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Development of a New Age-Appropriate, Chewable Tablet of Mebendazole 500 mg for Preventive Chemotherapy of Soil-Transmitted Helminth Infections in Pre-School and School-Age Children

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1. ABSTRACT

The aim of this study was to develop an age-appropriate tablet of mebendazole 500 mg to be used in large donation programs by the World Health Organization (WHO) for preventive chemotherapy of soil-transmitted helminth (STH) infections in pre-school and school-age children living in tropical and subtropical endemic areas. To that end, a new oral tablet formulation was developed that can be either chewed or given to young (≥1 year old) children by spoon after rapid disintegration to a soft mass with the addition of a small amount of water directly on the spoon. Although the tablet was manufactured using conventional fluid bed granulation, screening, blending, and compression processes, one of the main challenges was to combine properties of a chewable, dispersible, and regular (solid) immediate release tablet to meet the predefined requirements. The tablet disintegration time was below 120 s, allowing for administration by the "spoon method". The tablet hardness was higher (160-220 N) than normally applicable for chewable tablets, permitting shipment along a lengthy supply chain in a primary 200-tablet count bottle packaging. In addition, the resulting tablets are stable for 48 months in all climatic zones (I-IV). In this article, several aspects of the development of this unique tablet are described, including formulation, process development, stability, clinical acceptability testing, and regulatory filing.

Abbreviations: STH = soil-transmitted helminth, ODT = Orally dispersible tablets, QTTP = quality target product profile, TAMC = total aerobic microbial count, TYMC = total combined yeast and mold count, NIR = near infrared, CQA = critical quality attribute, PAR = proven acceptable range, SKU = single stock keeping unit, DBP = double-

blind treatment phase, OLP = open-label phase, NDA = new drug application, WHO-PQ = WHO pre-qualification, eCTD = electronic common technical document

Keywords

STH, neglected tropical disease, mebendazole, tablet, pediatric, chewable, rapidly-disintegrating, dispersible

2. INTRODUCTION

Intestinal worm infections or STH infections are the most widespread of the neglected tropical diseases, affecting more than one billion people in low- and middle-income countries, including an estimated 762 million school-age and 310 million pre-school age children, respectively [1]. STH infections are mainly caused by Ascaris lumbricoides, Trichuris trichiura (whipworm), and two hookworm species, Necator americanus and Ancylostoma duodenale. Symptoms of STH infections are non-specific and only become evident in persons with high worm burdens, who suffer from nausea, diarrhea, abdominal pain, and fatigue, which cause malnutrition and increase anemia rates [2,3]. To control STH, WHO recommends an integrated approach of sanitation, hygiene education, and preventive chemotherapy with anthelmintic drugs, either albendazole or mebendazole for high-risk populations in endemic areas. Between 2010 and 2020 an estimated total of 3.3 billion albendazole and mebendazole tablets were manufactured by GlaxoSmithKline and Johnson & Johnson for distribution by WHO in large donation programs. See a recent overview by Montresor et al. for a discussion of the progress made to date, the remaining challenges and WHO targets for 2030 [4,5].

To include pre-school age children in the above-mentioned preventive chemotherapy programs for STH, Johnson & Johnson committed in 2012 to develop a new pediatric formulation of mebendazole [6]. The project team was tasked with developing a single formulation to (i) deliver a single dose of 500 mg, regardless of age and body weight, (ii) design a suitable oral solid formulation for all children from 1 to 16 years of age with suitable palatability, and (iii) replace the currently used oral solid 500 mg tablet (to be swallowed whole or crushed) in the donation program for school-aged children. While the approach of a single pediatric formulation for such a wide age range is highly unusual, it is consistent with current STH treatment guidelines for mebendazole, a locally acting benzimidazole, and is motivated by the need to expand this program to pre-school age children. The request of WHO to develop a solid formulation is driven by the need to keep transport volumes and weight low and to guarantee the simplest possible transport logistics. As individual packaging would increase dosing complexity and slow down dosing rate for the WHO health care providers in the mass treatment setting, the WHO preferred bulk packaging containing 200 units. Additionally, individual packaging would have a negative impact on environmental sustainability (increase packaging waste) and would increase the manufacturing dose unit cost.

Multiple oral solid pediatric formulation platforms were considered, and the development of a chewable dispersible formulation was selected as the most suitable, considering the WHO requirements and the acceptability for the intended age range (1-16 years) [7]. In Table 1, the multiple oral solid formulation platforms considered are listed with some brief rationale why they were not selected for the development of this pediatric medicine.

Table 1: Oral solid dosage forms not selected for development

Dosage form	Reason why not selected
Monolithic solid capsules or tablets to be swallowed intact	Considering the high dose (500 mg), capsule and tablet size will be too big towards swallowability and the intended age range.
Minitablets	Considering the high dose (500 mg), multiple units are needed. This will require a too complex dosing device or individual packaging not warranted by the WHO.
Orally dispersible tablets (ODT)	Considering the high dose (500 mg), total tablet weight will exceed the FDA recommended maximum weight of 500 mg for an ODT formulation [8], compromising patient safety.
Granules or multiparticulates	Such formulation systems require individual packaging's per dose, not warranted by WHO.
Sprinkle capsules filled with granules or multiparticulates	This type of formulation will require a too complex compounding step (mixing content of the capsule with food/ liquid) for the WHO health care provider.

Requirements for this new formulation were captured in a Quality Target Product Profile (QTPP) and are summarized in Table 2. Establishing a QTTP is highly recommended for projects like the one described, particularly when multiple stakeholders are involved [9]. The QTPP is also a suitable tool to capture and document new requirements as they arise during the development cycle and as new regulatory requirements are introduced.

Table 2: QTPP of the new mebendazole chewable tablet 500 mg

Product attribute	QTPP attribute
Dosage form	Chewable dispersible tablet with suitable palatability
Dosage strength	500 mg of mebendazole
Route of administration	Oral
Pediatric population 1 to 16 years	Ability to dose smallest children by disintegrating tablet on a spoon (age range 1-3)[a] Children above 3 years can chew the tablet[a]
Drug release	Immediate release
Purity	Sufficiently low level of impurities/degradation products, complying with the ICH requirements
Polymorph purity	Predominantly polymorph C at release and over shelf-life, conforms with the International Pharmacopoeia (Ph. Int.)
Microbial purity	Sufficiently low level of microbial burden, complying with the ICH requirements
Stability	Minimum 24 months shelf-life in all climatic zones (without special storage requirements)
Container closure system	200-tablet count high-density polyethylene (HDPE) bottle with no child-resistant closure

