mini matrixtablet(s)	matrix minitablet(s)
multiparticulate dosage form(s)	multiparticular dosage form(s)

compile all documents on mini-tablets from the very beginning until today using a structured review analysis for a balanced discussion of the available sources, to evaluate the recent advancements in both pharmaceutical and clinical investigations and to propose a scientifically based standardization scheme. These data comprise generally acceptable terms and definitions, appropriate formulations and manufacturing procedures and some suitable characterization methods for this challenging, but promising class of relatively new drug dosage forms.

2. Methods

A systematic research based on the PRISMA scheme (Fig. 1) was applied for the screening of the scientific databases ScienceDirect, Scopus, PubMed and Web of Science. The variety of terms used to describe the dosage form in publications proved to be a challenge. In some publications, mini-tablets were even referred to as "granules", thus the general terms "multiparticulate" or "multiparticular" dosage forms were also used for the screening to cover as wide a range as possible. Another difficulty was the fact that the keywords may also be applied in other technical areas, e.g. in the field of automobiles (matrix mini) or in the field of telecommunications including modern handheld computers (micro- or mini-tablets) or headsets. With the aim of obtaining a broad collection of publications on pharmaceutical mini-tablets, 14 search terms were selected for the screening of the databases (Table 1).

The plural form of each keyword was also considered, as some databases distinguish between singular and plural versions. The use of inverted commas ensured that all sources with the quoted search term could be collected. Cut-off date for the literature research was December 31st, 2023. Besides the systematic research, additional literature sources from other sources dealing with mini-tablets were added and labelled as "additional sources". After removal of duplicates 3,409 publications were reviewed for relevance by following the algorithm of the PRISMA Flow Diagram [16], see Fig. 1. Books, excerpts from books and general review papers were excluded. In total, 496 sources were assessed for eligibility of the topic. 333 publications thereof were finally included for the deeper analysis. Hereby, articles in other languages than English as well as non-accessible sources were discarded. In this review, mini-tablets are defined as tablets with a diameter less than 4 mm and all publications covering tablets of this size limit were enclosed. A final tableting step was required for inclusion into the review. For instance, thin slits from hot-melt extruded strands were not included. In total, 298 publications were finally identified to fit into the scope of this review.

3. Results

Relevant sources dealing with mini-tablets have been published in patent literature since 1940 and an increase in research can be observed as the number of publications significantly rised over time (Fig. 2). The graph includes mini-tablets with size of less than 4 mm and manufactured by final tableting step. Important milestones along the years may be represented by the establishment of the Paediatric Regulation in the European Union in 2007 [18] or also the reflection paper of the WHO Informal Expert Meeting on Dosage Forms of Medicines for Children in 2008 which concluded solid formulations to be most suitable [6]. According to Hoppu in 2016, this requested shift towards solid dosage forms was already ongoing [19]. Further clinical acceptability studies of mini-tablets, underlining their benefit in administering APIs to children, might have additionally led to the huge growth in research in the last decade [20–24].

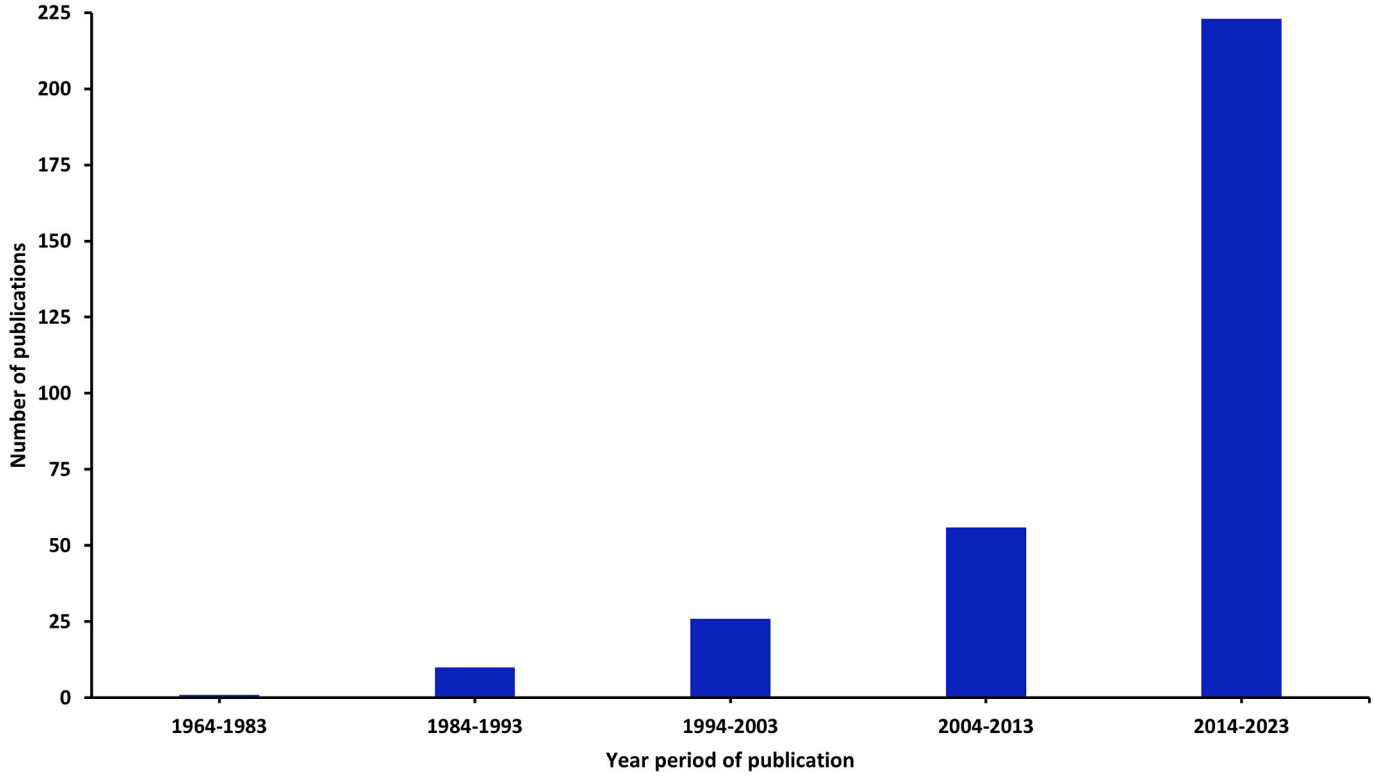

Fig. 2. Publication counts over time.

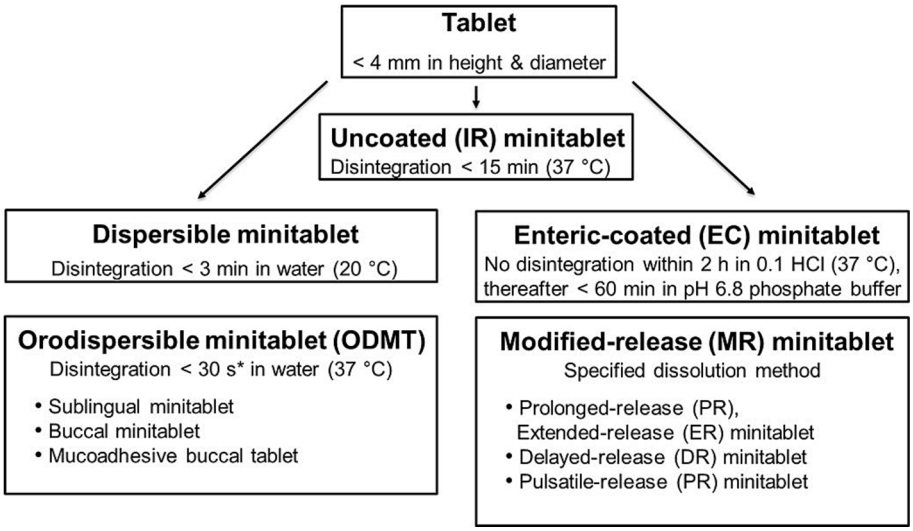

Fig. 3. Proposed classification scheme for mini-tablets. The terms define one monolithic mini-tablet; a compilation of various mini-tablets per single dose (multi-particulates) may be referred to as "granules", "multiparticulates" or "sprinkles". Recommendations for dissolution testing are provided under Ph.Eur. 5.17.1. * 30 s is a FDA specification [24] and is clinically more relevant; Ph.Eur. specifies 3 min as the maximum disintegration time [25].

Table 2
Overview of suitable pharmaceutical excipients for preparing ODMTs.

Excipient	Contained ingredients	Source reference
Cellulose nanofibers	–	[27]
F-Melt®	mannitol microcrystalline cellulose xylitol dibasic calcium phosphate anhydrous crospovidone	[28,29]
galenIQ™ 721	isomalt	[29–32]
Granfiller-D	mannitol microcrystalline cellulose carmellose crospovidone	[29,31,33]
Hisorad	D-mannitol microcrystalline cellulose croscarmellose sodium	[33]
Lactose monohydrate	–	[27,34]
Ludiflash®	D-mannitol polyvinylacetate dispersion crospovidone	[9,29,30,32,33,35–38]
Mannitol	–	[39–42]
Microcrystalline cellulose	–	[39–42]
MicroceLac®	lactose monohydrate microcrystalline cellulose	[34]
Parteck® ODT	mannitol croscarmellose sodium	[9,28,29,32,33,43,44]
Pearlitol® Flash	mannitol maize starch	[9,28,29,33]
Pharmaburst®	mannitol sorbitol silicon dioxide crospovidone	[9,29,45,46]
Prosolv® ODT	mannitol fructose microcrystalline cellulose silicon dioxide crospovidone	[9,29,32,33]
Smart Ex®	D-mannitol polyvinyl alcohol low-substituted hydroxypropylcellulose	[28,29,33,47]
StarLac®	lactose maize starch	[34,48]
SuperTab® 50 ODT	lactose	[32]

4. Subtypes of mini-tablets

Mini-tablets may be classified by the site of administration or by the patient subpopulation, e.g. paediatric mini-tablets or mini-tablets for veterinary use. The type may also be determined by properties of the tablet, which are for instance dependent on the manufacturing technique or the composition. In the following, mini-tablets are categorized in accordance with Ph. Eur. based specifications regarding functionality and performance (Fig. 3).

4.1. Orodispersible mini-tablets

Orodispersible tablets are defined as tablets with a disintegration time limit of 3 min in water at 25 °C according to the European Pharmacopeia (Ph. Eur.). A Guidance for Industry released in 2008 by the U. S: Food and Drug Administration (FDA) on "Orally disintegrating tablets" specifies a disintegration time of "approximately 30 s or less" [25,26]. In scientific papers, the more challenging limit of 30 s is often targeted and in most cases the produced mini-tablets fulfill this specification.

The term orodispersible mini-tablet (ODMT) was introduced by Stoltenberg and Breitkreutz in 2011 [9]. The aim of their work was to manufacture low-dosed solid dosage forms for paediatric use containing enalapril maleate (EM) or hydrochlorothiazide (HCT) using different commercial co-processed excipients (CPEs). In their initial work, several CPEs based on the filler mannitol were investigated for 2 mm mini-tablets [9]. Various investigations were subsequently conducted for screening and testing the suitability of different types of pharmaceutical excipients. Table 2 provides an overview of the identified excipients for the manufacturing of ODMTs including various fillers, binders and superdisintegrants. Some of the CPEs even contain the abbreviation ODT as part of their trademark.

Lura et al. added Isomalt as a suitable excipient for the production of ODMTs containing EM or HCT and compared it to the previous formulations made with Ludiflash® [30]. Recently, two novel CPEs were investigated by Kokott et al. with a focus on low-dosed EM preparations. The best results were obtained using Ludiflash® and Hisorad®, as the lowest acceptance values (AV) and coefficient of variations (CV) were accomplished when using these CPEs. The authors highlight that the choice of the appropriate excipient depends on the API properties [33]. Recently, also cellulose nanofibers were found to decrease the disintegration time while maintaining the mechanical strength of 3 mm ODMTs

manufactured by direct compression [27].

A systematic screening by Hejduk et al. on CPEs for the development and manufacturing of ODMTs focused on the morphology of the powder blends. In particular, the solidity (overall concavity of a particle) and circularity (quotient of circumference of equivalent area circle and actual particle circumference) were found to be the most critical morphological properties affecting the resulting ODMT properties [29]. An analysis of model mixtures with micronized and coarse grade melatonin showed that high solidity values resulted in high homogeneity of the mixture, whereas high circularity supported the flowability of the formulation. A level of solidity $>$ 20 % and circularity $>$ 25 % were stated as beneficial quality attributes of CPEs [29].

As the disintegration time is the major critical quality attribute (CQA) of ODMTs, some studies focus on the functionality of added (super)disintegrants. In particular crosslinked polyvinyl pyrrolidone (xPVP) showed the best results in improving the disintegration time in drug-free formulations containing either microcrystalline cellulose or mannitol, followed by cross-linked carmellose. Cross-linked carboxymethyl starch and calcium alginate did not show the same improvement in disintegration time [40,41]. The various authors point out the urgent need for linking *in vitro* disintegration testing with *in vivo* conditions, as in their studies *in vitro* disintegration times were often much shorter than the *in vivo* results. An overall correlation could not be found [40]. In another study, the use of two different xPVP grades in several ODMT formulations for two APIs resulted in meeting the specifications for disintegration [30]. In order to find the best formulation, various authors showed the benefit of implementing systematic methods either by a statistical approach or by applying a compaction simulator [31,35,36,39,43,49].

Lubrication can have a major impact on key properties of ODMTs. A comparison of conventionally sized orodispersible tablets and ODMTs showed that a higher amount of lubricant is needed for mini-tablets in order to accomplish sufficiently low ejection forces. This can be explained by the high specific surface of ODMTs and, as a consequence, elevated adhesion and friction forces compared to larger tablets. Particularly, mannitol-based CPEs revealed sensitivity to the type and the concentration of the lubricant with respect to the two key attributes mechanical properties and disintegration time. In general, studies revealed that ODMTs containing sodium stearyl fumarate disintegrated faster than ODMTs with the same amount of magnesium stearate. External lubrication may prolong disintegration times considering the high specific surface area covered with lubricant [32].

One of the major challenges faced in the development of ODMTs is the impact of the unpleasant taste of the API and the resulting lack of patient compliance [28,45,50]. To overcome this challenge, Wasilewska et al. masked the bitter drug substance rupatadine fumarate with an aqueous dispersion of ethylcellulose (Surelease®) by a spray drying process. Different formulations were manufactured and the bitterness score was determined by healthy volunteers, *in vitro*-drug release and electronic tongue measurements. The lowest bitterness score of the ODMT preparations was achieved using the combination of Pearlitol® Flash and Surelease® [28]. Bebawy et al. developed risperidone ODMTs on the basis of lipid based granules to mask the bitter taste of the API [50].

Another potential challenge is the impact of scale-up process on the quality of ODMTs. An increase in batch size during transfer and scale-up may lead to a loss of functionality of the pharmaceutical excipients, due to heating up of the equipment or possible over-lubrication in the feed frame. Potential sintering processes due to an increase in product temperature have been described for the excipients isomalt as well as mannitol, which might have deteriorated the disintegration time. Therefore, in addition to formulation development, process understanding and appropriate (in-process) control strategies are important to ensure the quality of ODMTs [35].

4.2. Immediate release mini-tablets for oral use

Due to the clinical profile an immediate release (IR) drug dosage form may be targeted. Various studies on IR mini-tablets without any special dissolution enhancement have been described in literature [51–62]. Ito et al. investigated acetaminophen mini-tablets with swelling and gelling properties after administration, elasticity upon swallowing pressure as well as low adhesiveness to avoid adherence to oral cavity and esophagus. Mini-tablets with 20–30 % of water soluble polymer κ-carrageenan showed best results and achieved a drug release of 80 % within 30 min [63].

