2.1.P.2 Pharmaceutical Development

Abbreviations

AS	Active substance
BCS	Biopharmaceutical Classification System
BE	Bioequivalence
CMA	Critical Material Attribute
CPP	Critical Process Parameters
CQA	Critical Quality Attribute
CU	Content Uniformity
EX	Experiment
FP	Final product
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
HPMC	Hydroxypropyl Methyl Cellulose
MCC	Microcrystalline Cellulose
QTPP	Quality target product profile

1 Development Summary

The pharmaceutical development report summarizes the development of Hydroxychloroquine MEDITOP 200 mg film-coated tablets for clinical investigation for treatment of COVID 19 virus. The reference product is the immediate release (IR) dosage forms of hydroxychloroquine film- coated tablets named Plaquenil 200 mg film-coated tablets developed and manufactured by Sanofi Co., Ltd.
Plaquenil 200 mg film-coated tablets are used at adults for treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight; at paediatric population for treatment of juvenile idiopathic arthritis (in combination with other therapies), discoid and systemic lupus erythematosus.
Plaquenil 200 mg film-coated tablets have been investigated for the treatment of COVID-19.
Hydroxychloroquine is a small polar molecule, its molecular weight of about 335. Its solubility in buffers of pH 1.2 is > 4.83 mg/mL, of pH 4.5 and pH 6.8 is > 4.97 mg/mL, therefore is an active substance of high solubility from the point of the BCS (1).

Hydroxychloroquine is 67-74% bioavailable. Bioavailability of the R and S enantiomers are not significantly different (3).
On the base of its solubility and permeability properties hydroxychloroquine belongs to the Class 3 of the BCS. In April 2020 FDA finalized its Guidance on Hydroxychloroquine Sulfate which suggest an BCS Class 3-based biowaiver option on this active substance (4).

At development 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 Hydroxychloroquine MEDITOP 200 mg film-coated tablets, these CQAs included assay, content uniformity, dissolution rate and impurities.

Taking into consideration the suggestion of FDA on BCS Class 3-based biowaiver option for this active substance at the development of the Hydroxychloroquine MEDITOP 200 mg film-coated tablets such product was developed that follows the composition and dissolution profile of the reference product. The dissolution method was determined as it is suggested in EMA Guideline on the investigation of bioequivalence, hereinafter GUIDELINE (5).

For formulation qualitatively the same types of excipients and near 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 high active substance content of the product the wet granulation process was chosen for preparation of the blend for compression. At the optimization process the following points were studied: quantity of the binder, the quantity of water (of the granulating liquid), the ratio of the inner and the outer phase of the blend.

Processing experience has been gained by manufacturing of three batches of 100.000 tablets in the GMP production site of Meditop. All the parameters of the tablets met with the predetermined acceptance criteria. The dissolution rate of the three batches was compared with the dissolution rate of the reference product according the GUIDELINE.

Data from stability studies performed in accordance with ICH guidelines show good stability of the product at the accelerated, the intermediate and long-term storage conditions.

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

The Reference Product is: Plaquenil 200 mg film-coated tablets

Active substance	hydroxychloroquine
ATC-code:	P01BA02
Marketing authorization holder:	Sanofi
Legal basis	Complete application
Authorization date	07. April 2020

The product is manufactured by Sanofi, Spain.

Based on the product labeling the composition of the reference products are listed into Table 1.

Table 2.1.P.2-1
Composition of the reference Plaquenil 200 mg film-coated tablets

Components	In one tablet
Hydroxychloroquine sulfate (Hydroyxchloroquine)	200 mg (155 mg)
Excipients	Lactose monohydrate, Maize starch, Magnesium stearate, Polyvidone Opadry OY-L-28900 (containing hypromellose, macrogol 4000, titanium dioxide (E171), lactose)

It can be concluded that the reference product contains well established excipients that conform the dosage form. The tablet core contains povidone as binder, lactose monohydrate as filler, maize starch as disintegrants and magnesium stearate as lubricant. The film coating of the tablets contains hypromellose as film forming polymer, titanium dioxide as opacifier macrogol 4000 as softener and lactose as binder to the tablet core.

The packaging of the product is 250 µm clear PVC/20 µm aluminum foil blister pack containing 56 or 60 tablets.

The weight of the Plaquenil 200 mg film-coated tablet is cc. 310 mg, therefore the tablet core weight is cc. 300 mg. Considering its SmPC the presumed composition of the composition of the reference product is the following:

Component	Quantity (mg)
Hydroxychloroquine sulfate	200
Lactose monohydrate	30
Maize starch	55-65
Povidone	5-10
Magnesium stearate	2-5
Film coating (Opadry OY-L-28900)	10
Total Mass (mg)	cc. 310

The reference product, Plaquenil 200 mg film-coated tablet is an immediate release product.
According to the BCS Class 3-based biowaiver the dissolution rate of the test and reference tablets should be very fast as measured by the paddle method at 50 rpm in 900 ml buffer of pH 1.2, 4.5 and 6.8 respectively.
During development, this method was used to control the dissolution rate of the reference Plaquenil and the Hydroxychloroquine MEDITOP 200 mg film-coated tablets as well.

The detailed data of the dissolution rate at given in *Part 2.1.P.2.2.3 Physicochemical and Biological Properties.*

Literature:
1./
Solubility Determination of Active Pharmaceutical Ingredients Which Have Been Recently Added to the List of Essential Medicines in the Context of the Biopharmaceutics Classification System – Biowaiver; G.F. Ploger et al. / Journal of Pharmaceutical Sciences 107 (2018) 1478-1488.)

2./
Chloroquine and hydroxychloroquine binding to melanin: Some possible consequences for pathologies; R.L. Schroeder, J.P. Gerber / Toxicology Reports 1 (2014) 963–968.

