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Original Article

MINITABLETS ENABLING DOSING AND DOSE INDIVIDUALIZATION IN ORAL SOLID DOSAGE FORMS: A CASE STUDY WITH ATOMOXETINE

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ABSTRACT

Minitablets represent a promising oral solid dosage form that allows for a wide range of doses within a single formulation. They are particularly suitable for pediatric and geriatric patients. Their small size facilitates administration by improving swallowability, making them an effective alternative for patients who have difficulty swallowing conventional tablets or capsules. This study describes the composition and manufacturing method of minitablets containing atomoxetine hydrochloride as a model drug. The minitablets were prepared using a direct compression method, utilizing the synergistic action of two fillers/diluents with different deformation properties: plastic microcrystalline cellulose and brittle anhydrous dibasic calcium phosphate. The resulting minitablets demonstrated satisfactory mechanical strength and met the required dosage unit uniformity. They also achieved dissolution rates consistent with the relevant monograph. Comparison with commercially available reference products in the form of hard capsules filled with a powder mixture confirmed the potential of minitablets as an effective alternative form of the drug.

KEYWORDS: minitablets, atomoxetine, swallowing difficulties, dose flexibility, calcium phosphate.

1. Introduction

Minitablets are a type of oral solid dosage form (OSDF), defined as tablets with a diameter of up to 3 mm. Their production does not require specialized manufacturing equipment. The main difference compared to the production of standard tablets lies in the use of special, highly precise tablet tooling, such as single- or multi-tip punches and dies [1-4].

Due to their small size, minitablets are a practical option for oral drug administration, especially for patients with swallowing difficulties, including children and the elderly. Their compact form facilitates ingestion, allows dose flexibility, and improves patient acceptability, making them a promising alternative to conventional dosage forms, such as tablets or capsules. It is worth noting that dosing is considerably more precise, and the reliability of drug release is more consistent with minitablets compared to the aforementioned traditional dosage forms [5-8].

Paediatric patients, in particular, represent a highly diverse group. They are typically divided into subgroups that differ significantly in physiological and pharmacokinetic characteristics, swallowing ability, and drug metabolism, necessitating tailored dosage forms and delivery systems [9,10]. Multiple studies have reported the high acceptability and practicality of minitablets in children. For instance, Klingmann et al. demonstrated that even very young children could swallow over 25 minitablets with 5 - 10 mL of syrup. Children aged 2–5 years tolerated up to 100 minitablets without difficulty [11]. Similarly, Mitsui et al. found that infants aged 6–11 months were able to swallow 4 minitablets more easily than fine granules dispersed in water [12]. Minitablets can be administered not only with water but also with beverages or even food, such as porridge, further enhancing their acceptability and ease of use [13].

The benefits of minitablets extend to elderly patients, particularly those suffering from dysphagia or managing polypharmacy. Research has long shown that the physical characteristics of tablets, such as size, shape, and texture, can significantly influence their transit through the pharynx and oesophagus [14-17]. However, it is also important to consider age-related

physiological changes that may affect drug bioavailability in the elderly, including delayed oesophageal transit and reduced fluid availability in the gastrointestinal tract, both of which can impact drug dissolution and absorption [18]. The small size and rapid dispersion of minitablets may help mitigate these challenges, making them a valuable option for improving medication adherence and therapeutic effects in this patient group. Minitablets, like granules or pellets, can be classified as multiple-unit dosage forms (MUDFs), which can enhance bioavailability and reduce the risk of issues such as dose dumping [19-21]. In the context of treatment involving multiple pharmaceuticals, minitablets offer an interesting option for the simultaneous administration of several drug substances. These can be delivered as separate minitablets enclosed within a single capsule (fixed-dose combination, FDC) [5]. An additional advantage of this approach is the mitigation of potential incompatibilities between different drug substances, which helps improve the stability of the final dosage form.

In a study utilizing the Sydney Swallow Questionnaire (SSQ), Liu et al. found that minitablets were among the most well-tolerated solid dosage forms in elderly patients, surpassed only by orodispersible and soluble tablets [22]. Additional studies have confirmed the high acceptability of minitablets among older adults, including those with swallowing difficulties [23].

Perhaps the greatest advantage of minitablets is their high degree of dose flexibility, which enables individualized therapy. By adjusting the number of units administered, a wide dosage range can be prepared from a single formulation. This is particularly important in pediatric pharmacotherapy, where dosing must be tailored to age, body weight, or body surface area. Minitablets are also an effective solution for drugs with a narrow therapeutic index or dose-dependent efficacy, as they provide a reliable and safe means of precise adjustment. In geriatric patients, the ability to rapidly modify doses can help mitigate or prevent adverse effects. Inconvenience related to unit counting can be addressed with dedicated dispensing devices, which offer a practical and accurate alternative to such methods as powder dispensing [24-27].

Of course, minitablets also have their drawbacks. From the user's perspective, such a small dosage form can present difficulties in counting, particularly when large quantities of tablets are required, especially for older patients. Therefore, additional dosing/counting devices may be necessary to facilitate this process. In the production of minitablets, achieving high precision can be challenging. Due to their low weight, even small standard deviations in mass can result in significant variations in the amount of API. This necessitates the development of formulations with excellent technological properties (e.g. flowability), which often requires the use of excipients specifically designed for direct compression. Similarly, with regards to tablet press equipment, dies and punches must exhibit very high precision and accuracy to minimize variability in the mass of the produced tablets [3,28].

The present study aimed to develop and evaluate minitablets containing atomoxetine hydrochloride as a model drug substance. Atomoxetine is a centrally acting sympathomimetic. Although its exact mechanism of action is not fully clarified, it is believed to act as a selective inhibitor of the presynaptic noradrenaline transporter. Atomoxetine is used to treat attention-deficit/hyperactivity disorder (ADHD) in children over 6 years of age and in adults. Treatment typically begins with a low dose, which is gradually increased until a therapeutic effect is achieved. The pharmacokinetics of atomoxetine are linear across the range of doses used and, importantly, are similar in both adults and children. No differences in linearity have been observed between slow and fast metabolizers (approximately 7% of the population are slow metabolizers) [29,30].

After oral administration, atomoxetine has an absolute bioavailability ranging from 63% to as high as 94%. The time to reach maximum plasma concentration is typically 1 to 2 hours. Approximately 98 - 99% of the drug binds to plasma proteins, primarily albumin. Atomoxetine is metabolized mainly by the cytochrome P450 enzyme CYP2D6. The elimination half-life is around 5 hours in extensive metabolizers but can extend up to 22 hours in poor metabolizers. The drug is primarily excreted by the kidneys in the form of its O-glucuronide metabolite. Due to differences in metabolism and treatment needs across patient populations, it is necessary to formulate atomoxetine in a wide range of doses [29-31]. Currently, the drug is available on the market as hard gelatine capsules containing atomoxetine in doses ranging from 10 to 100 mg (i.e., 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, and 100 mg) [32,33]. The wide range of available doses makes the minitablet form an attractive alternative, not only for patients, due to the potential for individualized dosing and easier dose adjustments (especially in paediatric use), but also for manufacturers, who can benefit from using a single formulation and production technology to prepare multiple dosage strengths of the drug product.