Different techniques have been investigated to enhance the dissolution rate of mini-tablet formulations, which do not significantly differ from larger sized IR tablets. One approach is the molecular complexation of the API with cyclodextrines [64]. Blends of ibuprofen and β-cyclodextrin inclusion complexes were investigated assessing influences of compaction forces and particle properties on the drug release [64]. For developing 2 mm prednisone mini-tablets for paediatrics, an amorphous API state was achieved by co-grinding with Neusilin®, an amorphous magnesium aluminosilicate with a surface area of about 300 m^2/g. Particle size, surface area and SEM analyses showed that prednisone was adsorbed to the surface of Neusilin® particles. The obtained amorphous co-ground prednisone-Neusilin® (1:7) complex was subsequently manufactured into 2 mm mini-tablets with silicified MCC, croscarmellose sodium and magnesium stearate. Dissolution profiles in simulated gastric fluid (pH 1.2) showed immediate release of 87 % drug within 20 min, followed by mini-tablets with prednisone in crystalline state (60 % in 20 min) [65]. A further approach to enhance the dissolution profile of the poorly soluble drug prednisone is presented by Poller et al. who manufactured 2 mm mini-tablets from electrospun drug loaded nanofibers. The mini-tablets fulfilled all USP requirements for content uniformity and friability, and showed complete drug release within 20 min [66]. Another approach targeting dissolution enhancement of lornoxicam mini-tablets was utilized by Tawfeek et al. [67]. Co-evaporation of lornoxicam and the non-ionic surfactant Pluronic® F-68 (1:5) led to dissolution enhancement and superior flow properties. The residual after evaporation was manufactured into 3 mm mini-tablets by using three directly compressible excipients, Cellactose® 80 (α-Lactose and cellulose), StarLac® (α-Lactose and maize starch) and Emcompress® (dicalcium phosphate). The formulation with StarLac® was chosen for further *in vivo* investigations due to suitable mechanical strength, content uniformity, rapid drug release profile and positive results in a 3-month stability study [67]. Stability monitoring of amorphous drugs incorporated in solid dosage forms, and hence also mini-tablets, is important in general. Bicalutamide solid dispersions compressed to mini-tablets demonstrated the relevance of the packaging material and its barrier properties [68]. Tawfeek et al. applied adsorption and co-adsorption methods using solid carriers with high specific surface area and surfactants to promote dissolution of glibenclamide [69].

Superior dissolution profiles could also be reached by bead layering or spray granulation of nanocrystalline irbesartan suspensions before compression into 3 mm mini-tablets. Spray granulation with mannitol was the superior method referring to the resulting *in vitro* dissolution profiles [70]. A further study revealed that 1.2 mm mini-tablets with low irbesartan loads (0.01 % – 0.5 %) could be manufactured with good content uniformity results meeting the USP acceptance criteria by nanocrystalline suspensions using high shear granulation [71].

There are also studies with the focus on combining IR mini-tablets with another drug delivery system. In the study of Rao and Venkatchalam, 3 mm IR mini-tablets with a loading dose of cefuroxime axetil were developed by fusion method with poloxamer 188 and Sylysia 350 due to its poor solubility [72]. These IR mini-tablets were combined in capsules with sustained release (SR) mucoadhesive mini-tablets to achieve a biphasic release [72].

IR mini-tablets can also be used for diagnostic purposes, for example

Table 3
Utilized matrix formers for SR mini-tablets.

Matrix formers		
Cellulose derivates	Cellulose acetate propionate	[89]
	Ethylcellulose	[75–77,89,93]
	Hydroxypropylcellulose	[83]
	Hypromellose (Hydroxypropylmethylcellulose)	[47,72,75,76,79,82,84,88,92–96]
	Methylcellulose	[83]
	Sodium carboxymethylcellulose	[72,83]
Other synthetic polymers	Methacrylic derivates	[86,89]
	Polyethylene oxide	[76,96]
	Polyvinylacetate/Polyvinylpyrrolidone	[76,85,87,89,93]
	Polyvinylalcohol	[89]
	Polyvinylpyrrolidone (Povidone)	[96]
Natural based polymers	Carrageenan	[81]
	Chitosan	[72]
	Karaya	[81]
	Locust bean	[81]
	Xanthan gum	[80,81]
Triglycerides	Glyceryl behenate	[76,78,93]
	Hard fat	[97]
	Triasterin	[74]
Other excipients	Carnauba wax	[74,77]
	Cholesterol	[74]
	Microcrystalline waxes	[90,91]

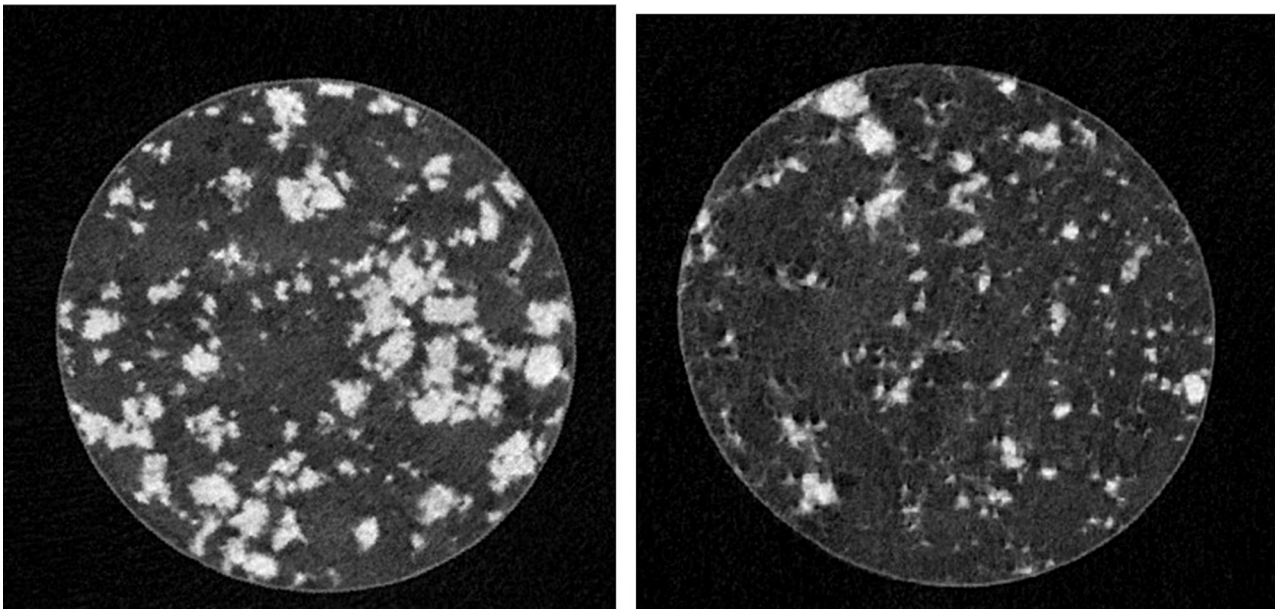

Fig. 4. µCT virtual slit images of Slenyto® film-coated matrix mini-tablets (3 mm) with 1 mg (left) and 5 mg melatonin (right) showing both taste-masking and coloring by thin film-coatings, but SR characteristics due to the Eudragit® RS matrix former in the tablet core. Areas with bright pixels encode locations of calciumhydrogenphosphate dihydrate particles.

phenotyping of cytochrome P450 enzymes for metabolic profiling. Usually, marketed products are used for phenotyping cocktails which are initially not developed for diagnostics. A novel strategy was developed by Camblin et al. [73]. The drug substances used in the so called 'Basel Cocktail' were loaded onto Fujicalin particles by solvent evaporation and subsequently manufactured to mini-tablets which showed immediate release profiles. The mini-tablets were subsequently filled into a so called CombiCap. Performance has been demonstrated *in vitro* and *in vivo*. According to the authors, the CombiCap strategy can be applied to various types of phenotyping cocktails as it is modular and scalable [73].

4.3. Modified-release mini-tablets for oral use

4.3.1. Matrix mini-tablets for oral use

Several efforts have been taken to develop sustained release (SR) matrix mini-tablets. Utilized matrix forming agents are summarized in Table 3. The investigations displayed that various factors may have an impact on the drug release profile. The nature or type of matrix former, e.g. whether predominantly hydrophobic or hydrophilic character [74–77], the quantity of matrix former [47,74,78–81] and its grade/particle size [80,82] were shown to be relevant. Furthermore, the tablet size is of importance, as with decreasing size the surface to volume ratio increases. This may lead to a relatively quick absorption of water and a rapid dissolution of the hydrophilic parts. Also, drug diffusion may be affected considering the reduced diffusion pathways. These consequences may lead to a higher drug release rate as in conventional tablets

[47,75,78–80,82,83]. API solubility was found to be another critical factor in the development of SR mini-tablets [79,84]. Besides, the type of manufacturing [74,85,86], settings of the tableting equipment [74] and further added excipients [87] may also play a major role. Some studies focus on pH-independent or pH-controlled release of drugs with pH dependent solubility by incorporation of pH modifiers [85,87,88]. In the year 2020, the PUMA product Slenyto® for the treatment of insomnia in specific paediatric patients was authorized and introduced by Neurim Pharmaceuticals in two dose strengths (1 and 5 mg). It is designed as a matrix SR mini-tablet of 3 mm diameter containing the API melatonin and ammonio methacrylate copolymer Type B (Eudragit® RS) as the matrix former and a thin film-coating of different colours (Fig. 4). The dissolution profile is a typical matrix-attributed behavior following a square-root-of-time kinetics.

One of the first approaches to develop matrix mini-tablets was utilized in 1985 by Ônay-Basaran and Olsen. However, the term mini-tablet was not established at that time and the authors called their products "compressed pellets" with a diameter of 1/8 in., which corresponds to 3.1 mm [74]. Different polymers, fatty acids, fatty alcohols and waxes were used for the formation of solid matrices and the release of the water soluble model drug quinacrine hydrochloride was investigated. Release times were prolonged by increasing tableting pressure and thus decreasing porosity. Drug diffusion was found to be dependent on matrix and surface structures of the mini-tablets. The authors concluded cholesterol to be a suitable matrix component taking into account its good compressibility, the nontoxic properties and its biodegradable property [74]. In the same year, Colombo et al. showed that diprophylline release could be prolonged by crosslinking the used polymers after the tablet compression, so that crosslinked barriers at the surface were formed acting like an intra-tablet membrane [89].

Combinations of hydrophobic waxes with hydrophilic starch derivatives were developed by De Brabander et. al [90,91] forming sustained release (SR) matrix mini-tablets. After melt extrusion, milling and a sieving process, 2 mm mini-tablets were manufactured with up to 60 % load of ibuprofen. The authors varied the *in vitro* drug release profile by varying the microcrystalline waxes with different melting ranges [90,91]. The impact of the amount of matrix forming agent on the dissolution profile could also be shown for glyceryl behenate and the soluble model drug theophylline. Higher concentrations were required to develop 2 and 3 mm SR mini-tablets in comparison to larger tablets, due to different physical dimensions and hence variations in diffusion processes from the matrix. Adjustments on the drug release profile were possible by change of lipophilic matrix excipient concentration or tablet size [78].

Mohamed et al. studied the effect of tablet size, HPMC concentration and drug solubility on drug release and tensile strength of hydrophilic matrix mini-tablets. Findings similarly showed that an increase of polymer level or tablet size decreased the dissolution rate. Furthermore, release of theophylline was generally more rapid than hydrocortisone considering its higher water solubility. Hence, drug solubility was a critical factor for the design of SR matrix mini-tablets [79,92].

In order to develop 3 mm SR mini-tablets of the poorly soluble API carbamazepine, Dzajkowska et al. tested the effects of various hydrophilic polymers such as HPMC or polyethylene oxide and hydrophobic matrix formers such as ethylcellulose, PVA/PVP and glyceryl behenate on carbamazepine release [76,93]. In general, hydrophobic matrix formers such as glyceryl behenate tended to slower drug release profiles. Among the hydrophilic matrix formers, the use of polyethylene oxide and highly viscous hypromellose (HPMC) resulted in slower drug release compared to low viscous HPMC [76,93]. In another setup, modified release mini-tablets containing high soluble morphine sulfate were investigated. Using HPMC as hydrophilic matrix former led to a slower release of the drug compared to immediate release mini-tablets without the matrix forming agent. Nevertheless, within the first hour, approximately 58 % of morphine sulfate were released and the authors described it as a burst effect [84]. The authors indicated that initially drug particles on the surface of hydrophilic matrix mini-tablets may be dissolved before the actual control took place. Hence, the swollen matrix, the entry of dissolution medium and the drug solubility were outlined as important factors controlling drug release [84]. In comparison, the study of Laicher and Profitlich exhibited that 2.8 mm SR mini-tablets with easily soluble metoprolol tartrate could not be achieved based on formulations with hydrophilic cellulose derivates like methylcellulose, hydroxypropylcellulose and sodium carboxymethylcellulose. Instead, SR profiles were only obtained for 7.0 mm or larger tablets [83]. Therefore, mathematical models were built to calculate the required dimensions and aspect ratio of hydrophilic polymer matrix systems, like HPMC, containing water soluble drugs to obtain desired release performances [94].

Another crucial material attribute is the particle size of the matrix components. HPMC grades with finer particle sizes reduced drug release of hydrocortisone, whereas faster drug release and a higher percolation threshold were obtained when using HPMC grades with larger particles. These effects were more pronounced for mini-tablets than for conventionally sized tablets. Tablet size and particle size were shown to impact percolation threshold. Thus, the authors concluded that particle size of HPMC has to be controlled to enable sustained release at suitable polymer concentrations [82]. A similar conclusion regarding concentration and particle size was drawn by Lazzari et al. for xanthan gum, chosen as a rate-controlling polymer for the development of alcohol-resistant matrix mini-tablets. In this study, the effects of ethanol in the dissolution medium, xanthan gum concentrations and particle sizes on theophylline release rate were investigated. Higher quantities of xanthan gum led to alcohol resistance regardless of the chosen polymer particle size. However, at lower concentrations, finer particle sizes allowed to adapt alcohol resistance by forming a less porous gel layer compared to larger particles, where a higher risk of alcohol-induced dose dumping was observed [80].

4.3.2. *Film-coated mini-tablets for oral use*

Film-coating of solid dosage forms may have different reasons. Besides protection from physical and chemical impacts or improving the

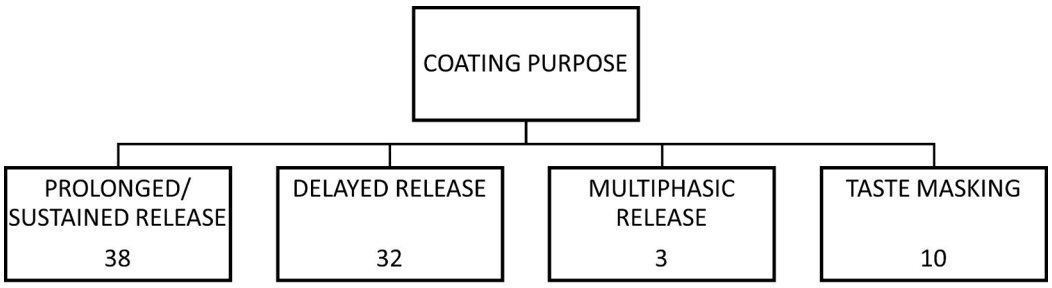

Fig. 5. Purposes of film-coating of mini-tablets. Delayed release includes gastro-resistant and colon-targeting mini-tablets; taste masking mini-tablets are displayed separately considering their significance in patient's acceptability; multiphasic release refers to biphasic and pulsatile release. Number of identified publications is displayed.

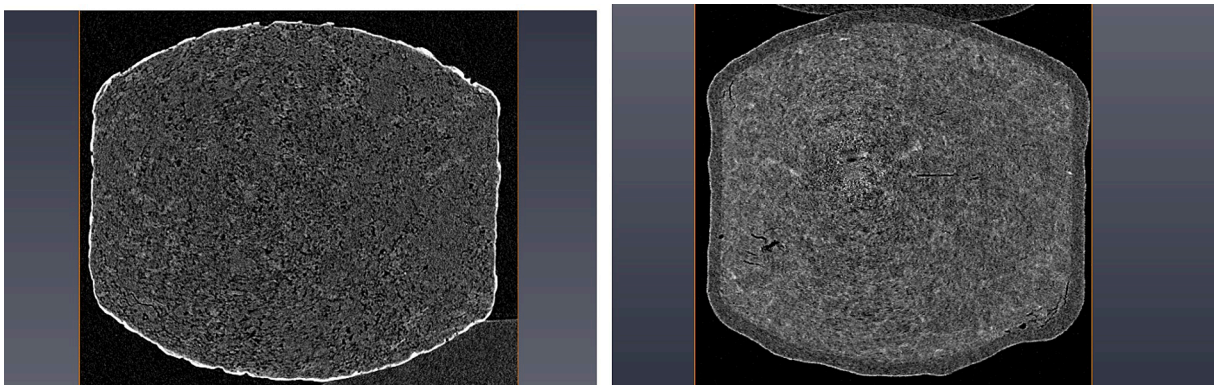

Fig. 6. µCT virtual slit images of levetiracetam 2 mm mini-tablet (Levetiracetam Desitin) with taste-masking coating (left) and sodium valproate mini-tablet (Orfiril® long by Desitin) with tablet cores of 1.7 mm and SR coating with a thickness of about 150 µm.