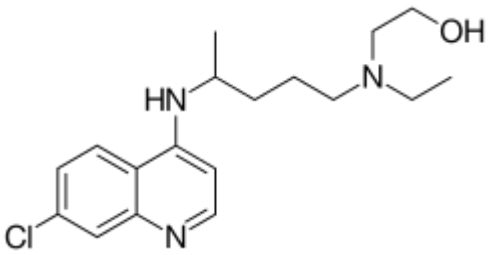
3./
(Furst DE: Pharmacokinetics of hydroxychloroquine and chloroquine during treatment of rheumatic diseases. Lupus. 1996 Jun;5 Suppl 1: S11-5. [PubMed:8803904]

4./
Guidance on Hydroxychloroquine; FDA Recommended Apr 2011; Finalizes Apr 2020
https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_009768.pdf

5./
Guideline on the investigation of bioequivalence; CPMP/EWP/QWP/1401/98 Rev. 1).
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf

2.1.P.2.1 Components of the Drug Product Drug substance

2.1.P.2.1.1 Drug Substance

INN name:	Hydroxychloroquine sulfate
IUPAC chemical name:	2-[4-[(7-chloroquinolin-4-yl)amino]pentyl-ethylamino]ethanol;sulfuric acid
Structural formula:	

Empirical Formula:	H_2SO_4
General formula:	$C_{18}H_{28}ClN_3O_5S$
CAS number:	747-36-4
Molecular weight:	434 g/mol
Chemical character:	base (possess three basic ionization sites)
pKa values:	pH 4.0, 8.3 and 9.7
Melting point:	90°C
Stability:	fairly stable

According to the data of PAR for Hydroxychloroquinesulfaat 200 mg film-coated tablets, the drug substance under the accelerated conditions (40°C/75 % RH) for 6 months, and under the long-term storage conditions (25°C/60 % RH) for 5 years the quality remained well within the proposed limits (https://db.cbg-meb.nl/Pars/h114949.pdf).

Pharmacokinetic data

Bioavailability:	74 %
Absorption:	t_{max} is 3.0-3.5 hours after single dose of 200 mg C_{max} average is 129.6 ng/mL
Terminal half-life:	2963 hours (123.5 days)

Solubility
Hydroxychloroquine sulfate is freely soluble in water

Solubility in buffers of different pH values (section *2.1.P.2.2.3 Physicochemical and Biological Properties*)

Solvent	**Solubility** (mg/100 mL)	**Solubility** (mg/250 mL)	**BCS* classification**
pH 1.2 buffer	1221.00	3052.5	Class I. or Class III.
pH 4.5 buffer	1213.12	3032.8	Class I. or Class III.
pH 6.8 buffer	1215.60	3039.0	Class I. or Class III.

Therefore, the unit dose of Hydroxychloroquine sulfate 200 mg film-coated tablets and its highest therapeutic dose (400 mg) dissolves in 250 ml buffer of the entire physiological pH range.

Taking into consideration of the permeability and solubility properties the hydroxychloroquine sulfate belongs to the BCS Class III.

Polymorphism
Hydroxychloroquine sulfate has two polymorphic forms. The usual form melts at 240°C the other at 198°C.

Hygroscopicity
The drug substance is not hygroscopic at 25°C/51 % to 93 % RH.

Particle size
The material used for the pilot scale manufacture of Hydroxychloroquine 200 mg film-coated tablets is manufactured by IPCA. Three batches were used for the three stability samples.

The investigation of the particle size shows that more than 95 % of the material consists of particles smaller than 250 µm that is appropriate for tablet manufacture by wet granulation technology.

By shifting method, the particle size distribution of the material is measured as follows:

	C63-200405 laboratory scale	**20140HS4R11 pilot scale**	**20137HS4R11 pilot scale**	**20131HS4R11 pilot scale**
abowe 250 µm	4.7 %	0.63 %	0.03 %	0.10 %
63-250 µm	93.2 %	75.29 %	65.59 %	62.15 %
below 63 µm	2.1 %	22.16 %	33.36 %	36.68 %

The material was processed without any further separate screening or milling.

Compatibility of the active substance with the excipients

A separate compatibility study between the hydroxychloroquine sulfate and the different excipients didn't make because all excipients which are used are components of the reference product as well: lactose monohydrate, maize starch, magnesium stearate, polyvidone, Opadry OY-L-28900 (containing hypromellose, macrogol 4000, titanium dioxide (E171), lactose).

The test product manufactured by GMP laboratory scale batch is put on stability test according to the ICH circumstances, and the result of the one, two and three months storing will be presented.

2.1.P.2.1.2 Excipients

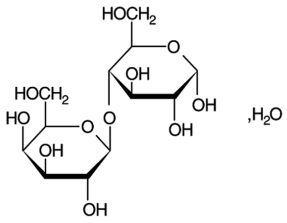
The same well-known excipients which the reference product has were used to develop the test product.

The tablet core has the following excipients:
- lactose monohydrate as filler
- povidone as binder
- maize (corn) starch as disintegrant
- magnesium stearate as lubricant

The film coating was made by the same pre-blended coating composition of Colorcon Ltd., type Opadry OY-L-28900, which contains hypromellose, macrogol 4000, titanium dioxide and lactose.

1 Lactose monohydrate

Ph.Eur:	Lactose *(Ph Eur monograph 0187)*
Synonyms:	lactosum; milksugar; saccharum lactis
Chemical Name:	O-β-D-Galactopyranosyl-(1→4)-β-D-glucopyranose
CAS Registry Number:	[63-42-3]
Empirical Formula:	$C_{12}H_{22}O_{11}$. H_2O
Molecular Weight:	360.30
Structural formula:	



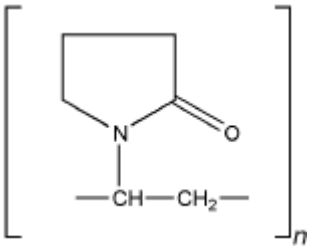
Definition:
Lactose monohydrate is the monohydrate of O-b-D-galactopyranosyl-(1®4)-a-D-glucopyranose. It may be modified as to its physical characteristics and may contain varying proportions of amorphous Lactose.