2. Materials and methods

Drug substance: atomoxetine (ATX) hydrochloride from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Anhydrous dibasic calcium phosphate (DCPA): PharSQ® Coarse A 60 from Chemische Fabrik Budenheim KG (Budenheim, Germany), Microcrystalline cellulose (MCC): Vivapur® 102 from JRS Pharma (Rosenberg, Germany). Croscarmellose sodium (CCS): Ac-Di-Sol® SD-711 from FMC BioPolymer (Brussels, Belgium). Magnesium stearate (MgSt): Ligamed® MF-2-V from Peter Greven Fett-Chemi (Venlo, The Netherlands). Transparent hard gelatin capsule shells, size “00” (Pharmapol Arzneimittelvertrieb GmbH, Daegeling, Germany). Strattera® 10 mg, 40 mg, and 100 mg hard capsules (Eli Lilly S.A., Madrid, Spain). Konaten 40 mg hard capsules (Glenmark Arzneimittel GmbH, Grobenzell, Germany).

2.1. Preparation and evaluation of a tableting blend

The formulation ingredients were selected to enable the preparation of minitablets by direct compression technique (DC). All ingredients listed in Table 1 (except MgSt), along with ATX in appropriate proportions, were thoroughly mixed in a mortar and then transferred to a Duran-type laboratory glass bottle. MgSt was subsequently added, and the mixture was blended using a rotary motion for 3 minutes.

The tabletting blend with the composition shown in Table 1, the drug substance, as well as both fillers/ diluents, DCPA and MCC, were evaluated for their flow characteristics. Flowability was assessed by measuring

the angle of repose (AoR) in accordance with the European Pharmacopoeia, 11th Edition (Ph. Eur. 11), Chapter 2.9.36 "Powder Flow", using a flowability tester BEP2 (Copley Scientific Ltd, Nottingham, United Kingdom). Three measurements were taken for each sample, and the flow properties were interpreted based on Carr's classification.

Table 1. Qualitative and quantitative composition of the tabletting blend

Ingredient	Amount [% w/w]	Role
Atomoxetine HCl	26.8	Drug substance
DCPA (PharSQ® Coarse A 60)	35.4	Filler/diluent
MCC (Vivapur® 102)	35.4	Filler/diluent
CCS (Ac-Di-Sol® SD-711)	1.2	Disintegrant
MgSt (Ligamed® MF-2-V)	1.2	Lubricant
Total	**100.0**	

2.2. Fabrication of minitablets and assessment of their properties

Minitablets were prepared using the direct compression method with a GTP-1 desktop tablet press (Gamlen Tableting Ltd, London, UK) equipped with flat punches of 3 mm diameter. A quantity of the tabletting blend equivalent to 5 mg of atomoxetine was placed in the die and compressed at a compaction pressure of 0.98 kN. Ph. Eur. 11 does not have a dedicated monograph on minitablets, so tests designed for traditional tablets were adapted to test the minitablets prepared in this research.

2.2.1. Tablet hardness

The tablet hardness (resistance to crushing) test was performed on 10 randomly selected tablets using a MultiTest 50 G2 tablet hardness tester (Sotax AG, Thun, Switzerland), in accordance with Ph. Eur. 11, Chapter 2.9.8 "Resistance to Crushing of Tablets". During the same operation, the device took automatic measurements of the thickness of the examined tablets. In accordance with Ph. Eur. requirements, the results are reported in Table 3 as mean values together with the corresponding minimum and maximum compaction forces obtained during testing.

2.2.2. Friability

The friability of the prepared minitablets was tested using an internally developed procedure based on Method B described in Chapter 2.9.41 "Friability of Granules and Spheroids" of Ph. Eur. 11. 20 randomly selected minitablets were de-dusted and weighed using an analytical balance. They were then placed in a 100 mL glass container (a Duran® laboratory glass bottle), which was tightly closed. The container was positioned horizontally in a WB 22 laboratory shaker (Memmert GmbH & Co. KG, Schwabach, Germany) and the test was conducted for 4 minutes at 300 rpm. After the test, the minitablets were de-dusted, reweighed, and the percentage of mass loss was calculated. The test was performed in triplicate. The acceptance criterion, in accordance with Ph. Eur. 11, Chapter 2.9.7, was set at a maximum mass loss of 1.0%.

2.2.3. Uniformity of mass and uniformity of content

The mass uniformity test was conducted on 20 randomly selected tablets in accordance with Ph. Eur. 11, Chapter 2.9.5 "Uniformity of mass of single-dose preparations", using an MC 1RC210D analytical balance (Sartorius AG, Goettingen, Germany).

The content uniformity of the minitablets was assessed for 10 randomly selected tablets using two approaches, in accordance with Chapter 2.9.40 "Uniformity of dosage units" and Chapter 2.9.6 "Uniformity of content of single-dose preparations" of the Ph. Eur. 11. A single minitablet was placed in water in a 100 mL volumetric flask and stirred with an LD-846 magnetic stirrer (Labinco BV, Breda, the Netherlands) for 10 minutes. The solution was then made up to volume with water. After mixing and filtration through a Millex-GN Nylon syringe filter, 0.2 µm (Merck Millipore, Billerica, MA, USA), the concentration of atomoxetine in the resulting solution was determined spectrophotometrically. A UV-Vis spectrophotometer (AV-650, Jasco Corporation, Tokyo, Japan), equipped with a 10 mm path-length cuvette, was employed for the measurements. The determination was carried out in triplicate at a wavelength of 270 nm.

2.2.4. Disintegration time

Disintegration time was analyzed using an internally developed method. The study was carried out in glass tubes equipped with a 20-mesh sieve (0.84 mm), which were placed in a 250 mL beaker containing 100 mL of distilled water maintained at 37 °C. The whole was placed in a WB 22 shaking water bath (Memmert GmbH & Co. KG, Schwabach, Germany) and operated at 15 rpm. Disintegration time was defined as the time required for the mass of the minitablet to completely pass through the sieve. The test was performed in 6 replicates. It should be noted that there is a lack of specific guidelines for minitablets, and this study was not intended to serve as a basis for product approval. Therefore, the results obtained should be considered only as predictive for dissolution testing.

2.2.5. Dissolution study

The dissolution study was conducted in accordance with the adopted monograph Atomoxetine Capsules (USP-NF 25). The test was performed using a Type II SR8 Plus Dissolution Test Station (Hanson Research, Chatsworth, CA, USA) (Apparatus II in accordance with Chapter 2.9.3, Ph. Eur. 11), with 900 mL of 0.1 M HCl as the dissolution medium, stirred at 50 rpm and maintained at 37 °C. The test lasted 40 minutes, with on-line spectrophotometric measurements carried out using an Agilent 8453 spectrophotometer equipped with flow cells Hellma Analytics made of quartz SUPRASIL® (Agilent Technologies, Shanghai, China) at 270 nm. Measurements were taken every 2 minutes during the first 30 minutes and additionally at 35 and 40 minutes.