Table 4
Utilized coatings for delayed release mini-tablets with gastro-resistant properties, sustained release mini-tablets and for taste masking purpose.

Coating polymers	Source reference
Coating polymers for delayed release mini-tablets with gastro-resistant properties	
Acryl-EZE®	[102]
Acryl-EZE II®	[100,113]
Eudragit® FS30 D	[114]
Eudragit® L30 D55	[99–101,113,115–120]
Eudragit® L100	[121,122]
Eudragit® L100-55	[123,124]
Eudragit® S100	[122,124]
Coating polymers for sustained release mini-tablets	
Ethylcellulose	[4,76,93,103,106,107,109,125,126]
Eudragit® RL	[76,93,103–105,109,126,127]
Eudragit® RS	[76,93,103–105]
Kollicoat® SR 30 D	[77,108]
Coating polymers for taste masking purpose	
Ethylcellulose	[57,110]
Eudragit® EPO	[57,65,111,112,128–130]
HPMC	[55]
Kollicoat® Smartseal 30D	[57]

patient compliance with regard to colour, the release characteristics of mini-tablets can be modified. For this purpose, Fig. 5 provides an overview of targeted release properties by means of film-coated mini-tablets and the associated number of relevant publications. The terminology of the modified release dosage forms has been aligned with the EMA Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms [98]. Exemplary µCT images for marketed coated mini-tablets (Levetiracetam and Orfiril® long by Desitin) were taken for a closer investigation of the film coating appearance (Fig. 6). The coating techniques are described in more detail in chapter 5.2.

4.3.2.1. Delayed release mini-tablets with enteric coatings. Mini-tablets can be enteric-coated with various suitable polymers in order to obtain gastro-resistant properties. The identified polymers used for mini-tablets are listed in Table 4.

Szczepanska et al. showed for 3 mm pantoprazole mini-tablets that a thin coating with Eudragit® L 30D 55 was sufficient to obtain gastro-resistant properties compared to 6 mm tablets. A higher release rate of the drug in phosphate buffer (pH 6.8) was observed for the mini-tablets compared to a 6 mm tablet, both with 80 µm film thickness. Under these conditions, the different thicknesses obviously did not affect the release profile [99]. Similar conclusions were drawn in another study with 3 mm pantoprazole mini-tablets which were compared to 5 mm tablets. A thinner film thickness was not sufficient for 5 mm tablets to match gastro-resistant properties contrary to the mini-tablets. Also, drug release rate in the buffer phase was higher when decreasing film thickness and decreasing the tablet size, regardless of the utilized coating apparatus. Use of gelatine capsules did not affect the drug release profile [100]. In a further study, 2 and 3 mm diclofenac sodium mini-tablets were manufactured and coated with Eudragit® L 30D 55 aiming film thicknesses of 40 µm and 60 µm. The required enteric film thickness seemed to be related to the mini-tablet size to obtain gastro-resistant properties, because swelling of only 3 mm mini-tablets in acidic medium was observed with the thinner film coating. Although, drug release was not observed in the acidic medium, the swelling effect slowed down the drug release at pH 6.8. This outcome was avoided by increasing the film thickness as a barrier to 60 µm for the 3 mm mini-tablets. The authors concluded that swelling did not occur with 2 mm mini-tablets due to a smaller surface area of an individual mini-tablet for the penetration of the medium compared to the 3 mm sized mini-tablet [101].

In a study by Omari, enteric coated 2.5 mm mini-tablets with esomeprazole and different coating weight gains (29 % and 32 %) were developed and tested against the marketed reference product Nexium®, which is an enteric-coated multiple-unit pellet system (MUPS). The developed formulations passed stability studies following ICH guidelines for six months at different storage conditions. *In vitro* testing revealed that drug release was faster in comparison to the reference product, but *in vivo* studies showed that the higher *in vitro* dissolution rate was not sufficient to meet the profile of Nexium® in fasting conditions, taking into account its higher number and specific surface area of the multiparticulates and corresponding fast gastric emptying. Therefore, increase in dissolution was targeted by choosing the lower amount of enteric coating and additionally adaption of core formulation. The disintegrant quantity was increased and also tablet mass was elevated, so that 28 instead of formerly 25 mini-tablets were filled into a capsule size 0. *In vivo* investigations under fasting conditions demonstrated bioequivalence to the market product [102].

4.3.2.2. Sustained release mini-tablets. Sustained release profiles of mini-tablets can be either achieved by a matrix core (see 4.3.1), by film-coating or both (see Table 4). The selection of the film former (polymer) is a critical step, as reported by several authors. Dzajkowska et al. formulated 2.5 mm carbamazepine mini-tablets coated either with ethylcellulose or different mixtures of Eudragit® RL and RS. Ethylcellulose, was not suitable due to low drug permeability and also poor mechanical film resistance despite added hypromellose as pore former. However, depending on Eudragit® ratio and film thickness sustained release profile of the poorly soluble drug (80 % in 14 h) could be achieved. The application of a pore former decreased the initial lag time [76]. Contrary results regarding the coating polymer were found by Gaber et al. [4]. Based on preliminary trials, ethylcellulose was preferred over Eudragit® RS 100 due to its superior integrity of the coat. Hence,

the study was continued with ethylcellulose coated 2 mm mini-tablets containing the highly water soluble venlafaxine hydrochloride. The authors elaborated that an elevation of weight gain from 2 up to 12 % led to a reduction of drug release from 95 % to 20 % after 8 h [4]. The dissolution profiles displayed a more delayed release profile compared with pellets (particle size range 1400–2000 μm) of the same coating weight gain (6 %). The authors concluded that mini-tablets are an alternative to pellets for controlled release multiparticulate delivery systems. Further, the mini-tablets showed better 6-month stability results in terms of dissolution in comparison to the pellets. The authors finally commented on the question if the number of mini-tablets in one vessel influenced the dissolution profile. To investigate this issue, single mini-tablets were subjected to dissolution apparatus and drug release at three timepoints was compared with the results for six mini-tablets. No significant difference in the release rate was found for this study [4].

Munday and Fassihi stated 1989 that coating composition and thickness influence the release profiles. Theophylline 3 mm mini-tablets were either film-coated with ethylcellulose and water soluble pore forming agents (PEG 1540, Eudragit® L, cellulose acetate phthalate, polysorbate 20) or with Eudragit® RL 100 and Eudragit® RS 100 without addition of pore forming agents. Film thickness displayed an effect on the initial lag time. A combination of mini-tablets with different thicknesses in one capsule enabled a constant dissolution profile. Mini-tablets with Eudragit® RL and Eudragit® RS led to shorter lag times at similar film thicknesses [103]. Antal et al. also developed theophylline 3 mm mini-tablets and used Eudragit® dispersion of RL and RS for coating purpose. The goal was to combine mini-tablets of different film thicknesses to achieve a modified drug release profile. They also showed that dissolution profiles of combinations (uncoated and coated mini-tablets) could be predicted from subunits [104]. The tablet core can also impact the drug release. In another study on theophylline 3 mm mini-tablets, matrix cores containing Eudragit® RL and RS were produced and non-matrix cores with subsequent film-coating at different thicknesses using a combination of Eudragit® RL and RS. Dissolution profiles revealed that a combination of matrix and coating techniques reduced the amount of polymers needed in the film for the required release profile. As the coating process with these polymers may show challenges in terms of sticking and obtaining a uniform film thickness, the authors underline the advantage to decrease coating time and polymer amount needed. The authors also assume that possible failures in coating film may be compensated with matrix mini-tablets regarding the dissolution profile [105]. The effect of coated matrix mini-tablets containing theophylline on dissolution was also investigated by Mohamed et al. Matrix mini-tablets were prepared with HPMC as matrix former and coated with different ratios of ethylcellulose and the pore former Opadry® and different film thicknesses. Drug release was then compared with coated non-matrix mini-tablets. Coated non-matrix mini-tablets showed fast release in the first 30 min at low weight gains or release of only a small amount (< 5 %) after 12 h at high weight gains. However, coated matrix mini-tablets decreased the drug release at low weight gains as swelling of matrix avoided disintegration, while increased the dissolution at high coating weight gains causing ruptures in the film. Additionally, the amount of the pore former and the coating weight gain impacted the lag time. Therefore, the authors concluded a combination of matrix and coating technique to be an alternative for tailoring controlled release of water soluble drugs [106].

Nart et al. displayed that metformin hydrochloride release can be modified by melt granulation of the highly soluble drug with carnauba wax and coating of the mini-tablets with different ratios of Kollicoat® SR 30 D and pore former Opadry® II and different coating weight gains [77].

In a recent study by Priese et al. drug release from 2 mm mini-tablets coated with ethylcellulose, and mini-tablets and larger tablets compressed from coated pellets were compared. These pellets consisted of a drug layer and an ethylcellulose layer. In all cases a release rate following first order kinetics was obtained. However, in contrast to the coated pellets, mini-tablets and tablets compressed from pellets did not show a lag time as the ethylcellulose layer might be damaged during tableting. In the case of coated mini-tablets, the authors point out that the thinner coating at the edges may be critical when compared to the spherical pellets. To minimize the burst effect, the critical thickness should be surpassed, specifically at the edges. The choice of different formulations and drug carrier (e.g. compressed pellets to mini-tablets) offer a great flexibility to target different release profiles [107].

An interesting approach to develop and optimize sustained release mini-tablets with metoprolol succinate mini-tablets was tested by Issa et al. by integrating DoE and physiologically based biopharmaceutics modeling (PBBM) in fasted and fed states. Experimental statistical design provided an insight into the relevant parameters for drug release, supporting to optimize the formulation. PBBM was used to receive PK model and biopharmaceutical data analysis in order to predict the drug absorption. In the end virtual bioequivalence studies (VBE) were applied with the best *in vitro* performed formulation via the GastroPlus® Software and together with the *in vitro* studies performance of that formulation was predicted and compared to a reference drug product [108].

A further aspect is the influence of stress parameters like temperature and relative humidity to the integrity of the film coating and the drug release. Munday and Fassihi exposed theophylline 3 mm mini-tablets, coated with ethylcellulose or Eudragit® RL, to different temperature and relative humidity ranges. Dissolution profiles of mini-tablets after storage were compared with profiles at the initial time point. Results indicated that coating integrity was not affected by storage conditions but dissolution behaviour was significantly hindered with increasing temperature, whereas relative humidity played a minor role. Munday and Fassihi assumed that this observation is correlated with the decrease of molecular diffusion rate through the film. Permeability of polymer film may be modified by alterations in crystallinity, glass transition temperature, polarity etc. The authors concluded that it is important to perform in-vitro dissolution studies of film coated mini-tablets after predefined storage conditions and periods [109].

4.3.2.3. Taste masking of mini-tablets. The taste of medicines has a major impact on the success of the therapy. Therefore, several approaches have been developed to mask the bitter taste of drugs in mini-tablets.

One approach is the coating with a suitable polymer (Table 4). Keser et al. succeeded in coating mini-tablets containing bitter acetaminophen using pH dependent polymers (Eudragit® EPO, Kollicoat® Smartseal 30D). No drug release could be determined within 5 min in artificial saliva. However, when using ethylcellulose, drug release could be already measured after 60 s. Besides taste masking purposes, one has to consider that a higher ethylcellulose film thickness could affect the further dissolution profile by prolonging drug release [57]. Nevertheless, in a study by Zhang et al., a suitable taste masking effect resulted with ethylcellulose in combination with HPC (75/25), without adversely affecting the dissolution profile [110]. Some more publications applied methacryl derivates with respect to taste masking, as shown for prednisone mini-tablets, when being dip-coated with Eudragit® EPO [65] or for valsartan mini-tablets coated with Eudragit® E [111]. In the latter publication, an electronic tongue system was used to characterize the release profile. Different experimental conditions were applied and results compared to pharmacopeial dissolution tests [111].

The feasibility of ultrathin coatings for mini-tablets with titanium dioxide using automatic layer deposition (ALD) technique was examined for mini-tablets with the bitter substance denatonium benzoate. However, ALD thin coating led to accelerated drug disintegration and reduced mechanical strengths of mini-tablets. Effective taste masking could not be obtained with the applied coating thickness using this a simple and rapid approach [112].

4.3.3. Gastroretentive mini-tablets for oral use

Physiological limitations as variable gastric emptying times (GET) ranging from minutes to 12 h and short gastric residence times (GRT) may lead to variations in the extent of absorption of the drug or also incomplete drug release, especially if the place of absorption of the drug is located in the upper part of gastrointestinal tract. The extension of GRT by gastroretentive dosage forms like floating, swelling/expanding, bioadhesive or high-density systems is an approach to counteract these challenges [131]. In contrast to multiple unit dosage forms like pellets or mini-tablets, monolithic single unit systems may lead to a higher variability based on the "all-or-nothing" emptying mechanism [131]. With regard to floating dosage forms, effervescent – both uncoated [132–139] and coated [133,134,140–143] – as well as non-effervescent [144–147] mini-tablets are described in literature. Rouge et al. identified that the use of gas generating excipient sodium bicarbonate and intermediate wet granulation was beneficial for buoyancy. The authors suppose that the emerging carbon dioxide was retained for a longer time in granulated form compared to the ungranulated form [133]. Formulation and size of mini-tablets also had an impact on drug release and floating properties according to Goole et al. Floating lag times increased along with increasing diameter, considering the greater tablet mass with increasing size [132]. Since the drug load in mini-tablets is limited by the required high amount of matrix-forming polymer, Goole et al. applied a coating with Eudragit® RL30D instead of a matrix to retain carbon dioxide in the tablet and modify drug release. Optimized mini-tablets showed a floating lag time of 20 min, floating duration of more than 13 h and sustained release of levodopa for over 20 h [140,141].

Another approach for non-effervescent floating mini-tablets is the use of lipophilic excipients [144,146,147]. Further literature sources deal with a proposal of a classification system for floating behaviour [148], with studies on reduction of sticking tendency of multiple floating mini-tablets filled in capsules [149], a comparative pharmacokinetic study of floating multiple-unit capsule, a high-density multiple-unit capsule and an immediate-release tablet containing atenolol [150] as well as with the mucoadhesive approach [151,152].

4.3.4. Colon targeting mini-tablets for oral use

Colon drug delivery may be intended for the purpose of systemic effects on the one hand, but also for local effects, especially in the treatment of inflammatory bowel diseases, when the focus is on achieving high efficacy while reducing side effects. Different approaches target physiological changes between the colon and the remaining GIT – as pH, microflora, hydrostatic pressure and residence time – to protect the dosage form during GIT passage and to allow release in the colon [153].

Mini-tablets may be film-coated using polymers with pH-dependent solubility. Hadi et al. applied film coatings with different ratios and concentrations of Eudragit® L100 and S100 on 3 mm mini-tablets with the goal to achieve release of naproxen in media with pH 7.2 and a lag time in media with pH 1.2, 6.5 and 6.8. The underlying idea was to take a HPMC capsule filled with mini-tablets at night to treat severe symptoms of rheumatoid arthritis in the early morning, when naproxen is released. [122]. Aleksovski et al. combined matrix mini-tablets with different film coatings to obtain a 24 h sigmoid extended release of paliperidone as an alternative to the market product Invega® (Janssen), an osmotic pump. The two matrix formers polyvinyl acetate and polyvinyl pyrrolidone extended the drug release, while the two polymers Eudragit® L30 D55 and Eudragit® FS30 D ensured onset of release in duodenum or the ileo-colonic region, respectively [154]. Ugurlu et al. employed Eudragit® S 100 to manufacture colon targeted mini-tablets containing dexketoprofen trometamol. They, however, concluded from their *in vitro* studies, that Eudragit® S 100 and Eudragit® L 100 alone were not ideal for establishing colon delivery and thus added an inner ethylcellulose coating with the pore former HPMC. They combined immediate release and colon targeting mini-tablets in a capsule to provide a pulsatile release profile [155].

Some research groups focused on multiple-layer systems to develop time-dependent colon targeting mini-tablets [156–159]. Del Curto et al. investigated erodible time-dependent systems, using hydrophilic erodible polymer coatings like HPMC, and an additional thin outer layer of Eudragit® NE 30 D to decelerate water entry to the HPMC layer and hence to additionally delay onset drug release of paracetamol through swelling or erosion. The introduced superdisintegrant as pore former in the outer layer enhanced the permeability. The thickness of the outer Eudragit® layer was relevant with respect to the delay of the water entry into the HPMC layer; also the HPMC layer had to swell to a higher degree to initiate disruption of the outer layer which may cause greater lag times [156,157]. Moutaharrik et al. developed a pH-, microbiota- and time-based drug delivery system containing an swellable inner HPMC layer and an outer Eudragit® S: pectin/chitosan layer [159].