Characters:
A white or almost white, crystalline powder, freely but slowly soluble in water, practically insoluble in alcohol.

Functional Category:
Tablet and capsule diluent; tablet and capsule filler.

Functionality-Related Characteristics:
The type of Lactose is a milled one under brand name Granulac 200 is a standard crystalline and milled lactose monohydrate for wet granulation process.
More than 90 % of the particles are smaller than 100 µm by air-jet-sieving.
The branded type is a guarantee for the proper particle size.

2 Polyvidonpyrrolidone

PhEur:	Povidonum
Synonyms:	Kollidon; Plasdone; polyvidone; polyvinylpyrrolidone
Chemical Name:	1-Ethenyl-2-pyrrolidinone homopolymer
CAS Registry No.:	[9003-39-8]
Empirical Formula:	(C6H9NO)n
Molecular Weight:	2500–3 000 000
Structural Formula	
Functional Category	Disintegrant; dissolution aid; suspending agent; tablet binder.

Applications in Pharmaceutical Formulation or Technology

In tableting, povidone solutions are used as binders in wet-granulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water.

Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

Typical Properties

Acidity/alkalinity:	pH = 3.0–7.0 (5% w/v aqueous solution).
Density (bulk):	0.29–0.39 g/cm3 for Plasdone.
Density (true):	1.180 g/cm3
Melting point:	softens at 150°C.
Moisture content:	povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative MEDITOPmidity.
Solubility:	freely soluble in acids, chloroform, ethanol, ketones, methanol, and water.

Storage Conditions
Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Safety
Povidone has been used in pharmaceutical formulations for many years. A temporary acceptable daily intake for povidone has been set by the WHO at up to 25 mg/kg body-weight.
LD50(mouse, IP): 12 g/kg

Handling Precautions
Eye protection, gloves, and a dust mask are recommended.

Regulatory Status
Accepted in Europe as a food additive.

3 Maize (Corn) Starch

PhEur:	Maydis amylum (maize starch)
Chemical Name:	Starch
CAS Registry Number:	[9005-25-8]
Empirical Formula:	(C6H10O5)n
Molecular Weight:	50 000–160 000 where n = 300–1000. Starch consists of amylose and amylopectin, two polysaccharides based on α-glucose.
Functional Category:	Glidant, diluent, disintegrant for tablets and capsules

Description:
Starch occurs as an odorless and tasteless, fine, white-colored powder comprising very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety.

Acidity/alkalinity:	pH = 5.5–6.5 for a 2% w/v aqueous dispersion of corn starch, at 25°C.
Density (bulk):	0.462 g/cm3 for corn starch.
Density (tapped):	0.658 g/cm3 for corn starch.
Density (true):	1.478 g/cm3 for corn starch.
Flowability:	Corn starch is cohesive and has poor flow characteristics.
Particle size distribution:	2–32 µm
Specific surface area:	0.41–0.43 m2/g

Moisture content:
corn starches is hygroscopic and rapidly absorb atmospheric moisture.
Approximate equilibrium moisture content values at 50% relative MEDITOPmidity are 11%.
Commercially available grades of corn starch usually contain 10–14% water.

Solubility:
Practically insoluble in cold ethanol (95%) and in cold water.
Starch swells instantaneously in water by about 5–10% at 37°C

Stability and Storage Conditions:
Dry, unheated starch is stable if protected from high MEDITOPmidity. Starch should be stored in an airtight container in a cool, dry place.

Safety:
Starch is widely used as an excipient in pharmaceutical formulations, particularly oral tablets.

Functionality-related characteristic:
None

4 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:	C36H70MgO4
Molecular Weight:	591.34
Structural Formula:	[CH3(CH2)16COO]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.

Description:

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

Typical Properties:

Crystalline forms:	high-purity Magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.
Density (bulk):	0.159 g/cm3
Density (tapped):	0.286 g/cm3
Density (true):	1.092 g/cm3
Flowability:	poorly flowing, cohesive powder.
Melting range:	117–150°C (commercial samples) 126–130°C (high purity Magnesium stearate)
Solubility:	practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).
Specific surface area:	1.6–14.8 m2/g

Stability and Storage Conditions:

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Functionality-related characteristic (Particle size distribution, specific surface area):

In the product magnesium stearate produced by Magnesia Co. is used.
The type of Magnesium stearate Magnesia 4264.
The specific surface area of the material is 1- 4 m2/g.
The branded type is a guarantee for the proper specific surface area.

5 Opadry OY-L-28900

Complete film-coating system manufactured by Colorcon Ltd.

Ph. Eur.:	non-compendial excipients mixture
Functional Category:	film-coating material
Description:	white powder.
Ash content:	23.80 – 32.20 %
Dispersion:	dispersible in water
Regulatory status	Fulfils the following requirements: GMO, TSE/BSE, Halal, Kosher, Aflatoxin, Metal Catalyst, Residual solvents, Irradiation/Ethylene Oxide, Dioxin

Quantitative formula:

Ingredient	Quantity % w/w	Grade	E Number	Quality
Lactose monohydrate	36.000	-	-	Ph. Eur.
HPMC 2910/ Hypromellose	28.000	15 mPas	E464	Ph. Eur.
Titanium dioxide	26.000	-	E171	Ph. Eur.
Macrogol	10.00	MW 4000	E1521	Ph. Eur.

