2.1.P.2 Pharmaceutical Development

AS	Active substance
BCS	Biopharmaceutical Classification System
BE	Bioequivalence
CMA	Critical Material Attribute
CPP	Critical Process Parameters
CQA	Critical Quality Attribute
CU	Content Uniformity
FP	Final product
GI	Gastro intestinal
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
QTPP	Quality Target Product Profile

1 Development Summary

The pharmaceutical development report summarizes the development work of the Ivermectin MEDITOP 3 mg tablets, generic version of the reference product, the immediate release (IR) dosage form of ivermectin named Stromectol 3 mg tablets was authorized in Europe by Merck Sharp & Dohm Co. Stromectol 3 mg tablets are used for treatment of the symptoms of certain parasite infections. Stromectol 3 mg tablets have been investigated now for COVID-19. Ivermectin also has some anti-viral activity against SARS-CoV-2 in vitro.

Ivermectin is an orally bioavailable macrocyclic lactone derived from Streptomyces avermitilis, with antiparasitic and potential anti-viral activities (National Institutes of Health, National Library of Medicine, National Center for Biotechnology Information: Ivermectin | C48H74O14 - PubChem (nih.gov)). Fermentation of Streptomyces avermitilis yields eight closely related avermectin homologues, of which B1a and B1b form the bulk of the products isolated. In a separate chemical step, the mixture is hydrogenated to give ivermectin, which is an approximately 80:20 mixture of the two 22,23-dihydroavermectin compounds H2B1a (molecular weight is about 875) and H2B1b (molecular weight is about 861. The difference is one methylene group. Ivermectin of Ph. Eur. quality should contain at least 90% of H2B1a component.

It is white or yellowish-white, crystalline powder, slightly hygroscopic. The molecule is extremely apolar, and the dissociation constant (pKa) is around 6.5. Practically insoluble in water (≤ 4 µg/ml), freely soluble in methylene chloride, soluble in alcohol according to the pharmacopeial term. Ivermectin solubility increases with the increasing of the pH of the solution.

Ivermectin is BCS (Biopharmaceutical classification system) class-II drug, which has high permeability and low water solubility which is responsible for its poor dissolution rate and ultimately leads to variable absorption (Formulation and evaluation of ivermectin solid dispersion / Somya Verma, Urmi Patel, Rakesh P. Patel (Journal of Drug Delivery and Therapeutics. 2017; 7(7):15-17)).

According to the specification of the BCS the generic versions can be authorized by BE study of the tests and reference product. (GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE, CPMP/EWP/QWP/1401/98 Rev. 1; hereinafter GUIDELINE).

Initially the quality target product profile (QTPP) was defined based on the properties of the drug substance, characterization of the reference products, and consideration of the reference product label and intended patient population.

Identification of critical quality attributes (CQAs) was based on the severity of harm to a patient (safety and efficacy) resulting from failure to meet that quality attribute of the drug product. For Ivermectin MEDITOP 3 mg tablets, these CQAs included assay, content uniformity, dissolution rate and stability.

For formulation qualitatively the same types of excipients and near of the same quantities as the reference product contains have been chosen. Risk assessment was used before the development to identify potentially high-risk formulation and process variables and to determine which studies were necessary to achieve product and process understanding in order to develop a control strategy.

Due to the low active substance content of the product the dry mixing process was chosen for preparation of the blend for compression. At the optimization process the following points were studied: particle size of the active substance, quantity of the antioxidant, the quantity of acidifying agent, the homogeneity of the blend and the hardness and disintegration time of the tablets.

Processing experience has been gained by manufacturing of batches of 1000-7000 tablets in the Laboratory site of MEDITOP. The parameters of the blends and tablets are controlled with the standard pharmacopeal methods. The dissolution rate of the tablets was compared with the dissolution rate of the reference product.

The quantities of the stabilizing components (buthyl hydroxy toluene and citric acid) were determined by stress stability test.

The risk assessment was then updated after development to capture the reduced level of risk based on our improved product and process understanding.

2 Analysis of the Reference Products

2.1 Composition

Stromectol 3 mg tablets are authorized in Europe by Merck Sharp & Dohm Co. The product is not commercialized in Hungary.

Product Name (in authorisation country)	MRP/DCP Authorisation number	National Authorisation Number	MAH of product in the member state	Member State where product is authorised
STROMECTOL 3 mg, comprimé	FR/H/0216/001	34009 352 388 5 6	MSD FRANCE	FR
STROMECTOL 3 mg, comprimé	FR/H/0216/001	34009 352 389 1 7	MSD FRANCE	FR
Stromectol 3 mg tabletten	FR/H/0216/001	RVG 28341	MERCK SHARP & DOHME BV	NL
STROMECTOL 3 mg, comprimé	FR/H/0216/001	34009 562 257 4 3	MSD FRANCE	FR
STROMECTOL 3 mg, comprimé	FR/H/0216/001	34009 357 506 6 2	MSD FRANCE	FR
STROMECTOL 3 mg, comprimé	FR/H/0216/001	34009 389 636 2 5	MSD FRANCE	FR

List of nationally authorized medicinal products:

(ivermectin (systemic use): List of nationally authorised medicinal products-PSUSA/00010377/201604 (europa.eu))

Well-known excipients of Ph. Eur. quality are used in the products.
The tablets have the following excipients:

- Ivermectin
- Microcrystalline cellulose
- Pregelatinized starch
- Magnesium stearate
- Butyl hydroxy anisole
- Citric acid anhydrous

The excipients belong to the usual ones applied in tablet products and no one has special effect on the absorption of the active substance.

2.2 Pharmacokinetics

Mechanism of Action
Ivermectin binds glutamate-gated Cl ion channels in invertebrate nerve and muscle cells; produces paralysis, death of parasite

Absorption
Ivermectin is moderately well absorbed, the peak serum time (Tmax) is approximately 4 hours. Absorption can be improved by high fat meal.

Distribution
Due to the high lipid solubility of ivermectin, this compound is widely distributed within the body. The volume of distribution is 3 to 3.5 L/kg and it does not cross the blood-brain barrier. Protein bound is about 93%.

Metabolism
Ivermectin is metabolized in the liver by hepatic enzymes (CYP3A4, CYP2D6, CYP2E1).

Elimination
Half-life: 16-18 hr (also reported at 22-28 hours)

Excretion
Ivermectin and/or metabolites of ivermectin are excreted almost exclusively in the faeces, with less than 1 % of the administered dose excreted in the urine.

2.3 Drug Release

Details of the dissolution method and results are given in part *2.1.P.2.2.3 Physicochemical and Biological Properties*.
Due to the low solubility of Ivermectin (< 3 mg/900 mL) the dissolution specification could be given as the lowest value of immediate release products: Q= 80% in 45 min, at pH 7.0 (0.01 M phosphate buffer with 0.5% of sodium dodecyl sulfate), 900 ml, 50 rpm, paddle method. These parameters of dissolution method are recommended by USP monographs.

2.4 Physicochemical Characterization

The physicochemical characterizations of the reference Ivermectin tablets are summarized in Table 1.

Table 1.
Physicochemical characterization of the reference tablets

Product	**Stromectol 3 mg tablets**	
Batch No.	R036228	T015953
Expiry date	10/2020	01/2022
Date of analysis	02/2021	05/2021
Description	Almost white, round, bevelled edge tablets, imprint on one side: “MSD”, and "32" on the other side	Almost white, round, bevelled edge tablets, imprint on one side: “MSD”, and "32" on the other side
Coating	None	None
Average mass (mg)	60.2	59.7

Product	**Stromectol 3 mg tablets**	
Mass variation (RSD %)	0.59	0.35
Diameter (mm)	5.5	5.5
Height (mm)	1.95	1.95
Disintegration time (sec)	30	28
Hardness (N)	45	41
Dissolution rate	Dissolution data are given in Part *2.1.P.2.2.3 Physicochemical and Biological Properties*	

Reference product is stored in ALU/ALU blister.

2.1.P.2.1 Components of the Drug Product

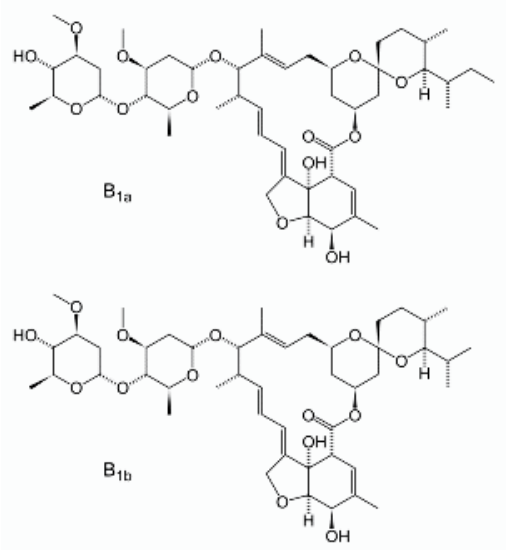
2.1.P.2.1.1 Drug Substance

1 Chemical properties

Chemical name:
A mixture of *Ivermectin component B1a* (2aE,4E,8E)-(5′S,6S,6′R,7S,11R,13R,15S,17aR,20R,20aR,20bS)-6′-(S)-sec-butyl-3′,4′,5′,6,6′,7,10,11,14,15,17a,20,20a,20b-tetradecahydro-20,20b-dihydroxy-5′,6,8,19-tetramethyl-17-oxospiro[11,15-methano-2H,13H,17H-furo[4,3,2-pq][2,6]-benzodioxacyclooctadecin-13,2′-[2H]pyran]-7-yl-2,6-dideoxy-4-O-(2,6-dideoxy-3-O-methyl-α-l-arabino-hexopyranosyl)-3-O-methyl-α-l-arabino-hexopyranoside) at least 90%,
and *Ivermectin component B1b* (2aE,4E,8E)-(5′S,6S,6′R,7S,11R,13R,15S,17aR,20R,20aR,20bS)-3′,4′,5′,6,6′,7,10,11,14,15,17a,20,20a,20b-tetradecahydro-20,20b-dihydroxy-6′-isopropyl-5′,6,8,19-tetramethyl-17-oxospiro[11,15-methano-2H,13H,17H-furo[4,3,2-pq][2,6]-benzodioxacyclooctadecin-13,2′-[2H]pyran]-7-yl-2,6-dideoxy-4-O-(2,6-dideoxy-3-O-methyl-α-l-arabino-hexopyranosyl)-3-O-methyl-α-l-arabino-hexopyranoside) less than 10 %.

Other names:	22,23-dihydroavermectin B1a, or H2B1a 22,23-dihydroavermectin B1b, or H2B1b
Molecular formula:	A mixture of Ivermectin component B1a ($C_{48}H_{74}O_{14}$) at least 90% and Ivermectin component B1b ($C_{47}H_{72}O_{14}$) less than 10%.
Chemical formula:	Ivermectin component B1a ($C_{48}H_{74}O_{14}$) Ivermectin component B1b ($C_{47}H_{72}O_{14}$)

Chemical structure:



Molecular mass:	875.106 g/mol (Ivermectin component B1a) 861.079 g/mol (Ivermectin component B1b)
CAS number:	70288-86-7

2 Physical properties

Description:	white or yellowish-white, crystalline powder, slightly hygroscopic
Solubility:	practically insoluble in water, freely soluble in methylene chloride, soluble in alcohol
Loss on Drying:	NMT 0.5 % (at 70 °C)
Polymorphism:	The drug substance produced by manufacturers exists in a unique crystalline form and does not show polymorphism.
Melting point:	about 155°C
Particle size:	D (90) 10-20 µm (CoA is Attached)
Powder fineness:	Micronized powder

The particle size distribution of the active ingredient during the development is as follows:

Table 2.
Particle size distribution of the tested APIs

	Ivermectin	
Batch No.	**20210020MIC**	**20210021MIC**
Result transformation type	**Particle size (µm)**	
D (90)	11.9	12.9

3 Compatibility with excipients

A pre-formulation study to test the compatibility with the potential excipients was not carried out because the same excipients are used in the test product that the reference product has.