In the course of a severe attack of inflammatory bowel diseases the pH in the colon may sink pathologically from 6.4 to 7 to 2.3–4.7. Leopold and Eikeler pursued the approach to apply coatings soluble in the pathologic acidic environment of the colon. They coated dexamethasone 3 mm mini-tablets with Eudragit® E or polyvinylacetal diethylaminoacetate (AEA®). They concluded that both polymers may be used for the purpose of release in acidic environment of the colon. They suggest to add an enteric coating such as HPMCAS for the final product to ensure gastroresistance and an intermediate layer of HPC to avoid ionic interactions between the layers [160,161].

Matrix mini-tablets have been also developed for colon targeting. Hadi et al. aimed at alleviation of peak symptoms of rheumatoid arthritis in the morning by providing 3 mm ileo-colonic targeted matrix mini-tablets with naproxen or lornoxicam. They investigated different formulations containing the pH sensitive polymers Eudragit® L100 and/or Eudragit® S100 as well as microsomal enzyme dependent polymers such as guar gum or sodium alginate [162,163]. Another approach of Hadi et al. for colon targeting was to fill uncoated 3 mm mini-tablets with lornoxicam into capsules, seal the capsule body and the cap with different polymers, and apply enteric coating to the entire capsule [164].

Another approach is the application of Nutriose, a branched dextrin from wheat starch, in 2 mm matrix mini-tablets containing the drug 5-aminosalicylic acid (5-ASA). Nutriose is subject to degradation by enzymes in the colon of patients with inflammatory bowel diseases and is hence a colon targeting excipient. A lipid was added to the formulation as a water-insoluble excipient limiting the drug release in the upper gastrointestinal tract. Choice of lipid and manufacturing methods, especially the curing conditions, had an effect on the release [165].

Finally, a study of Adkin et al. explored whether there is an influence of tablets dimensions (3, 6, 9 and 12 mm) on gastrointestinal transit by dual isotope gamma scintigraphy in humans. Colon transit was characterized by high inter and intra variability. The transit through ileo-caecal junction did not seem to be dependent on tablet size. 3 mm mini-tablets and 6 mm tablets stayed in the ascending colon for a comparatively longer length of time, hence the authors suggested that a reduction in tablet size might be beneficial when targeting ascending colon. They also suppose that not only diameter but also the volume of tablets could have an influence on the streaming of the tablets. Streaming refers here to the solid phase passing faster than the liquid phase in the colon [166].

4.4. Ophthalmic mini-tablets

A major challenge of the drug application for ocular diseases is the significant drug loss caused via clearance and tear turnover. Highly concentrated solutions, however, may be irritating to the eye. Absorption in nasal mucosa after tear drain may cause systemic side effects. Hence, modern drug development is moving further towards ocular delivery systems with increased residence time at the conjunctival site and sustaining the drug release [167]. For this purpose, several studies are concerned with SR mini-tablets as ophthalmic inserts.

Ceulemans et al. prepared 2 mm mini-tablets containing sodium fluorescein as a model drug and a physical polymer mixture of Carbopol® 974P and drum dried waxy maize starch (DDWM) with the aim to extend the drug release. This solid dosage form was then compared with a hydrated polymer dispersion *in vivo* in humans. The application of mini-tablets led to higher concentrations of fluorescein sodium in the tear film and anterior chamber compared to the dispersion or an aqueous reference solution. Also, the enhanced concentrations were retained for some hours, displaying the mini-tablets to be suitable for diseases involving the cornea or anterior chamber. Hydration of the mini-tablet was completed after about 2 h and in the end, it was converted to a gel. Finally, acceptability was shown to be similar to the dispersion [168]. Several studies investigated different bioadhesive polymers considering drug release and mucosal irritation [11,12,169–175].

Weyenberg et al. investigated the influence of tableting pressure on physical properties, *in vitro* and *in vivo* drug release. Elevation of tableting pressure extended *in vivo* release in humans. In total, the tableting pressure was regarded as an easily adaptable parameter to adjust characteristics of the mini-tablets. Different methods to determine *in vitro* release were tested, among these the shaking bath method was found to be appropriate to investigate the dependency of the tableting pressure on *in vivo* drug release [172]. Another study focused on effects of roller compaction parameters on the preparation of ocular mini-tablets [176].

For ocular application, sterility of the mini-tablets has to be ensured. Gamma sterilization of ciprofloxacin 2 mm mini-tablets, containing DDWM and Carbopol® 974P, was a more suitable approach compared to dry heat sterilization as it compromised physical properties of mini-tablets to a lesser extent. Both methods influenced *in vitro* drug release. *In vivo* analysis of the gamma-irradiated mini-tablets indicated high concentrations of the drug in tear film for over 8 h [11]. Further investigations in volunteers and by mucosal-irritation test demonstrated tolerance and no mucosal irritation by these mini-tablets [173].

Another approach to obtain mini-tablets with SR profile for ocular administration is the application of a film coating. Saettone et al. produced 3.5 mm mini-tablets film-coated with Eudragit® RS and RL achieving suitable *in vitro* timolol maleate release by changing type and quantity of polymers. [177]. In a study in rabbits, these mini-tablets showed an extended release profile with regard to reference eye drops and no irritation in rabbits' eyes [178].

Mini-tablets for ocular use show major advantages towards liquid formulations and emphasize the versatility of the application of mini-tablets. A more detailed review on mini-tablets for ocular use can be found elsewhere [179].

4.5. Other types of mini-tablets

The majority of the identified sources deal with mini-tablets for oral use. However, there are also a few investigations on oromucosal [180–182], vaginal [183], nasal [10] or parental use of mini-tablets [184–186].

Kottke et al. developed a composite dosage form of a mini-tablet and a buccal mucoadhesive carrier film and performed ex-vivo studies on controlled lidocaine oromucosal absorption [180,181]. A similar approach was utilized for mini-tablets containing desmopressine acetate for buccal administration for the treatment of primary nocturnal enuresis [182].

Hiorth et al. targeted the development of mucoadhesive mini-tablets for vaginal drug delivery of hexyl aminolevulinat hydrochloridum. The mini-tablets based on HPMC or HPC showed suitable mechanical strength and superior bioadhesive properties for the vaginal tissue. Furthermore, pH independent drug release could be achieved, which supports the treatment of women independent from their vaginal pH levels [183].

A mucoadhesive mini-tablet was designed for nasal application of sumatriptan [10]. Mucoadhesive polymers were manufactured into 3 mm mini-tablets and an *in vitro* nasal diffusion study was conducted. Mini-tablets based on either chitosan or polyacrylic acid or both showed the most promising results, with respect to mechanical and mucoadhesive properties and also drug release for up to seven days [10].

A parenteral application was proposed for mini-tablets containing 20 % of theophylline and 80 % PLGA nanoparticles, which could be designed towards specific release patterns based on molecular weight or copolymer ratio of PLGA [184]. Haupt et al. developed 2 mm lipid based mini-tablets for the controlled release of trospium chloride in the urinary bladder. However, these mini-tablets were considered as less appropriate, as comparably fast drug release was recorded within the first hours and consequently an overdose of the drug substance in the urinary bladder may not be excluded [185]. Wang et al. developed floating controlled released 2 mm mini-tablets containing 5-fluorouracil for intravesical application aiming at local treatment of bladder cancer. The lipid glyceryl tristearate was used which is supposed to preserve intactness in the bladder for a long time. The density of the used lipid is lower than the urine ensuring floating properties. Mini-tablets exhibited drug release for several days [186].

5. Manufacturing

5.1. Tableting

For industrial manufacturing mini-tablets are produced on conventional rotary presses using special tooling systems. The authors would like to highlight some guidance for mini-tableting regarding tablet presses, which can impact process robustness and product quality. Considering the smaller mass compared to conventionally sized tablets, a smaller filling curve may be beneficial. Optimal adjustments of the feed frame as part of product and process development, like speed, rotational direction (clockwise; counterclockwise) and geometry of the paddles ensure adequate filling and improve weight variation. A crucial part is also the position of the scraper to avoid any mini-tablets to remain on the die table during the process and being ejected at a later point. This would impact product quality if e.g. process parameters are adjusted

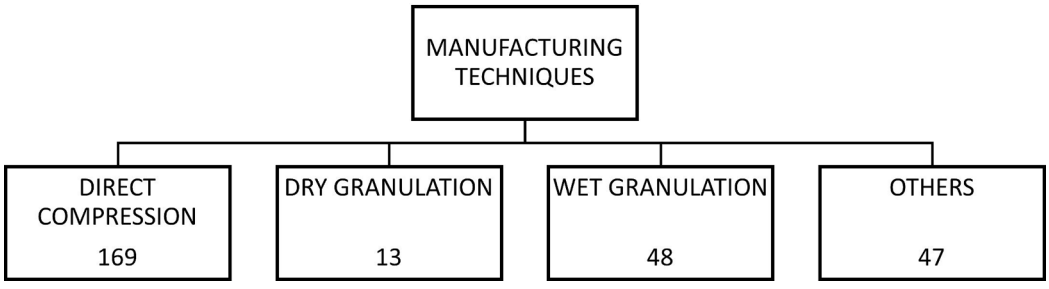

Fig. 7. Overview of the manufacturing techniques, classified according to Manufacturing Classification System. Category "Others" includes: prior melt granulation, melt extrusion, lyophilisation and manufacturing of amorphous solid dispersions before tableting, use of drug loaded excipients and encapsulation of API in nanoparticles etc. Number of publications displayed.

during the process and a temporal allocation is not possible anymore. Mini-tablets should not be damaged at the gap between scraper and die table, as well. In the case of large tablets, individual tablet rejection during the process is usually used to ensure that tablets out of specified ranges are rejected. For mini-tableting with multi-tip tooling it is required to address which approach would be feasible.

Similar to conventionally sized tablets, mini-tablets can be manufactured via direct compression or by prior dry or wet granulation. Fig. 7 provides an overview of the applied production routes of mini-tablets in the literature together with the associated number of publications. Based on the Manufacturing Classification System a classification into 4 processing routes was made: Direct Compression, Dry Granulation and subsequent compression, Wet Granulation and subsequent compression and Other Technologies [187]. The category 'Others' comprises melt granulation, melt extrusion, lyophilisation and manufacturing of amorphous solid dispersions, drug-loaded excipients and encapsulation of API into nanoparticles. Direct compression is the most often applied technology for the manufacturing of mini-tablets among the publications. If prior granulation is required, wet granulation is more often used than dry granulation according to Fig. 7.

5.1.1. Role of tablet size

There have been several observations on the differences in the manufacturing of mini-tablets and conventionally sized tablets. Pich & Moest reported in a patent [188] that 10 mm tablets containing 99.5 % pancreatin have poor mechanical strength and high friability, making further processing difficult. Reduction of the tablet size to less than 2.5 mm improved the tableting process and the mini-tablet properties. Lennartz & Mielck showed for formulations containing paracetamol, a model drug with poor tableting properties, that tablets with higher mechanical strength were obtained with decreasing size at high compaction pressures. Higher drug load was feasible compared to 5 mm tablets because of lower capping tendency. The authors provide a possible explanation for this observation by referring to the enlarged surface-to-volume ratio with decreasing tablet size. As a result, more material is in direct contact with the punch toolings and the dies. This causes a wider distribution of relative density over the volume of tablet and hence to more binding locations forming a protective shell which may reduce capping [2]. Mini-tablets with a diameter of 1 mm were produced by Tissen et al. using different manufacturing strategies. High drug loads were achieved by direct compression (90 % quinine hydrochloride, 90 % dried gentian extract) or intermediate dry granulation (70 % ibuprofen). From this study, no conclusion could be derived about the role of the mini-tablet dimensions regarding tensile strength [53]. A systematic investigation of the impact of tablet size (1, 2, 3 and 8, 11.28 mm) and industrially relevant tableting pressures on the mini-tablet characteristics was recently reported by Lura et al. The study used various pharmaceutical excipients known for different deformation behaviour. The results did not indicate a higher degree of plasticity of materials when decreasing the tablet size. A correlation between 1, 2 and 3 mm mini-tablets and the change in yield pressure could not be established. In contrast, higher compactibility for mini-tablets was obtained, which means that higher tensile strengths at a specific solid fraction were attained compared to conventionally sized tablets. Taking into account the tabletability profiles, mini-tablets did not show significantly varying tabletability characteristics [189]. Gómez et al. confirmed these observations by mechanistic modeling. The stress and density distribution during tableting are comparable for both, mini-tablets and conventionally sized tablets. However, little localized differences could be detected depending on tablet dimensions, proposing a potential higher risk for defects for larger tablets [190].

5.1.2. Tooling

An important difference in the production of mini-tablets compared to other tablets is the tooling system. Hershberg patented the first multi-tip tooling system for mini-tablets in 1965 [191]. Work on multi-tip tooling systems has been progressed since that. Customized multi-tip tooling systems are available nowadays and can be designed in various ways: A multi-tip system tablet punch can consist of a single solid steel monoblock to enable tooling stability and shorter cleaning times. On the other hand, when a single tip has been damaged, the entire punch has to be substituted. Pin fixing describes a type of tooling system where individual tips are fixed with pins and can be replaced easily. Finally, there is also a differentiation between external and internal cap fixing. Tools with internal cap fixing mitigate the risk of damaging the punch guide and contamination, as the cap is fixed inside the punch body. Punch sets with an external cap fixing to the punch body may enable more tips to be placed on the punch, however there is a higher risk of damaging the punch guides and seals. Both types allow the substitution of single damaged tips. A drawback of these two systems is the time consuming step of dismantling before cleaning [192].

Multi-tip toolings are beneficial with respect to higher yields and comparably lower process time. Lura & Breitkreutz studied the impact of the tooling system on properties of mini-tablets. Using single-tip, 7-tip and 19-tip tooling systems, 2 and 3 mm mini-tablets were produced on a compaction simulator and evaluated regarding tabletability and compactibility. In most cases compactibility was enhanced when using the 19-tip tooling, so the authors suggest to use multiple tips if poorly compactible powders have to be compacted. However, it should be considered that experiments were performed by manual die filling only and the results have to be verified on a fully automated rotary press. The change of the tooling systems did not show a systematic effect on tabletability, but some excipients tended towards better tabletability using 2 mm 19-tip toolings. Furthermore, this study did not exhibit an impact of the tooling system or the number of tips on deformation behaviour. Only in some cases significantly lower yield pressures were obtained when using a single-tip tooling. Apart from that, it should be noted that a growing number of tips implies an increase of ejection force which might impact mechanical characteristics of mini-tablets, particularly if a formulation is prone to sticking or capping. Therefore, the authors propose to check the formulation with regard to predefined properties as tensile strength before scaling-up. It has been also highlighted that higher deviation can be assumed with a higher number of tips regarding mass and content variation of mini-tablets. On top of that, maintenance is more challenging, as increased abrasion can be expected with a higher number of tips [193]. In a study by Usuda et al. the position of the dies during the filling phase had the most significant impact on weight variation of 3 mm mini-tablets compared to other factors like granule properties [194]. These findings stress that the impact of the tooling system on final quality attributes of mini-tablets is not negligible.

5.1.3. Compaction simulator, transfer and scale-up

During formulation development, it is preferred to work with small material quantities which is enabled by use of compaction simulators. Lura et al. conducted an indicative study on a potential transfer of manufactured orodispersible drug-free mini-tablets with the fillers isomalt or Ludiflash®, from the compaction simulator STYL'One Evo to the rotary press Korsch XM 12. Similar tabletability and compactibility profiles as well as disintegration times were obtained [35]. A subsequent scale-up process changing mini-tablet batch size by factor 10 according to FDA guidance [195] was conducted and revealed that the pre-defined critical quality attributes (CQA) mass variation, tensile strength and disintegration time were impacted to varying degrees. Investigations highlighted that an elevated product temperature over time caused by friction forces may be the reason for the increased disintegration times of some mini-tablets, possibly leading to sintering processes and hence impeding water penetration. Also, in order to mitigate a decline in tensile strength and increase in disintegration time, lubrication and lubricant sensitivity should be taken into account [35]. In a further study transfer and scale-up considerations were investigated with a losartan potassium based formulation. With magnesium stearate as the lubricant over-lubrication issues were detected during the transfer from STYL'One

Evo to Korsch XM 12 with an impact on tabletability and compactibility. During scale-up the CQAs weight, content uniformity, disintegration and tensile strength were monitored over time and at different tableting speeds [196]. External lubrication may be an alternative in case of severe over-lubrication challenges. In a recent study this lubrication system has been systematically investigated for mini-tableting on a rotary tablet press with focus on the tensile strength [197].