Functionality-related characteristic: none

2.1.P.2.2 Drug Product

1 Drug Product Development Strategy

At the development of the Hydroxychloroquine MEDITOP 200 mg film-coated tablets, the same excipients were used as the reference product has both int tablet core and in the film-coating as well.

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

For manufacture the wet granulation method was chosen due to the high active substance content (2/3 part) 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 less than 0.6 % at the end of shelf life. 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 85% of drug substance released within 15 minutes in buffer of pH 4.5. Similar to the safety justification, efficacy is assured by application of the pharmacopoeial acceptance criteria for uniformity of dosage units.

Table 2.1.P.2.2-1
Target Product Profile of Hydroxychloroquine MEDITOP 200 mg film-coated tablets

Description	White or almost white, round, biconvex film-coated tablets with plain surfaces on both sides.
Identification	Positive
Assay	Labelled amount ± 5 %
Uniformity of dose units	Meets pharmacopoeial acceptance criteria
Total impurities	Not more than 0.6 %
Dissolution	Very rapid dissolution (Q=80 % in 15 minutes)
Microbiological limits	Meet pharmacopoeial acceptance criteria

3 Quality Attributes of the Drug Product

Table 2.1.P.2.2-2 summarizes the quality attributes of the Hydroxychloroquine MEDITOP 200 mg film-coated 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 2.1.P.2.2-2
Critical Quality Attributes of Hydroxychloroquine MEDITOP 200 mg film-coated 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 15 min in 0.1 M HCl, volume 900 ml, rpm 50	**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
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 pharmacopoeial 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 (hydroxychloroquine), 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.

2.1.P.2.2-1
Preliminary Hazard Analysis (PHA) of development of Hydroxychloroquine MEDITOP 200 mg film-coated tablets

CQA	**CMA**					**CPP**			
	AS assay	AS impuri-ties	AS particle size	AS sensitivity	Type and rate of excipients	Working conditions	Wet granulation	Final blending	Tableting
Appearance	N	N	M	L	L	L	N	N	M
Assay	H	L	N	N	N	L	N	L	M
CU	N	N	L	N	N	N	L	L	M
Dissolution	N	N	L	N	H	N	L	N	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

2.1.P.2.2-2
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)	L	Inappropriate particle size of AS may have effect on CU of product.	The wet granulation process leads to a low effect of particle size on FP content uniformity.
	Dissolution	L	Too large particle size has effect on dissolution rate of the final product (FP)	The high solubility of the active ingredient leads to low effect on the dissolution rate.
	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.	The stability of the AS leads to low effect on the impurity level.
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
	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.	However, the composition of test product is very similar to them the reference product has the rate of excipients should be optimized by dissolution test.
	Dissolution	H		
	Impurities	L		

2.1.P.2.2-3
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
Manufacturing 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 not hygroscopic and not sensitive to heat. With standard working condition and packaging the risk can be eliminated.
	Assay	L		
	Impurities	L		
Wet granulation	CU	L	Pre-blending/wetting/aggregation/drying/milling process affects particle size of the blend for compression. Inappropriate particle size affects flowability of the blend, and may have an influence on the content uniformity and may affect the dissolution rate of the AS.	Due to the high AS content and high solubility of the AS the inappropriate particle size has low risk for CU and dissolution rate. With standard working the required particle size can be can be ensured.
	Dissolution	L		
Final blending	Assay	L	The final blending might have risk from the point of the Assay and CU.	Due to the high AS content of the tablets with standard working the required Assay and CU can be ensured.
	CU	L		
Tableting	Appearance	M	The tableting may affect the appearance of the tablets and their Assay and CU values.	With proper control of the tableting process the required appearance, Assay and CU can be ensured.
	Assay	M		
	CU	M		
Film-coating	Appearance	L	The coating may affect the appearance of the product.	With standard control of the coating process the required appearance can be ensured.

Therefore, in the case of the development of Hydroxychloroquine MEDITOP 200 mg film-coated tablets, the quality of the active substance and the quantities of excipients pose a high risk only. 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 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
  - film-coated tablets ~ 310 mg
  - tablet core ~ 300 mg

- lactose content given in the SmPC of the reference product (35,5 mg)
- the presumed lactose content of the film coating (5,5 mg)
- the presumed lactose content of the tablets is 30 mg
- the usual quantities of the other excipients of the whole tablets mass:
  - maize starch 10 – 25 %
  - povidone 2 – 10 %
  - magnesium stearate 0,5 – 3 %

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

- hydroxychloroquine 200 mg
- lactose 30 mg
- maize starch 60 mg
- povidone 7 mg
- magnesium stearate 3 mg

Taking into consideration the compositions in the first series of experiments the effect of the quantity of the binder and disintegrant was studied.

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

- ProCept 4m8 high shear mixer with 1 Litre pot
- ProCept 4m8 fluid bed dryer with 1 Litre capacity
- IKA mill with 2 mm screen
- Korsch EK 0 eccentric tablet machine.

Manufacturing process

The materials to be granulated were shifted through a sieve of 0.8 mm and filled into the pot of the ProCept equipment (with 1 Litre capacity) and blended for 1 minute at impeller speed of 370 rpm without chopper. The granulating liquid (aqueous solution of povidone) was added to the powder blend at continuous stirring at impeller speed of 300 rpm and chopper speed of 500 rpm.

The wetted material was granulated further at mixing rate of 500/700 rpm.

The granulated material is dried in fluid bed dryer and milled by IKA mill through a screen of 2.0 mm and then the materials of the outer phase are blended to the granulated material.

The final blend is compressed into tablets of 200 mg weight by round biconvex tablet tools of 10 mm on a Korsch EK0 single punch tablet press.