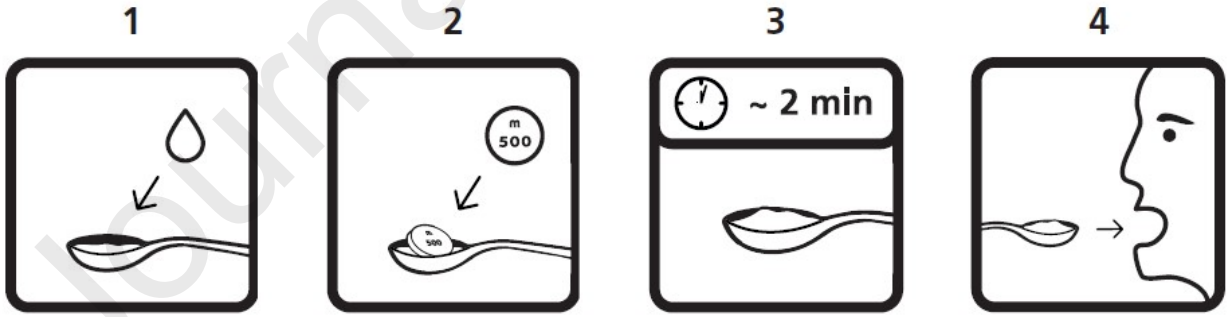
[a] Age range and acceptability of these dosing pathways conform to the recommendations as outlined in article of Mistry et al. [7].

The unique formulation concept behind the new mebendazole chewable tablet 500 mg consists of combining the advantages of a chewable tablet and a dispersible tablet, while developing a chemically and physically stable product suitable for a lengthy distribution chain and storage in tropical climates.

The new chewable dispersible tablet can be administered to children in 2 alternate ways. First, older children can chew the tablet (and rinse the mouth with a small amount of water, if available). Second, the drug can be administered to younger children (e.g., ≤3 years, or older children with difficulties chewing) as follows: a teaspoon (nominally 5 mL capacity) is filled approximately half full with water (corresponding to approx. 2-3 mL, no exact measurement needed). This volume is within the recommended range. The maximum volume to be administered to young children should be equal to the volume of a swallow, which is 4.5 mL for children from 15 months to 3.5 years. This corresponds to a volume of 0.27 mL/kg [7]. A single chewable tablet is then carefully placed into the liquid on the spoon. The chewable tablet immediately absorbs the water and within 2 min rapidly forms a "soft white mass" with a consistency like "baby foods" and without any hard lumps. The entire dose is then administered by mouth using the spoon without the need for further manipulations.

The new chewable tablet has been developed for donation programs, and therefore will be administered by health care providers or trained staff conducting mass administration campaigns. To facilitate the use of the new chewable tablet at mass administration, a "dosing card" (depicted in Figure 1) was developed. Of note, during development, the impact of the order of addition onto the spoon towards soft mass consistency and ease of tablet administration was investigated, i.e., first water on the spoon followed by the addition of the tablet versus first the tablet on the spoon followed by the addition of water. No considerable differences on water uptake/soft mass consistency were observed suggesting that the order of addition has no influence on soft mass consistency after wetting and hence on patient administration. Another advantage of this alternate administration (spoon method) is that it significantly reduces the risk of choking associated with crushed or broken solid and chewable tablets [10].

Figure 1: Instructions for administration by the "spoon method" (dosing card): (**1**) fill a teaspoon approximately half full with drinking water (approximately 2-3 mL), (**2**) place the tablet in the water on the spoon, (**3**) wait up to 2 min for the tablet to absorb the water and become a semi-solid soft mass, and (**4**) dose by mouth.



While the challenges of developing pediatric dosage forms have been widely documented [7, 10-17], this article describes the development and launch of a unique, single-strength, "one-size-fits-all" formulation of mebendazole, suitable for children 1-16 years of age.

The physicochemical properties of the Mebendazole drug substance are presented in Table 3.

Table 3: Physicochemical properties of the drug substance

Physicochemical property	Mebendazole drug substance
Solubility	The drug substance is practically insoluble or insoluble in water and aqueous buffered solutions. Water (pH 6.8): <0.001 solubility in g/100 mL solution 0.1 N HCl (pH 1.2): 0.006 solubility in g/100 mL solution 0.01 N HCl (pH 2.3): 0.001 solubility in g/100 mL solution Citrate-HCl buffer (pH 2.1): 0.001 solubility in g/100 mL solution Citrate-HCl buffer (pH 4.0): <0.001 solubility in g/100 mL solution Citrate-NaOH buffer (pH 5.9): <0.001 solubility in g/100 mL solution Borate-HCl buffer (pH 8.0): <0.001 solubility in g/100 mL solution Borate-KCl-NaOH buffer (pH 10.0): <0.001 solubility in g/100 mL solution 0.1 N NaOH (pH 12.2): 0.016 solubility in g/100 mL solution
Particle size	d_v50 of approximately 5 μm
Crystalline form	Mebendazole exhibits polymorphism with 3 polymorphs identified and referred to as polymorph A, B, and C. Polymorph C is now the generally accepted polymorph.
Flow properties	
Compressibility index	39.14%
Hausner ratio	1.64
Angle of repose	45.56°
Impurities	Highly pure material conform the Ph. Eur.

Table 3: Physicochemical properties of the drug substance

Physicochemical property	Mebendazole drug substance
Stability	Chemically very stable compound

3. MATERIALS AND METHODS

3.1 Materials

Formulation development: Mebendazole microfine grades with similar quality properties were obtained from Shaanxi Hanjiang Pharmaceutical Group Co., Ltd (Hanzhong City, Shaanxi Province, China) and Changzhou Yabang-QH Pharmachem Co., Ltd. (Changzhou City, Jiangsu Province, China).

Povidone (Ashland, Texas City, USA), microcrystalline cellulose (MCC) low moisture grade with nominal particle size of 100 μm (FMC, Cork, Ireland), crospovidone (BASF, Ludwigshafen, Germany), sucralose (Tate & Lyle, McIntosh Alabama, USA), strawberry flavor (Symrise, Holzminden, Germany), magnesium stearate (Peter Greven, Venlo, The Netherlands) and purified water were purchased commercially.

Dissolution experiments and stability data: Methanol (Merck, Maharashtra, India) and acetonitrile (Merck, Maharshtra, India) were of HPLC or HPLC gradient grade. Hydrochloric acid (HCl) (min 35%, Merck, Maharashtra, India), sodium lauryl sulphate (SLS) (Merck, Darmstadt, Germany), ammonium acetate (Fluka, Seetze, Germany), formic acid (98-100%, Merck, Espoo, Finland), and trifluoro acetic acid (Sigma-Aldrich, L' lsle D'Abeau Chesnes, France) were of analytical grade. For the preparation of the dissolution medium for the dissolution experiments, deionized water was used. For the preparation of the mobile phase for HPLC analysis, milli-Q water, or water of HPLC grade was used.

3.2 Granulation and Tableting

The new mebendazole chewable tablet 500 mg was manufactured using fluid bed granulation, screening, blending, and compression processes.