5.1.4. Impact of API and excipient properties

In addition to the various production techniques and equipment, there are some criteria to be met in direct compression by the formulation. Particularly, flowability of the powder blend is an essential characteristic influencing various steps in the production like mixing and tableting [198]. Common methods according to European Pharmacopeia for characterization of flowability are the determination of angle of response, Hausner ratio or Carr index, the flow rate through an orifice or shear cell measurements [26]. However, all these methods depend on experimental conditions and cannot be directly compared. Kotlowska et al. applied a rheological measurement, i.e. dynamic tests with variation of speed and shear forces [199].

Flemming & Mielck performed investigations on flow rates and powder properties of directly compressible excipients. They compared experimental with predicted flow rates from parameters calculated from powder densities and found varying results. With regard to orifice diameter they also stated that the maximum particle size becomes more relevant when reducing the orifice diameter. In their studies, it appears that the largest particle should not exceed 1/3 of the orifice diameter [198]. Although intermediate granulation processes can improve the flow properties, it is still important to avoid large particles and wide particle size distributions (PSD) which could obstruct the die. Therefore, according to Zhao et al., PSD should be considered as the major property next to the flow properties supporting the findings from Flemming & Mielck and confirming that largest particles should not be larger than 1/3 of the die diameter [200]. Yohannes et al. investigated the effect of particle size on compaction, tensile strength and heterogeneity of microstructure in tablets via compaction experiments of a metallic powder to 3 mm mini-tablets and related simulations. They indicated that compaction profiles were reproducible when particle sizes were below 1/6 of the die diameter [201]. The orifice length also plays a major role with regard to the flow rate. According to Kachrimanis et al. this is the third most influencing factor after orifice diameter and particle size, followed by bulk density, difference between bulk and tapped densities, and particle convexity [202]. There are also investigations on the possibly greater influence of non-cohesive arching on smaller orifices, which may be alleviated by staying below the critical particle size, which implies the relevance of particle size and particle size distribution for this phenomenon. In case of small orifice diameters, non-cohesive arching led to reduction of die filling with increasing particle size in the study of Goh et al. However, if larger orifice diameters were used, then, on the contrary, die filling was increased, as the interparticular friction was then reduced [203]. A discrete element method (DEM) simulation was performed by Xu et al. to simulate segregation processes during die filling in mini-tableting. The authors concluded that segregation during die filling is mostly affected by percolation and friction between the particles and die wall [204].

The properties of the API also play an important role in mini-tableting. Chen et al. showed that for a cohesive and poorly compactable API manufacturability could be improved by a particle design approach. The API was wet and hammer milled prior to tableting. Compared to hammer milling, high shear wet milling led to an API with smoother surface, a narrow particle size distribution and consequently better flow properties. The obtained mini-tablets with a high wet milled API load (87.5 %) exhibited better mass variation and lower friability [205]. Another approach for micronized API with poor flowability and strong cohesivity was suggested by Loo et al. Fine paracetamol powders were silicified in different concentrations. Optimal fumed silica concentrations were found between 0.7–0.9 %. Subsequently, silicified paracetamol was further processed via fluid bed granulation. The prepared mini-tablets showed lower weight variability and suitable mechanical properties compared to non-granulated powder mixtures [206]. In a later study, Loo et al. improved manufacturability of highly drug loaded 3 mm paracetamol mini-tablets by intermediate wet granulation: Here, high shear granulation represented a more robust process compared to fluid bed granulation without the need to add fumed silica [207].

A different way to overcome challenging API properties in mini-tableting was utilized by Elezaj et al. For manufacturing of high drug loaded 2 mm losartan mini-tablets the excipient silicified microcrystalline cellulose (SMCC 50) helped to reduce sticking to punches in initial direct compression trials. Because of compaction phenomena in the hopper an intermediate dry granulation step had to be implemented [55].

Targeted attributes of tablets are low weight variation and high content uniformity. Mitra et al. evaluated the impact of drug particle size, dosing per mini-tablet (3–25 %) and tablet size (1.2–2.5 mm) on content uniformity of single mini-tablets. They identified that greater tablet size and higher drug load led to lower variability in content uniformity [208]. Implementation of an intermediate high shear wet granulation step enabled manufacturing of qualitatively acceptable low dose mini-tablets at lower drug loads and larger drug particle sizes compared to directly compressed mini-tablets in the study of Gupta et al. They observed that in general higher loads and smaller particle sizes reduced CU variability [209]. To achieve proper content uniformity for low API doses, a nanomilled Irbesartan was sprayed as a suspension onto a powder bed during high shear wet granulation and compared to high shear wet granulation with micronized API. 1.2 mm mini-tablets manufactured with the prior nanomilled drug showed acceptable content uniformity according to USP for drug loads from 0.16 to 8 μg, whereas mini-tablets manufactured with the micronized Irbesartan failed in content uniformity studies for the low doses 0.16 and 0.8 μg [71]. In general, appropriate content uniformity is easier to obtain when mini-tablets are applied as multiparticulates and not as a single unit according to Mitra et al. [46].

5.1.5. Impact of equipment set-up and process parameters

Further, the influence of tableting conditions on tablet weight variation has been investigated. Goh et al. studied the influence of type of wheel paddle, paddle speed and turret speed on weight variations of 1.8 and 3 mm mini-tablets. Flat paddles and high paddle speeds led to higher fill densities due to more effective fluidization of material in the feed frame. Also, higher inter-cycle weight variation and decreased tensile strengths with regard to a potential overlubrication were observed. Turret speed did not show a significant influence on weight variation or tensile strength in this study. The number of paddle passes in the die filling area was related to die fill performance [210]. Goh et al. also adapted a new method to investigate die filling variations by combining data on tablet weight and data from compression roller displacement. In this study 1.8 and 3 mm mini-tablets were produced, both showing similar inter-cycle weight variation, but 1.8 mm mini-tablets had a higher intra-cycle weight variation because of the smaller diameter of die. Potential differences between fill mechanisms with varying tablet sizes were found: Gravity fill impacted intra-cycle die fill variation of 3 mm mini-tablets whereas for smaller mini-tablets suction fill was the predominant die fill mechanism for this variation [211]. In another study of Cho et al., die filling performance of conventionally sized tablets and mini-tablets were compared by variation of cam type, fill depth and rotational speed on a rotary press. It was shown that for mini-tablets a deeper fill cam and high rotational speed was needed to increase die filling and decrease weight variation indicating that the suction effect was important here. Also, the suction effect might be beneficial in overcoming arch formation by interlocking between granules, which may be observed more often on smaller dies, as

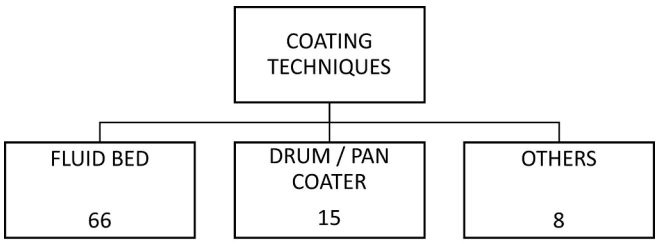

Fig. 8. Overview of classic coating techniques. Category "Others" includes dipping of tablets, Atomic Layer Deposition (ALD) coating etc. Number of associated publications displayed.

the ratio of diameter of granules to die diameter increases. However, these settings had a detrimental influence on weight variation in the production of conventionally sized tablets, underlining that knowledge of die filling behavior is important for production of mini-tablets with desired properties [212]. Finally, Kurashima et al. demonstrated that weight variation was decreased when replacing the open feeder by a forced feeder [213].

5.1.6. Others

Additionally, the mixing operation also affects final attributes of mini-tablets. Non-homogenous mixtures can lead to mini-tablets with inadequate properties. Hagen et al. investigated the use of interactive mixtures containing mannitol of different particle size fractions as carrier and micronized sodium salicylate to obtain 2 mm mini-tablets. They studied the impact of mixing time, type of mixer, sample size and carrier particle sizes on homogeneity of mini-tablets [214].

Iurian et al. recommended the early integration of dynamic compaction analysis within a Quality by Design (QbD) approach next to the inclusion of desired quality attributes of mini-tablets [36]. Within the frame of QbD there is also research on applying DoE experiments with artificial intelligence regression techniques to investigate the influence of critical material properties in the manufacturing of mini-tablets [215].

Finally, there are also studies on multiple unit (orodispersible) mini-tablets [216,217]. Hiew et al. investigated which positions of a coated pellet in a 3 mm mini-tablet led to higher damage of film by manufacturing single pellet in a mini-tablet (SPIM) system. This SPIM system revealed that especially pellets peripherally positioned were prone to get damaged by the tableting pressure. Thus, the authors concluded that one should not exceed the critical pellet volume fraction in order to reduce the count of pellets in the periphery when manufacturing MUPS tablets [218].

5.2. Film-Coating

In 4.3.2 various purposes for film-coating of mini-tablets have been described. In the following chapter the focus is placed on the coating equipment and technologies. Fig. 8 gives an overview of the applied coating techniques of mini-tablets used in literature sources.

From an industrial perspective the most common used equipment for commercial coating processes are drum/pan coaters. With the possibility to utilize differently sized pans with smaller perforations or optional application of meshes there are possibilities to execute coating processes of mini-tablets in drum/pan coaters. Hence, more research to develop and optimize the coating process in pan/drum coaters is required. Fluid bed coating is by far the most often used technology cited in literature (Fig. 8). The low mass of the mini-tablet cores enable a stable fluid-bed in the coating apparatus. Mini-tablets have been compared to pellets and granules with respect to the coating process. Reproducibility in terms of size and weight and hence low intra- and inter-batch variability as well as the smooth surface enable even film-coating with possibly less coating material needed compared to pellets or granules [4,126]. Gaber et. al compared 2 mm coated mini-tablets with pellets containing venlafaxine as a freely water soluble model drug. A further comparison to the market product Effexor® XR was performed. The pellets needed a higher weight gain of coating polymer to reach the same modified release effect as for the coated mini-tablets. In fact, the mini-tablets provided similar release profiles compared to the market product Effexor® XR pellets. From an industrial point of view, production of mini-tablets from 5 kg of powder took 1 h, whereas pelletization was performed within 4 h. The loss of mass because of dusting during the production amounted 2.3 % for mini-tablets and 20–30 % for pellets [4].

Several studies deal with the influence of process parameters on the fluid bed process [118,128,219]. Frankiewicz and Sznitowska demonstrated that the design of experiments (DoE) enables the creation of a design space and optimization of the film coating process. However, they emphasized that this statistical tool should be applied on an individual basis only in order to optimize the fluid bed process, because alterations of the sub-coat, mini-tablet size and mass, as well as coating and core composition may lead to different parameters which are critical. Already minor alterations like change of coating composition of the same polymer or changing composition and mass of same-size mini-tablets may lead to differences in the film coating process [113]. Szczepanska et al. applied another statistical DoE concept (full factorial design) to investigate critical parameters and find optimal ranges in two laboratory fluid bed apparatuses with different geometries and spraying patterns. This approach may be helpful in scale-up processes to identify and estimate critical process parameters. Analyzed parameters were the inlet air flow rate, the product temperature, the coating mixture flow rate and the spray pressure, whereas the response values included film thickness of the 3 mm enteric coated mini-tablets, standard deviation of the film thickness and amount of API released after a certain time in dissolution test. The results displayed that not every parameter combination led to good quality of the film-coated mini-tablets. Some combinations provoked blocking of the nozzle or sticking. The larger chamber enabling effective drying was less sensitive to a change in coating mixture flow rate than the smaller chamber. On the other hand, a suitable range of inlet air flow rate was required for that chamber to enable a good working process. In comparison, the fluid bed coater with the smaller chamber showed less sensitivity of to the inlet airflow rate [118].

Turk et al. also used a statistical approach – a DoE based on the Taguchi method – in combination with the calculated minimum fluidization velocity to optimize the coating process of mini-tablets and pellets of different dimension in a fluid bed apparatus. The choice of optimal parameters was determined with regard to film thickness. In their study, the spraying pressure had the biggest influence, as this parameter impacts size of coating mixture droplets. The authors also concluded that the coating of the edges of mini-tablets is more challenging than on flat areas. They assume that this may be the result of the rather turbulent air movement in the surrounding boundary air layer in combination with the geometry of mini-tablets. Minimum fluidization velocity increased with core diameter. Thereby, experimental and theoretical results were generally more consistent for pellets than for mini-tablets, which may be attributed to the non-spherical shape of mini-tablets. The influence of the shape on fluidization is also underlined by the fact that the relative difference between theoretical and experimental values increased with the size of mini-tablets from 2.0 to 2.5 mm [128].

Šibanc et al. investigated the coating variability of the coating process of 2.0, 2.5 and 3.0 mm mini-tablets in two different Wurster fluid bed apparatuses (equipped with classic or swirl chambers) by determination of dye content. In total, inter-particle coating variability ranged between 3.1–19.1 % in both coaters. In general, the swirl chamber displayed superior performance in case of all three sizes of mini-tablets with a maximum coating variability of 4.8 %. Regardless of coater type, coating of smaller mini-tablets always led to a smaller coating variability. The authors assume that bigger mini-tablets undergo a less

uniform circulation since the gap size stayed the same being an obstruction for the lager mini-tablets [220]. In this regard, the differing coating time for various tablet sizes to achieve the same level of film thickness is also of relevance [220,221]. Additionally, mini-tablet cycle time measurements were performed using photoluminescent coating and a detection setup on top of the Wurster insert. The finding was that number of passes variability amounted to 5–28 % of the total coating variability. Further transmittance studies gave a hint at the dynamics in the system and the proportion of mini-tablets in the Wurster insert and may therefore indicate whether particles are sheltering other particles from the spraying nozzle. Hence, these studies may be an indicator for inter-particle shielding from the nozzle which may contribute to the "per pass variability" of applied coating amount [220].

In another study further focus was placed on the different inlet air distributors of fluid bed devices and their impact on coating uniformity. A chamber with a classical Wurster distributor (perforated, flat) and a swirl distributor (curved, thicker circular center segment with inclined gaps) were compared. Bottom spray was applied and mini-tablets of 2.0, 2.5 and 3.0 mm were coated with hypromellose at the same film thickness. Tartrazine served as a colorant in the coating mixture to determine coating uniformity by spectrophotometric method. Film thickness was also investigated by colorimetric analysis (scanner method) based on hue. Both distributors led to successful coating. Nevertheless, with the swirl distributor better coating uniformity was obtained for all three mini-tablet sizes (relative standard deviation max. 5.0 %). In general, the larger mini-tablets of 3 mm always showed higher coating variability at the same process parameters. The authors assume that mixing in the annulus bed area and the gap size may be restricting factors for film thickness variability. An elevation of air flow rate improved coating uniformity. A high correlation of the two analytical methods with respect to inter-tablet variability was found, showing that the scanner method – a non-destructive technique – might be applicable [221].

Another way to optimize process parameters for coating in a fluid bed device is suggested by Wong et al., they used an acoustic levitator with an ultrasonic atomizer. They conducted a DoE to investigate which parameters have an effect on the mass of film thickness; coating material was a povidone solution. After transfer to a fluid bed apparatus, the results concerning mass of film thickness were comparable. Scanning electron microscopy images of coated mini-tablets at 40 °C in the acoustic levitator and fluid bed showed comparable surfaces. The stated advantage for the transfer from an acoustic levitator to the fluid bed device is saving time and resources [222].

The determination of the film thickness is also of important relevance. Czajkowska et al. examined the method dynamic image analysis by use of Camsizer XT to measure the film thickness of pellets (0.7–0.8 mm) and mini-tablets (2.0, 2.5 mm). In case of mini-tablets, they determined minimum and maximum Feret diameters from coated and uncoated mini-tablets and calculated the film thickness at the edges and the wall. This tool was then compared to scanning and stereoscopic microscopy. The results indicated a good correlation between this method and the microscopic methods for pellets and 2.0 mm mini-tablets, whereas statistically significant differences between the methods were observed for the measurement of 2.5 mm mini-tablets exhibiting a non-isometric shape. The limited measuring span of the Camsizer XT (1 μm – 3 mm) has to be considered hereby. The authors propose that this method may be used in the field of quality control for mini-tablets up to 2 mm due to several benefits as the large sample analyzed, the small amount of time required and the lack of sample preparation [223]. In comparison to this off-line method, Podrekar et al. described an in-line method to determine the film thickness of mini-tablets by applying visual imaging. This system was placed to the observation window of the fluid bed device. Results were compared to calculations of thickness based on weight gain as well as to optical microscope measurements. Highest accuracy was achieved for band coating thickness compared to the microscope reference method with a root mean square error (RMSE) of 1.30 μm. The developed window cleaning mechanism was important for the measurements leading to decrease of RMSE. Due to the absence of the need for product-related calibration and the lack of sensitivity to formulation or colour of coating, this approach offers a reasonable alternative for coating thickness determination [224].