In process control
- control of the loss on drying of the dried granules and the final blend
- control of the flowability of the final blend by funnel of 10 mm
- control of the bulk density and tapped density of the final blend
- control of the particle size distribution 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 tests were done according to the methods given in the part 2.3.P.

In the first series of experiments the active substance batch C63-200405 was used.

The results were the followings:

Table 3.2.P.2.2.1-1
Tablet core compositions and blend parameters

Components (g)	**Number of experiments**		
	VAXVIII172	**VAXVIII184**	**VAXIX046**
Hydroxychloroquine sulfate	200	200	200
Lactose monohydrate	30	30	30
Povidon	7	7	7
Maize starch	60	57	53
Magnesium stearate	3	6	9
Purified water	12	12	12
Blend parameters			
Loss on drying (%)	3.6	2.9	2.1
Flowability (100 g) (s)	9	19	25
Bulk density (g/mL)	1.43	0.83	0.82
Hausner ratio (-)	1.17	1.22	1.25

Table 3.2.P.2.2.1-2
Parameters Hydroxychloroquine MEDITOP 200 mg tablets

Tablet parameters/Nr. of exp.	**VAXVIII172**	**VAXVIII040**	**VAXIX046**
Average weight (mg)	300.0	299.6	302.8
Weight variation (%)	0.44	1.7	1.5
Height of the tablets (mm)	4.62	4.15	4.23
Hardness (N)	86	128	95
Friability (%)	-	0.08	0.26
Disintegration time (min)	6.5	6.5	7.0
Appearance	Sticking	Suitable	Suitable
Dissolution rate (%) at 5 min.	-	56.5	39.0
Dissolution rate (%) at 15 min	-	87.7	67.5
Dissolution rate (%) at 30 min	-	98.6	86.3

In the second series of experiments the active substance batch 20140HS4R11 was used.

The results were the followings:

Table 3.2.P.2.2.1-3
Tablet core compositions and blend parameters

Components (g)	**Number of experiments**		
	VAXX002	**VAXX014**	**VAXX022**
Hydroxychloroquine sulfate	200	200	200
Lactose monohydrate	30	30	30
Povidon	7	3.5	3.5
Maize starch	57	63.5	69.5
Magnesium stearate	6	3.5	3.5
Purified water	12	12	14
Blend parameters			
Loss on drying (%)	2.2	1.8	1.7
Flowability (100 g) (s)	35	22	27
Bulk density (g/mL)	0.81	0.75	0.82
Hausner arány (-)	1.22	1.22	1.27

Table 3.2.P.2.2.1-4
Parameters Hydroxychloroquine MEDITOP 200 mg tablets

Tablet parameters/Nr. of exp.	**VAXX002**	**VAXX014**	**VAXX022**
Average weight (mg)	308.5	300.6	308.5
Weight variation (%)	1.0	0.97	0.6
Height of the tablets (mm)	4.33	4.28	4.31
Hardness (N)	107	93	108
Friability (%)	0.01	0.28	0.23
Disintegration time (min)	7.0	6.2	6.5
Appearance	Suitable	Suitable	Suitable
Dissolution rate (%) at 5 min.	41.2	44.4	55.3
Dissolution rate (%) at 10 min	78.7	79.5	84.9
Dissolution rate (%) at 15 min	87.3	95.4	98.3

On the basis of the optimization process above the final composition of the test product was chosen as the following:

Hydroxychloroquine sulfate	200.0 mg
Lactose monohydrate	30. 0 mg
Povidon	3.5 mg
Maize starch	69.5 mg
Magnesium stearate	3.0 mg

2 Revised risk assessment after formulation development

The initial risk assessment and risk mitigation strategy tables were presented in Part 3.2.P.2.2; 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 and povidone had to be changed because in the case of the first choice sticking occurred during tableting.

Table 2.1.P.2.2.1-5
Hazard Analysis (HA) of manufacture of Hydroxychloroquine MEDITOP 200 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	N	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 2.1.P.2.2.1-6
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.	The compaction granulation process leads to a low effect of particle size on FP content uniformity.	Low risk on quality attributes No investigations was needed.	L
	Dissolution	M	Too large particle size has effect on dissolution rate of the final product (FP)	The slightly solubility of the active ingredient leads to medium 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

Overages were not applied in this preparation.

2.1.P.2.2.3 Physicochemical and Biological Properties

1 *In vitro* dissolution

Scientific databases. official monographs and guidelines (issued by EMA. FDA. ICH) as well as the data presented by the manufacturer of reference product (Plaquel 200 mg film-coated tablets – Sanofi-Aventis Ltd.) 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 products.

The dissolution method given in the USP Monograph of Hydroxychloroquine Sulfate tablets applies 900 ml water as dissolution medium and the Apparatus 2 (paddle) with 50 rpm stirring rate. The dissolution rate of the Plaquel 200 mg film-coated tablets was more than 85 % in these circumstances that offers the possibility of the BCS based biowaiver process for the generic development.

However, the BCS-based biowaiver process requires the dissolution comparison of the test and reference product in different buffers of the physiological pH range, therefore these media were used at the development.

As a basic test, the solubility of Hydroxychloroquine was evaluated in these buffers. Based on the literature data (Drugbank.ca) the pKa value of this active substance is 9.7 and 8.3. Because these values are out the physiological range, consequently the solubility at these pH-s wasn't tested.

- 500 ml media was filled into a vessel of dissolution tester (Apparatus 2)
- it was tempered to 37°C
- API was added gradually to the media and intensively stirred (paddle with 100 rpm) and the solubility was tested visually
- if the solubility is not complete, liquid was filtered through 0.45 µm cellulose ester filter
- API content was determined by UV method (details are described in section 1.2.1)

Table 2.1.P.2.2.3-1
Solubility of hydroxychloroquine

Solvent	**Solubility** (g/100 ml)	**Ph.Eur. definition**	**Solubility** (mg/250 ml)	**BCS* classification**
water	1203.36	very soluble	3008.4	-
pH 1.2	1221.00	very soluble	3052.5	Class I./Class III.
acetate buffer at pH 4.5	1213.12	very soluble	3032.8	Class I./Class III.
phosphate buffer at pH 6.8	1215.60	very soluble	3039.0	Class I./Class III.