4 Human bioavailability

Following oral administration of ivermectin, plasma concentrations are approximately proportional to the dose. In two studies, after single 12-mg doses of ivermectin tablets in fasting healthy volunteers (representing a mean dose of 165 mcg/kg), the mean peak plasma concentrations of the major component (H2B1a) were 46.6 (±21.9) (range: 16.4-101.1) and 30.6 (±15.6) (range: 13.9-68.4) ng/mL, respectively, at approximately 4 hours after dosing. Ivermectin is metabolized in the liver, and ivermectin and/or its metabolites are excreted almost exclusively in the feces over an estimated 12 days, with less than 1% of the administered dose excreted in the urine. The elimination of ivermectin is multi-phasic with an initial half-life of approximately 18 hours and a longer terminal half-life of approximately 53 hours following oral administration (*Notes on the Design of Bioequivalence Study: Ivermectin, WHO/PQT: medicines, Guidance Document, 16 April 2019*).

2.1.P.2.1.2 Excipients

Well-known excipients were used to develop the test product.

The Ivermectin MEDITOP 3 mg tablets have the following excipients:

1 Microcrystalline Cellulose

Ph. Eur.:	Cellulosum microcristallinum
Chemical Name:	Cellulose
CAS Registry Number:	9004-34-6
Empirical Formula:	$(C_6H_{10}O_5)_n$
Molecular Weight:	≈36 000, where n ≈220.
Functional Category:	Adsorbent; tablet and capsule diluent; tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology
Microcrystalline Cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulation. Cellulose, Microcrystalline also has some lubricant and disintegrant properties that make it useful in tableting.

Description
White, odorless, tasteless, crystalline powder composed of porous particles.

Functionality-related characteristic (Particle size distribution)
The type of microcrystalline cellulose is Vivapur 302.
Vivapur 302 is a medium size standard MCC grade, suited for the majority of directly compressible actives. Combines good flow and high compatibility.
Average Particle Size by laser diffraction is 90 to 150 µm
Bulk density is 0.35 – 0.50 g/ml
The branded type is a guarantee for the proper particle size.

2 Pregelatinized starch

Nonproprietary Names	
BP:	Pregelatinised starch
PhEur:	Amylum pregelificatum
USPNF:	Pregelatinized starch
Synonyms	Compressible starch; Instastarch; Lycatab C; Lycatab PGS; Merigel; Pharma-Gel; Prejel; Sepistab ST 200; Spress; Starch 1500 G;
Chemical Name:	Pregelatinized starch
CAS Registry Number:	[9005-25-8]
Empirical Formula:	(C6H10O5)
Molecular Weight:	n where n = 300–1000.

Pregelatinized starch is a starch that has been chemically and/or mechanically processed to rupture all or part of the starch granules and so render the starch flowable and directly compressible. Partially pregelatinized grades are also commercially available. Typically, pregelatinized starch contains 5% of free amylose, 15% of free amylopectin, and 80% unmodified starch. PhEur 2002 (Suppl 4.1) specifies that pregelatinized starch is obtained from maize (corn), potato, or rice starch.

Functional Category
Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder.

Description
Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odorless and has a slight characteristic taste.

Typical Properties

Acidity/alkalinity:	pH = 4.5–7.0 for a 10% w/v aqueous dispersion.
Angle of repose:	40.7 ° (6)
Compressibility:	see Starch.
Density (bulk):	0.586 g/cm3
Density (tapped):	0.879 g/cm3
Density (true):	1.516 g/cm3
Flowability:	18–23% (Carr compressibility index)(17)
Moisture content:	< 7 %
Particle size distribution:	30–150 µm, median diameter 52 µm.
Specific surface area:	0.26 m2/g (Colorcon)

Stability and Storage Conditions
Pregelatinized starch is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.

Functionality-related characteristic:
None

3 Magnesium stearate

Ph. Eur.:	Magnesii stearas
BP:	Magnesium stearate
USPNF:	Magnesium stearate
Chemical Name:	Octadecanoic acid magnesium salt
CAS Registry Number:	557-04-0
Empirical Formula:	$C_{36}H_{70}MgO_4$
Molecular Weight:	591.34
Structural Formula:	$[CH_3(CH_2)_{16}COO]_2Mg$ The Ph.Eur. 2002 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and palmitic acid and in minor proportions other fatty acids.
Functional Category:	tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Magnesium stearate is widely used in pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w.

Description

Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Functionality-related characteristic: particle size distribution, or specific surface area

Magnesia 4264 which has the usual specific surface area of 1- 4 m^2/g was tested at product development. Based on the results, it seemed to be proper, therefore, it was chosen to be applied in the final composition. The branded type is a guarantee for the proper particle size and specific surface area.

4 Butyl hydroxy anisole

Nonproprietary Names	
BP:	Butylated Hydroxy anisole
Ph. Eur:	Butyl hydroxy anisole
USP NF:	Butylated Hydroxy anisole
Synonyms:	BHA, Tenox BHA, Nipanox BHA, tercier-butyl-4-methoxyphenol
Chemical Name:	2-tert-Butyl-4-methoxyphenol
CAS Registry Number:	[25013-16-5]
Empirical Formula:	$C_{11}H_{16}O_2$;
Molecular Weight:	180.25
Functional Category	Antioxidant

Description
Butylated hydroxy anisole occurs as a white or almost white crystalline powder or yellowish-white waxy solid a faint characteristic aromatic odor.

Typical Properties

Density (true):	1.117 g/cm3
Flash point:	130°C
Melting point:	47°C
Solubility:	Practically insoluble in water

Stability and Storage Conditions
Exposure to light causes discoloration and loss of activity. BHA should be stored in a well-closed container, protected from light, in a cool, dry place.

Functionality-related characteristic:
None

5 Citric acide anhydrous

Nonproprietary Names	
BP:	Citric acid anhydrous
Ph. Eur:	Citric acid anhydrous
USP:	Citric acid anhydrous
Synonyms:	Anhydrous citric acid, acidum citricum anhydricum, citric acid
Chemical Name:	2-Hydroxy-1,2,3-propanetricarboxyic acid
CAS Registry Number:	[77-92-9]
Empirical Formula:	$C_6H_8O_7$
Molecular Weight:	192.12
Functional Category:	Acidifying agent, antioxidant, chelating agent, preservative.

Description
Anhydrous citric acid occurs as colorless or translucent crystals, or a white crystalline powder. It is odorless and has a strong acidic taste.

Typical Properties

Density (true):	1.542 g/cm3
Acidity:	pH 2.2 (1 % aqueous solution)
Melting point:	153°C
Solubility:	Soluble 1 in 1 of water and ethanol (95%)

Stability and Storage Conditions
The bulk material should be stored in airtight container in a cool, dry place.

Functionality-related characteristic:
None

All components are Ph. Eur. quality.

2.1.P.2.2 Drug Product Development

1 Drug Product Development Strategy

At the development of the Ivermectin MEDITOP 3 mg tablets, the same excipients were used as the reference product has.

The characteristics of the reference products are given in part of *2.1.P.2-2 Analysis of the Reference Products.*

For manufacture the dry mixing process was chosen due to the low active substance content of the tablet core.

2 Target Product Profile

The target product profile summarises the quality attributes of the product required to meet the needs for safety and efficacy of the patient. Safety is assured by ensuring limits for assay and uniformity of dosage units to prevent the administration of excess drug substance and the total impurities is no more than 5.0 % at the end of shelf life. (In accordance with the Ph. Eur requirements for ivermectin.) Meeting globally-agreed limits for any microbiological contamination and application of appropriate GMP standards during manufacture assure the adequate microbiological quality.
Efficacy is assured by application of a dissolution limit according to equal to or greater than 80% of drug substance released within 45 minutes in buffer of pH 7 with 0.5% sodium dodecyl sulfate. Similar to the safety justification, efficacy is assured by application of the pharmacopeial acceptance criteria for uniformity of dosage units.

Table 3.
Target Product Profile of Ivermectin MEDITOP 3 mg tablets

Description	White/white capsules of sizes #0
Identification	Positive
Assay	Labelled amount ± 5 %
Uniformity of dose units	Meets pharmacopoeia acceptance criteria
Total impurities	Not more than 5.0 %
Dissolution	Q ≥ 80 % in 45 minutes
Microbiological limits	Meet pharmacopeial acceptance criteria

3 Quality Attributes of the Drug Product

Table 4. summarizes the quality attributes of the Ivermectin MEDITOP 3 mg tablets developed and indicates which attributes were classified as drug product critical quality attributes (CQAs). For the products assay, content uniformity (CU), dissolution and degradation products were identified as the subset of CQAs that have the potential to be impacted by the formulation and/or process variables and therefore will be investigated and discussed in detail in subsequent formulation and process development studies.

Table 4.
Critical Quality Attributes of Ivermectin MEDITOP 3 mg tablets

Quality Attributes of the Drug Product	Target	Is this CQA?	Justification
Appearance	No visual tablets defects observed.	No	Colour, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical.
Odour	No	No	The odour is not directly linked to safety and efficacy therefore it is not critical.
Size	Conform to size of tablets	No	The size is not directly linked to safety and efficacy. Therefore, it is not critical.
Imprint	No	No	The imprint is not directly linked to safety and efficacy. Therefore, it is not critical.
Identification	Positive	Yes*	Formulation and process variables do not impact identity.
Assay	100% w/w of label claim	**Yes**	Assay variability will affect safety and efficacy. Process variables may impact the assay of the drug product.
Content Uniformity (CU)	Conforms to Ph. Eur.	**Yes**	Variability in content uniformity affects safety and efficacy. Both formulation and process variables impact the content uniformity.
Dissolution	Q ≥ 80% at 45 min in buffer of pH 7 with 0.5% sodium dodecyl sulfate, volume 900 ml.	**Yes**	Variability in the dissolution rate can impact the efficacy. Both formulation and process variables affect the dissolution profile.

Quality Attributes of the Drug Product	Target	Is this CQA?	Justification
	rpm 50		
Degradation products	Conforms to Ph. Eur.	**Yes**	Failure to meet the degradation specification can affect safety and efficacy. Both formulation and process variables impact the chemical stability
Residual Solvents	Conform to ICH	Yes*	Formulation and process variables applied do not impact the residual solvent.
Loss on drying	NMT 6.0% w/w	Yes*	Formulation and process variables applied do not impact the water content.
Microbial Limits	Meet relevant pharmacopoeia criteria	Yes*	Formulation and process variables applied do not impact the water content.

* This CQAs will not be discussed in detail during formulation and process development.

4 Preliminary Hazard Analysis

Considering the properties of the active substance (ivermectin), the excipients and the manufacture process a Preliminary Hazard Analysis (PHA) was done as initial risk assessment, that help to establish the required experimental work.