The studies evaluated free minitablets (FMT) in doses corresponding to 10 mg of atomoxetine (2 minitablets) and 100 mg (20 minitablets). Equivalent doses of minitablets were also placed in size "00" hard gelatin capsules (CMT), with sinkers used to prevent capsule flotation. For comparison, the original preparation, Strattera® hard capsules, was tested at 10 mg and 100 mg. In an additional test, eight free minitablets corresponding to 40 mg of atomoxetine were examined, along with the same dose placed in size "00" hard gelatin capsules. Two marketed preparations, Strattera® and the generic Konaten hard capsules, were included as references. The

acceptance criteria defined in the Atomoxetine Capsules (USP–NF 25) monograph were used to evaluate the minitablets quality. Furthermore, compliance with the requirements of Ph. Eur. 11, Chapter 2.9.3, applicable to oral immediate-release dosage forms, was also assessed.

3. Results

The tabletting blend, with the composition listed in Table 1, was tested for its flow properties along with the drug substance and the two fillers/diluents present at their highest concentrations in the formulation. Flowability was assessed by measuring the angle of repose (AoR), as described in section 2.1. of the Materials and Methods. The results presented in Table 2 show the mean AoR in degrees, along with the standard deviation (SD). The evaluation of the powder flow results was followed as described in Ph. Eur. 11, Chapter 2.9.36 "Powder Flow".

Table 2. Evaluation of powder flowability by means of the angle of repose (AoR)

Ingredient	Mean AoR ± SD [deg.]	Flow property
Atomoxetine HCl	39.72 ± 1.30	Fair (aid not needed)
DCPA (PharSQ® Coarse A 60)	26.55± 0.38	Excellent
MCC (Vivapur® 102)	31.61 ± 1.14	Good
Tabletting blend	32.84 ± 1.05	Good

The tabletting blend was compressed into minitablets with a diameter of 3 mm and analyzed for their physical and chemical properties as described in Section 2.2 of the Materials and Methods. The results obtained are compiled in Table 3.

Table 3. Summary of selected physical and chemical properties of the minitablets

Property	Average	SD
Tablet weight [mg]	21.38	0.50
Tablet thickness [mm]	2.12	0.03
Tablet hardness [N]	16.01 Min 14.0 Max 17.3	0.98
Friability [%]	0.47	0.24
Disintegration time [s]	72.74	4.53
Drug content [mg]	5.40	0.18

3.1. Uniformity of mass and uniformity of content

According to Ph. Eur. 11, Chapter 2.9.5, for uncoated tablets weighing less than 80 mg, no more than two individual masses may deviate from the average mass by more than 10%, and none may deviate by more than twice that value. In this study, the minitablets showed an average relative standard deviation of about 2.02%, with no individual tablet exceeding 3.79%. Therefore, they complied with the defined compendial requirements.

To demonstrate the uniformity of content of the minitablets fabricated in this study, Test A, as described in Chapter 2.9.6 of Ph. Eur. 11, was adopted. According to the test requirements, each individual content should fall within the range of 85–115% of the average content. The determined range was 94.8–105.7%, indicating that the examined minitablets met this requirement.

Additionally, consistency of dosage units was demonstrated using the content uniformity method, as required by Ph. Eur. 11, Chapter 2.9.40, for uncoated tablets containing less than 25 mg of a drug substance. The maximum allowed acceptance value (AV) was set at L1 = 15.0. In the case of the prepared minitablets, the AV was calculated to be 14.5, demonstrating compliance with compendial requirements.

3.2. Dissolution testing

The dissolution behaviour of the minitablets developed in this study was examined as described in Section 2.2.5 of the Materials and Methods. The dissolution conditions were adopted from the performance test in the USP–NF 2025 monograph for Atomoxetine Capsules, which specifies that not less than 85% of the labeled amount of the drug substance should dissolve within 30 minutes (with a Q value of 80%). Both forms of the minitablets, i.e. FMT (minitablets immersed directly in the dissolution medium) and CMT (minitablets placed in hard gelatin capsules and tested as such), were evaluated. The study compared the extreme strengths, i.e. 10 mg and 100 mg, with the corresponding doses of the reference drug product, Strattera® hard capsules (Fig. 1 and 3). For the intermediate strength of 40 mg, the results were compared with two commercial products, i.e. Strattera® hard capsules and Konaten hard capsules (Fig. 2). The time needed for 85% of the labeled amount of atomoxetine to dissolve from the examined preparations is summarized in Table 4. Both evaluated minitablet forms, i.e., FMT (minitablets immersed directly in the dissolution medium) and CMT (minitablets filled into hard gelatin capsules), complied with the requirements of USP–NF 25 and Ph. Eur. 11 at the Q1 acceptance level.

Table 4. Time to achieve 85% dissolution of atomoxetine from tested preparations

Tested preparation	Calculated time to release 85% of the dose [measurement time range]	Compendial requirement
Strattera® 10 mg hard capsules	9 min [8-10 min]	30 min
ATX 10 mg FMT	7.5 min [6-8 min]	
ATX 10 mg CMT	13 min [12-14 min]	
Strattera® 40 mg hard capsules	9.5 min [8-10 min]	
ATX 40 mg FMT	13 min [12-14 min]	
ATX 40 mg CMT	17.5 min [16-18 min]	
Konaten 40 mg hard capsules	> 30 min	
Strattera® 100 mg hard capsules	10.5 min [10-12 min]	
ATX 100 mg FMT	13.5 min [12-14 min]	
ATX 100 mg CMT	23 min [22-24 min]	