It can be concluded, that based on the GUIDELINE the solubility this active substance on the base its dose can be classified as a high solubility compound in the physiological pH range.

1.1 Parameters used for comparative analysis of *In vitro* dissolution profiles

1.1.1 Description of the dissolution method in 0.1 M hydrochloric acid

Instrumentation:	ERWEKA DT-80 dissolution tester Agilent 708-DS dissolution tester UNICAM UV2 UV-VIS spectrophotometer Cary 60 UV-VIS spectrophotometer
Media:	900 mL of 0.1 M hydrochloric acid
Method:	paddle
Agitation rate:	50 rpm
Temperature:	37 ± 0.5°C
Sample amount:	1 tablet per vessel
Time points:	5, 10, 15, 30 and 45 min
Detection:	343 nm
Type of cuvette:	1 cm quartz

Preparation of dissolution medium - 0.1 M hydrochloric acid
Dissolve 8.3 mL cc. hydrochloric acid in 1000 ml purified water.

Preparation of standard solution
Dissolve 28,0 mg of Hydroxychloroquine working standard in 25 mL dissolution media (with the use of ultrasound) and filter it through filtering paper and 0.45 µm CA (cellulose acetate) filter. Dilute this sample 100 times with dissolution media.

Sampling
Withdraw 5.0 ml of sample at the specified time points and filtered through 0.45 µm CA filter.
Dilute this sample 20 times with dissolution media.

Calculation

$$\text{Dissolution (\%)} = \frac{A_s}{A_{sta}} \cdot \frac{W}{}$$

where:
A_s = absorbance of the sample solution
A_{std} = absorbance of the standard solution
W_{std} = dose weight of the reference material, mg
St = strength, mg
x_{dilut} = dilution ratio
P_{std} = potency of the reference material, %

Calculation:

$$\text{Dissolution (\%)} = \frac{A_s}{A_{std}} x \frac{W_{std}}{x_{dilut}} x P_{std}$$

where:
As = absorbance of the sample solution
Astd = absorbance of the standard solution
Wstd = weight of the reference material, mg
xdilut = dilution rate of sample
Pstd = potency of the reference material, %

1.1.2 Description of the dissolution method at pH 4.5

Instrumentation:	ERWEKA DT-80 dissolution tester Agilent 708-DS dissolution tester UNICAM UV2 UV-VIS spectrophotometer Cary 60 UV-VIS spectrophotometer
Media:	900 mL of dissolution media
Method:	paddle
Agitation rate:	50 rpm
Temperature:	37 ± 0.5°C
Sample amount:	1 tablet per vessel
Time points:	5, 10, 15, 30 and 45 min
Detection:	343 nm
Type of cuvette:	1 cm quartz

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.

Preparation of standard solution
Dissolve 28,0 mg of Hydroxychloroquine working standard in 25 mL dissolution media (with the use of ultrasound) and filter it through filtering paper and 0.45 µm CA (cellulose acetate) filter. Dilute this sample 100 times with dissolution media.

Sampling
Withdraw 5.0 ml of sample at the specified time points and filtered through 0.45 µm CA filter.
Dilute this sample 20 times with dissolution media.

Calculation

$$\text{Dissolution (\%)} = \frac{A_s}{A_{std}} \times \frac{W_{std}}{St} \times P_{std} \times X_{dilut}$$

where:
A_s = absorbance of the sample solution
A_{std} = absorbance of the standard solution
W_{std} = dose weight of the reference material, mg
St = strength, mg
x_{dilut} = dilution ratio
P_{std} = potency of the reference material, %

Calculation:

$$\text{Dissolution (\%)} = \frac{A_s}{A_{std}} x \frac{W_{std}}{x_{dilut}} xP_{std}$$

where:
As = absorbance of the sample solution
Astd = absorbance of the standard solution
Wstd = weight of the reference material, mg
xdilut = dilution rate of sample
Pstd = potency of the reference material, %

1.1.3 Description of the dissolution method at pH 6.8

Instrumentation:	ERWEKA DT-80 dissolution tester Agilent 708-DS dissolution tester UNICAM UV2 UV-VIS spectrophotometer Cary 60 UV-VIS spectrophotometer
Media:	900 mL of dissolution media
Method:	paddle
Agitation rate:	50 rpm
Temperature:	37 ± 0.5°C
Sample amount:	1 tablet per vessel
Time points:	5, 10, 15, 30 and 45 min
Detection:	343 nm
Type of cuvette:	1 cm quartz

Preparation of dissolution medium – pH 6.8 (Phosphate buffer)
Mix 250.0 mL of 0.2 M potassium dihydrogen phosphate and 112 mL of 0.2 M sodium hydroxide and dilute to 1000.0 mL with purified water. The acidity of the medium is set to pH= 6.8.

Preparation of standard solution
Dissolve 28,0 mg of Hydroxychloroquine working standard in 25 mL dissolution media (with the use of ultrasound) and filter it through filtering paper and 0.45 µm CA (cellulose acetate) filter. Dilute this sample 100 times with dissolution media.

Sampling
Withdraw 5.0 ml of sample at the specified time points and filtered through 0.45 µm CA filter.
Dilute this sample 20 times with dissolution media.