Table 5.
Preliminary Hazard Analysis (PHA) of development of Ivermectin MEDITOP 3 mg tablets

CQA	CMA					CPP			
	AS assay	AS impuri-ties	AS particle size	AS sensiti-vity	Type and rate of ex-cipients	Working conditions	Pre-blending	Final blending	Tabletting
Appearance	N	N	M	L	L	L	N	L	M
Assay	H	L	N	N	N	L	M	L	M
CU	N	N	M	N	N	N	M	L	M
Dissolution	N	N	H	N	H	N	N	M	M
Impurities	N	H	L	L	L	L	N	N	N

Color coding for relative risk ranking:

High risk/H	affect quality attributes - further investigations and controls needed in order to reduce risk
Medium risk/M	potential to affect quality attributes - further investigations and controls may be needed in order to reduce risk
Low risk/L	low impact on quality attributes - no further investigations needed
No risk/N	no impact on quality attributes - no further investigations needed

Table 6
Risk Assessment Plan for Justification and Risk Mitigation Strategies for Risks of CMAs

CMA	CQA	Initial risk	Description of CMA's effect on FP CQAs	Risk mitigation Strategy / Control Strategy Action points
AS Assay	Assay	H	Product assay depends on the AS assay.	During weighing calculate the AS weight based on AS assay of the relevant AS CoA.
AS impurities	Assay	L	Product may have low assay due to the high impurity level of API.	Control the impurity profile of the AS with analytical measurements according to the AS specification.
	Impurities	H	Product may have high impurity content due to the high impurity level of API.	
AS particle size	Content Uniformity (CU)	M	Inappropriate particle size of AS may have effect on CU of product.	Appropriate particle size can reduce risk.
	Dissolution	H	Particle size has effect on dissolution rate of the final product (FP).	The low solubility of the active ingredient leads to high effect on the dissolution rate. Appropriate particle size can reduce risk.
	Impurities	L	It is anticipated that potential degradation of active substance may be faster for smaller particle size, since it corresponds to the larger surface area.	Appropriate particle size can reduce risk.
AS sensitivity	Appearance	L	Sensitivity of AS to any environmental parameter (oxygen. temperature. moisture or light) may influence the appearance of the product. and may have impact on FP appearance and impurity levels.	According to the DMF of the AS is hygroscopic and sensitive to heat. With standard working condition at manufacture and packaging the risk can be eliminated
	Impurities	L		
Type and rate of excipients	Appearance	L	Inappropriate type and rate of excipients may negatively affect the appearance, dissolution ate and degradation products of FP.	The composition of the test product is very similar to that of the reference product has, the rate of excipients should be optimized by dissolution and stability test.
	Dissolution	H		
	Impurities	L		

Table 7.
Risk Assessment Plan for Justification and Risk Mitigation Strategies for Risks of CPPs

CPP	CQA	Initial risk	Description of CPP's effect on FP CQAs	Risk mitigation Strategy / Control Strategy Action points
Working conditions	Appearance	L	Sensitivity of the components to any environmental parameter (oxygen. temperature. moisture or light) may influence the appearance of the product. and may have impact on FP appearance. assay and impurity. if the air condition in the manufacturing place is not proper.	According to the DMF of the AS is hygroscopic and sensitive to heat. With proper working condition and packaging the risk can be eliminated.
	Assay	L		
	Impurities	L		
Pre-blending	Assay	M	The dry mixing might have risk from the point of the Assay and CU.	Due to the low AS content of the tablets with proper working methods the required Assay and CU can be ensured.
	CU	M		
Final blend-ing	Dissolution	M	The time of final blending might have risk from the point of the disin-tegration time and dissolution rate	With proper blending time the risk can be eliminated.
Tableting	Appearance	M	The tableting may affect the appearance of the tablets and their Assay, CU values and the dissolution rate of the AS.	With proper control of the tableting process the re-quired appearance, Assay, CU and dissolution can be ensured.
	Assay	M		
	CU	M		
	Dissolution	M		

Therefore, in the case of the development of Ivermectin MEDITOP 3 m tablets, the quality and particle size of the active substance and the quantities of excipients pose a high-risks. Because the quality of the active substance can't be changed at pharmaceutical development and the excipients are the same as the reference product has, the main issue of the development is the determination of the optimal particle size of ivermectin and the composition from the point of tablet hardness and dissolution rate.

2.1.P.2.2.1 Formulation Development

1 Development of tablet composition

The initial composition was determined by the following aspects:

- the qualitative composition of the reference products
- the weight of the reference product
  - tablet core ~ 60 mg
- the usual quantities of the other excipients of the whole tablet's mass:
  - microcrystalline cellulose 60 – 90 %
  - maize starch (pregelatinized) 5 – 25 %
  - butyl hydroxy anisole 0.05 - 0.15 %
  - citric acid 0.2 - 1 %
  - magnesium stearate 0.5 – 2 %

On the base of the aspects above the initial composition of the test product was the following:

- ivermectin 3.00 mg*
- microcrystalline cellulose 53.11 mg**
- maize starch pregelatinized 3.00 mg
- butyl hydroxy anisole 0.06 mg
- citric acid 0.20 mg
- magnesium stearate 0.30 mg

* calculated on measured "as is" of the active substance (based on quality control measurements of MEDITOP),

** amount of microcrystalline cellulose is reduced by the amount of ivermectin overages

Taking into consideration the compositions in the first series of experiments the effect of the quantity of the antioxidant, buffering agent and particle size of the active substance was studied.

The experiments were made at laboratory scale using the following equipment:

- ProCept 4m8 high shear mixer with 1 Liter pot
- Hand sieve with 0.8 mm screen
- IKA mill with 1 mm screen
- Wynka Kompressor Developer tablet machine
- Korsch EK 0 eccentric tablet machine

Manufacturing process

The butyl hydroxy anisole is a crystalline powder; therefore, it was milled by IKA mill through a screen of 1.0 mm with a portion of microcrystalline cellulose, because of the low melting point (48-63°C) of butyl hydroxy anisole. The milled powder, ivermectin, maize starch and citric acid were homogenized in a beaker, sieved through a 0.8 mm sieve and added to a 1L container of ProCepT. The remaining microcrystalline cellulose was sieved through a 0.8 mm sieve, then added to the pre-homogenate in a 1L container of ProCepT and homogenized with stirring at 100 rpm (impeller speed) for 10 minutes.

- The final blend is compressed into tablets of 60 mg weight by round flat-faced and beveled edge tools (of 6 mm on a Wynka Kompressor Developer tablet press or Korsch EK 0 eccentric tablet machine).

In process control
- control of the loss on drying of the final blend
- control of the flowability of the final blend by funnel of 15 mm
- control of the bulk density and tapped density of the final blend

Control of the tablets
- control the weight of the tablets
- control of the height of the tablets
- control of the hardness of the tablets
- control of the friability of the tablets
- control of the disintegration time of the tablets
- control of the dissolution rate of the tablets

The pharmaceutical tests were done according to the methods of the Analytical Methods of Ivermectin Meditop 3 mg tablets.

The results were the followings:

Table 8.
Tablet core compositions and blend parameters

Components (g)	Number of experiments		
	VAXX104	VAXX116	VAXX152
Ivermectin	(micronized) 3.30	(micronized) 3.30	(non-micronized) 3.30
Microcrystalline Cellulose	(Type: 102) 56.58	(Type: 302) 53.03	(Type: 302) 53.06
Corn Starch, pregelatinized	3.00	3.00	3.00
Citric acid (anhydrous)	0.36	0.36	0.30
Magnesium-stearate	0.15	0.30	0.30
Butylated hydroxy anisole	0.06	0.06	0.04
Nominal weight of tablet	60.00	60.00	60.00
Blend parameters			
Flowability (100 g) (s)	12	13	8
Bulk density (g/mL)	0.39	0.51	0.49
Tapped density (g/mL)	0.49	0.60	0.63
Hausner ration (-)	1.25	1.17	1.29

Table 9.
Parameters Ivermectin MEDITOP 3 mg tablets

Tablet parameters/Nr. of exp.	VAXX104	VAXX116	VAXX152
Average weight (mg)	59.5	60.5	60.1
Weight variation (%)	1.01	0.75	0.81
Height of the tablets (mm)	1.87	1.75	1.81
Hardness (N)	36	35	26
Friability (%)	0.0	0.0	0.0
Disintegration time (sec)	35	15	10
Appearance	Sticking	Suitable	Suitable
Dissolution rate (%) at 15 min.	-	81.4	39.1
Dissolution rate (%) at 30 min	-	92.4	56.6
Dissolution rate (%) at the end*	-	95.2	78.4

*at 60 min, 250 rpm stirring

As it can be seen in Table 9, 0.15 mg magnesium stearate is not sufficient for proper lubrication because the tablets stick to the punches and the tablet surface appearance wasn't acceptable. In the case of 0.30 mg of magnesium stearate the lubrication was good. Due to improving the poor flowability of the final blend the type of 302 of microcrystalline cellulose was chosen. The quantity of maize starch seems to be good from the point of the tablet-disintegration-time and the dissolution rate as well; therefore, these quantities were chosen for the manufacturing process optimization and scale up.

For evaluation of the effect of micronizing, the dissolution rates of the tablets prepared by the non-micronized ivermectin was measured as well as it is written in section *2.1.P.2.2.3 Physicochemical and Biological Properties.*

Table 10.
Dissolution of Ivermectin from tablets (batch number: VAXX152) prepared by non-micronized ivermectin in 0.01 M phosphate buffer, pH 7 with 0.5% sodium dodecyl sulfate (dissolved amount in %)

	15 min	**30 min**	**45 min**
1.	36.4	52.2	61.3
2.	43.8	63.8	76.2
3.	39.2	55.9	65.7
4.	34.6	52.5	63.8
5.	42.8	61.5	73.3
6.	37.7	53.5	61.9
Average	39.1	56.6	67.0
SD	3.6	4.9	6.3
CV (%)	9.2	8.7	9.3

Summary tablets and charts are prepared to promote the comparison of the products.

Table 11.
Dissolution of Ivermectin from the reference, and the test product prepared by micronized and non-micronized active substance in 0.01M phosphate buffer, pH 7 with 0.5% sodium dodecyl sulfate (average of dissolved amount in %)

Minutes	**Reference product**	**Test product**	
		Micronized ivermectin	**Non-micronized ivermectin**
	TO15953	**VAXX180**	**VAXX152**
15	67.0	67.6	39.1
30	87.3	84.8	56.6
45	94.6	90.1	67.0

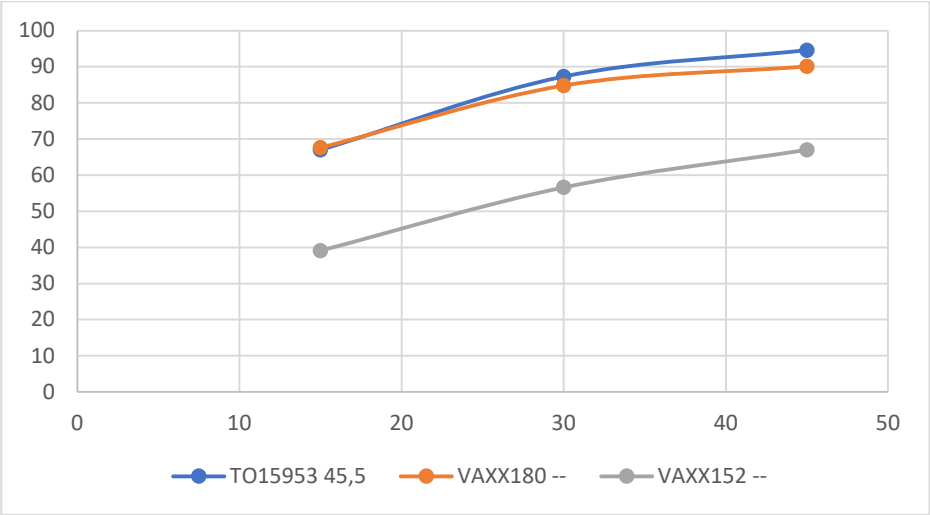


Figure 1
Dissolution of Ivermectin from the reference, the test product and prepared by non-micronized active substance in 0.01M phosphate buffer, pH 7 with 0.5% sodium dodecyl sulfate (average of dissolved amount in %)

Examining the particle size of the drug, it was concluded that the micronized sample should be selected to achieve a rapid dissolution result.