With the Atomic Layer Deposition (ALD) a new approach for ultra-thin coating of mini-tablets is presented by Hautala et al. [112]. These titanium dioxide (TiO_2) nanolayers were created via chemical reactions between gaseous precursors on a solid substrate surface. Number of reaction cycles determined the layer thickness. Hautala et. al. coated bitter tasting mini-tablets of denatonium benzoate with three different TiO_2 nanolayer thicknesses to mask the taste of the mini-tablets. The study indicated minimal growth in mass and dimensions of mini-tablets with ALD coating. However, these mini-tablets showed lower mechanical strength and faster disintegration process. Also, the goal of taste masking was not achieved with the applied ALD layers. In this regard, further investigations are therefore necessary. Nevertheless, this novel coating system provides advantages over the typical coating systems due to the absence of spraying and drying processes and the lower risk of collision processes [112].

Table 5
Selection of marketed products modified from [253].

Marketed product and company	Drug and dosage strength	Size	Packaging	Indication
Aqumeldi Proveca Pharma Limited, Ireland	Enalapril maleate 0.25 mg	2 mm	50, 100 and 200 count bottles with dosing device (spoon)	Heart failure
Kalydeco® oral granules Vertex Pharmaceuticals, Ireland	Ivacaftor 25, 50, 75 mg	2 mm	Sachets	Cystic fibrosis
Lamisil® Oral Granules Novartis, Switzerland	Terbinafine 125, 187.5 mg	2.1 mm	Sachets	Tinea capitis
Levetiracetam Desitin® Desitin, Germany	Levetiracetam 250, 500, 1000 mg	2 mm	Sachets	Epileptic seizures
Orfiril® long Desitin, Germany	Sodium valproate 150, 300, 500, 1000 mg	2 mm	Capsule (150 and 300 mg) Sachets (500 and 1000 mg)	Epileptic seizures
Rhythmol SR Glaxo Smith Kline, England	Propafenone 225, 325, 425 mg	2 mm	Capsule	Cardiac arrhythmias
Slenyto® Neurim Pharmaceuticals, France	Melatonin 1 and 5 mg	3 mm	Blistered as single dose	Insomnia with autism spectrum disorder

6. Drug substances and marketed products

This chapter outlines which drug substances have been used in the manufacturing of mini-tablets in published literature: In addition to the mini-tablet size, the dosage is given in milligrams (mg) and percentage (%) in Table S1 in Supplementary Materials. If there was no information on the drug loads in both units, they were converted to the other unit by the authors (if possible). The list of drug substances in Table S1 did not necessarily result in marketed products but should provide an overview across scientific publications. The cited sources in Table S1 can be found in the References section of this article. Some of these sources [227,228,230–238,241,244,245,247–249,251,252] do not appear in the main text of the article but are included in Table S1 to provide a comprehensive overview of the use of drug substances. Additionally, in

Table 5 a selection of marketed products has also been compiled.

7. Characterization of mini-tablets

So far, there is no dedicated monograph for mini-tablets in USP and Ph.Eur. with respect to uniform characterization methods. The smaller size of the mini-tablets compared to conventionally sized tablets imposes difficulties in using conventional devices for their characterization as described in the pharmacopoeia for tablets. The focus here is therefore to provide an overview of the different approaches already applied in literature to determine tensile strength, friability and disintegration of mini-tablets. To the authors' opinion mini-tablets should match compendial test methods for tablets and not those of granules, as they are usually produced by compacting and are generally classified as tablets, but certain limitations must be considered with respect to the procedures and specifications of the pharmacopeial standard methods.

7.1. Tensile strength

The use of conventional hardness testers to determine the diametrical breaking force imposes the limitation of low sensitivity due to the small size and weight of mini-tablets [254,255]. An alternative approach is the use of a Texture Analyser enabling a higher sensitivity with a set speed [53,254,255]. In Fig. 9 an overview of applied devices to determine the breaking force are presented.

In general, the tensile strength may be calculated by the equation of Fell and Newton [256] or of Pitt and Newton [257]. The equation of Fell and Newton, which takes thickness and diameter of a tablet into account, is usually applied for flat-faced tablets, whereas the other equation is used for determination of tensile strength of biconvex tablets. Lennartz and Mielck decided for the first equation even though their mini-tablets were biconvex, because mini-tablets usually have an aspect ratio of almost 1, but the tablets in the study of Pitt and Newton show a thickness to diameter ratio of 0.06–0.3 [2,257]. Lura et al. used both equations for calculation of the tensile strengths of placebo mini-tablets with different excipients and different sizes (1, 2 and 3 mm) and showed that the resulting tensile strengths from the two calculations did not differ significantly for all batches [189].

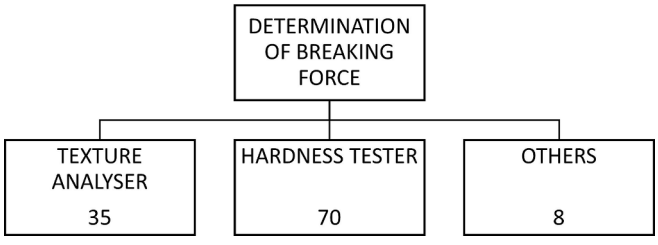

Fig. 9. Overview of methods to determine breaking force of mini-tablets. Number of associated publications displayed.

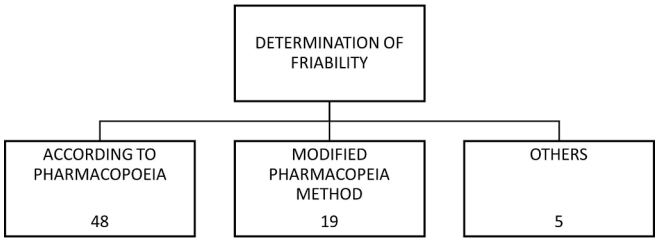

Fig. 10. Overview of methods to determine friability of mini-tablets. Number of associated publications displayed. Pharmacopoeia method refers to the test of tablets.

7.2. Friability

On the one hand, there is the possibility to apply the methods of Ph. Eur. to determine the friability of mini-tablets (Fig. 10). However, it should be considered that the surface to volume ratio is higher for mini-tablets [189], and when using the same mass of mini-tablets as for conventionally sized tablets, it may be reasonable to reconsider the recommended limit in Ph.Eur. On the other hand, approaches to determine friability of multiparticulate dosage forms, such as pellets or granules, are described [9,39,56]. However, the classification of mini-tablets as tablets suggests the use of compendial methods for tablets while considering certain limitations on the procedures and specifications.

7.3. Disintegration

The conventional disintegration apparatus described in Ph. Eur. contains mesh sizes at the bottom that are partly wider than the size of the mini-tablets, so that they would pass through during the disintegration test. To overcome this limitation, the modified method for pellets by Kleinebudde may be employed. Hereby, a single mini-tablet is placed in a plexiglas® cylinder with a height of 15 mm and an inner diameter of 10 mm, covered at the top and bottom with a mesh of 710 µm. These cylinders are transferred to a conventional disintegration apparatus and can be weighted down with a metal cylinder [258].

For ODMTs different techniques for the determination of disintegration time are described in literature. The simulated wetting test-time – not to be mistaken with the disintegration time – by Park et al. [259] is modified and applied for ODMTs by Stoltenberg and Breitkreutz [9,254]. Here, the simulated wetting test-time is the time that a blue dye solution, which is only on the bottom of the tablet, will need to entirely wet the tablet, which is detected visually [9,254]. In several studies the Texture Analyser is utilized in general for orodispersible tablets [260–263] and this method of disintegration time determination in the presence of defined mechanical forces was also applied for ODMTs by Stoltenberg [254].

Sieber et al. investigated the applicability of the OD-mate (Higuchi Inc., Tokyo, Japan) and the Hermes tester designed by Hermes for ODTs and ODMTs. They compared the findings with the disintegration times obtained by the method according to Ph. Eur. and in case of mini-tablets according to the modified method by Kleinebudde; they also did a qualification for both apparatuses. In the OD-mate, a piston contains an inner and outer weight and is positioned on the top of a tablet. The tablet is in turn deposited on a mesh sieve being then placed in a beaker with the medium and stirrer. An automatic stop of the measurement is done when a preselected distance of the inner weight has been reached in the course of the disintegration of the tablet. The automated Hermes tester designed for ODMTs works by measuring the electrical resistance in a gap between the upper and lower contact where the tablet is located and where the tablet is loaded with a preset force by the upper piston which is supposed to simulate the force exerted by a human tongue. In addition, a small volume of disintegration medium can be used. Sieber et al. found out that small relative standard deviations (RSDs) were obtained for the two testers (16.9 % OD-mate, 15.2 % Hermes tester with respect to 32.3 % for the Ph. Eur. method). Given the findings, they suggest to apply differing threshold values for the repeatability or RSDs in dependence on the mean disintegration time, which also should be validated. Sieber et al. noted an enhanced applicability of the two devices compared to the modified Ph. Eur. method by Kleinebudde because of among other things the automatic endpoint determination [3,264]. However, according to Lura et al. a major limitation of an apparatus like the Hermes tester is the need to self-construction and standardization as well as qualification and validation, increasing the effort to establishment in GMP area [35].

7.4. Quality control and monitoring

Another important property to monitor is the content uniformity of mini-tablets. A study intended to compare content uniformity of quartered hydrocortisone tablets to 3 mm mini-tablets for paediatric use revealed that the hydrocortisone mini-tablets outperform the split tablets regarding mass and content uniformity [58]. Besides the traditional offline methodologies for determination of content uniformity, Kandpal et al. observed that results obtained by hyperspectral imaging (HSI) linked with methods of multivariate analysis may be promising for the establishment as an in-line method in production. HSI is a spectroscopic technique already applied for content determination in single tablets and tablets with larger size, but not yet in bulk mini-tablets according to the authors [265]. In other studies, Kandpal et al. propose that Fourier transform near infrared (FT-NIR) spectroscopy and line-scan Raman hyperspectral imaging (RHSI) may also be alternative options for the determination of content uniformity and of mini-tablets, in case of the FT-NIR technique also hardness of mini-tablets was determined [266,267]. Wagner-Hattler et al. use the method of synchrotron X-ray microtomography and image clustering, and conclude that it may be applied for determination of drug content and drug distribution within tablets, for example for the optimization of formulations [243]. There is also research on laser-induced breakdown spectroscopy (LIBS) hyperspectral imaging [268].

A study by Gerberich et al. used a computational model to investigate the probability of mini-tablets filled in sachets or capsules not passing the content uniformity targets. Following factors were taken into account: sachet fill count, weight, potency RSD and fill error probability. The model should support to find the sufficient fill count for a given mini-tablet weight and potency RSD and to evaluate permissible limits for the fill error frequency. Overall, the authors recommend fill counts of more than five mini-tablets per sachet [269].

Schilderink et al. investigated the utility of tiny-TIM system for assessment of *in vivo* behavior of oral dosage forms, amongst others modified-release mini-tablets [270]. Niessen et al. systematically tested different biorelevant *in vitro* assays, including MicroDiss, two-stage, transfer model and tiny-TIM, for ASD-based mini-tablets containing the poorly soluble ritonavir with the aim to support development of ASD pediatric formulations. With the designed staged testing protocol consisting of these assays disintegration, dissolution, supersaturation and precipitation as well as their interaction were investigated in dependence of various physiological conditions [250].

There is also work on artificial neural networks to find relevant formulation and process factors with the aim of prediction of *in vitro* dissolution of sustained release mini-tablets [271]. Karkossa et al. developed a dissolution model for biorelevant simulation of gastrointestinal environment in children considering small volumes and pH conditions, with the purpose to possibly reduce the amount of pharmacokinetic studies in children; here *in vitro* dissolution studies were carried out with an extended release valproate formulation [272,273]. Most recently Borjigin et al. used X-ray computed tomography to predict the dissolution performance of 2 mm enteric coated mini-tablets [119].

8. Dosing devices and administration aids

Besides the focus on formulation and process, the packaging and dosing of mini-tablets is also of pertinence. Various options as encapsulation or filling in sachets/stick packs are feasible but in terms of personalized medicine with the requirement for flexible dosing there have been additional development strategies to assure accurate dosing for mini-tablets and hence also patients' safety.

A more comprehensive overview of dosing devices has been recently compiled by Hejduk & Lulek [15].

One of the very first dosing devices was a spoon with 50 gaps for 2 mm pancreatin mini-tablets by Knoll AG in 1999 [274]. A limitation, however, may be the risk of losing mini-tablets during application or incomplete filling of all gaps leading to inadequate dosing. Also, dosing flexibility is not yet fully enabled with this device [275].

Another alternative is offered by devices that deliver one mini-tablet per operation. According to this concept Warren and Dobkin designed cylindrical devices, dispensing tablets by rotating the container, and also further approaches based on these exist. It is important to note, though, that patients are required to count the delivered single mini-tablets, which might also be a source of error [275–277]. Therefore, it would be desirable to find devices that provide the individually required number of mini-tablets. The dosing device by Knoll AG/Schuster in 1988 [278] was advanced by Breitkreutz and Wazlawik [279] for the dosing of solid multiparticulates, including mini-tablets [275]. The dosing device is set up with a rotating disc, gaps to load mini-tablets and a container for the mini-tablets. With the help of a display the patient can set the amount of needed mini-tablets [279]. The dispenser with a digital display described by Bredenberg et al. electronically determines the required amount of mini-tablets and was investigated in 20 patients with Parkinson's disease with regard to acceptability. Patients were generally satisfied with the device, however several patients criticized the size and weight of the dispenser as well as the small display [240].

Furthermore, the company Sensidose AB offers the dispensers OraFID, a mechanical disposable device, and the electronic MyFID (My Flexible Dosing) for levodopa/carbidopa mini-tablets. MyFID provides an improved touch screen with an implemented reminder and a diary for the patients with Parkinson's disease. The physicians can further set a fixed dosing regimen or allow the patient to individualize the dosing. The device further saves the data of dispensed mini-tablets and informs the user, for instance, if the cassette has to be replaced [280,281]. The user-friendliness for MyFID was stated by Senek et al. [282]. In 2016, EMA approved this treatment (medicinal product Suades or Flexilev 5 mg/1.25 mg) in 13 EU countries apart from Sweden [283].

Zalviso® (15 μg sufentanil sublingual microtablet system) for acute pain management in hospitals received approval by the European Commission in 2015, but is no longer maintained. The device regulates the dosing regimen by providing only one 3 mm mini-tablet within 20 min between doses (blocking time) and a maximum dosing of 45 μg (3 mini-tablets) within one hour. The preprogrammed device works with a radio-frequency thumb-identification, so that only the patient can use the device. The mini-tablet is put under the tongue with the help of the dispensing device. Before handing out to the patient, one should ensure that he has been well instructed. A phase III *meta*-analysis by Minkowitz et al. highlights the product's earlier onset of action and simple handling compared to intravenous (IV) patient controlled analgesia (PCA) with morphine [284–286].

Philipps-Medisize developed a mini-tablet dispenser which is compatible with standard bottle necks and can be mounted on these bottles. This provides the benefit that mini-tablets are protected from the environment until they are dispensed. For dosing, the amount of mini-tablets can be set manually. Then the bottle is flipped and shaken so that the mini-tablets enter the chamber with the preset number of gaps. Then the bottle is placed upright again and shaken lightly until the mini-tablets get into the gaps and the rest returns to the bottle. Hence, a visual check on complete filling of the preset number of gaps can be performed before dispensing the mini-tablets [287].

In addition to dosing devices, there are also studies on vehicles for the administration of mini-tablets. The current EMA guideline on pharmaceutical development of medicines for paediatric use recommends to investigate alternatives of administration – even if they are already considered child-appropriate as such, for example by mixing solid dosage forms with food or beverages [7]. Kluk and Sznitowska investigated hydrogels as an alternative vehicle besides (semisolid) food where interactions might take place between API and ingredients in the food [288]. Another study deals with the influence of liquid (water, milk and apple juice) and semisolid (2 % carmellose and 0.5 % carbomer gels) vehicles on disintegration time and drug release of 2.5 mm mini-tablets with the API diazepam [61]. Studies were also conducted with enalapril

Table 6.1
Acceptability studies with placebo-containing mini-tablets.
Table 6.1. Studies in the paediatric population.