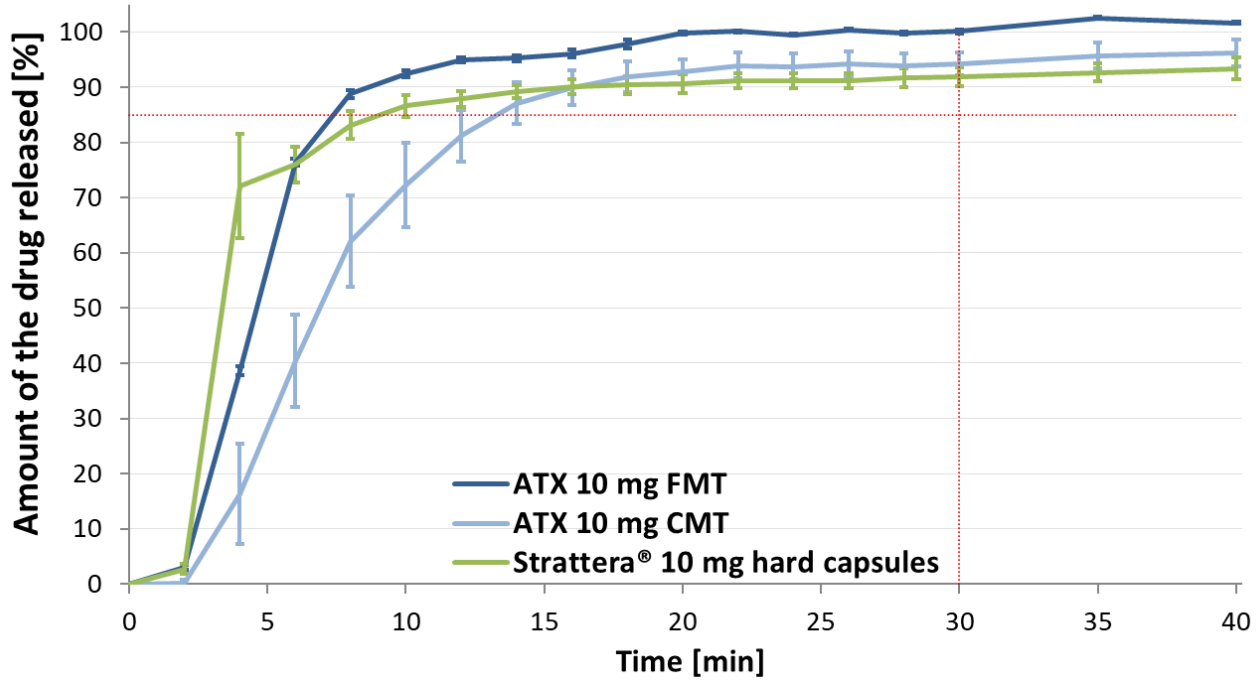

Fig. 1. Comparison of the dissolution profiles of ATX free minitablets (FMT) and encapsulated minitablets (CMT) at a 10 mg strength with the corresponding dose of the reference product, Strattera® hard capsules (mean of *n* = 6; SD indicated by error bars).

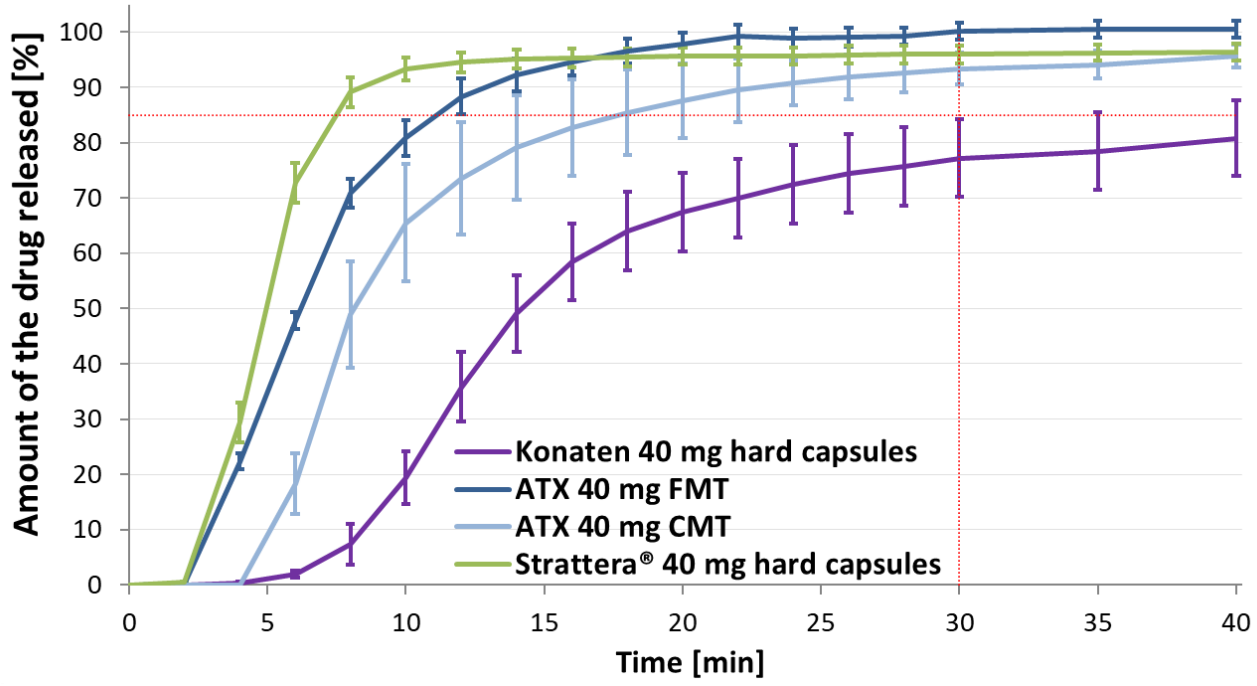

Fig. 2. Comparison of the dissolution profiles of ATX free minitablets (FMT) and encapsulated minitablets (CMT) at a 40 mg strength with the corresponding doses of the reference products, Strattera® hard capsules and Konaten hard capsules (mean of *n* = 6; SD indicated by error bars).

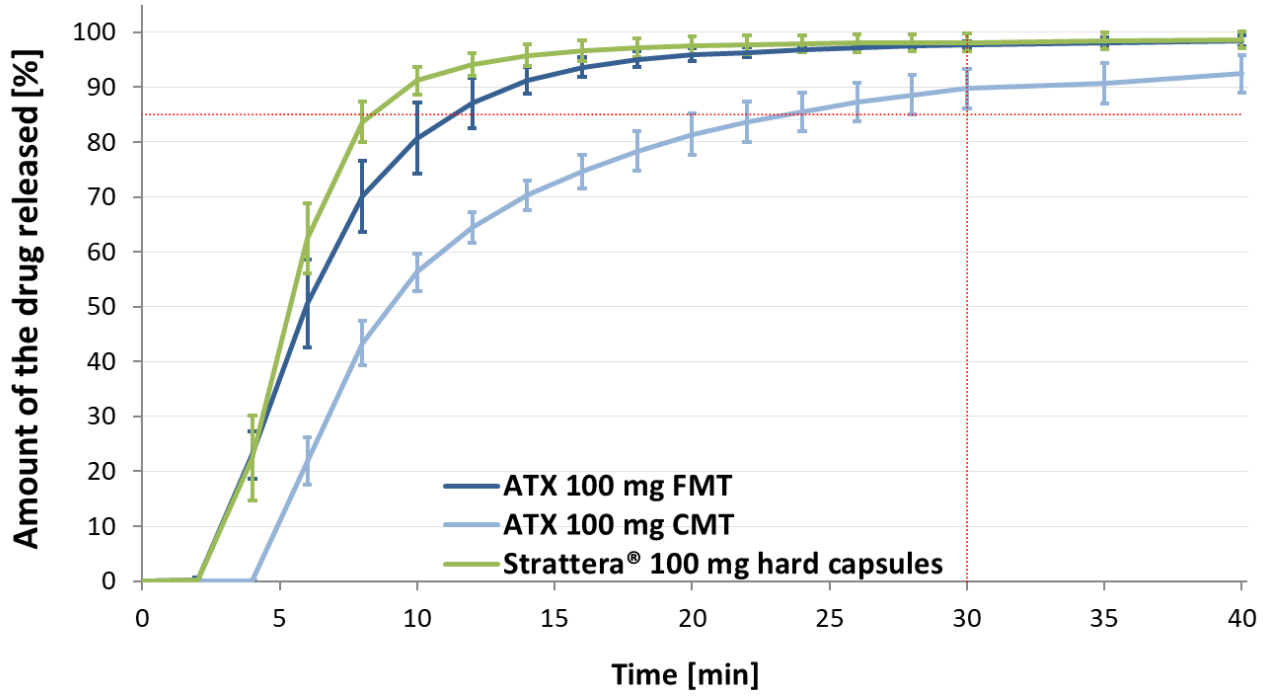

Fig. 3. Comparison of the dissolution profiles of ATX free minitablets (FMT) and encapsulated minitablets (CMT) at a 100 mg strength with the corresponding dose of the reference product, Strattera® hard capsules (mean of *n* = 6; SD indicated by error bars).