2 Revised risk assessment after formulation development

The initial risk assessment and risk mitigation strategy tables were presented in Part 4.; Drug Product; 4 Preliminary Hazard Analysis.
For those attributes that could have a high/medium impact on the drug product CQAs. actions were taken to control the medium and high risks. Whereas those attributes that had low impact on the drug product CQAs required no further investigation.

As regards the Assay and impurity of the Active Substance their effects can be decrease by applying Active Substance of proper properties.

As regards the effect of the rate of excipients on the properties of tablets prepared by the initial composition the quantity of the magnesium stearate had to be changed because in the case of the first choice sticking occurred during tableting.

Based on the literature data the following compositions are applied for Ivermectin tablets.
During the formulation experiments, it was important to examine the ratio of antioxidant to buffering agent in the ivermectin tablets. Table 3. contain the selected options.

Table 12.
Experimental matrix for first formulation screen – ratio of antioxidant / buffering agent

Material	**Quantity (mg/tablet)**				
Nr. of exp.	VAXX124	VAXX126	VAXX128	VAXX130	VAXX132
Ivermectin	3.33	3.33	3.33	3.33	3.33
Microcrystalline cellulose	53.15	52.91	52.95	53.11	53.03
Pregelatinized starch	3.00	3.00	3.00	3.00	3.00
Citric acid anhydrous	0.20	0.40	0.40	0.20	0.30
Butilhydroxy anisole	0.02	0.06	0.02	0.06	0.04
Magnesium stearate	0.30	0.30	0.30	0.30	0.30
Nominal weight of tablets	**60.00**	**60.00**	**60.00**	**60.00**	**60.00**

The composition of the blends and the property of tablets are summarized in the following table. This composition was made at laboratory scale, size of the batch was 2000 or 3000 pcs of tablets.

Table 13.
Experimental matrix for first formulation screen – ratio of antioxidant / buffering agent
Parameters of the blend

Composition	Quantity (g/batch)				
	VAXX124	**VAXX126**	**VAXX128**	**VAXX130**	**VAXX132**
Ivermectin	6.66	6.66	9.99	6.66	9.99
Microcrystalline cellulose	106.30	105.82	158.85	106.22	159.09
Pregelatinized starch	6.00	6.00	9.00	6.00	9.00
Citric acid anhydrous	0.40	0.80	1.20	0.40	0.90
Butyl hydroxy anisole	0.04	0.12	0.06	0.12	0.12
Magnesium stearate	0.60	0.60	0.90	0.60	0.90
Weight of batch	**120.00**	**120.00**	**180.00**	**120.00**	**180.00**
Parameters of the blend					
Flowability 15mm (s/100g)	10	14	15	9	14
Bulk density (g/100ml)	0.52	0.52	0.52	0.51	0.50
Tapped density (g/100ml)	0.60	0.61	0.61	0.60	0.60
Hausner ratio (-)	1.17	1.18	1.18	1.18	1.20
Homogenized assay (%)	97.6	97.7	98.1	97.2	96.5
Standard deviation (%)	1.8	2.9	3.3	2.0	0.6
RSD (%)	1.9	3.0	3.4	2.1	0.6

The above-mentioned compositions of final blends were examined on stress circumstance. The samples were stored for two weeks at 50°C in closed container.

Table 14.
Experimental matrix for first formulation screen – ratio of antioxidant / buffering agent
Stability test results (Circumstance of stability test: two weeks, 50°C in closed container)

Nr. of exp.	**VAXX124**	**VAXX126**	**VAXX128**	**VAXX130**	**VAXX132**	
Homogenized assay (%)	91.4	91.2	90.5	92.8	89.2	
Standard deviation (%)	7.4	3.0	4.1	5.4	0.6	
RSD (%)	8.1	3.3	4.5	5.8	0.7	
Related substances						**Requirements**
Imp "D" (%)	0.022	0.024	0.030	0.033	0.031	NMT 2.0%
Imp RRT 1,3 (%)	0.010	0.009	0.009	0.009	0.008	NMT 2.7%
Imp RRT 1,4 (%)	0.077	0.074	0.076	0.077	0.075	NMT 2.7%
Imp RRT 1,5 (%)	0.007	0.004	0.005	0.005	0.005	NMT 2.7%
Any unspecified impurity (in all) (%)	0.091	0.084	0.094	0.106	0.094	NMT 1.0 % / pcs
Total impurities (%)	0.208	0.194	0.213	0.229	0.213	NMT 6.0%

The effect of ratio of antioxidant and buffer on stability data did not show significant differences. The most preferred composition was VAXX132, where the assay decreasing was the lowest. The impurity profile for each sample is well below the expected value.

Table 15.
Experimental matrix for first formulation screen – ratio of antioxidant / buffering agent
Parameters of the tablets

Composition	**VAXX128**		**VAXX132**	
Parameters of the tablets	12 kN (at the beginning of the tablet process)	12 kN (at the end of the tablet process)	12 kN (at the beginning of the tablet process)	12 kN (at the end of the tablet process)
Appearance	appropriate	appropriate	appropriate	appropriate
Average mass (mg)	60.4	61.1	60.8	61.2
Weight variation (%)	1.49	1.40	1.30	1.34
Height (mm)	1.81	1.82	1.77	1.79
Hardness (N)	42	39	41	42
Friability (%)	0.0	0.0	0.0	0.0
Disintegration time (sec)	57	23	27	21
Tablet assay (%)	94.3	96.6	96.0	93.1
Standard deviation (%)	1.0	0.2	0.3	0.8
RSD (%)	1.0	0.2	0.3	0.8

3 Conclusion

During the tableting process, size separation of the particles was not observed, the standard deviation of tablet assay is NMT 1%.

Table 16.
Experimental matrix for second formulation screen –
effect of the batch size increasing for assay of the homogenate

Material	**Quantity (mg/tablet)**		
Product	**VAXX132**	**VAXX150**	**VAXX180**
Ivermectin	3.33	3.33	3.38*
Microcrystalline cellulose	53.03	53.03	53.06
Pregelatinized starch	3.00	3.00	3.00
Citric acid anhydrous	0.30	0.30	0.20
Butyl hydroxy anisole	0.04	0.04	0.06
Magnesium stearate	0.30	0.30	0.30
Nominal weight of tablets	**60.00**	**60.00**	**60.00**
			*3% overages
Composition	**Quantity (g/batch)**		
	VAXX132 (3000 pieces)	VAXX150 (12 000 pieces)	VAXX180 (12 000 pieces)
Ivermectin	9.99	39.84	40.56
Microcrystalline cellulose	159.09	636.48	636.72
Pregelatinized starch	9.00	36.00	36.00
Citric acid anhydrous	0.90	3.60	2.40
Butyl hydroxy anisole	0.12	0.48	0.72
Magnesium stearate	0.90	3.60	3.60
Weight of batch	**180.00**	**720.00**	**720.00**
Parameters of the blend			
Loss on drying (at 105°C) (%)	4.60	4.08	4.05
Flowability 15mm (s/100g)	14	14	13
Bulk density (g/100ml)	0.50	0.52	0.51
Tapped density (g/100ml)	0.60	0.62	0.62
Hausner ratio (-)	1.20	1.20	1.22
Homogenized assay (%)	96.5	97.0	101.8
Standard deviation (%)	0.6	0.3	1.3
RSD (%)	0.6	0.3	1.3
Tablet assay (%)	96.0	97.9	100.0
Standard deviation (%)	0.3	0.5	0.8
RSD (%)	0.3	0.5	0.8

4 Conclusion

Without overage, the active substance content was about 3% lower than expected. Increasing the batch size (VAXX150), the homogenized assay was measured higher, than in case of VAXX132. Using 3% overages (VAXX180), the appropriate assay was measured in the homogenate and tablets too. The standard deviation of homogenized assay and the tablet assay are below 1.5%.

Table 17.
Hazard Analysis (HA) of manufacture of Ivermectin MEDITOP 3 mg tablets from the point of Critical Quality Attributes

CQA	CMA				
	AS assay	AS impurities	AS particle size	AS sensitivity	Type and rate of excipients
Appearance	N	N	M	L	L
Assay	L	L	N	N	N
CU	L	N	L	N	N
Dissolution	N	N	L	N	L
Impurities	N	L	L	L	L

Color coding for relative risk ranking:

High/H	affect quality attributes – further investigations and controls needed in order to reduce risk
Medium/M	potential to affect quality attributes – further investigations and controls may be needed in order to reduce risk
Low/L	low impact on quality attributes – no further investigations needed
Low/L	low impact on quality attributes – risk is mitigated.
No risk/N	no impact on quality attributes – no further investigations needed

Based on the activities performed in the formulation development, the related risks of the Critical Quality Attributes could be decreased to low level

Table 18.
Revised Risk Assessment for Justification and Risk Mitigation Strategies for Risks of CMAs

CMA	CQA	Initial risk	Description of CMA's effect on FP CQAs	Risk mitigation Strategy / Control Strategy Action points	Results/ Summary	Revised risk
AS Assay	Assay	H	Product assay depends on the AS assay.	During weighing calculate the AS weight based on AS assay of the relevant AS CoA.	With the proposed AS specification control in place. the risk is considered to be low.	L
AS impurities	Assay	M	Product may have low assay due to the high impurity level of API.	Control the impurity profile of the AS with analytical measurements according to the AS specification.	With the proposed AS specification control in place. the risk is considered to be low.	L
	Impurities	H	Product may have high impurity content due to the high impurity level of API.			L
AS particle size	Content Uniformity (CU)	L	Inappropriate particle size of AS may have effect on CU of product.	Appropriate particle size can reduce risk.	With the proposed AS particle size specification, the risk is considered to be low.	L
	Dissolution	H	Too large particle size has effect on dissolution rate of the final product (FP)	The low solubility of the active ingredient leads to high effect on the dissolution rate. Appropriate particle size can reduce risk.	With the proposed AS particle size specification, the risk is considered to be low.	L
	Impurities	L	It is anticipated that potential degradation of active substance may be faster for smaller particle size. since it corresponds to the larger surface area.	Appropriate particle size can reduce risk.	Low risk on quality attributes No investigations was needed.	L
AS sensitivity	Appearance	L	Sensitivity of AS to any environmental parameter (oxygen. temperature. moisture or light) may influence the appearance of the product. and may have impact on FP appearance and impurity levels.	According to the DMF of the AS is not hygroscopic and not sensitive to heat. With standard working condition and packaging the risk can be eliminated	Low risk on quality attributes No investigations was needed.	L
	Impurities	L			Low risk on quality attributes No investigations was needed.	L
Type and rate of excipients	Appearance	L	Inappropriate type and rate of excipients may negatively affect the appearance. dissolution ate and degradation products of FP.	As the test composition is similar to the reference product the rate of excipients should be approved by dissolution and stability test.	Low risk on quality attributes No investigations was needed.	L
	Dissolution	H			With quantities of the excipients chosen the risk is considered to be low.	L
	Impurities	L			Low risk on quality attributes No investigations was needed.	L

2.1.P.2.2.2 Overages

3 % overages were applied in this preparation, due to the active substance lost during the manufacturing process which was caused by the low particle size of the micronized active substance.