First, the binder solution was prepared in a granulating solutions reactor by dissolving povidone in purified water at room temperature using a dissolution mixing speed of 2860 rpm for 10 min.

Next, fluid bed granulation at appropriate speed was performed followed by drying of the granules using a Huttlin fluid bed granulator/dryer HDG 300 (Huttlin, Schopfheim, Germany). Next, the dried granules were screened using a stainless-steel sieve with a sieve size of 2.5 mm and a Frewitt Coniwitt 200 mill (Huttlin, Schopfheim, Germany) at a rotor speed of 500 rpm. The screened granules were mixed for 2 min at 12 rpm and then blended with the external phase (MCC low moisture grade, crospovidone, sucralose and strawberry flavor) using a Tumbler IBC (Zanchetta, Lucca, Italy) for 10 min at 12 rpm. Next, the blend was lubricated with sieved magnesium stearate in a blender (Tumbler IBC) at 12 rpm for 5 min, followed by compression using a Manesty Unipress Diamond tablet press (Manesty, Liverpool, England) at a compression speed of 78000 tph.

3.3 Physical Testing

Disintegration testing was conducted as described in current USP <701> using an ED2AL disintegration tester (Electrolab, Mumbai, India). Friability was determined according to USP <1216> using an EF-2 friability tester (Electrolab, Mumbai, India). The hardness of the tablets was measured according to USP <1217> using a TBH hardness tester (Erweka, Langen, Germany). Uniformity of dosage units was assessed according to Ph. Eur. 2.9.40/USP <905>.

3.4 Dissolution

Dissolution experiments were performed with n=6 at 37.0 ± 0.5 °C in 900 mL 0.01 N HCl with 1.0% SLS using a paddle USP 2 apparatus (Distek, North Brunswick, NJ, USA). One dosage unit was placed per vessel and the rotation speed was set to 75 rpm. Samples (10 mL volume) were taken after 5, 10, 15, 30, 45, 60 and 90 min without medium replacement. Each sample was filtered through a membrane filter (GHP Acrodisc 0.45 µm membrane 25 mm diameter filter or, alternatively, wwPTFE Acrodisc 0.45 µm membrane 25 mm membrane filter / Whatman Spartan 30/0.45 µm RC (regenerated cellulose) membrane 30 mm diameter filter) discarding at least the first 2 mL of the filtrate. After attaining room temperature, the filtrate sample solution was immediately further diluted from 5 mL to 25 mL with dissolution medium. The dissolution samples were analyzed by means of reversed phase HPLC (Waters or Agilent) (X-Bridge Shield RP-18 column 150 x 4.6 mm, 3.5 µm particle size) at 25 °C using an isocratic elution with a mobile phase of 55:45 20 mM ammonium acetate:acetonitrile. The injection volume was 10 µL and the flow rate was 1.2 mL/min. The run time was 5 min. Mebendazole was detected with UV detection at 250 nm after approximately 3.2 min.

3.5 Stability Testing

3.5.1 Identity, Assay and Chromatographic Purity

The identification of mebendazole and the determination of the concentration of mebendazole and its degradation products was based on gradient reversed phase HPLC with UV detection. Stability samples were prepared as follows. First, 10 mebendazole 500 mg chewable tablets were accurately weighed, grinded and reduced to fine powder. Next, an amount of homogenized powder equivalent to 100 mg mebendazole was accurately weighed and transferred to a 100 mL amber glass volumetric flask. After the addition of 30 mL formic acid, sonication was performed for 20 min. Thereafter, 60 mL of dilution solvent (water and methanol v/v 40/60) was added, followed by a mixing step. After equilibration to room temperature, dilution to volume was done using dilution

solvent and mixing was performed by manual shaking. Thereafter, again, a 10-fold dilution with dilution solvent was performed followed by mixing. Last, the sample solution was filtered through a 0.45 µm GHP membrane filter or a 0.45 µm chemical resistance filter. The stability samples were analyzed on a HPLC instrument (Waters or Agilent) equipped with a Zorbax SB C18, 5 µm particle size, 150 × 4.6 mm column. The column was equilibrated at 40 °C, while the autosampler was maintained at 5 °C. The mobile phase consisted of 0.025% trifluoro acetic acid in water (mobile phase A) and acetonitrile (mobile phase B). The injection volume was 10 µL. Elution was performed at a flow rate of 1.50 mL/min with mobile phase B using a linear gradient of 10% to 30% in 20 min, followed by an increase to 70% mobile phase B in 9 min after which the column was equilibrated at 10% mobile phase B for 5 min (total run time 35 min). Detection was performed with a UV detector at 250 nm.

3.5.2 Microbial Purity

Microbial purity tests (including microbial enumeration tests 'total aerobic microbial count (TAMC) and total combined yeast and mold count (TYMC)) and the specified micro-organisms test 'Escherichia coli' were respectively conducted according to Ph. Eur. 2.6.12/USP <61> and Ph. Eur. 2.6.13/USP <62>.

3.5.3 Polymorphism

Mebendazole polymorphs A, B, and C are known to differ in terms of thermodynamic stability, physicochemical properties (e.g. solubility), and efficacy. Polymorph A is the most thermodynamically stable, and as such the lowest soluble form and is reported to have no/poor anthelmintic activity [18]. Polymorph C is more stable than polymorph B, and both polymorphs have higher solubility than polymorph A and possess appropriate efficacy [18]. Polymorph C is the polymorph of choice for therapeutic use in human (and veterinary) medicine [18-21], as reflected in the reference standards of the current Ph. Eur. monograph and the WHO International Pharmacopoeia monograph [22, 23]. As such, mebendazole polymorph C has been registered extensively worldwide and is the primary polymorph used in marketed and donated mebendazole products.

The polymorphic form purity of mebendazole was determined using a near infrared (NIR) test. Note that initially, an XRD method was developed to determine the polymorphic content. Using the XRD method as a reference, a more efficient NIR method for routine analysis was developed and used for the stability studies. The NIR test identified the predominant polymorphic form of mebendazole present in the new mebendazole chewable tablet 500 mg. The predominant polymorphic form was identified by a visual comparison of the recorded NIR spectra with the NIR reference spectra of the different phase forms and by an evaluation of the specific band position. If the predominant polymorph was identified as polymorph C, quantification of polymorph A was performed using an in-house chemometric calibration model (range 5.0-30.0%). A Bruker MPA FT-NIR spectrometer in combination with OPUS version 7.0 software was used. Sample preparation and sample analysis was as follows: A tablet was gently placed in the center of the radiation beam and covered with an inner black coated holder. The NIR spectrum of both sides of the tablet was recorded in the reflection mode using the integrating sphere with the recording parameters detailed in Table 4.

Table 4: NIR recording parameters

Range (minimal) (cm^{-1})	12000-4000
Resolution (cm^{-1})	8
Number of scans background	64
Number of scans sample	64
Aperture setting	Open
Optic gain background[a]	Ref
Optic gain sample	Ref
Source setting	High Intensity NIR (Tungsten) or equivalent
Detector setting	Room temperature (Rt)-Pbs or equivalent

[a] Background measurements are performed with exactly the same recording parameters.