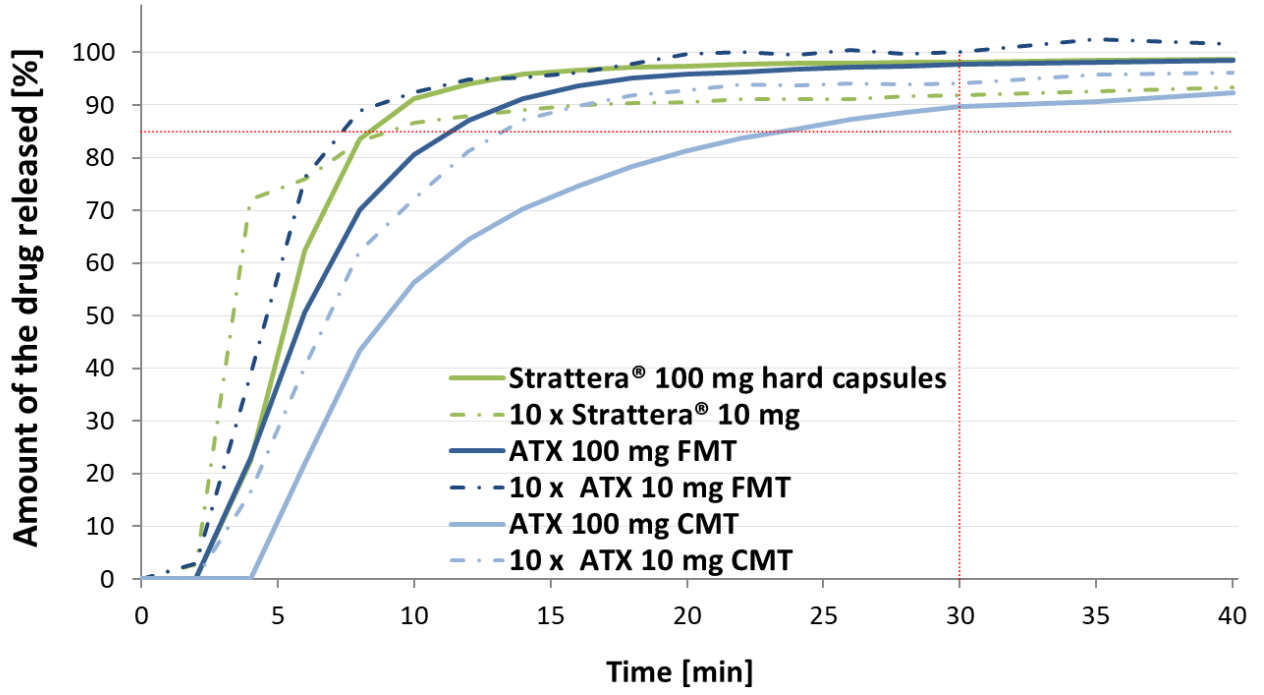

Fig. 4. Comparison of experimental dissolution profiles for Strattera® 100 mg hard capsules, ATX free minitablets (FMT), and encapsulated minitablets (CMT) at a 100 mg strength with profiles predicted by simple dose multiplication from 10 mg to 100 mg.

4. Discussion

Atomoxetine is a centrally acting sympathomimetic that exhibits substantial interindividual variability in its elimination half-life, ranging from approximately 4 to over 20 hours. This pharmacokinetic variability necessitates individualized dose adjustment within a broad therapeutic range. Consequently, the original product (Strattera® hard capsules) is marketed in multiple strengths: 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, and 100 mg [30-36].

The need for a large number of drug doses, especially over a wide dosage range, presents a significant technological challenge. For drugs like atomoxetine, using a proportional powder composition for all strengths can result in excessively large dosage forms at higher doses. This may compromise patient comfort during ingestion and potentially lead to discontinuation of therapy. Commercially available products are typically hard gelatin capsules filled with non-proportional powder blends,

requiring a separate formulation for each strength. This approach adds complexity to the manufacturing process [40]. In such cases, selecting minitablets as the dosage form offers a highly beneficial alternative. Their modular nature enables flexible dose adjustments across the broad therapeutic range required for both paediatric and adult patients, supporting individualized pharmacotherapy. Additionally, the small size of minitablets facilitates swallowing, which is especially advantageous for patients suffering from dysphagia, potentially improving compliance with pharmacotherapy and overall treatment [19,37-39].

In this study, minitablets containing 5 mg of atomoxetine were developed to allow flexible dosing (see Table 1). Patients can adjust their dose to match any of the commercially available strengths from 10 mg to 100 mg, with the exception of the 18 mg formulation. Such a dosing approach may offer some practical advantages. Minitablets can be administered directly from a suitable dispensing device or supplied in hard gelatin capsules containing the appropriate number of units. In cases where dose adjustment is required, patients would not need to purchase a new drug product but could instead modify the dose by adjusting the number of minitablets taken, either directly from dispensers or after removing them from capsules. Similar dosing strategies for other drugs have been reported elsewhere in scientific literature [39-41].

The use of minitablets for atomoxetine formulation can also offer significant advantages from a manufacturing perspective. The minitablets developed in this study enable dose-proportional preparations, where dose adjustment is achieved simply by varying the number of units placed in the capsule shells. This approach can significantly simplify the production process.

The minitablets fabricated in this study had a relatively straightforward composition. Apart from the drug substance, they contained two fillers/diluents, a disintegrant, and a lubricant (see Table 1). The two fillers/diluents, i.e. MCC and DCPA, which made up over 70% w/w of the minitablet mass, were directly compressible grades. This enabled the application of the DC method and resulted in tablets with good mechanical properties and performance (see Table 3). During compression, the ductile MCC and brittle DCPA exhibited distinct deformation mechanisms, producing a synergistic effect, a phenomenon previously reported in the literature [41,42]. Among various directly compressible DCPAs, the dense type with round particles and excellent flow properties was selected for this study [46-48]. This choice ensured the blend maintained the flowability necessary for efficient DC process (see Table 2) [46,47]. As a result, the minitablets achieved the required uniformity of mass and content, despite their relatively low weights and strengths (see Section 3.2 of the Materials and Methods).

Another aspect examined in the present study was the dissolution behaviour of the developed minitablets under compendial conditions. Dissolution studies demonstrated that, using the model drug atomoxetine, it was possible to develop an alternative dosage form to the commercially available powder-filled capsules. Both free minitablets (FMT) and encapsulated minitablets (CMT) exhibited rapid drug dissolution, meeting pharmacopoeial requirements by releasing at least 85% of the labelled amount within 30 minutes in 0.1 M HCl (Q value set at 80%) (see Table 4).