Without overage, the active substance content was about 3% lower than expected. Increasing the batch size (VAXX150), the homogenized assay was measured higher, than in case of VAXX132. Using 3% overages (VAXX180), the appropriate assay was measured in the homogenates and tablets too. The standard deviation of the homogenized assay and the tablet assay are below 1.5%.

2.1.P.2.2.3 Physicochemical and Biological Properties

1 *In vitro* dissolution

1.1 Introduction

Scientific databases, official monographs and guidelines (issued by EMA, FDA, ICH) as well as the data presented by the manufacturer of reference product (Stromectol 3 mg tablets - Merck Sharp & Dohm BV) had been overviewed and assessed before the *in vitro* dissolution method development and the subsequent *in vitro* dissolution studies to compare the in vitro performance of the reference product and the newly developed test product.

However, due to the low solubility of ivermectin the complete dissolution in the usual aqueous buffers cannot be achieved at all. Therefore, the comparative dissolution method and QC meth-od were chosen based on the USP Monograph of Ivermectin tablets that uses a dissolution medium 0.01M phosphate buffer of pH 7 with 0.5% sodium dodecyl sulfate (SDS). Similarly, 0.5% sodium dodecyl sulfate was applied in the buffer of pH 4.5 as well. In the case of buffer pH 1.2, the solubility and dissolution of ivermectin can't be measured due to the acidic degradation of the product.

Using of Apparatus 2 with 50 rpm agitation speed is adequate to test and compared the in vitro character of the formulations. Complete dissolution of this active agent can be achieved for 900 ml dissolution medium containing 0.5% anionic surface-active SDS. Because this is the suggested USP method and its discriminative power was observed in the case of micronized and non-micronized active substance as well, other discriminatory tests were not made. Validation of the dissolution method was also executed and these data also supported the adequate solution stability, which is required for solubility trials as well.

In vitro dissolution character of the reference and test products were compared to support the development and planning of bioequivalence study. One batch of the reference product with Stromectol 3 mg tablets - Merck Sharp & Dohm BV and the one batch of the test product Ivermectin MEDITOP 3 mg tablets produced in laboratory scale and its three batches manufactured in pilot scale were compared to evaluate the similarity.

Because the QC method is the same as the dissolution method in 0.01M phosphate buffer, pH 7 with 0.5% sodium dodecyl sulfate separates tests weren't made.

As a basic test, the solubility of Ivermectin was evaluated in these buffers. Based on the literature data (Drugbank.ca) the pKa values of this active substance are 12.47 and -3.4. Since this value is not within the physiological range, consequently the solubility at these pH-s was not tested.

- 250 ml media was filled into a vessel of dissolution tester (Apparatus 2)
- it was temperated to 37°C
- API was added gradually to the media and intensively stirred (paddle with 150 rpm) and the solubility was tested visually
- if the solubility is not complete, liquid was filtered through 10 µm cellulose ester filter
- API content was determined by HPLC method (details are described in section 1.4)

Table 19.
Solubility of Ivermectin

Media*	Measured solubility (mg/mL)	Maximum capacity of 900 mL dissolution media (mg)	Maximum capacity of 250 mL dissolution media (mg)	Evaluation according to BCS criterion (Critical limit: 18 mg/250 mL)**	pH value after stirring for 1 hour
acetate buffer at pH 4.5	<LOD	<LOD	<LOD	low solubility	4.52
acetate buffer at pH 4.5 + 0.5% SDS	0.34	308.03	85.56	high solubility	4.52
pH 7.0 (0.01 M Phosphate buffer)	<LOD	<LOD	<LOD	low solubility	7.03
pH 7.0 (0.01 M Phosphate buffer) + 0.5 % SDS	0.34	309.91	86.09	high solubility	7.02

*Compositions of the media are given in section 1.3 In vitro dissolution profile of test products manufactured in pilot scale.

**The maximum single dose is ~ 200 mcg/kg, therefore ~ 18 mg according to the SMPC of Stromectol tablets.

1.2 *In vitro* dissolution profile of test products manufactured in laboratory scale

1.2.1 Methods used for *In vitro* dissolution profile tests according to USP Monograph

Instrumentation:	ERWEKA DT-80 dissolution tester Agilent 708-DS dissolution tester with Agilent 850-DS sampling station Shimadzu Nexera X2 UHPLC Shimadzu LC-20AD
Media:	900 mL - pH 7.0 (0.01 M Phosphate buffer)
Method:	paddle
Agitation rate:	50 rpm
Temperature:	37 ± 0.5°C
Sample amount:	1 tablet per vessel
Time points:	15, 20, 30, 45 min +10 min with 250 rpm stirring
Mobile phase:	water for HPLC : MeOH : ACN = 12 : 35 : 53
Column:	Zorbax SB C18; 250 x 4,6 mm; 5 µm or equivalent + ballast column
Wavelength:	245 nm
Flow rate:	1.2 ml/min
Injection volume:	50 µl
Run time:	25 min
Oven temperature	30 °C

Sampling

Withdraw 5.0 ml of sample at the specified time points and filtered through 0.45 µm CA filter.
Agilent 850-DS sampling station uses 10 µm polyethylene full flow filters.

Calculation

$$Fx = \left(\left(\frac{Asam(x)}{Astd(x)}\right) * \left(\frac{ConcStd}{ConcMax}\right) * TabStr + M(x-1) + \ldots + M(x - m)\right)/TabStr$$

where:

Conc(x-1)	= (Asam(x-1)/Astd(x-1))*ConcStd
Fx	= fraction of active dissolved at time x
Asam(x)	= area of sample at time x
Astd(x)	= area of standard at time x
ConcStd	= concentration of standard solution (milligrams/milliliter)
ConcMax	= maximum theoretical concentration of sample (milligrams of dissolved drug/milliliter of dissolution medium)
Tab Str	= tablet or capsule strength (milligrams of drug/tablet or capsule)
M(x-1)	= milligrams of dissolved drug substance removed at time (x-1) = Conc(x-1) x mL:
Conc(x-1)	= concentration (milligrams/milliliter of dissolved drug substance in dissolution vessel at time (x-1).
mL	= milliliters of medium removed at each time point.

1.2.2 Evaluation of results

The results obtained in these comparative *in vitro* dissolution tests were evaluated according to *Guideline on the Investigation of Bioequivalence CPMP/QWP/EWP/1401/98 Rev. 1.* Consequently. where more than 85% of the drug is dissolved within 15 minutes. dissolution profiles may be accepted as similar without further mathematical evaluation. In case more than 85% is not dissolved at 15 minutes. dissolution similarity is determined by using the f_2 statistic.

$$f_2 = 50 \times \log\left[100 / \left(1 + (1/n)\sum_{t=1}^{n}\left|R_t - T_t\right|^2\right)^{-0.5}\right]$$

where f_2 is similarity factor. n is the number of observations. R_t is percentage drug dissolved from reference formulation. and T_t is percentage drug dissolved from test formulation. All the following requirements of the abovementioned guideline for the calculations were taken into account.

- A minimum of three time points (zero excluded)
- The time points should be the same for the two formulations
- Twelve individual values for every time point for each formulation
- Not more than one mean value of > 85% dissolved for any of the formulations.
- The relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less than 10% from second to last time point.

1.2.3 Tested products

Reference product:

- Stromectol 3 mg tablets – Merck Sharp & Dohm BV
  - batch numbers: TO15953

Test product:

- Ivermectin MEDITOP 3 mg tablets
  - batch numbers: VAXX180

1.2.4 Results

In vitro dissolution test results of 12 tablets of reference product (Stromectol 3 mg tablets) and 12 tablets of test product (Ivermectin MEDITOP 3 mg tablets) are summarized in the following tables.

Table 20.
Dissolution of Ivermectin from the reference product (batch number: TO15953), in 0.01M phosphate buffer, pH 7 with 0.5% sodium dodecyl sulfate (dissolved amount in %)

	10 min	15 min	30 min	45 min
1.	49.4	70.6	89.1	94.6
2.	38.6	60.2	83.4	91.1
3.	48.4	69.3	90.6	97.2
4.	45.0	67.3	88.3	95.5
5.	47.1	68.4	88.9	94.8
6.	44.3	66.1	83.5	94.3
Average	45.5	67.0	87.3	94.6
SD	3.9	3.7	3.1	2.0
CV (%)	8.5	5.5	3.5	2.1

Table 21.
Dissolution of Ivermectin from the test product (batch number: VAXX180) in 0.01 M phosphate buffer, pH 7 with 0.5% sodium dodecyl sulfate (dissolved amount in %)

	10 min	15 min	30 min	45 min
1.	--	65.3	83.9	90.6
2.	--	66.3	84.1	89.9
3.	--	73.0	87.0	88.9
4.	--	60.0	81.3	90.7
5.	--	68.9	86.1	91.5
6.	--	72.4	86.3	88.9
Average	--	67.6	84.8	90.1
SD	--	4.9	2.1	1.1
CV (%)	--	7.2	2.5	1.2

Summary tablets and charts are prepared to promote the comparison of the products.

Table 22.
Dissolution of Ivermectin from the reference and the test product in 0.01M phosphate buffer, pH 7 with 0.5% sodium dodecyl sulfate (average of dissolved amount in %)

Minutes	Reference product	Test product
	TO15953	VAXX180
10	45,5	--
15	67,0	67,6
30	87,3	84,8
45	94,6	90,1

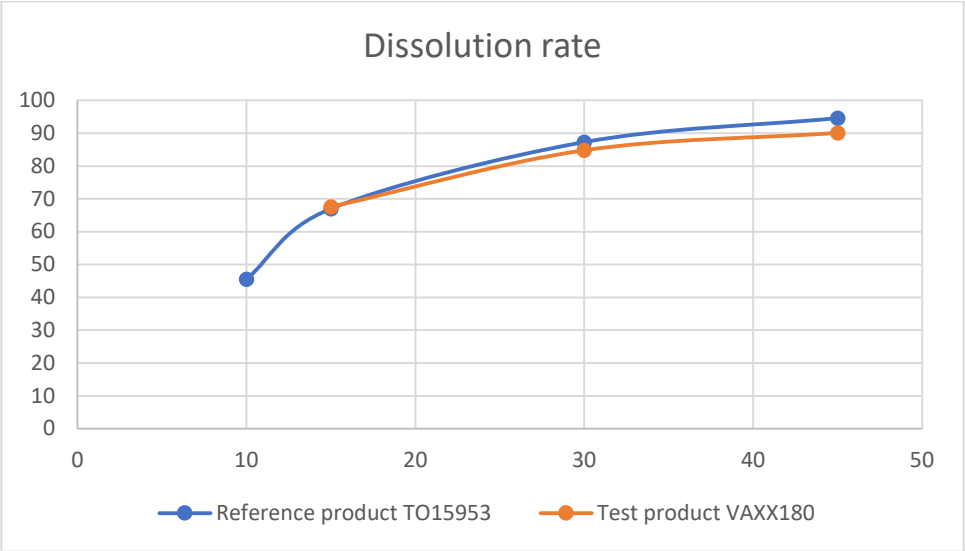


Figure 2
Dissolution of Ivermectin from the reference and test product at 0.01M phosphate buffer, pH 7 with 0.5% sodium dodecyl sulfate (average of dissolved amount in %)

It can be concluded, that more than 80% of the active agent is dissolved within 30 minutes from both samples. The f2 comparison value for the dissolution profiles is 75, therefore they can be considered as similar.
Finally, it can be concluded that for the manufacture technology of Ivermectin 3 mg test tablets developed in laboratory scale is appropriate for scale up.