3.5.4 Water Content

The water content of the new mebendazole chewable tablet 500 mg was determined using a direct volumetric Karl Fischer in accordance with the USP.

4. RESULTS & DISCUSSION

4.1 Formulation Development

The final qualitative and quantitative composition of the new mebendazole chewable tablet 500 mg is shown in Table 5. Micronized drug substance is used, and all excipients are well characterized and widely used in pediatric pharmaceutical preparations.

Table 5: Qualitative and quantitative composition of the new mebendazole chewable tablet 500 mg

Component	Function	Quantity per unit (mg)	Quantity (%)
Mebendazole (micronized)[a]	Active	500.00	50.00
Povidone	Binder	10.00	1.00
Purified water[b]	Processing agent	q.s.	q.s.
Microcrystalline cellulose (MCC), low moisture grade	Filler	412.00	41.20
Crospovidone	Disintegrant	50.00	5.00
Sucralose	Sweetener	8.00	0.80
Strawberry flavor	Flavor	5.00	0.50
Magnesium stearate	Lubricant	15.00	1.50
Total		1000.00	100.00

[a] Polymorph C

[b] Removed during processing

q.s. = quantum satis

First, a formulation concept selection study was performed to determine the feasibility to achieve chewable tablets with an acceptable disintegration time (ability to dose smallest children by

disintegrating tablet on a spoon) and that also conform to the intended critical quality attributes (CQAs) of the chewable tablet.

Due to the poor flow characteristics of the drug substance (demonstrated by typical batch results for the compressibility index, the Hausner ratio, and the angle of repose in Table 6), direct compression was not pursued. Dry granulation using compaction was also excluded because of the high dose of the drug substance required for the drug product, and the sticky and low-density characteristics of the drug substance.

Table 6: Flow properties of a representative drug substance batch

Property	Result
Compressibility index (%)	38.89
Hausner ratio	1.64
Angle of repose (°)	45.56

As a result of the poor flow properties of the drug substance and the required large processing scales, a fluid bed granulation process was implemented. Various concepts were prepared using fluid bed granulation of which the compositions were selected based on experience with other tablet formulations.

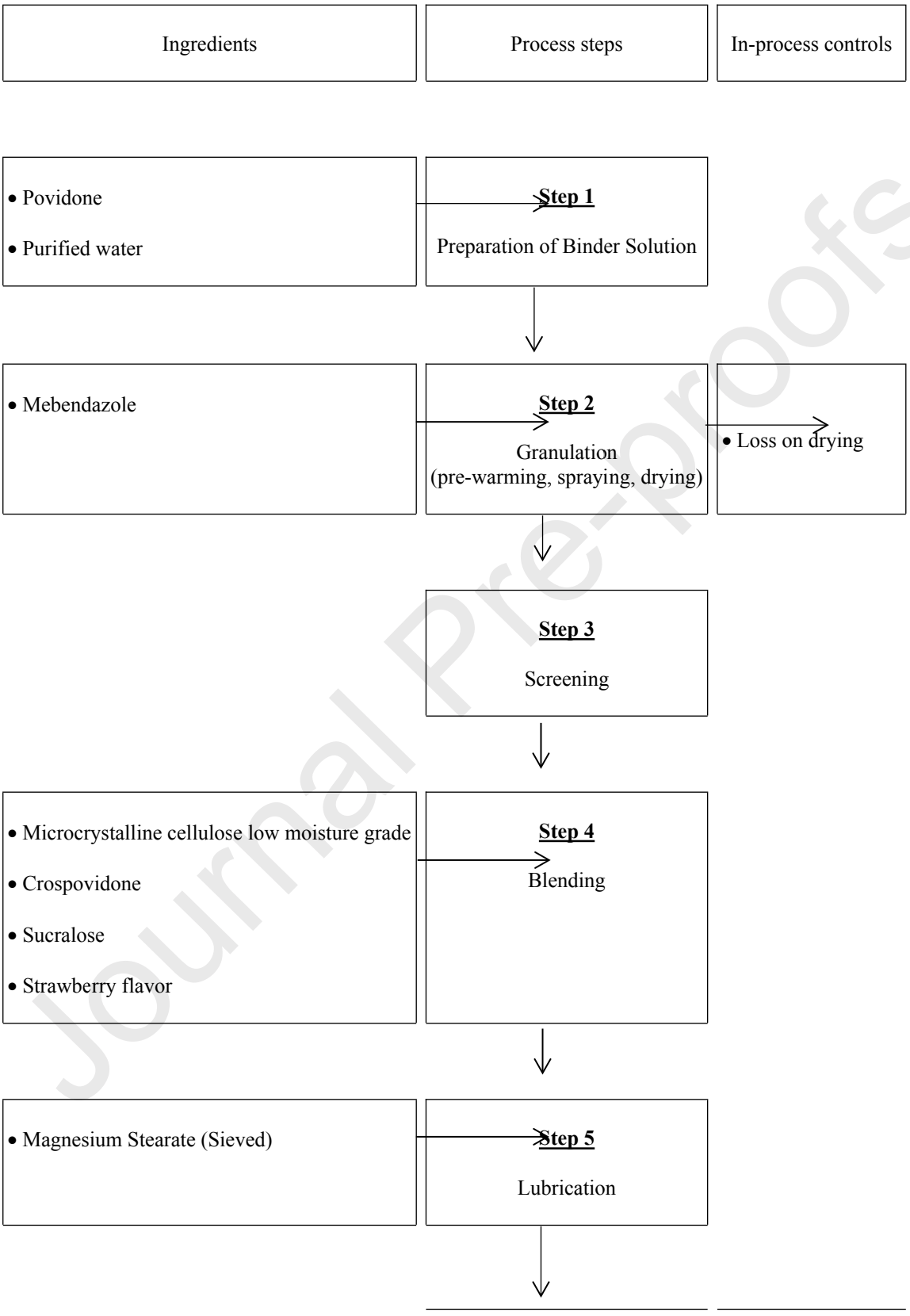
A concept in which the drug substance is initially granulated with an aqueous povidone binder solution was selected for further optimization due to its capacity to form granules with adequate properties for blending, a suitable compression profile (i.e., proper tablet hardness and no defects), and a desirable tablet disintegration time. When additional fillers (e.g., lactose monohydrate, MCC) were used in the fluid bed granulation process to increase the particle size of the granules, the tablet disintegration time became too long. The formulation concept that was selected produced a high drug-loaded granulate consisting of 98% mebendazole and 2% povidone to which MCC (filler) and crospovidone (disintegrant) were added extra-granularly. In addition, the formulation was optimized for taste by the extra-granular addition of sucralose (as a sweetener) and strawberry flavor. Also, the MCC grade was changed to a low moisture grade to minimize the amount of moisture in the final drug product and therefore reduce the risk for potential polymorph conversion during storage, which can be catalyzed by the presence of moisture [24]. The change to the low moisture grade of MCC had no impact on the compression step (tablet hardness and appearance were not affected) and on the CQAs (Table 7) of the drug product. The knowledge obtained about the different polymorphs of mebendazole A, B and C will be discussed elsewhere (article in preparation).