Calculation

$$\text{Dissolution (\%)} = \frac{A_s}{A_{std}} \times \frac{W_{std}}{St} \times P_{std} \times X_{dilut}$$

where:
A_s = absorbance of the sample solution
A_{std} = absorbance of the standard solution
W_{std} = dose weight of the reference material, mg
St = strength, mg
x_{dilut} = dilution ratio
P_{std} = potency of the reference material, %

Calculation:

$$\text{Dissolution (\%)} = \frac{A_s}{A_{std}} x \frac{W_{std}}{x_{dilut}} x P_{std}$$

where:
As = absorbance of the sample solution
Astd = absorbance of the standard solution
Wstd = weight of the reference material, mg
xdilut = dilution rate of sample
Pstd = potency of the reference material, %

1.2 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.

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

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.

1.3 Tested products

Reference product:
Plaquenil 200 mg film-coated tablets – Sanofi Co., Ltd.
batch number: **OR161**

Test product:
Hydroxychloroquine MEDITOP 200 mg film-coated tablets – Meditop Pharmaceuticals Ltd.
batch numbers: **HI12001**
HI12002
HI12003

1.4 Results

1.4.1 *In vitro* dissolution profiles at pH 1.2

Table 2.1.P.2.2.3-2
Dissolution of Hydroxychloroquine from the reference product (batch number: OR161) in 0.1N HCl (dissolved amount in %)

	5 min	**10 min**	**15 min**	**30 min**	**45 min**
1.	59.4	88.0	98.7	92.2	92.8
2.	55.9	83.4	94.1	92.1	92.6
3.	53.0	86.5	94.4	97.3	97.9
4.	67.4	92.5	96.0	98.4	98.0
5.	64.0	87.7	95.9	99.8	100.5
6.	70.1	91.1	97.1	99.5	98.9
7.	56.6	85.6	96.0	99.0	99.4
8.	65.2	88.7	96.4	98.7	98.3
9.	60.5	87.5	96.6	100.4	99.4
10.	71.6	95.5	100.8	101.7	101.4
11.	70.7	93.3	97.6	98.4	97.8
12.	71.3	91.9	99.2	101.5	101.3
Average	**63.8**	**89.3**	**96.9**	**98.2**	**98.2**
SD	6.6	3.6	1.9	3.1	2.8
CV (%)	10.4	4.0	2.0	3.2	2.9

Table 2.1.P.2.2.3-3
Table Dissolution of Hydroxychloroquine from the test product (batch number: HI12001) in 0.1N HCl (dissolved amount in %)

	5 min	**10 min**	**15 min**	**30 min**	**45 min**
1.	51.9	88.9	100.9	102.6	102.7
2.	50.6	88.6	102.1	103.6	103.7
3.	49.6	86.4	99.8	101.9	102.1
4.	52.7	88.4	97.9	101.7	101.9
5.	49.1	86.8	99.0	104.0	104.2
6.	38.8	73.0	94.4	104.3	104.7
7.	52.2	90.3	101.8	104.4	104.6
8.	48.9	86.2	101.3	103.2	103.4
9.	52.1	89.0	100.2	102.9	103.1
10.	53.3	90.0	98.9	102.2	102.3
11.	51.2	88.6	98.8	101.3	101.4
12.	53.6	92.2	101.8	105.5	105.8
Average	**50.3**	**87.4**	**99.7**	**103.1**	**103.3**
SD	4.0	4.8	2.2	1.3	1.3
CV (%)	7.9	5.5	2.2	1.2	1.3

Table 2.1.P.2.2.3-4
Dissolution of Hydroxychloroquine from the test product (batch number: HI12002) in 0.1N HCl (dissolved amount in %)

	5 min	**10 min**	**15 min**	**30 min**	**45 min**
1.	41.1	87.6	104.1	104.5	104.3
2.	40.8	87.4	100.2	102.2	102.2
3.	43.4	88.9	100.1	101.2	101.1
4.	28.8	67.7	92.2	102.9	103.0
5.	31.9	77.1	100.3	104.5	104.7
6.	42.2	86.2	100.6	102.2	102.1
7.	36.7	79.7	102.1	104.3	104.1
8.	46.3	91.3	104.3	104.7	104.6
9.	26.8	67.9	92.6	103.9	104.2
10.	43.6	87.8	101.5	102.5	102.5
11.	39.7	84.4	99.1	101.2	101.5
12.	44.5	90.0	101.9	102.4	102.4
Average	**38.8**	**83.0**	**99.9**	**103.0**	**103.1**
SD	6.4	8.2	3.8	1.3	1.3
CV (%)	16.5	9.9	3.8	1.3	1.2

Table 2.1.P.2.2.3-5
Dissolution of Hydroxychloroquine from the test product (batch number: HI12003) in 0.1N HCl (dissolved amount in %)

	5 min	10 min	15 min	30 min	45 min
1.	54.5	91.7	101.8	103.5	103.6
2.	51.7	89.4	99.2	101.5	101.4
3.	53.7	91.4	100.4	101.9	101.9
4.	48.8	86.3	99.7	101.7	101.9
5.	57.2	91.7	101.0	102.3	102.6
6.	45.8	84.4	99.5	102.7	102.8
7.	55.6	93.5	101.6	102.7	103.1
8.	49.5	87.1	102.3	103.3	103.3
9.	67.6	88.3	102.8	102.9	103.0
10.	59.6	88.2	96.7	98.6	98.6
11.	58.9	90.1	100.6	104.1	104.2
12.	49.7	89.5	101.2	104.1	104.2
Average	**54.4**	**89.3**	**100.6**	**102.4**	**102.6**
SD	6.0	2.6	1.6	1.5	1.5
CV (%)	10.9	2.9	1.6	1.4	1.5

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

Table 2.1.P.2.2.3-6
Dissolution of Hydroxychloroquine from the reference and the test product in 0.1N HCl (average of dissolved amount in %)