1.3 *In vitro* dissolution profile of test products manufactured in pilot scale

1.3.1 Methods used for *in vitro* dissolution profile test according to GUIDELINE

Instrumentation:	ERWEKA DT-80 dissolution tester Agilent 708-DS dissolution tester with Agilent 850-DS sampling station Shimadzu Nexera X2 UHPLC Shimadzu LC-20AD
Media:	900 mL of dissolution media
Method:	paddle (Apparatus 2)
Temperature:	37 ± 0.5°C
Agitation rate:	50 rpm
Time points:	15, 20, 30, 45 min +10 min with 250 rpm stirring
Detection:	HPLC

Preparation of dissolution medium – pH 4.5 (Acetate buffer)
Dissolve 2.99 g of sodium acetate trihydrate in 500 mL of purified water and add 14.0 mL of 2M
acetic acid for the preparation of 1000 mL dissolution medium. Mix well and dilute to 1000.0
mL with purified water. The acidity of the medium is set to pH= 4.5 with NaOH solution or hydrochloric acid

Preparation of dissolution medium – pH 4.5 (Acetate buffer) with 0.5 % sodium dodecyl sulfate
Dissolve 2.99 g of sodium acetate trihydrate in 500 mL of purified water and add 14.0 mL of 2M
acetic acid for the preparation of 1000 mL dissolution medium. Mix well and dilute to 1000.0
mL with purified water. The acidity of the medium is set to pH= 4.5 with NaOH solution or hydrochloric acid
Then add 0.5 % sodium dodecyl sulfate and control the pH.

Preparation of dissolution medium – pH 7.0 (0.01 M Phosphate buffer)
Dissolve 0.53 g of potassium phosphate monobasic in 500 mL of purified water and add 20.53 g of disodium hydrogen phosphate dihydrate for the preparation of 1000 mL dissolution medium. Mix well and dilute to 1000.0 mL with purified water. The acidity of the medium is set to pH= 7.0 with NaOH solution or phosphoric acid.

Preparation of dissolution medium – pH 7.0 (0.01 M Phosphate buffer) with 0.5 % sodium dodecyl sulfate
Dissolve 0.53 g of potassium phosphate monobasic in 500 mL of purified water and add 20.53 g of disodium hydrogen phosphate dihydrate for the preparation of 1000 mL dissolution medium. Mix well and dilute to 1000.0 mL with purified water. The acidity of the medium is set to pH= 7.0 with NaOH solution or phosphoric acid.
Then add 0.5 % sodium dodecyl sulfate and control the pH.

Preparation of standard solution
Dissolve 33.0 mg of Ivermectin CRS standard in 100.0 mL methanol. Dilute this sample 100 times with the dissolution media.

Description of the analytical method

Mobile phase:	water for HPLC : Methanol : ACN : 12 : 35 : 53
Flow:	1.2 mL/min
Column:	Zorbax SB C18; 250 x 4,6 mm; 5 µm or equivalent + ballast column
Detection:	UV at 245 nm
Injection volume (sample):	50 µl
Column temperature:	30 °C
Flow rate:	1.2 mL/min
Rack temperature:	ambient
Runtime:	25 min
Retention time for Ivermectin:	~20 min

Sampling
Withdraw 5.0 mL of sample at the specified time points and filtered through 0.45 µm CA filter. Agilent 850-DS sampling station uses 10 µm polyethylene full flow filters.

Calculation

Fx=((Asam(x)/Astd(x))┤ *(ConcStd/ConcMax)*TabStr+M(x-1)+...+M(x-m))/TabStr

Conc(x-1)	= (Asam(x-1)/Astd(x-1))*ConcStd
Fx	= fraction of active dissolved at time x
Asam(x)	= area of sample at time x
Astd(x)	= area of standard at time x
ConcStd	= concentration of standard solution (milligrams/milliliter)
ConcMax	= maximum theoretical concentration of sample (milligrams of dis solved drug/milliliter of dissolution medium)
Tab Str	= tablet or capsule strength (milligrams of drug/tablet or capsule)
M(x-1)	= milligrams of dissolved drug substance removed at time (x-1) = Conc(x-1) x mL:
Conc(x-1)	= concentration (milligrams/milliliter of dissolved drug substance in dissolution vessel at time (x-1).
mL	= milliliters of medium removed at each time point.

1.3.2 Description of the dissolution method in pH 7.0 (0.01 M Phosphate buffer)

Instrumentation:	ERWEKA DT-80 dissolution tester Agilent 708-DS dissolution tester with Agilent 850-DS sampling station Shimadzu Nexera X2 UHPLC Shimadzu LC-20AD
Media:	900 mL of pH 7.0 (0.01 M phosphate buffer)
Method:	paddle
Agitation rate:	50 rpm
Temperature:	37 ± 0.5°C
Sample amount:	1 tablet per vessel
Time points:	15, 20, 30, 45 min +15 min with 250 rpm stirring
Mobile phase:	water for HPLC : MeOH : ACN = 12 : 35 : 53
Column:	Zorbax SB C18; 250 x 4.6 mm; 5 µm or equivalent + ballast column
Wavelength:	245 nm
Flow rate:	1.2 ml/min
Injection volume:	50 µl
Run time:	25 min
Oven temperature	30 °C

Preparation of standard solution
Dissolve 33.0 mg of Ivermectin CRS standard in 100.0 mL methanol. Dilute this sample 100 times with methanol.

Sampling
Withdraw 5.0 mL of sample at the specified time points and filtered through 0.45 µm CA filter.
Agilent 850-DS sampling station uses 10 µm polyethylene full flow filters.

Evaluation of results
The results obtained in these comparative in vitro dissolution tests were evaluated according to Guideline on the Investigation of Bioequivalence CPMP/QWP/EWP/1401/98 Rev. 1. Consequently. where more than 85% of the drug is dissolved within 15 minutes. dissolution profiles may be accepted as similar without further mathematical evaluation. In case more than 85% is not dissolved at 15 minutes. dissolution similarity is determined by using the $f2$ statistic.
where f2 is similarity factor. n is the number of observations,
Rt is percentage drug dissolved from reference formulation,
and Tt is percentage drug dissolved from test formulation.
All the following requirements of the abovementioned guideline for the calculations were taken into account.
A minimum of three time points (zero excluded)
The time points should be the same for the two formulations
Twelve individual values for every time point for each formulation
Not more than one mean value of > 85% dissolved for any of the formulations.
The relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less than 10% from second to last time point.

1.3.4 Description of the dissolution method in pH 4.5 acetate buffer with 0.5 % so dium dodecyl sulfate

Instrumentation:	ERWEKA DT-80 dissolution tester Agilent 708-DS dissolution tester with Agilent 850-DS sampling station Shimadzu Nexera X2 UHPLC Shimadzu LC-20AD
Media:	900 mL of pH 4.5 acetate buffer with 0.5 % sodium do-
decyl sulfate	
Method:	paddle
Agitation rate:	50 rpm
Temperature:	37 ± 0.5°C
Sample amount:	1 tablet per vessel
Time points:	15, 20, 30, 45 min +15 min with 250 rpm stirring
Mobile phase:	water for HPLC : MeOH : ACN = 12 : 35 : 53
Column:	Zorbax SB C18; 250 x 4.6 mm; 5 µm or equivalent + ballast column
Wavelength:	245 nm
Flow rate:	1.2 ml/min
Injection volume:	50 µl
Run time:	25 min
Oven temperature	30 °C

Preparation of standard solution
Dissolve 33.0 mg of Ivermectin CRS standard in 100.0 mL methanol. Dilute this sample 100 times with the dissolution media.

Sampling
Withdraw 5.0 mL of sample at the specified time points and filtered through 0.45 µm CA filter.
Agilent 850-DS sampling station uses 10 µm polyethylene full flow filters.

1.3.5 Tested products

Reference product:
- Stromectol 3 mg tablets – Merck Sharp & Dohm BV
  - batch numbers: TO15953

Test products:
- Ivermectin MEDITOP 3 mg tablets
  - batch numbers: IM15001, IM15002, IM15003

1.3.6 Bioequivalence trial information

Table 23
Test and reference product information

Product Characteristic	Test product	Reference product
Name	Ivermectin MEDITOP 3 mg tablets	Stromectol 3 mg tablets
Strength	3 mg	3 mg
Dosage form	Tablet	Tablet
Manufacturer	MEDITOP Pharmaceutical Ltd.	Merck Sharp & Dohm Co.
Batch number	IM15001	TO15953
Batch size	100.000 pcs	
Measured content (% of label claim	97.95	101.3
Commercial batch size	300.000 pcs	
Expiry date (Retest date)	11/2021	01/2022
Location of Certificate of Analysis	Pilisborosjenő	Pilisborosjenő
Member State where the reference product was purchased from		Netherland
This product was used in the following trials	Study ID:	Study ID:

1.4 Result

1.4.1 *In vitro* dissolution profiles at pH 7.0 + 0.5% SDS

Table 24.
Dissolution of Ivermectin from reference tablets (batch number: TO15953) at pH 7.0 + 0.5 % SDS (dissolved amount in %)

	15 min	20 min	30 min	45 min	+15 min with 250 rpm stirring
1.	65.8	75.9	84.0	89.1	92.0
2.	68.3	77.3	84.6	87.4	91.4
3.	71.2	79.8	86.8	90.6	93.5
4.	62.7	78.5	85.9	92.2	96.8
5.	68.6	78.5	86.4	89.7	92.8
6.	66.3	76.8	88.6	93.7	96.5
7.	70.0	80.9	87.8	92.7	95.0
8.	67.3	78.5	89.4	95.1	98.2
9.	64.9	77.6	88.5	93.7	96.4
10.	72.9	83.5	91.7	97.1	99.4
11.	73.2	82.1	89.0	93.1	95.4
12.	71.2	80.1	87.8	92.5	94.8
Average	**68.5**	**79.1**	**87.5**	**92.2**	**95.2**
SD	3.3	2.2	2.1	2.7	2.5
CV (%)	4.8	2.8	2.4	2.9	2.6

Table 25.
Dissolution of Ivermectin from test tablets (batch number: IM15001) at pH 7.0 + 0.5 % SDS (dissolved amount in %)