A detailed analysis of the dissolution profiles of the drug substance from the tested formulations revealed interesting findings (see Figs. 1–3). The reference product, Strattera, was presented as hard gelatine capsules with SLS filled with a powder composed of atomoxetine HCl and excipients such as pregelatinized starch and dimethicone [49]. The dissolution profiles showed a short 2–4-minute lag phase, corresponding to the partial dissolution of the capsule shell, and subsequent release of its content. Following this, the drug substance dissolved quickly due to high exposure to the dissolution medium and is probably accelerated by the SLS present in the capsule shell. The second reference product also a hard gelatine capsule with SLS formulation containing a powder blend of atomoxetine HCl, pregelatinized starch, dimethicone, and an additional excipient, colloidal silica [50], exhibited a significantly slower dissolution rate of the drug substance (see Fig. 2). These observations highlight substantial variability in dissolution characteristics among commercially available atomoxetine hydrochloride formulations. Compared to the reference drug product, Strattera, the dissolution rate of the free minitablets (FMT) was slightly slower, as they first needed to fully disintegrate before releasing the entire drug substance. A further decrease in dissolution rate was observed when the minitablets were enclosed in capsules (CMT). It should be mentioned that, in the formulation developed in this study, standard hard gelatin capsules that did not contain SLS were employed. This effect was likely due to the dissolution characteristics of the gelatin capsule shells, which initially softened, swelled, and could partially cover the minitablets. This hindered the penetration of the dissolution medium, making it more difficult to wet the minitablets and consequently slowing the release and dissolution of atomoxetine. Similar behavior of gelatin capsules has been reported previously [48]. Nevertheless, even in this case, the amount of drug released met pharmacopoeial requirements, with more than 85% dissolving within 30 minutes. This observation is crucial, as under physiological conditions, absorption of atomoxetine occurs predominantly in the small intestine following its gastric dissolution. However, interindividual variability (e.g. age, sex, comorbidities) and prandial state can significantly influence gastric emptying half-life [31,51-53]. Given these physiological variations and the interindividual variability in atomoxetine half-life, the minor differences observed in dissolution times among formulations are unlikely to result in clinically meaningful differences in therapeutic efficacy.

In the final stage of work on Strattera and minitablets (both FMT and CMT), a mathematical simulation was carried out to evaluate whether there is a correlation between the experimental dissolution rate and those predicted by simple dose multiplication from 10 mg to 100 mg. The simulated dissolution profiles (see Fig. 4) exhibited slightly faster dissolution dynamics compared to the experimental results at the 100 mg dose. This was likely influenced by the larger mass / volume of powders / minitablets at higher doses. Exceeding sink conditions at higher strengths does not appear to be an issue, as the solubility of atomoxetine hydrochloride is approximately 18–20 mg/mL in 0.1 M HCl (based on unpublished in-house research). A measurable difference was observed in the

case of minitablets closed in gelatin capsules, highlighting the critical role of the capsule shell. Nevertheless, even in this case, as noted above, the atomoxetine formulations developed in this study successfully released the required amount of drug substance.

5. Conclusions

The presented research provides a method for preparing minitablets containing atomoxetine hydrochloride, as an alternative oral solid dosage form (OSDF) to commercially available hard capsules filled with a powder mixture. The formulation of the minitablets was based on two fillers/diluents with differing deformation behaviors during compression, namely anhydrous dibasic calcium phosphate and microcrystalline cellulose, enabling application of a direct compression (DC) method.

The resulting minitablets demonstrated the desired mechanical strength as well as satisfactory mass and dose uniformity, despite their low weight and content of the active pharmaceutical ingredient. The drug dissolution rates met the requirements specified in the relevant pharmacopoeial monograph. However, the tests revealed a significant influence of the capsule shells on the dissolution rate of atomoxetine.

The study demonstrated that minitablets may offer a favorable alternative to existing solid dosage forms of atomoxetine, particularly in therapies requiring gradual dose adjustment or for patients with special needs, such as children, the elderly, or patients with swallowing difficulties (dysphagia).

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References

1. Goh, H.P.; Sia Heng, P.W/; Liew, C.V. The Effects of Feed Frame Parameters and Turret Speed on Mini-Tablet Compression. *J. Pharm. Sci.* **2019**, *108(3*), 1161-1171. DOI: 10.1016/j.xphs.2018.09.005
2. De Souter, L.; Nitert, B.J.; De Beer, T. The effect of material properties and process parameters on die filling using double-tip tooling: A PLS-model-based analysis. *Int. J. Pharm.* **2025**, *671*, Art. No: 125229. DOI: 10.1016/j.ijpharm.2025.125229
3. Lura, A.; Breitkreutz, J. Manufacturing of mini-tablets. Focus and impact of the tooling systems. *J. Drug Deliv. Sci. Technol.* **2022**, *72*, Art. No: 103357. DOI: 10.1016/j.jddst.2022.103357
4. Page, S.; Rode, T.; Breitkreutz, J.; Wagner-Hattler, L. Minitablets current use and future opportunities – An APV course on manufacturing, packaging, characterization and use of minitablets. *Eur. J. Pharm. Biopharm.* **2024**, *199*, Art. No: 114294. DOI: 10.1016/j.ejpb.2024.114294
5. Meruva, S.; Singaraju, A.B.; Vinjamuri, B.P.; Ternik, R.; Stagner, W.C. Current State of Minitablet Product Design: A Review. *J. Pharm. Sci.* **2024**, *v113(5)*, 1123-1154. DOI: 10.1016/j.xphs.2024.02.016
6. Mitra, B.; Thool, P.; Meruva, S.; Aycinena, J.A.; Li, J.; Patel, J.; Patel, K.; Agarwal, A.; Karki, S.; Bowen, W. Decoding the small size challenges of mini-tablets for enhanced dose flexibility and micro-dosing. *Int. J. Pharm.* **2020**, *574*, Art. No: 118905. DOI: 10.1016/j.ijpharm.2019.118905
7. Klingmann, V.; Langenickel, T.H.; Meissner.; Meissner T.; Mayatepek E.; Moeltner A.; Breitkreutz J.; Bosse H.M. Acceptability of Multiple Uncoated Minitablets in Infants and Toddlers: A Randomized Controlled Trial. *J. Pediatr.* **2018**, *201*, 202-207.
8. Klingmann, V.; Hinder, M.; Langenickel, T.H.; Chen, F.; Khder, Y.; Breitkreutz, J.; Bosse, H.M. Acceptability of multiple coated mini-tablets in comparison to syrup in infants and toddlers: a randomised controlled study. *Arch. Dis. Child.* **2023**, *108(9)*, 730-735. DOI: 10.1136/archdischild-2022-325264
9. Lopez, F.L.; Ernest, T.B.; Tuleu, C.; Gul, M.O. Formulation approaches to pediatric oral drug delivery: benefits and limitations of current platforms. *Expert Opin. Drug Deliv.* **2015**, *12(11)*, 1727-1740. DOI: 10.1517/17425247.2015.1060218
10. Al-Japairai, K.; Hamed Almurisi, S.; Almonem Doolaanea, A.; Mahmood, S.; Alheibshy, F.; Alobaida, A.; Abdul-Halim, N.; Chatterjee, B. A review on taste masked multiparticulate dosage forms for paediatric. *Int. J. Pharm.* **2023**, *632*, Art. No: 122571. DOI: 10.1016/j.ijpharm.2022.122571
11. Klingmann, V.; Linderskamp, H.; Meissner T.; Mayatepek, E.; Moeltner, A.; Breitkreutz, J.; Bosse, H.M. Acceptability of Multiple Uncoated Minitablets in Infants and Toddlers: A Randomized Controlled Trial. *J. Pediatr.* **2018**, *201*, 202-207.e1. DOI: 10.1016/j.jpeds.2018.05.031
12. Mitsui, N.; Hida, N.; Kamiya, T.; Yamazaki, T.; Miyazaki, K.; Saito, K.; Saito, J.; Yamatani, A.; Ishikawa, Y.; Nakamura, H.; Nakamura, A.; Harada, T. Swallowability of Minitablets among Children Aged 6-23 Months: An Exploratory, Randomized Crossover Study. *Pharmaceutics* **2022**, *14(1)*, Art. No: 198. DOI: 10.3390/pharmaceutics14010198
13. Kluk, A.; Sznitowska, M.; Brandt, A.; Sznurkowska K.; Plata-Nazar K.; Mysliwiec M.; Kaminska B.; Kotlowska H. Can preschool-aged children swallow several minitablets at a time? Results from a clinical pilot study. *Int. J. Pharm.* **2015**, *485(1-2)*, 1-6. DOI: 10.1016/j.ijpharm.2015.02.068
14. Channer, K.S.; Virjee, J.P. The effect of formulation on oesophageal transit. *J. Pharm. Pharmacol.* **1985**, *37(2)*, 126-129. DOI: 10.1111/j.2042-7158.1985.tb05021.x
15. Evans, K.T.; Roberts, G.M. The ability of patients to swallow capsules. *J. Clin. Hosp. Pharm.* **1981**, *6(3)*, 207-208. DOI: 10.1111/j.1365-2710.1981.tb00994.x