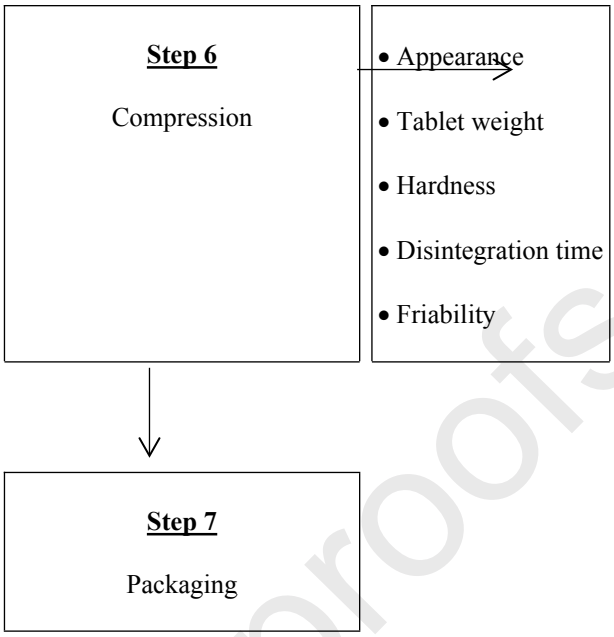
4.2 Process Development

The new mebendazole chewable tablet 500 mg is manufactured using conventional fluid bed granulation, screening, blending, and compression processes. The flowchart of the manufacturing process together with the in-process controls is given in Figure 2.

The manufacturing process starts with dissolving povidone in water (Step 1, preparation of binder solution). Next, the drug substance is granulated using the povidone solution (Step 2, granulation) and the dried granules are screened (Step 3, screening). The screened granules are blended with MCC low moisture grade, crospovidone, sucralose and strawberry flavor (Step 4, blending). Consequently, the blend is lubricated with magnesium stearate in a blender (Step 5, lubrication), after which the lubricated blend is compressed into tablets (Step 6, compression).

Figure 2: Flowchart of the new mebendazole chewable tablet 500 mg





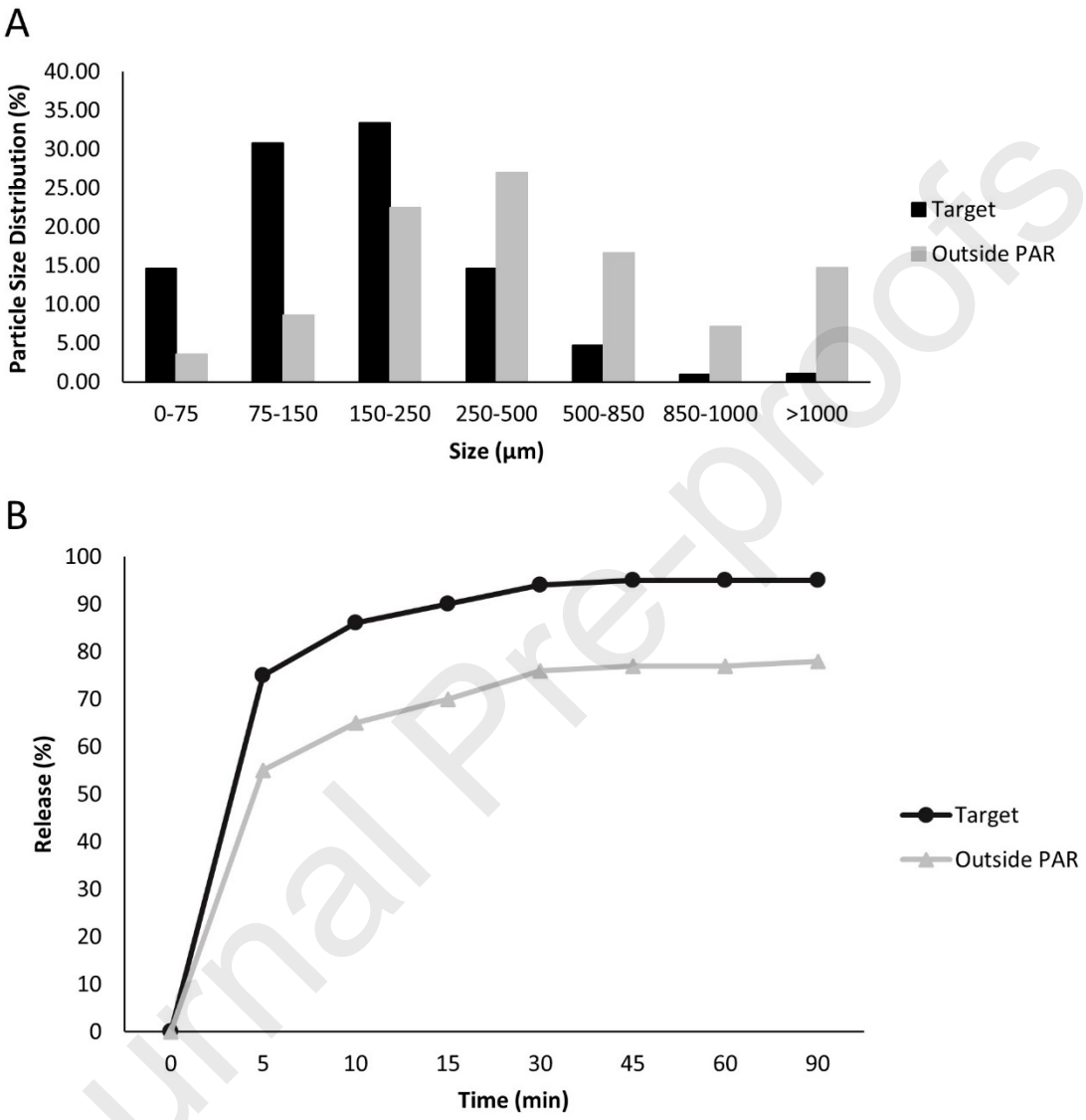
Fluid bed granulation was selected to enlarge the particle size of the granulate sufficiently to ensure an appropriate flow of the blend and to minimize blend segregation risks.