	15 min	20 min	30 min	45 min	+15 min with 250 rpm stirring
1.	66.0	81.2	89.9	96.1	99.8
2.	72.3	86.7	93.6	98.3	98.6
3.	76.4	89.6	96.7	100.2	99.6
4.	64.1	81.3	90.5	96.1	99.7
5.	64.7	77.4	85.2	90.1	92.1
6.	67.6	83.7	92.9	97.6	100.1
7.	69.2	82.2	94.4	95.8	84.9
8.	66.9	79.2	91.9	93.7	91.6
9.	70.3	85.7	90.2	92.8	88.5
10.	68.3	83.0	94.4	96.0	88.6
11.	66.1	82.0	92.1	94.5	94.8
12.	77.6	89.5	92.9	88.2	96.3
Average	**69.1**	**83.5**	**92.1**	**94.9**	**94.5**
SD	4.3	3.8	2.9	3.4	5.3
CV (%)	6.3	4.5	3.2	3.5	5.6

Table 26.
Dissolution of Ivermectin from test tablets (batch number: IM15002) at pH 7.0 + 0.5 % SDS (dissolved amount in %)

	15 min	20 min	30 min	45 min	+15 min with 250 rpm stirring
1.	65.6	81.1	89.5	92.3	93.2
2.	68.7	81.5	89.4	95.2	97.2
3.	72.2	82.5	88.6	92.6	93.6
4.	66.1	79.3	85.8	90.8	93.9
5.	75.7	84.4	89.2	92.1	97.5
6.	65.7	79.3	87.5	93.4	94.9
7.	62.2	77.3	86.3	91.3	93.7
8.	69.3	78.1	83.2	88.9	91.2
9.	75.4	84.2	87.0	87.9	88.8
10.	63.0	78.5	85.4	90.3	91.2
11.	72.3	82.6	87.2	89.8	88.7
12.	67.5	81.6	87.3	92.0	94.8
Average	**68.7**	**80.9**	**87.2**	**91.4**	**93.2**
SD	4.5	2.4	1.9	2.0	2.8
CV (%)	6.5	2.9	2.1	2.2	3.0

Table 27.
Dissolution of Ivermectin from test tablets (batch number: IM15003) at pH 7.0 + 0.5 % SDS (dissolved amount in %)

	15 min	20 min	30 min	45 min	+15 min with 250 rpm stirring
1.	69.4	88.3	96.5	99.8	101.0
2.	67.2	79.5	86.6	94.2	97.1
3.	74.2	88.1	100.2	102.1	103.0
4.	67.2	83.3	90.1	94.5	97.5
5.	67.1	81.7	90.2	96.2	99.5
6.	71.1	85.1	90.9	95.6	97.2
7.	70.3	83.2	89.7	92.0	95.4
8.	75.7	85.3	90.1	92.0	92.9
9.	82.0	89.3	89.8	93.2	93.9
10.	67.5	79.9	86.6	91.2	93.3
11.	70.5	80.5	86.9	89.8	91.2
12.	91.9	93.6	93.7	94.8	95.5
Average	**72.8**	**84.8**	**90.9**	**94.6**	**96.5**
SD	7.5	4.3	4.1	3.5	3.5
CV (%)	10.2	5.1	4.5	3.7	3.6

Table 28.
Dissolution of Ivermectin from the reference and test product at pH 7.0 + 0.5 % SDS (average of dissolved amount in %)

Minutes	Reference product	Test product		
	TO15953	IM15001	IM15002	IM15003
15	68.5	69.1	68.7	72.8
20	79.1	83.5	80.9	84.8
30	87.5	92.1	87.2	90.9
45	92.2	94.9	91.4	94.6
60	95.2	94.5	93.2	96.5

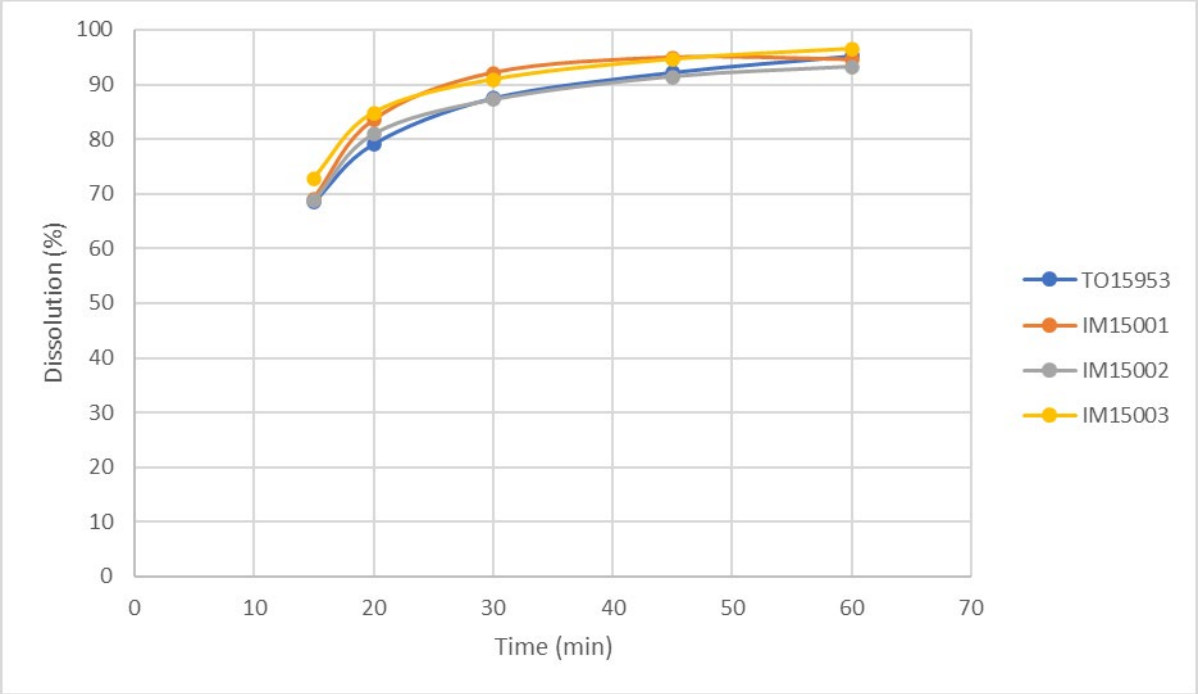


Figure 3
Dissolution of Ivermectin from the reference and test product at pH 7.0 + 0.5 % SDS (average of dissolved amount in %)

1.4.1.1 Conclusion

The evaluations are made in pairs to compare all the test products for both reference products and compare them to each other.

- Comparing TO15953 to IM15001 – f2 = 71
- Comparing TO15953 to IM15002 – f2 = 92
- Comparing TO15953 to IM15003 – f2 = 66
- Comparing IM15001 to IM15002 – f2 = 74
- Comparing IM15001 to IM15003 – f2 = 79
- Comparing IM15002 to IM15003 – f2 = 69

Since all the calculated similarity factors are higher than 50, it can be concluded that not only the similarity of the three batches of developed and the batch of reference products are proven, but also the similarity of the different batches of the developed products, consequently the robustness of the manufacturing process was also supported from this perspective.

1.4.2 *In vitro* dissolution profiles at pH 4.5 + 0.5% SDS

In this case the comparison of the dissolution rate of the "bio batches" was compared.

Table 29.
Dissolution of Ivermectin from reference tablets (batch number: TO15953) at pH 4.5 + 0.5 % SDS (dissolved amount in %)

	15 min	**20 min**	**30 min**	**45 min**	**+15 min with 250 rpm stirring**
1.	75.4	85.2	95.6	97.0	98.0
2.	76.7	85.5	92.5	94.5	94.8
3.	75.7	88.3	94.5	95.2	95.6
4.	73.6	84.7	91.2	93.9	95.0
5.	80.6	86.1	94.6	96.8	97.5
6.	77.3	87.5	93.9	97.0	97.1
7.	75.5	82.0	93.5	93.9	94.4
8.	76.4	82.2	91.6	92.8	92.9
9.	74.2	82.1	91.5	92.3	92.0
10.	75.7	86.2	91.9	94.9	95.2
11.	73.7	81.1	84.5	86.6	85.8
12.	74.1	82.6	88.8	92.3	93.9
Average	**75.7**	**84.4**	**92.0**	**93.9**	**94.3**
SD	1.9	2.4	3.0	2.9	3.2
CV (%)	2.6	2.9	3.3	3.1	3.4

Table 30.
Dissolution of Ivermectin from test tablets (batch number: IM15001) at pH 4.5 + 0.5 % SDS (dissolved amount in %)

	15 min	20 min	30 min	45 min	+15 min with 250 rpm stirring
1.	69.9	84.6	88.4	90.5	90.6
2.	68.2	80.1	84.5	87.8	88.8
3.	65.4	84.1	87.5	88.6	89.0
4.	64.3	78.5	82.5	85.5	88.8
5.	63.3	78.6	83.2	85.8	84.4
6.	69.6	82.1	85.0	88.3	86.3
7.	65.2	80.7	84.6	85.9	87.8
8.	65.2	75.1	78.4	80.4	84.1
9.	71.6	79.3	80.6	82.7	83.8
10.	67.3	79.1	83.0	86.7	88.8
11.	70.7	81.7	86.4	82.5	91.6
12.	69.6	78.4	81.2	87.8	85.8
Average	**67.5**	**80.2**	**83.8**	**86.0**	**87.5**
SD	2.8	2.7	2.9	2.9	2.6
CV (%)	4.1	3.3	3.5	3.4	3.0

Table 31.
Dissolution of Ivermectin from the reference and test product at pH 4.5 + 0.5 % SDS (average of dissolved amount in %)

Minutes	Reference product	Test product
	TO15953	IM15001
15	75.7	67.5
20	84.4	80.2
30	92.0	83.8
45	93.9	86.0
60	94.3	87.5

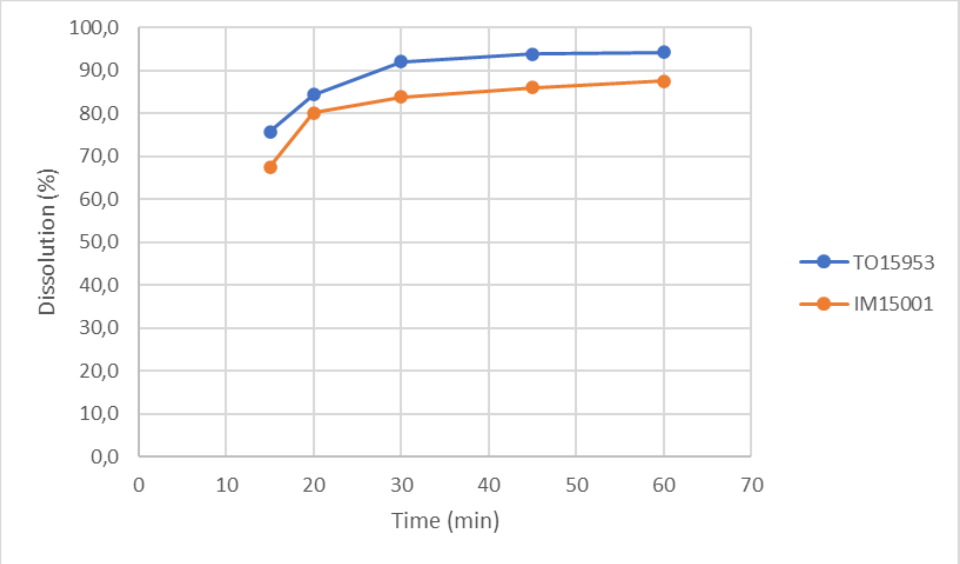


Figure 4
Dissolution of Ivermectin from the reference and test product at pH 4.5 + 0.5 % SDS (average of dissolved amount in %)

1.4.2.1 Conclusion

The evaluations are made to compare the test product and the reference product by f2 probe.