16. Hey, H.; Jørgensen, F.; Sørensen, K.; Hasselbalch, H.; Wamberg, T. Oesophageal transit of six commonly used tablets and capsules. *Br. Med. J. (Clin. Res. Ed.)* **1982**, *285(6356),* 1717-1719. DOI: 10.1136/bmj.285.6356.1717

17. Overgaard, A.B.; Højsted, J.; Hansen, R.; Møller-Sonnergaard, J.; Christrup, L.L. Patients' evaluation of shape, size and colour of solid dosage forms. *Pharm. World Sci.* **2001**, *23(5),* 185-188. DOI: 10.1023/a:1012050931018

18. Khan, M.S.; Roberts, M.S. Challenges and innovations of drug delivery in older age. *Adv. Drug Deliv. Rev.* **2018**, *135*, 3-38. DOI: 10.1016/j.addr.2018.09.003

19. Aleksovski, A.; Dreu, R.; Gašperlin, M.; Planinšek, O. Mini-tablets: a contemporary system for oral drug delivery in targeted patient groups. *Expert Opin. Drug Deliv.* **2015**, *12(1),* 65-84. DOI: 10.1517/17425247.2014.951633.

20. Lura, V.; Lura, A.; Breitkreutz, J.; Klingmann, V. The revival of the mini-tablets: Recent advancements, classifications and expectations for the future. *Eur. J. Pharm. Biopharm.* **2025**, *210*, Art. No: 114655. DOI: 10.1016/j.ejpb.2025.114655

21. Giatti, F.; Malavolti, M.; Ferrini, F.; Funaro, C. Taste Masking Minitablets Using a Drum Coater. *Tablets & Capsules Magazine*. **2020**, 18(3). Available at https://www.tabletscapsules.com/3641-Technical-Articles/585212-Taste-masking-minitablets-using-a-drum-coater/ (accessed on June 23, 2025)

22. Liu, F.; Ghaffur, A.; Bains, J.; Hamdy, S. Acceptability of oral solid medicines in older adults with and without dysphagia: A nested pilot validation questionnaire based observational study. *Int. J. Pharm.* **2016**, *512(2),* 374-381. DOI: 10.1016/j.ijpharm.2016.03.007

23. Walsh, J.; Ranmal, S.R.; Ernest, T.B.; Liu F. Patient acceptability, safety and access: A balancing act for selecting age-appropriate oral dosage forms for paediatric and geriatric populations. *Int. J. Pharm.* **2018**, *536(2),* 547-562. DOI: 10.1016/j.ijpharm.2017F.07.01

24. Gorkem Buyukgoz, G.; Kossor, C.G.; Ji, S.; Guvendiren, M.; Davé, R.N. Dose Titration of Solid Dosage Forms via FDM 3D-Printed Mini-Tablets. *Pharmaceutics* **2022**, *14(11),* Art. No: 2305. DOI: 10.3390/pharmaceutics14112305

25. Hejduk, A.; Lulek, J. Dispensing of minitablets - Has the problem been resolved? *Int. J. Pharm.* **2022**, 619, Art. No: 121666. DOI: 10.1016/j.ijpharm.2022.121666

26. Van Riet-Nales, D.A.; Kozarewicz, P.; Aylward, B.; de Vries, R.; Egberts, T.C.; Rademaker, CM.; Schobben, A.F. Paediatric Drug Development and Formulation Design-a European Perspective. *AAPS PharmSciTech.* **2017**, *18(2),* 241-249. DOI: 10.1208/s12249-016-0558-3

27. Bredenberg, S.; Nyholm, D.; Aquilonius, S.M.; Nyström, C. An automatic dose dispenser for microtablets--a new concept for individual dosage of drugs in tablet form. *Int. J. Pharm.* **2003**, *261(1-2),* 137-146. DOI: 10.1016/s0378-5173(03)00294-1

28. Minitablets: Manufacturing, Characterization Methods, and Future Opportunities | American Pharmaceutical Review - *The Review of American Pharmaceutical Business & Technology n.d. Available online:* https://www.americanpharmaceuticalreview.com/Featured-Articles/190921-Minitablets-Manufacturing-Characterization-Methods-and-Future-Opportunities/ (accessed on March 20, 2026)

29. Mechler, K.; Banaschewski, T.; Hohmann, S.; Häge, A. Evidence-based pharmacological treatment options for ADHD in children and adolescents. *Pharmacol. Ther.* **2022**, *230*, Art. No: 107940. DOI: 10.1016/j.pharmthera.2021.107940

30. Witcher, J.W.; Long, A.; Smith, B.; Sauer, J.M.; Heilgenstein, J.; Wilens, T.; Spencer, T.; Biederman, J. Atomoxetine pharmacokinetics in children and adolescents with attention deficit hyperactivity disorder. *J. Child Adolesc. Psychopharmacol.* **2003**, *13(1*), 53-63. DOI: 10.1089/104454603321666199

31. Sauer, J.M.; Ring, B.J.; Witcher, J.W. Clinical pharmacokinetics of atomoxetine. *Clin. Pharmacokinet.* **2005**, *44(6),* 571-590. DOI: 10.2165/00003088-200544060-00002