Multiple characterization batches were made at commercial scale to identify target process parameters and proven acceptable ranges (PAR) for the critical fluid bed process parameters (spray rate, air flow rate, inlet air temperature) [25], guaranteeing that fluid bed process settings within this range result in a robust downstream manufacturing compression process and tablets in compliance with the CQA criteria (Table 7). When a coarser granulate was produced in an attempt to improve the flow properties of the blend by using granulation parameters at significant wetter conditions outside the PAR (Figure 3 A), the dissolution profile was substantially slower and incomplete compared to the batch produced at target parameters (reference batch used in pivotal Phase III clinical study) (Figure 3 B). Variation of the granulation process parameters within the PAR resulted ultimately in the production of a granulate with good manufacturability, an adequate dissolution profile, and appropriate flow.

To guarantee an appropriate and robust flow of the blend from batch to batch, additional technical adjustments were implemented such as the use of extra air vents at the piping between the bin and the tablet press and the use of a specially designed hopper. These modifications facilitated the flow, and thus, the production of tablets at high throughput (rotary tablet press) with tablet weight and content uniformity in-process control tests within the predefined acceptance criteria.

The development of the manufacturing process for the drug product was initiated at smaller scale at development sites. The process was then transferred to the manufacturing site where it was scaled up for the manufacturing of drug product for clinical studies, registration stability studies (260 kg batch size), and eventually for the mass donation program (1300 kg batch size). Scaling-up from 260 kg to a batch size as large as 1300 kg is accomplished by repeating process steps 1 to 3, i.e., the production of screened granules, at 260 kg scale 5 times and blending 5 granulation batches together with the external phase to yield one large batch for compression. Hence, no changes were implemented in the granulation or the compression process steps, with only the blending process adapted to accommodate the scale-up to 1300 kg.

Figure 3: Batch produced at target versus outside PAR parameters: (**A**) particle size distribution results and (**B**) dissolution results



4.3 Primary Packaging Development, Storage & Stability

To accommodate the expected large volume forecast for a mass administration program and the complex supply chain logistics, a single stock keeping unit (SKU) of 200 chewable tablets in a single HDPE bottle of approx. 350 mL was used as the primary container closure. The packaging system consists of HDPE bottles with induction seals (tamper evidence), HDPE non-child-resistant closures for ease of handling at donation centers and does not contain any desiccant. However, to minimize the risk for polymorph conversion during storage due to moisture ingression, the HDPE bottles used are high moisture barrier containers specifically designed to contain moisture-sensitive products. The stability of the product was tested under ICH conditions, with 30 °C/75% RH selected for "long-term" conditions. These conditions are considered worst case compared to 25 °C/60% RH and are more appropriate given the intended geographical use of the tablet (climatic zone IVb). A shelf-life of 24 months was originally approved by regulatory authorities and then further extended to 48 months post-approval for all climatic zones (I-IV) (Table A.1). The chewable tablets were chemically stable, and no significant polymorph conversion (C to A) was detected over this period.

However, once the bottle is opened, polymorph conversion in the chewable tablets is theoretically possible when the bottles are daily opened and stored under high humidity and temperature. As such an in-use stability study was set up, simulating the opening and closing of the bottle by the health care provider and studying the effect of the daily refreshment of the headspace in the bottle on the chemical and physical quality of the tablets. During this in-use stability study, bottles were opened daily 2, 3 or 4 months before the end of shelf-life. More details on the design of the in-use study can be found in the appendix. No significant chemical (stable assay and purity profile) nor physical degradation (no trend in the dissolution and polymorphic content data) was observed. Consequently, an in-use period of 1 month was granted at the time of regulatory approval, and later extended to 3 months, supported by additional stability data (Table A.2).

4.4 Physical Properties and Controls

The new pediatric formulation is a chewable dispersible tablet, specifically designed to provide a single, age-appropriate formulation for children 1-16 years of age. To achieve this, normally contradicting physical characteristics had to be designed into a single product, combining properties of a chewable, dispersible, and regular (solid) immediate release tablet. The resulting controls and acceptance limits are summarized in Table 7.

Table 7: Analytical control strategy of selected CQAs of the new mebendazole chewable tablet 500 mg

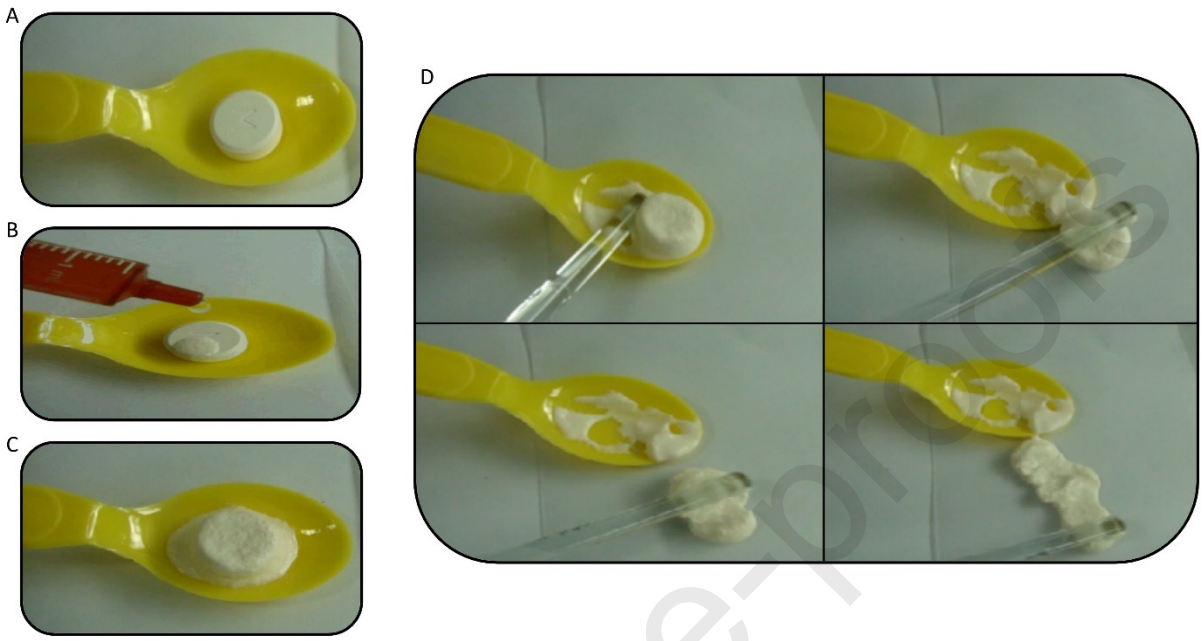
Quality attribute	Release & stability test (acceptance limits)	In-process controls (acceptance limits)
Appearance	Yes	Yes
Dissolution rate (%)	Q = 75at 45 min	NA
Disintegration time (s)	<120	<120
Friability (%)	NA	≤1.0
Tablet hardness (N)	NA	160-220
Tablet weight	NA	conform USP

NA = Not applicable

The new chewable tablet formulation and manufacturing processes were designed such that the tablet disintegration time was consistently below 120 s, when tested in the USP apparatus 2 (release and stability test). The acceptance criterion of <120 s is more stringent as compared to what is required for dispersible tablets (<3 min according to the Ph. Int.). While meeting this criterion, the chewable tablets also disintegrated rapidly and softened when exposed to 2-3 mL of water, allowing for administration by the "spoon method" to younger children or children with difficulties swallowing (illustrated in Figure 4).