- Comparing TO15953 to IM15001 – f2 = 57

Since the calculated similarity factor is higher than 50, it can be concluded the similarity of the reference and the test product (bio batches).

1.5 Summary of in vitro dissolution test

Ivermectin has low solubility in water at the physiological pH range moreover it degrades at low pH values. Therefore, the comparison of the dissolution rate of the test and reference product can be made by the dissolution method suggested by USP and WHO Monograph that apply 0.01M phosphate buffer of pH 7 with 0.5% sodium dodecyl sulfate (SDS). Similarly, 0.5% sodium dodecyl sulfate could be applied in the buffer of pH 4.5 as well. In the case of buffer pH 1.2, the solubility and dissolution of ivermectin can't be measured due to the acidic degradation of the product.

At laboratory development the dissolution rate of test tablets manufactured by micronized and non-micronized active substance it was found that for ensuring similar dissolution to the reference product the micronizing is necessary.

The dissolution of the three batches of the test product manufactured in pilot scale were compared to the reference product by the USP method. For comparison the f2 probe was used and it was found that the f2 value is higher than 50 in all paired combination that means similarity for all cases and suggest the robustness of the manufacture process too.

For QC dissolution method the USP/WHO method was chosen as well.

For clinical study the test product batch IM15001 was chosen.
As supportive data the dissolution rate comparison of the clinical batches of the test and reference product was made in buffer of pH 4.5 0.5% sodium dodecyl sulfate as well. The value of f2 probe show similar dissolution profile in that case too.

Therefore, on the basis of the in vitro dissolution tests there may be a good probability of bioequivalence of the test and the reference batches.

2.1.P.2.3 Manufacturing Process Development

Predetermined target product profile and the related preliminary risk assessment are presented before. These methodologies were considered, so the composition of the drug product had been successfully developed for the related manufacturing process development and scale up.

Taking into consideration the target product profile and risk assessment the critical quality attributes and the critical process parameters had been identified for the complex evaluation of the manufacturing process. The critical quality attributes (CQAs) are physical and chemical property or characteristic of the drug, excipients and intermediate(s) that must be controlled directly or indirectly to ensure the quality of the product. The critical process parameters (CPP) are process inputs that have a direct and significant influence on the critical quality attributes of the intermediate(s) or the critical quality attributes of the product when they are varied within regular operation range, CPP and CQAs are linked by risk assessment of the process, so the understanding their connection leads up a product with predefined quality and it decreases the risk of failure.

The CQA of the active ingredient:	particle size
The CQA of the excipients:	particle size
The CQAs of the intermediate:	flow properties of the final blend
	content uniformity of the final blend
	average weight of the tablets
	weight uniformity of the tablets
	disintegration time
The CQAs of the product:	visual attributes
	average weight of the product
	assay
	uniformity of dose unit
	dissolution
	impurities

Taking into account the well-known CQAs and CPPs of a manufacturing process of an immediate release tablets produced by dry mixing, the following matrix with the most relevant relationship can be compiled.

Table 34.
CPP of the manufacturing process and CQAs of the intermediates and of the products

Unit operation	Process parameter	Critical Quality Attributes
Pre-blending	Blending speed Blending time	Particle size Bulk density Flowability
Final blending	Blending speed Blending time	Blend uniformity
Tableting	Filling position	Average weight Assay
	Filling speed	Weight uniformity Uniformity of dose unit
	Compression force	Hardness Disintegration time Dissolution rate

Based on the abovementioned general matrix and speciality of the current development the following evaluations had been identified to understand the manufacturing process, and minimize the related risks.

- Evaluation of effect of the particle size of the active substances
- Evaluation of effect of the particle size of the excipients
- Testing of the blending process
- Testing the tableting process

1 Evaluation of effect of the particle size of the active substances

It is well-known that the particle size of the ivermectin has large effect on the solubility. From the point of dissolution in the case of ivermectin due to the its low solubility the particle size of the active substance has large effect as well.

As the active substance content of the Ivermectin MEDITOP 3 mg tablets is low. Therefore, the particle size has risk from the point of the homogeneity too. Thus, micronized ivermectin was used in experiments.

Consequently. the particle size of ivermectin batch no. 20210020MIC and 20210021MIC considered good for manufacture of the clinical sample.

2 Evaluation of effect of the particle size of the excipients

In case of Cellulose. microcrystalline (MCC), the following types might come into consideration (using of data presented by JRS for the Vivapur grade).

Table 35.
Parameters of the potential Cellulose. microcrystalline

Type of MCC	Average particle size	Bulk density
101	65	0.26 – 0.31
102	130	0.28 – 0.33
302	130	0.35 – 0.50
112	180	0.30 – 0.36
200	250	0.31 – 0.37

From the types of Cellulose. microcrystalline Type 101 has too small particle size therefore it is not suitable for direct compression. Type 112 and 200 have large particle size therefore there are not suitable for next to micronized active substance. Type 102 and 302 proved to be good however from better flowability point of view the Type 302 has been chosen.

3 Testing of the manufacturing process of tablet making

Concerning the manufacturing process development, the granulating, the blending and compression parameters (especially compression force and time) were identified as possible process inputs which could affect the product quality.
Because the composition had been determined, the influence of the parameters of the different manufacturing steps on the product quality were tested. namely:

1. mixing time: at addition of magnesium-stearate
2. effect of compression force
3. effect of compression speed

The experiments were made at laboratory scale using the following equipment:

- Hand sieve with 0.8 mm mesh size
- ProCepT 4m8 high shear mixer with 1 Litre capacity
- Korsch EK0 single punch tablet press
- Wynka Kompressor Developer tablet press

1. Mixing time

Product	**VAXX104**		
Mixing time (min)	10	+10	+2 with magnesium stearate
Homogenized assay (%)	95.4	95.0	94.8
Standard deviation (%)	4.9	2.7	1.5
RSD (%)	5.1	2.8	1.5

The standard deviation was reduced with increasing time of mixing. Consequently. the selected mixing time was 20 minutes. then plus 2 minutes with magnesium stearate.

2. Effect of compression force and speed

	VAXX150								
Turret speed (rpm)	5	5	5	10	10	10	20	20	20
Compression force (kN)	8	10	12	8	10	12	8	10	12
Weight (mg)	60.8	60.5	60.8	60.8	60.3	60.1	61.3	61.2	62.4
Weight variation (%)	0.86	0.76	0.60	1.04	1.60	1.20	0.91	1.18	1.23
Height (mm)	1.81	1.80	1.74	1.86	1.80	1.76	1.86	1.82	1.80
Hardness (N)	33	36	44	31	34	39	31	36	40
Friability (%)	0.01	0.14	0.05	0.14	0.13	0.13	0.06	0.1	0.03
Disintegration time (sec)	25	28	30	15	28	31	16	28	30

In this case the hardness value did not change significantly with increasing the turret speed. Each compression force can result the same hardness each turret speed.

Table 36.
Hazard Analysis (HA) of manufacture of Ivermectin MEDITOP 3 mg tablets from the point of Critical Quality Attributes

CQA	CPP			
	Working conditions	Pre-blending	Final blending	Tablet press
Appearance	L	N	N	L
Assay	L	L	L	L
CU	N	L	L	L
Dissolution	N	L	L	N
Impurities	L	N	N	N

Color coding for relative risk ranking:

High/H	affect quality attributes – further investigations and controls needed in order to reduce risk
Medium/M	potential to affect quality attributes – further investigations and controls may be needed in order to reduce risk
Low/L	low impact on quality attributes – no further investigations needed
Low/L	low impact on quality attributes – risk is mitigated.
No risk/N	no impact on quality attributes – no further investigations needed

Table 37.
Revised Risk Assessment for Justification and Risk Mitigation Strategies for Risks of CMAs

CPP	CQA	Initial risk	Description of CPP's effect on FP CQAs	Risk mitigation Strategy / Control Strategy Action points	Results/ Summary	Revised risk
Working conditions	Appearance	L	Sensitivity of the components to any environmental parameter (oxygen. temperature. moisture or light) may influence the appearance of the product. and may have impact on FP appearance. assay and impurity. if the air condition in the manufacturing place is not proper.	Low risk on quality attributes. No investigations were needed.	Low risk on quality attributes No investigations was needed.	L
	Assay	L				L
	Impurities	L				L
Pre-blending	Assay	M	The dry mixing might have risk from the point of the Assay and CU.	Due to the low AS content of the tablets with proper working methods the required Assay and CU can be ensured.	With standard pre-blending method the required Assay and CU can be ensured	L
	CU	M				L
Final blending	Dissolution	M	The time of final blending might have risk from the point of the disintegration time and dissolution rate	With proper blending time the risk can be eliminated.	With standard blending time the required dissolution can be ensured	L
Tableting	Appearance	M	The tableting may affect the appearance of the tablets and their Assay. CU values and the dissolution rate of the AS.	With standard control of the tableting process the required appearance. Assay. CU and dissolution can be ensured.	With standard control of the tableting process the required appearance. Assay. CU and dissolution can be ensured.	L
	Assay	M				L
	CU	M				L
	Dissolution	M				L

Finally, it can be concluded that as a result of the formulation development and the related manufacturing process development, the product and process understanding are suitable for the adequate control strategy, consequently, the potential risks of the non-conformance for Ivermectin MEDITOP 3 mg tablets were minimized to an acceptable level.

2.1.P.2.4 Container and closure system

Package size for clinical study:
10 tablets in Alu//Alu blister

1 Primary packaging materials

Alu//Alu blister

- Soft tempered Aluminium foil for cold forming
- Aluminium foil hard tempered Primer for printing on the mat side and thermosealable lacquer to PVC/PVdC on the bright side, 20 µm

Specifications of Soft tempered Aluminium foil

- ALU-Thickness 45.00 ± 5.0 µm
- Polyamide 25.00 ± 2.0 µm
- PVC 60.00 ± 8.0 µm
- Weight 213.8 -261.4 g/m2
- Identification (IR) Identical

Specifications of Aluminium foil for closing

- ALU-Thickness 18.4 – 21.6 µm
- Heat-seal lacquer 7.00 ± 1.0 g/m^2
- Print lacquer 1.0 ± 0.4 g/m^2
- Identification (IR) Identical

2 Secondary packaging materials

None.

2.1.P.2.5 Microbiological Attributes

The microbiological impurity of the preparation is examined.

- at release
- at the end of the 40°C/75%RH storage.
- at the end of the 30°C/65%RH storage.
- at the end of the 25°C storage.

The microbiological impurity of the finished product meets the requirements for oral administration of the Ph.Eur. Category 3/A.

Microbiological impurity:	TAMC $\leq 10^3$ CFU/g
	TYMC $\leq 10^2$ CFU/g
	Absence of Escherichia coli/g

The microbiological impurity of the finished product is controlled annually.

2.1.P.2.6 Compatibility

The type of compatibility is not appropriate for the product.