Investigated age groups	Number of participants	Author, year	Formulation type	Control	Study design and research question	Results
2 – 28 days	N = 151	Klingmann V, 2015 [22]	2 mm uncoated mini-tablet	Glucose syrup	Open, randomized, prospective cross-over study. To investigate the acceptability and swallowability of an uncoated mini-tablet compared with glucose syrup.	The mini-tablet showed high acceptability and swallowability in comparison to syrup and proved to be a valuable alternative to syrup for term neonates.
1 month – 5 years	N = 320	Münch J, 2023 [302]	2 mm and 2.5 mm coated mini-tablets	None	Open, randomized, single-dose, cross-over study. To investigate the acceptability, swallowability, and palatability of a high quantity (7–31) of 2 mm coated mini-tablets compared to a low quantity (4–15) of 2.5 mm coated mini-tablets.	Across all tablet sizes, quantities and age groups, acceptability rates were high (at least 87 %). Swallowability and palatability were high as well.
6 – 23 months	N = 40	Mitsui N, 2022 [303]	2 mm uncoated mini-tablets	Fine granules (263.2 ± 107.8 μm), sucrose liquid	Randomized, controlled, three-way, single administration cross-over study. To investigate the swallowability of multiple drug-free mini-tablets (depending on age 4 or 5) compared to fine granules and liquid.	Significantly more children (80 %, 95 % CI: 56–94 %) aged 6–11 months could swallow the mini-tablets than those who could swallow all the dispersed fine granules and liquid formulations (22 %, 95 % CI: 6–47 % and 35 %, 95 % CI: 15–59 %, respectively). No significant differences were observed in children aged 12–23 months.
6 months − 5 years	N = 60	Spomer N, 2012 [20]	2 mm uncoated mini-tablet	Glucose syrup	Open, randomized cross-over exploratory pilot study. The study hypothesis was that children would accept the liquid formulation better than the solid mini-tablets.	Acceptability of mini-tablets was higher or at least equal to that of syrup.
6 months − 5 years	N = 306	Klingmann V, 2013 [21]	2 mm uncoated mini-tablet and 2 mm coated mini-tablet	Glucose syrup	Open, randomized cross-over study. To investigate the acceptability and swallowability of mini-tablets compared to glucose syrup.	In all age groups the acceptability and swallowability of uncoated mini-tablets was superior to syrup. Uncoated and coated mini-tablets were comparable.
6 months − 5 years	N = 372	Klingmann V, 2018 [23]	2 mm uncoated mini-tablets	Glucose syrup	Randomized, controlled, three-way, single administration cross-over study. To investigate the acceptability and swallowability of multiple uncoated mini-tablets (depending on age 25, 100, and 400) in comparison to glucose syrup.	Administration of 25 mini-tablets was well tolerated, feasible and safe in children aged from 6 months, and was superior to the equivalent dose of syrup. Children aged above 2 years accepted up to 400 mini-tablets, even better than the equivalent dose of syrup.
1 – 5 years	N = 50	Klingmann V, 2023 [304]	2 mm coated mini-tablets	Glucose syrup	Open, randomized cross-over study. To compare acceptability and swallowability of multiple (16–28) coated mini-tablets compared to glucose syrup.	In all age groups, administration of multiple coated mini-tablets and syrup showed good acceptability (mini-tablets 80 %–100 %, syrup 90 %–100 %) and swallowability (mini-tablets 30 %–70 %, syrup 20 %–80 %) without any clinically meaningful difference.
1 – 5 years	N = 280	Münch J, 2021 [296]	2 mm uncoated mini-tablets	Glucose syrup, oblong tablet (2.5 x 6 mm)	Randomized, controlled, single dose, two-way cross-over design in two parallel study arms. To investigate the acceptability, swallowability and palatability of mini-tablets, oblong tablets and glucose syrup.	Mini-tablets and oblong tablet showed similar results for acceptability, swallowability and palatability. Acceptability, swallowability and palatability for syrup were lower.
2 – 3 years	N = 60	Kluk A, 2015 [129]	2 and 3 mm coated mini-tablets	None	Exploratory study. To assess swallowability of 5 and 10 mini-tablets (2 mm or 3 mm) suspended in a fruity jelly (semisolid gel) on a spoon.	The swallowing of mini-tablets (with or without chewing) was registered for 75 % of 2-year-olds and for 93 % of 3-year-olds. Most of the children were fully capable of swallowing all units without chewing (2 years 50 %; 3 years 64 %).
2 – 6 years	N = 100	Thomson A, 2009 [24]	3 mm coated mini-tablets	None	Single dose study to investigate the swallowability of a single mini-tablet.	Swallowability of mini-tablets increased with age (46—85 %).
2 – 6 years	N = 300	Münch J, 2023 [305]	3 mm coated mini-tablets	None	Open, randomised, parallel-group study. To investigate the acceptability, swallowability, and palatability of multiple (16 or 32) mini-tablets administered with soft food or water.	The rates of acceptability, swallowability, and palatability were ≥ 80.0 %, ≥42.0 %, and ≥ 82.0 %, respectively, across the study groups (administration with soft food or water).

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Table 6.1 (*continued*)

Investigated age groups	Number of participants	Author, year	Formulation type	Control	Study design and research question	Results
2 – 8 years	N = 65	Miyazaki K, 2022 [306]	2 mm uncoated mini-tablets	Fine granules (263.2 ± 107.8 μm), sucrose liquid	Randomized, controlled, three-way, single administration cross-over exploratory study. To measure acceptability and swallowability of mini-tablets (depending on age 6, 9, and 12), fine granules (depending on age 360, 540, and 720 mg) and liquid (depending on age 5, 5, and 10 ml).	Most subjects accepted all formulations, although mini-tablets showed lower swallowability compared to fine granules and liquid formulations. Fine granules and liquid formulations showed good acceptability and swallowability, and mini-tablets were accepted, although the swallowability was lower, likely because children tend to chew on mini-tablets.

maleate ODMTs (Aqumeldi®) in order to investigate the dispersion procedure, the physicochemical stability and compatibility of ODMTs in various beverages and the feasibility of administration through nasogastral tubes of different sizes and materials. Dispersion of ODMTs in an oral syringe showed better results than dispersion in a container in terms of dose precision and flexibility. The ODMTs were stable in the tested beverages, however the authors suggest dispersion in tap water, because longer disintegration times were observed in the other beverages [37,38].

9. Clinical investigations

The clinical investigation of mini-tablets' suitability in patients is still a rather young field of research.

Especially the oral drug therapy of young children is often not evidence-based, but empirical and with medicines lacking marketing authorization for this age group. Thus, even today, most medicines are administered to young children in hospitals off-label and without an age-appropriate dosage form [289]. The generation of scientifically sound efficacy and tolerability data is methodologically complex and lengthy due to small concerned patient populations and difficult to perform clinical assessment and bioanalytical methods. The development of paediatric dosage forms for these small patient populations is often economically not interesting for pharmaceutical companies. Introduced in 2007, the Paediatric Regulation [18] of the European Commission requires the development of more medicines suitable for children with age-appropriate galenic formulations and defines the uniform legal conditions, ethical obligations and regulatory expectations for the European Economic Area. The manufacturers of new substances are obliged to examine their medicines, developed for adults, also for their suitability for children, offered in age-appropriate galenic preparations. Due to the limited number of cases and the ethical and methodological difficulties of studies in children, it is of great importance to identify the most promising galenic application form for different age groups as early as possible in the development process by systematically collecting the necessary information in paediatric patients with validated assessment methods that allow statistically sound comparison of acceptability rates in the shortest possible time frame. As at this stage in the development process only placebo-containing formulations are available, the acceptability assessment methods need to be particularly sensitive and able to distinguish the formulations' suitability solely based on their size and shape. The pre-selected

Table 6.2
Studies in the adult / geriatric population.

Investigated age groups	Number of participants	Author, year	Formulation type	Control	Study design and research question	Results
22.5 ± 1.0 years	N = 18	Hayakawa Y, 2016 [307]	3 mm uncoated mini-tablets (MTs)	Orally disintegrating mini-tablet (ODMT, 3 mm), conventional tablet (CT, 8 mm), conventional orally disintegrating tablet (ODT, 8 mm)	Randomized, controlled, cross-over study in two parts. Part 1: Measurement of the amount of water required for ingestion of one of the formulations each and evaluation of the ease of taking the tablets using a VAS (visual analogue scale). Part 2: Random intake of 1 CT or one unit containing 1, 2, 5, or 10 MTs with water. Measurement of the amount of water required for ingestion of the formulations and evaluation of the ease of taking the tablets using a VAS (visual analogue scale).	The VAS score for the ease of intake and the amount of water required for intake of MTs was significantly lower than those of CTs. An ODMT required the least amount of water and smallest VAS score for the ease of taking a tablet. ODTs showed similar results to MTs.
Adult volunteers	Unknown	Podczeck F, 2007[308]	3.2 mm non-disintegrating mini-tablets of different densities	/	Transit behaviour of mini-tablets of different densities in the gastrointestinal tract, observed with gamma-scintigraphy at various intervals.	The median emptying time of the light tablet was significantly shorter than that for the dense tablet, but the total emptying time and the time for the last tablet to empty for both sets of tablets were not statistically different. The median time for initial and final emptying of the mini-tablets from the stomach was significantly longer than that for larger tablets (data from literature).

Table 7.1
Clinical studies with active ingredient containing mini-tablets, including Pharmakokinetic / Pharmacodynamic (PK / PD) studies with mini-tablets.
Table 7.1 Studies in the paediatric population.

Active ingredient	Trade name	Author, year	Investigated age groups	Number of participants	Formulation type	Control	Indication	Study design, research question	Results	Acceptability of mini-tablets investigated?
Artesunate (AS)-Amodiaquine (AQ)–Methylene Blue (MB)	/	Coulibaly B, 2015 [242]	6 – 59 months	N = 221	Methylene blue (MB) in 2 mm mini-tablets. No information on tablet size of the other active ingredients.	AS-AQ	Falciparum Malaria	Randomized controlled phase IIb study. Gametocyte prevalence Plasmodium falciparum during follow-up.	Gametocyte prevalence of Plasmodium falciparum was significantly lower in AS-AQ-MB than in AS-AQ group.	Yes, MB mini-tablets were acceptable for mothers and caretakers.
Enalapril	/	Bajcetic M, 2019 [309]	0 − <12 years	N = 85	Orodispersible mini-tablets (ODMT, 2 mm)	/	Dilated cardiomyopathy and congenital heart disease	Study protocol for phase II/III, open-label, multicentre study. Creation of PK/PD and safety profile of Enalapril.	No results.	Acceptability investigation foreseen in the study protocol.
Enalapril	/	Laeer S, 2022 [229]	1 day − <12 years	N = 102	Orodispersible mini-tablets (ODMT, 2 mm)	/	Heart failure due to dilated cardiomyopathy (DCM) and congenital heart disease (CHD)	Phase II/III open-label, multicentre PK bridging study. Bioavailability of enalapril (area under the curve (AUC) within a dosing interval of 12 h, Cmax and Tmax), and descriptive PK investigation.	Rate and extent of enalapril and its active metabolite enalaprilat Described. Etiology and age could be identified as potential PK modifying factors.	Yes, according to study protocol. But no results of acceptability and palatability investigation reported in this publication.
Hydro-cortisone	/	Madathilethu J, 2017 [62]	/	/	3 mm mini-tablets	Quartered tablets (size unknown)	Cortisol replacement therapy	To determine dose variation obtained from quartered hydrocortisone tablets (10 mg) and to ascertain whether better uniformity could be attained from mini-tablets (2.5 mg).	Quartering 10 mg hydrocortisone tablets produces unacceptable dose variations. Production of mini-tablets is feasible, containing more accurate doses.	No.
Melatonin	/	Gringras P, 2017 [310]	2 – 17.5 years	N = 125	3 mm prolonged-release mini-tablet (PedPRM)	Placebo	Insomnia in children and adolescents with autism spectrum disorder (ASD) and neurogenetic disorders (NGD)	Randomized, double blind, placebo-controlled study. Efficacy and safety of PedPRM versus placebo for insomnia in children with ASD and NGDs.	Participants slept longer at night with PedPRM compared to placebo.	Yes. No need to crush the mini-tablets, high acceptability.
Melatonin	Slenyto	Malow B A, 2021[311]	2 – 17.5 years	N = 80	3 mm prolonged-release mini-tablet (PedPRM)	Placebo	Insomnia in children and adolescents with autism spectrum disorder (ASD)	Randomized, double blind, placebo- controlled study. Examination of long-term effects of PedPRM treatment on sleep, growth, body mass index, and pubertal development.	Improvements in child sleep disturbance and caregiver satisfaction. Changes in mean weight, height, body mass index, and pubertal status within normal ranges for age.	Yes. Principal investigators reported that children were Able to swallow the mini-tablets without crushing, thus confirming acceptability and suitability of 3 mm mini-tablets for children ≥ 2 years of age.
Melatonin	Slenyto	Vivas E A, 2022 [312]	4 – 18 years	N = 23	3 mm prolonged-release mini-tablet (PedPRM)	/	Insomnia in children and adolescents with	Prospective descriptive study on the efficacy of PedPRM after at least 6	Improvement of sleeping behaviour.	Yes. No problems with ingestion of the mini-tablets.

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Table 7.1 (*continued*)

Active ingredient	Trade name	Author, year	Investigated age groups	Number of participants	Formulation type	Control	Indication	Study design, research question	Results	Acceptability of mini-tablets investigated?
							autism spectrum disorder (ASD)	months of use measured by anamnesis (total sleep time, sleep latency and awakenings) as well as with objective scales.		
Pancrelipase	/	Van de Vijver E, 2011 [313]	6 – 30 months	N = 16	2 mm enteric coated mini-tablets	/	Cystic Fibrosis	Phase II randomized, single-blind, parallel-group pilot study. Medication efficacy of different dose regiments assessed by fecal fat excretion.	None of the dose regimens significantly influenced the fecal fat excretion.	Yes. Palatability (ease of swallowing) was scored fair to good by the parents.

formulations can then be pharmaceutically developed with active substance, and their acceptability confirmed in the subsequent efficacy and safety trials with patients suffering from the respective disease applying the same acceptability assessment methods. However, comparison of publicly available acceptability results is difficult as currently the acceptability assessment methods in children are very heterogenous, range from standardised patients' swallowability and palatability observation and assessment by investigators and blinded raters to preference surveys in children, parents, paediatricians and nurses.

9.1. Oral paediatric dosage forms

The traditionally preferred oral forms of administration in paediatric patients, syrup or oral solution, do not meet the requirements for a reliable form of therapy in several relevant aspects according to various scientific findings (e.g. dosing errors by parents in liquid medication administration, unknown drug quantities of rinses out of the mouth, spit-outs etc.), especially not in newborns and infants [290]. Among the innovative paediatric formulations like small oblong or round coated, uncoated or orodispersible tablets, buccal films or granules, mini-tablets have proven to be a safe, child-friendly and reliable alternative oral drug formulation. Several clinical trials have been performed investigating the acceptability, swallowability, and palatability of mini-tablets (see Table 6). This has provided scientifically sound data that is now used as a reference. The results of the clinical trials have led to a rethink in European paediatric drug development and a change in recommendations regarding child-friendly dosage forms. For example, in its final version of the Guideline on pharmaceutical development of medicines for paediatric use [7] of 2013, the European Medicines Agency withdrew its previous recommendation not to administer solid oral dosage forms to children under 6 years of age and instead welcomed the use of alternative dosage forms in this age group. Also, the FDA Draft guidance [291] generally asks for "the ethical acceptability" testing of paediatric dosage forms.

The results from the paediatric formulation studies stimulated clinical and regulatory needs discussion and research interest in the swallowability and palatability of solid dosage forms in other patient populations, such as geriatric patients and patients with certain neurological diseases (e.g. Alzheimer's disease, Parkinson's disease) [292]. The 2020 Reflection Paper on the pharmaceutical development of medicines for use in the older population [293] now also calls for appropriate studies and data on the swallowability and palatability of oral dosage forms in respective adult patient populations.

9.2. Acceptability testing of mini-tablets

Acceptability testing of different mini-tablet sizes, composition and numbers per application was conducted by different research groups in various ways, mostly in the paediatric population (see Table 6). In some cases, the mini-tablets were compared against the former gold standard syrup, in others against other oral dosage forms. In most cases, however, no comparison was made. The assessment criteria varied as well. Each research group developed its own method. Also, the investigated age groups varied, but the focus was on children younger than 7 years of age. The first study examined the acceptance of 3 mm mini-tablets. However, most of the following studies investigated 2 mm tablets. To further studies with 2 and 3 mm tablets, the new size of 2.5 mm was added (Table 6.1).

There were hardly any studies dedicated to acceptability testing of mini-tablets in adults. Only two studies investigated the acceptability of 3 and 3.2 mm tablets (Table 6.2).