Figure 4: Illustration of the new mebendazole chewable tablet 500 mg turning into a soft mass with (**A**) placing the tablet on a spoon, (**B**) adding approx. 2 mL of purified/potable water (drop-wise), (**C**) waiting for

120 s during dispersion, and (**D**) spreading the soft mass on a solid surface to check for the absence of lumps or hard mass.



In addition, the chewable tablets needed to be "soft" enough to be chewed by older children, while hard enough for packaging in a 200-count bottle and withstanding the shipping shear stresses along a lengthy supply chain. Considering these opposing requirements, appropriate in-process acceptance limits for tablet hardness and friability were established.

The new chewable tablet is relatively hard (in-process acceptance limit of 160-220 N) and exceeds the typical range for chewable tablets, however, meets the requirements of the August 2018 US FDA guidance on "Quality Attribute Considerations for Chewable Tablets" [26]. This guidance states that hardness for chewable tablets should be low (<12 kp/117.6 N) to be considered chewable, but that a higher hardness value may be acceptable if exposure to saliva (~30 s) (before chewing) results in significant disintegration and/or reduction in hardness. Such a study may be performed in *vivo* using human volunteers or *in vitro* using 1 mL of simulated salivary fluid for 30 s. The new chewable tablet was studied *in vitro,* and the results indicated that the tablet disintegrates so rapidly that the hardness can no longer be measured once the fluid is added, confirming a significant reduction in hardness.

Friability was selected as an additional in-process test to ensure adequate tablet integrity. The acceptance criterion of ≤1.0% is typical of standard (solid) tablets and thus an indicator that the new chewable tablet is suitable for packaging and shipment in bottles.

In conclusion, the inherent physicochemical properties of the new chewable tablet and the chosen set of in-process, release and stability tests and acceptance criteria were found adequate for the intended use, particularly with the two alternate methods of administration: chewing of the intact tablet or softening of the tablet with a small amount of water and dosed by spoon.

Although dissolution is not directly correlated to clinical activity as mebendazole is a locally acting drug of which more than 90% remains in the gastrointestinal tract after oral administration, the development of a dissolution method was a regulatory requirement. The dissolution method was developed based on the method described in the Mebendazole Tablets (100 mg) USP Monograph. To achieve a complete dissolution with the new chewable tablet containing a higher dose of mebendazole (500 mg), the dissolution medium was modified: instead of 0.1 N HCl with 1.0% SLS, 0.01 N HCl with 1.0% SLS was required. Importantly, this newly developed dissolution method has been adopted by the WHO as compendial method for Mebendazole Chewable Tablets, 500 mg in the Ph. Int. The parameters of the original USP method, the Ph. Int. method, and the developed dissolution method for the new mebendazole chewable tablet 500 mg are shown in Table 8. The acceptance criterion for the release and stability dissolution test is Q = 75% at 45 min.

Table 8: Parameters of the USP, Ph. Int., and the new mebendazole chewable tablet 500 mg dissolution methods

Parameter	USP method Mebendazole Tablets, 100 mg	New Mebendazole Chewable Tablet, 500 mg	Ph. Int. method Mebendazole Chewable Tablets, 500 mg
Dissolution apparatus	USP Apparatus 2 (Paddle)	USP Apparatus 2 (Paddle)	Not specified
Dissolution medium temperature (°C)	37.0 ± 0.5	37.0 ± 0.5	37.0 ± 0.5
Dissolution medium volume (mL)	900	900	900
Dissolution medium	0.1 N HCl with 1.0% SLS	0.01 N HCl with 1.0% SLS	0.01 N HCl with 1.0% SLS
Rotation speed (rpm)	75	75	75
Sample filter	Inert	0.45-µm GHP Acrodisc membrane filter (diameter 25 mm)	In line filter
Assay method	HPLC with UV detection at 250 nm	HPLC with UV detection at 250 nm	HPLC with UV detection at 250 nm

HPLC = high performance liquid chromatography; UV = ultraviolet

4.5 Acceptability of the New Chewable Tablet

The acceptability of the new chewable tablet has been assessed in a clinical safety and efficacy study (MEBENDAZOLGAI3003), conducted in Ethiopia and Rwanda. Clinical supplies for this study were manufactured with the final formulation and at the intended commercial manufacturing site. Chewable tablets (active and matching placebo) were packaged in aluminum blisters. Information on tolerability and acceptability was collected at the study site, using a questionnaire, first during the double-blind treatment phase (DBP; single chewable tablet, active or placebo),

followed by the open-label phase (OLP; single chewable tablet, active only) approximately 3 weeks after the initial treatment (DBP). Results of this clinical safety and efficacy study have been published and the respective acceptability results are summarized in Table 9 [27].

Table 9: Tolerability of the new chewable tablet in the DBP of the clinical safety/efficacy study [27]

	<3 years		3 to 6 years		7 to 16 years	
	Placebo (N=12)	Mebendazole 500 mg (N=12)	Placebo (N=24)	Mebendazole 500 mg (N=31)	Placebo (N=104)	Mebendazole 500 mg (N=101)
Ease of administration						
How was the medication administered?						
Chewed	0	0	24 (100.0%)	30 (96.8%)	104 (100.0%)	101 (100.0%)
Swallowed	0	0	0	0	0	0
Mixed with water and given with spoon	12 (100.0%)	12 (100.0%)	0	1 (3.2%)	0	0
Tolerability						
Choking						
Yes	0	0	0	0	0	0
No	12 (100.0%)	12 (100.0%)	24 (100.0%)	31 (100.0%)	104 (100.0%)	101 (100.0%)
Gagging						
Yes	1 (8.3%)	2 (16.7%)	0	0	0	0
No	11 (91.7%)	10 (83.3%)	24 (100.0%)	31 (100.0%)	104 (100.0%)	101 (100.0%)

Table 9: Tolerability of the new chewable tablet in the DBP of the clinical safety/efficacy study [27]

Vomiting						
Yes	0	0	0	0	0	0
No	12 (100.0%)	12 (100.0%)	24 (100.0%)	31 (100.0%)	104 (100.0%)	101 (100.0%)
Difficulty swallowing						
Yes	2 (16.7%)	0	0	0	0	0
No	10 (83.3%)	12 (100.0%)	24 (100.0%)	31 (100.0%)	104 (100.0%)	101 (100.0%)
Consumed medication						
None	0	0	0	0	0	0
Less than half	0	0	0	0	0	0
More than half	2 (16.7%)	1 (8.3%)	0	0	0	0
All	10 (83.3%)	11 (91.7%)	24 (100.0%)	31 (100.0%)	104 (100.0%)	101 (100.0%)
Spit out the medication						
Yes	2 (16.7%)	0	0	0	0	0
No	10 (83.3%)	12 (100.0%)	24 (100.0%)	31 (100.0%)	104 (100.0%)	101 (100.0%)
Refuse to take the medication						
Yes	2 (16.7%)	0	0	0	0	0

Table 9: Tolerability of the new chewable tablet in the DBP of the clinical safety/efficacy study [27]

No	10 (83.3%)	12 (100.0%)	24 (100.0%)	31 (100.0%)	104 (100.0%)	101 (100.0%)

Note: Percentages calculated with the number of relevant patients in each group as denominator.
Note: In the placebo group, two subjects reported difficulty swallowing, consumed medication more than half, spit out the medication, and refused to take the medication; one subject reported gaging. In the mebendazole group, one subject consumed medication more than half; two subjects reported gaging. All subjects were less than 3 years old.