32. Yu, G.; Li, G.F.; Markowitz, J.S. Atomoxetine: A Review of Its Pharmacokinetics and Pharmacogenomics Relative to Drug Disposition. *J. Child Adolesc. Psychopharmacol.* **2016**, *26(4),* 314-26. DOI: 10.1089/cap.2015.0137

33. Eli Lilly and Company, Strattera (atomoxetine HCl), 2007. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021411s004s012s013s015s021lbl.pdf (accessed on June 23, 2025)

34. Childress, A.C. A critical appraisal of atomoxetine in the management of ADHD. *Ther. Clin. Risk Manag.* **2015**, *12*, 27-39. DOI: 10.2147/TCRM.S59270

35. Seabright, J. Strattera dosing guide. 2025. Available at https://www.medicalnewstoday.com/articles/drugs-strattera-dosage (accessed on June 23, 2025)

36. Chalon, S.A.; Desager, J.P.; Desante, K.A.; Frye, R.F.; Witcher, J.; Long, A.J.; Sauer, J.M.; Golnez, J.L.; Smith, B.P.; Thomasson, H.R.; Horsmans, Y. Effect of hepatic impairment on the pharmacokinetics of atomoxetine and its metabolites. *Clin. Pharmacol. Ther.* **2003**, *73(3)*, 178-191. DOI: 10.1067/mcp.2003.25

37. Münch, J.; Sessler, I.; Bosse, H.M.; Wargenau, M.; Dreesen, J.D.; Loforese, G.; Webb, N.J.A.; Sivasubramanian, R.; Reidemeister S.; Lustenberger, P.; Klingmann, V. Evaluating the Acceptability, Swallowability, and Palatability of Film-Coated Mini-Tablet Formulation in Young Children: Results from an Open-Label, Single-Dose, Cross-Over Study. *Pharmaceutics* **2023**, *15(6),* Art. No: 1729. DOI: 10.3390/pharmaceutics15061729

38. Spomer, N.; Klingmann, V.; Stoltenberg, I.; Lerch, C.; Meissner, T.; Breitkreutz, J. Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study. *Arch. Dis. Child.* **2012**, *97(3)*, 283-286. DOI: 10.1136/archdischild-2011-300958

39. Mitra, B.; Chang, J.; Wu, S.J.; Wolfe, C.N.; Ternik, R.L.; Gunter, T.Z.; Victor, M.C. Feasibility of mini-tablets as a flexible drug delivery tool. *Int. J. Pharm.* **2017**, *525(1)*, 149-159. DOI: 10.1016/j.ijpharm.2017.04.037

40. Buck, J.; Huwyler, J.; Kühl, P.; Dischinger, A. Pediatric Dispersible Tablets: a Modular Approach for Rapid Prototyping. *Pharm. Res.* **2016**, *33(8)*, 2043-2055. DOI: 10.1007/s11095-016-1946-9.

41. Andersen, B.K. Unique minitablet dispenser meets flexible oral dosing need. *ON Drug Delivery Magazine*. **2020**, *109*, 22–24. Available online: https://ondrugdelivery.com/unique-minitablet-dispenser-meets-flexible-oral-dosing-need/ (accessed on 29 September 2025)

42. Salmon Pharma GmbH. Immediate release dosage forms of Atomoxetine. European Patent EP3069715A1, 21 September **2016**. Available online: https://patents.google.com/patent/EP3069715A1/en (accessed on 29 September 2025)

43. Zakowiecki, D.; Edinger, P.; Papaioannou, M.; Hess, T.; Kubiak, B.; Terlecka, A. Exploiting synergistic effects of brittle and plastic excipients in directly compressible formulations of sitagliptin phosphate and sitagliptin hydrochloride. *Pharm. Dev. Technol*. **2022**, *27(6)*, 702-713. DOI: 10.1080/10837450.2022.2107013.

44. Zakowiecki, D.; Kukuls, K.; Cal, K.; Pelloux, A.; Mohylyuk, V. Investigating the Mechanical Behaviour of Viscoelastic and Brittle Pharmaceutical Excipients during Tabletting: Revealing the Unobvious Potential of Advanced Compaction Simulation. *Pharmaceutics* **2025**, *17(12)*, Art. No: 1606. DOI: 10.3390/pharmaceutics 17121606

45. Zakowiecki, D.; Lachmann, M.; Hess, T. Eye on excipients. *Tablets Capsul*. **2019**, *17*, 39–43. Available online: https://www.researchgate.net/publication/333207856_Eye_on_Excipients_Tablets_Capsules_Magazine (accessed on 29 September 2025)

46. Worku, Z.A.; Kumar, D.; Gomes, J.V.; He, Y.; Glennon, B.; Ramisetty, K.A.; Rasmuson, Å.C.; O'Connell, P.; Gallagher, K.H.; Woods, T.; Shastri, N.R.; Healy, A.M. Modelling and understanding powder flow properties and compactability of selected active pharmaceutical ingredients, excipients and physical mixtures from critical material properties. *Int. J. Pharm.* **2017**, *531(1)*, 191-204. DOI: 10.1016/j.ijpharm.2017.08.063.

47. Lindberg, N.O.; Berdal, A.; Enstad, G.; Seifert, E.; Lundstedt, T. Investigation of flow properties of powders by means of a uniaxial tester, in relation to direct tablet compression. *Drug Dev. Ind. Pharm.* **2002**, *28(1)*, 15-28. DOI: 10.1081/ddc-120001482

48. U.S. Food and Drug Administration. Strattera (atomoxetine) capsules: prescribing information, **2022**. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021411s050lbl.pdf (accessed on 9 October 2025).

49. Neuraxpharm. Konaten. Charakterystyka Produktu Leczniczego (ChPL), **2025**. Available online: https://static.neuraxpharm.com/wp-content/uploads/sites/18/2025/06/04112358/konaten-chpl.pdf (accessed on 9 October 2025).

50. Wu, Y.; Zhao, F.; Paborji, M. Effect of fill weight, capsule shell, and sinker design on the dissolution behavior of capsule formulations of a weak acid drug candidate BMS-309403. *Pharm. Dev. Technol*. **2003**, *8(4)*, 379-83. DOI: 10.1081/pdt-120024691

51. Simpson, D.; Plosker, G.L. Atomoxetine: a review of its use in adults with attention deficit hyperactivity disorder. *Drugs* **2004**, *64(2)*, 205-222. DOI: 10.2165/00003495-200464020-00005

52. Lovecchio, F.; Kashani, J. Isolated atomoxetine (Strattera) ingestions commonly result in toxicity. *J. Emerg. Med*. **2006**, *31(3)*, 267-268. DOI: 10.1016/j.jemermed.2005.12.024

53. Grimm, M.; Koziolek, M.; Kühn, J.P.; Weitschies W. Interindividual and intraindividual variability of fasted state gastric fluid volume and gastric emptying of water. *Eur. J. Pharm. Biopharm*. **2018**, *127*, 309-317. DOI: 10.1016/j.ejpb.2018.03.002