What all studies had in common was the fact that mini-tablets were very well accepted by all age groups studied and regardless of the size of the tablets.

Initially, all studies focused on the acceptability of mini-tablets determined by their swallowability. Later-on, palatability was

Table 7.2
Studies in the adult / geriatric population.

Active ingredient	Trade name	Author, year	Investigated age groups	Number of partici-pants	Formulation type	Control	Indication	Study design, research question	Results	Acceptability of mini-tablets investigated?
Acetyl-salicylic acid	/	Hida N, 2023 [225]	Healthy adult volunteers, 20 – 45 years, male	N = 6	3 mm mini-tablets	Acetylsalicylic acid powder	/	Pharmacokinetic study in two periods (Period 1: Powder; Period 2: Mini-tablets) to investigate the pharmacokinetic parameters of salicylic acid and acetylsalicylic acid in the blood.	No significant differences between the pharmaco-kinetic parameters of mini-tablet and powder formulations.	No.
Asciminib	/	Hoch M, 2023 [226]	Healthy adult volunteers	N = 24	40 x 1-mg coated mini-tablets with a diameter of 2 mm	40-mg tablet	/	Randomized, single-dose, open-label, four period crossover study to investigate the relative bioavailability of a single 40-mg dose of asciminib in mini-tablets compared with the reference adult tablet.	Under fasted conditions, asciminib exposure was similar for both formulations. Food decreased the bioavailability of the asciminib administered with mini-tablets.	Yes. The mini-tablets were assessed to be easy to ingest with good palatability (question-naire).
Atenolol	/	Rouge N, 1998 [150]	Healthy adult volunteers	N = 6	3 mm mini-tablets (floating multiple-unit capsule and high-density multiple-unit capsule)	Immediate-release tablet Tenormin® submite	/	Bioavailability and pharmacokinetic study to evaluate the possible advantages of floating and high-density dosage forms and their influence on pharmacokinetic parameters. Atenolol was chosen as a model drug.	The bioavailability of the two gastroretentive preparations with sustained release characteristics was significantly decreased when compared to the immediate-release tablet. The floating mini-tablets seemed to be retained longer in the stomach than the high-density dosage form.	No.
Enalapril	/	Faisal M, 2019 [314]	Healthy adult volunteers	N = 24	2 mm orodispersible mini-tablets (ODMTs)	Market authorized reference tablet (Renitec®)	/	Crossover, two periods, two treatments phase I study. To perform a detailed model informed population PK analysis of prodrug enalapril and its active metabolite enalaprilat in serum and urine.	Enalapril is absorbed 5 min earlier when administered using ODMTs compared to Renitec®. This implies that the ODMTs allow for a faster absorption of the drug. The developed model can be useful in predicting the serum and urine concentrations and pharmacokinetics of the inactive prodrug enalapril and its active metabolite, enalaprilat.	No.
Enalapril	/	Van Hecken A, 2019 [315]	Healthy adult volunteers	N = 24	2 mm orodispersible mini-tablets (ODMTs)	Market authorized reference tablet (Renitec®)	/	Bioavailability open-label, randomized 3-way crossover study. Comparing the bioavailability of enalapril in the ODMT with that of Renitec®.	The method of administration of the ODMT, swallowed or dispersed, did not significantly affect the bioavailability of enalapril.	No.
Enalapril	/	Faisal M, 2019 [316]	Healthy adult volunteers	N = 24	2 mm orodispersible mini-tablets (ODMTs)	Market authorized reference tablet (Renitec®)	/	Phase I study. PK profile of enalapril administered using two treatments of ODMTs (ODMTs with 240 mL water, and ODMTs dispersed in the mouth with 20 mL water) and Renitec® (240 mL water).	Compared with Renitec®, enalapril administered from ODMTs administered with 240 mL water appeared 4 min earlier in serum. No other differences were observed in absorption, elimination, and relative	No.

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Table 7.2 (*continued*)

Active ingredient	Trade name	Author, year	Investigated age groups	Number of participants	Formulation type	Control	Indication	Study design, research question	Results	Acceptability of mini-tablets investigated?
									bioavailability of drug between the three treatment arms.	
Ibuprofen	/	De Brabander C, 2000 [91]	22 – 57 years, healthy volunteers	N = 8	2 mm mini-tablets (filled into hard gelatin capsules), sustained-release formulation	Ibu-slow® 600, sustained-release formulation	/	Randomized cross-over study. Bioavailability of ibuprofen from matrix mini-tablets compared to a commercial matrix formulation.	Relative bioavailability of mini-tablets 116±22.6% compared to Ibu-slow®. Data demonstrate that mini-tablets can be used to formulate sustained-release dosage forms.	No.
Levodopa & carbidopa	/	Goole J, 2008 [239]	Healthy adult volunteers	N = 10	3 mm sustained-release floating mini-tablets, Levo-Form 1 (matrix, uncoated) and 2 (coated). 20 mini-tablets each filled in a capsule.	Prolopa® HBS 125 (levodopa/ benserazide)	/	Randomized open single-dose, three-treatment, three-period cross-over study. Radiolabelling of the formulations to evaluate their gastric residence time using γ-scintigraphy.	It was shown that the three formulations offered almost the same mean gastric residence time.	No.
Levodopa & carbidopa	LC-5; Levodose	Nyholm D, 2012 [317]	Healthy adult volunteers	N = 19	3 mm mini-tablets	Levodopa/ carbidopa, 100/25 mg (LC-100), and dispersible levodopa/ benserazide, 100/ 25 mg (LB-100)	/	Single-dose, open, randomized, 3-way cross-over study. Bioavailability and pharmacokinetics of levodopa, carbidopa, and the metabolite 3-O-MD were determined after intake of 100 mg of levodopa, that is, one tablet of reference formulations and 20 microtablets of the new formulation.	The LC-5 mini-tablets were bioequivalent to LC-100 and LB-100 Tablets.	No.
Levodopa & carbidopa	LC-5; Levodose	Nyholm D, 2013 [318]	Healthy adult volunteers	N = 11	3 mm mini-tablets	Levodopa/ carbidopa/ entacapone (LCE), Stalevo®	/	Randomized, crossover study. Plasma concentrations of levodopa, carbidopa and 3-O-methyldopa were determined after intake of 300 mg levodopa during the day, either as three intakes of 100/ 25/200 mg LCE or as a morning dose of 75/18.25 mg followed by five repeated doses of 45/11.25 mg levodopa/carbidopa mini-tablets.	Fractionation of levodopa with levodopa/carbidopa mini-tablets into small, frequent administrations as compared to standard administrations of LCE decreased the fluctuation index in plasma for both levodopa and carbidopa by nearly half.	No.
Levodopa & carbidopa	Flexilev®	Johansson D, 2017 [319]	>18 years	N = 28	3 mm mini-tablets	/	Parkinson's disease (PD)	Observational study. Collection of clinical data on mini-tablets delivered from a dosing device (MyFID®) and effect of adjusting dosage based on recordings of measurement of PD motor symptoms based on a wearable technology.	Introducing a levodopa mini-tablet dispenser and individualized accelerometry-guided dose adjustments can improve PD symptoms and disease-related quality of health in the short term.	Yes. The treatment adherence to mini-tablets was high.
Levodopa & carbidopa	Flexilev®	Senek M, 2017 [283]	>18 years	N = 19	3 mm mini-tablets	/	Parkinson's disease (PD)	PK study to investigate the PK profiles of levodopa-carbidopa and the motor function	In the PD population, following levodopa/carbidopa mini-tablet administration the bioavailability	No.

(*continued on next page*)

Table 7.2 (*continued*)

Active ingredient	Trade name	Author, year	Investigated age groups	Number of participants	Formulation type	Control	Indication	Study design, research question	Results	Acceptability of mini-tablets investigated?
								following a single-dose mini-tablet administration in Parkinson's disease.	was found to be higher compared with results from a previous study in young, healthy subjects. A large between subject variability in response and duration of effect was observed, highlighting the importance of a continuous and individual assessment of motor function in order to optimize treatment effect.	
Levodopa & carbidopa	Flexilev®	Senek M, 2018 [320]	>18 years	N = 46	3 mm mini-tablets	/	Parkinson's disease (PD)	Population PK analysis to characterize the pharmacokinetics (PK) of levodopa and carbidopa after mini-tablet administration.	The presented models adequately described the PK of levodopa and carbidopa, following mini-tablet administration.	No.
Omecamtiv mecarbil	/	Trivedi A, 2021 [246]	Healthy volunteers, 18 – 55 years	N = 20	2.5 mm mini-tablets: slow-release mini-tablets and fast-release mini-tablets	Matrix modified-release tablet	/	Phase I randomized, 5-period, cross-over study. To determine the bioavailability of the mini-tablets relative to the adult matrix modified-release formulation tablets.	The slow- and fast-release mini-tablets display approximately dose-proportional pharmacokinetics. Relative bioavailability of slow-release mini-tablets was demonstrated to be similar to the adult matrix modified-release formulation.	
Sufentanil	/	Singla N K, 2014 [321]	18 – 80 years	N = 100	3 mm mini-tablets	Placebo	Postoperative analgesia	Randomized, double-blind, placebo-controlled study. Time-weighted summed pain intensity difference to baseline over 12 h after administration of two different doses of sufentanil (20 or 30 μg) or placebo.	The 20 μg dosage strength was not superior to placebo. The 30 μg may be an effective, noninvasive alternative to opioids for the management of moderate-to-severe acute pain.	No.
V565 (Anti-TNFα antibody)	/	Nurbhai S, 2019 [322]	>18 years	N = 15	3 mm coated mini-tablets in capsules	/	Inflammatory bowel disease (IBD)	Assessment of 1. oro-ileal recovery of V565. 2. V565 concentrations in faecal, urine and blood samples. 3. V565 tissue localisation and activity.	Enteric coating of V565 mini-tablets provided protection in the stomach with gradual release in intestinal regions affected by IBD. Immunostaining revealed V565 tissue penetration and association with inflammatory cells, while decreased phosphoproteins after 7d oral dosing was consistent with V565-TNFα engagement and neutralising activity. Overall these results are encouraging for the clinical utility of V565 in the treatment of IBD.	No.
Valproate	Orfiril long	Graf W, 2009 [323]	18 – 67 years	N = 27	2 mm prolonged-release mini-tablets	/	Focal or generalized epilepsy	Single dose, 2 study arms (10 – 17 mg/kg and 18 – 24 mg/kg body weight) pilot study. Valproate serum concentration over a course of 24 h and their correlation with the value measured at 9:00 am.	Therapy with valproate prolonged-release at a dose rate of 24 mg/kg preparation given as a single dosage in the evening will be sufficient for seizure control in most patients.	No.

Table 7.3
Studies in both, the paediatric and adult population.

Active ingredient	Trade name	Author, year	Investigated age groups	Number of participants	Formulation type	Control	Indication	Study design, research question	Results	Acceptability of mini-tablets investigated?
Pancreatin	Kreon and Panzytrat 20 000	Stern M, 1988 [324]	2 – 24 years	N = 17	Mini-tablets (size unknown) in capsules	/	Cystic Fibrosis	Observational study. Collection of clinical data in patients with severe pancreatic Insufficiency under treatment with two different pancreatin products.	No significant differences in clinical outcome parameters between the two products.	No.
Sulfadoxine-pyrimethamine & amodiaquine	/	Dicko A, 2018 [325]	5 – 50 years, male	N = 80	Methylene blue in 2 mm mini-tablets. No information on tablet size of the other active ingredients.	Sulfadoxine-pyrimethamine & amodiaquine + single dose of primaquine, Dihydroartemisinin-piperaquine, Dihydroartemisinin-piperaquine + methylene blue	Falciparum Malaria	Phase II, single-blind, randomised controlled study. Median within-person percentage change in mosquito infectivity during follow-up.	Adding a single dose of primaquine to sulfadoxine-pyrimethamine and amodiaquine or methylene blue to dihydroartemisinin-piperaquine was highly efficacious for preventing P falciparum transmission.	No.
Valproate	Orfiril long	Stefan H, 2005 [326]	12 – 86 years	N = 359	Sustained release mini-tablets	/	Epilepsy	Observational study (prospective, open, uncontrolled) under routine clinical setting. Collection of clinical data after administration of once daily evening dosing of valproate sustained release mini-tablets.	Reduction of mean seizure frequency.	Yes. Good compliance with and acceptance of mini-tablets.

acknowledged as an important element of acceptability and therefore added to the acceptability test methodologies. Palatability is the visible reaction like mimic or gestures on e.g. oral pain, discomfort, mouth feeling, taste sensations, smell, etc. after formulation administration. The EMA guideline [7] highlights that the patients' acceptability is determined by both clinical aspects, the swallowability as well as the palatability, but that also other aspects ultimately play a role in patients' acceptability of a formulation like appearance, complexity of the modification to be conducted by the child or its caregivers prior to administration, the required dose, the required dosing frequency and duration of treatment, the selected administration device, the primary and secondary container closure system, and the actual mode of administration to the child and any related pain or discomfort. This results in the need for a holistic acceptability evaluation of the mini-tablets intended to achieve marketing authorisation. Acceptability was also assessed as expression of preference among a choice of different galenic formulations assessed in surveys or interviews.

In order to standardize the acceptability measurement, our research group invented and validated a meanwhile internationally applied (e.g. in Japan and the United Kingdom) comparative assessment methodology, the Composite Acceptability Endpoint Method [294]. This Composite Acceptability Endpoint is based on validated assessment methods for swallowability and palatability [20–23,295–297] in children of different age groups using different galenic placebo formulations, in line with the EMA criteria [7] for assessing acceptability in children from newborn to 18 years of age. Data from two studies investigating mini-tablets, oblong tablets, orodispersible films, and syrup were analyzed retrospectively with this new method [295,296] and prospectively validated in a dedicated study over all paediatric age groups to establish the validity, expediency, and applicability of the suggested composite acceptability assessment tool. The measurement methods developed for paediatrics can also be adapted to the conditions of other age groups and transferred as a measurement method to the adult population.

9.3. *Mini-tablets with active ingredients*

When evaluating the publications on mini-tablets with active ingredients, it is noticeable that some research groups have published various studies on one active ingredient each. Mostly enalapril, melatonin, and levodopa were investigated. Most of the studies were conducted with adults, or studies for the use of the mini-tablets in adults (Table 7.2 and 7.3). Few mini-tablet studies have been conducted in children with the active ingredient (Table 7.1 and 7.3). It is striking that the focus was on PK/PD and the mode of action of the substances, and everyday use of the mini-tablets. Different publications report about assessments of patient suitability of mini-tablets by investigators and care givers. A systematic investigation of acceptability, however, did not take place in most cases. All reports, however, show good acceptability, both in paediatric and adult patients.

Regardless of whether the acceptability of mini-tablets with or without an active ingredient was investigated, there were a few questionnaire studies that investigated the preference by means of surveys and questionnaires. The participants and/or their parents in the case of paediatric participants, did not have to swallow mini-tablets in this case. They were only asked various questions about their supposed acceptability of mini-tablets. Statements from such questionnaire studies are less reliable than studies in which participants actually take the mini-tablets. However, here, too, the mini-tablets were found to be fundamentally suitable from the toddler age onwards [282,298–301].

10. Conclusion

The present review clearly reveals, that there are good reasons for the present hype comprising the mini-tablet concept. Most technical issues have been solved by scientific research, e.g. by introducing new pharmaceutical excipients for orodispersible mini-tablets or by advanced film-coating materials for controlled drug delivery, so that conventional production equipment may be used for mini-tablet production even at economically reasonable scales.

The advantages of mini-tablets especially regarding drug stability and ease of drug administration to 'special populations' such as children and the geriatric patients advocates the increased use of mini-tablets based on clinical and societal aspects. International organizations like WHO see a further demand in these products.

Although being on the pharmaceutical market for almost 40 years now, there is still a lack in regulatory guidance for these dosage forms. The pharmacopoeias have not defined the 'mini-tablets' and have inappropriately addressed them in the characterization methods (e.g. disintegration, tensile strength, friability), clinical guidelines for conducting acceptability studies and adapting the superior flexible dosing opportunities of mini-tablets are still missing, too. Further, reliable dosing devices ("counters") are being seen at the horizon, but have not been commercially marketed so far. If these hurdles can be overcome in the upcoming years, mini-tablets have the potential to become one of the most often used solid dosage form in the future.

CRediT authorship contribution statement

Valentinë Lura: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization, Investigation. **Ard Lura:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization, Investigation. **Jörg Breitkreutz:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization, Writing – original draft. **Viviane Klingmann:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization, Visualization.

Declaration of competing interest

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpb.2025.114655.

Data availability

No data was used for the research described in the article.

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