The study demonstrated that the mebendazole chewable tablet can be used safely in children aged 1-16 years and is found to be efficacious. For patients <3 years of age, mixing the chewable tablet with water (without crushing) allowed for easy and safe administration as a semisolid mass to 25 patients. Two patients in the mebendazole group reported gagging in DBP and 1 instance of difficulty in swallowing and 2 instances of spitting out medication after swallowing were reported in OLP, but there were no instances of choking or vomiting.

In addition, a survey was conducted among the study subjects to rate how much the child liked the medication ("satisfaction"). Results from the DBP are shown in Table 10. All subjects responded "good" or "really good" on a five-point scale after the study medication administration except for the few subjects who were too young to provide an evaluation of the response. The results of the response survey conducted during the OL follow-up phase were consistent with those seen during the DBP. An independent study by the Swiss Tropical & Public Health Institute in Tanzania came to a similar conclusion and recommended an additional rinsing step with water when chewing the tablet [28].

Table 10: New mebendazole chewable tablet 500 mg: response survey "Satisfaction with Administered Drug" in the DBP, DB safety analysis [27]

Satisfaction, n (%)	Placebo (n = 140)	Mebendazole 500 mg (n = 144)	Total (n = 284)
Really good	59 (42.1)	60 (41.7)	119 (41.9)
Good	71 (50.7)	72 (50.0)	143 (50.4)
Not sure	0	0	0

Table 10: New mebendazole chewable tablet 500 mg: response survey "Satisfaction with Administered Drug" in the DBP, DB safety analysis [27]

Satisfaction, n (%)	Placebo (*n* = 140)	Mebendazole 500 mg (*n* = 144)	Total (*n* = 284)
Bad	0	0	0
Really bad	0	0	0
Not applicable – too young to evaluate the response	10 (7.1)	12 (8.3)	22 (7.7)

4.6 Regulatory Approval and Launch

Considering the change in dosage form and the extended age-range (down to 1 year of age) compared to the current tablet, the sponsor first decided on conducting an additional clinical safety and efficacy study with the new chewable tablet. Taking into account the intended distribution for large donation programs, as well as the fact that mebendazole is already on WHO's list of essential medicines, the sponsor embarked on a tiered regulatory strategy: (i) obtaining approval from "Stringent Health Authority", (ii) WHO full pre-qualification (WHO-PQ), and (iii) acceptance of WHO standards for local submissions, where applicable. The overarching objective was to develop a single product (one SKU) with a single set of quality standards, including analytical testing and specifications. In a first step, the sponsor obtained US FDA approval in 2016 for the new chewable tablet (new drug application, NDA 208398). Next, the sponsor submitted a dossier to request Pre-Qualification to the WHO. This process is available for drugs listed on the Essential Medicine List, for which a WHO-PQ Invitation for Expression of Interest is published and intended to set international quality standards by the originator product and subsequently for generic products. WHO prequalification may facilitate local approval processes and may be a prerequisite of international organizations that procure products on the open market for their donation programs. The WHO prequalification submission package is based on the ICH eCTD structure with additional content and formatting requirements. WHO prequalification was achieved in 2019 [29].

Following WHO prequalification, the new chewable tablet has been successfully launched in donation programs in more than twenty countries to replace the solid oral tablet. Informal feedback from the launch sites confirmed the acceptability of the new chewable tablet across all age groups.

In the meantime, the efficacy of the new chewable tablet has been found equivalent in a head-to-head comparison with the older solid tablet in an independent study of the Swiss Tropical & Public Health Institute, conducted in Tanzania [28].

Recently, and after completion of this development work, a new guideline regarding BE study for mebendazole has been published by the WHO [30].

5. CONCLUSIONS

The work presented in this article describes the development of a new, age-appropriate, chewable tablet of mebendazole 500 mg to include pre-school age children in preventive chemotherapy programs run by WHO for STH. To develop a single pediatric formulation for children 1 to 16 years of age, a tablet formulation concept was chosen that combines the advantages of a chewable tablet and a dispersible tablet but is as well suitable for a lengthy distribution chain and storage in tropical climates. As such, the tablet can be either chewed or given to young (≥1 year old) children by spoon after rapid disintegration to a soft mass with the addition of a small amount of water directly on the spoon. The new mebendazole chewable tablet 500 mg was manufactured by fluid bed granulation using an aqueous povidone binder solution, followed by screening, blending, and compression processes. The resulting granules from the fluid bed granulation were relatively fine to meet the predefined dissolution requirements. Furthermore, the formulation was optimized for taste by the extra-granular addition of sucralose and strawberry flavor. To achieve development of this unique tablet, normally contradicting physical characteristics had to be designed into a single product. A tablet with the following physical characteristics was developed: a disintegration time of <120 s, a hardness of 160-200 N, and a friability of ≤1.0%. In addition, a dissolution method was developed for the new mebendazole chewable tablet 500 mg, which has been adopted by the WHO as compendial method for Mebendazole Chewable Tablets, 500 mg in the Ph. Int. The tablets were packaged per 200 in HDPE bottles serving as high moisture barrier containers to minimize the risk for polymorph conversion during storage due to moisture ingression. A shelf-life of 48 months for all climatic zones (I-IV) could be established. Furthermore, it was demonstrated that the new mebendazole chewable tablet 500 mg can be used safely in very young children (12-36 months), that “good to really good satisfaction” was obtained after administration of the tablet, and that no choking occurred.

In conclusion, this study describes the challenging and successful development of a new, age-appropriate “one-size-fits-all” formulation of mebendazole. The work presented can serve as a case study on how the development of tablets can be fine-tuned to result in an appropriate pediatric dosage form for a wide age range with high flexibility in administration.

DECLARATION OF COMPETING INTEREST

D.Sch. retired from Janssen and is an independent consultant, advising pharmaceutical companies, academic, and governmental organizations.

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7. APPENDIX A – SUPPLEMENTARY MATERIAL

The following are the Supplementary data to this article.