Minutes	Reference product	Test product		
	OR161	HI12001	HI12002	HI12003
5	63.8	38.8	50.3	54.4
10	89.3	83.0	87.4	89.3
15	96.9	99.9	99.7	100.6
30	98.2	103.0	103.1	102.4
45	98.2	103.1	103.3	102.6

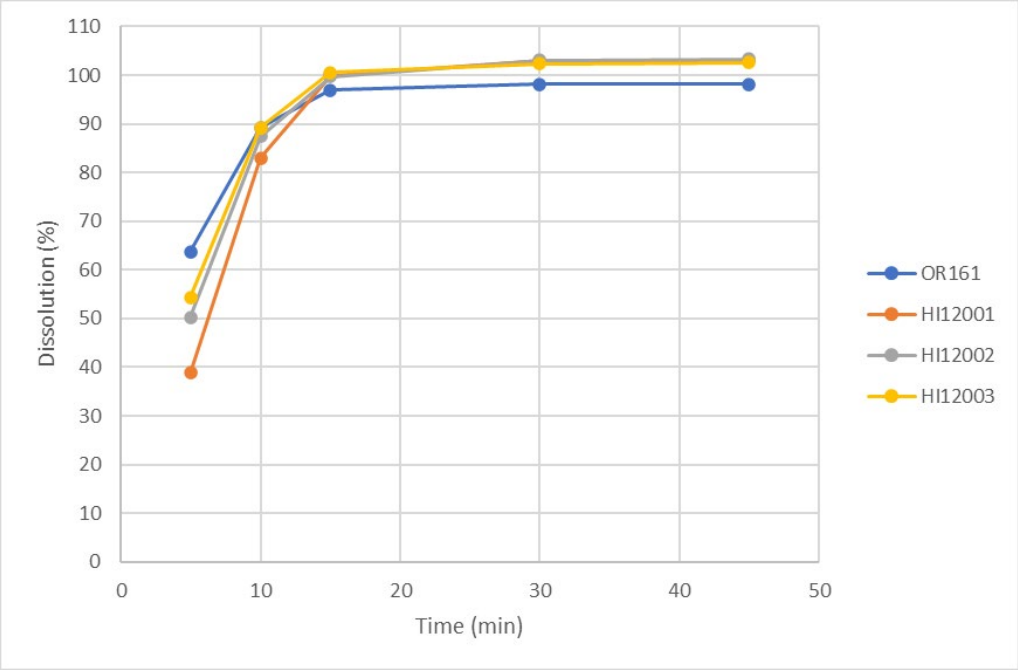


Figure 1 Dissolution of Hydroxychloroquine from the reference and the test product in 0.1N HCl (average of dissolved amount in %)

It can be concluded, that more than 85% of the active agent is dissolved within 15 minutes for all the samples, consequently according to *Guideline on the Investigation of Bioequivalence CPMP/QWP/EWP/1401/98 Rev. 1.* all of these products have not to be compared by using of similarity factor. The dissolution profiles may be accepted as similar without further mathematical evaluation.

Table 2.1.P.2.2.3-7
Dissolution of Hydroxychloroquine from the reference product (batch number: OR161) at pH 4.5 (dissolved amount in %)

	5 min	10 min	15 min	30 min	45 min
1.	59.0	81.6	88.8	91.0	93.4
2.	68.4	90.7	96.4	97.8	99.6
3.	49.5	76.8	87.9	91.7	94.1
4.	53.1	75.1	84.7	89.9	93.7
5.	59.4	85.2	97.9	99.9	100.7
6.	62.9	86.9	95.7	97.6	98.9
7.	51.5	72.5	87.0	88.0	88.7
8.	47.3	74.5	81.1	92.5	95.1
9.	50.6	78.6	87.6	98.9	100.8
10.	57.2	78.8	93.3	98.9	100.1
11.	56.5	82.7	93.4	93.6	97.9
12.	46.2	76.4	87.5	89.8	91.1
Average	**55.1**	**80.0**	**90.1**	**94.1**	**96.2**
SD	6.6	5.5	5.2	4.2	4.0
CV (%)	12.0	6.9	5.7	4.5	4.2

Table 2.1.P.2.2.3-8
Table Dissolution of Hydroxychloroquine from the test product (batch number: HI12001) at pH 4.5 (dissolved amount in %)

	5 min	10 min	15 min	30 min	45 min
1.	52.8	88.8	100.4	104.5	104.3
2.	44.9	80.2	97.5	101.3	101.3
3.	52.4	90.5	101.5	104.4	103.8
4.	49.1	82.1	97.5	101.3	101.0
5.	55.0	89.5	100.6	103.5	103.3
6.	48.7	87.7	102.6	105.2	104.8
7.	50.3	83.3	99.9	102.1	101.7
8.	42.6	76.7	96.4	103.2	103.1
9.	47.4	83.7	98.4	103.7	103.0
10.	42.9	76.6	95.2	101.4	101.0
11.	47.2	84.1	99.2	102.3	102.1
12.	40.5	76.2	96.4	103.0	102.7
Average	**47.8**	**83.3**	**98.8**	**103.0**	**102.7**
SD	4.5	5.1	2.3	1.3	1.3
CV (%)	9.4	6.2	2.3	1.3	1.2

Table 2.1.P.2.2.3-9
Dissolution of Hydroxychloroquine from the test product (batch number: HI12002) at pH 4.5 (dissolved amount in %)

	5 min	10 min	15 min	30 min	45 min
1.	46.7	82.3	98.0	102.9	102.9
2.	48.7	84.4	100.4	102.8	102.8
3.	46.0	82.0	98.6	102.2	102.3
4.	46.0	81.4	98.9	101.9	101.9
5.	45.1	81.8	98.1	102.0	102.3
6.	47.6	85.6	99.0	102.0	102.4
7.	46.7	83.2	98.5	102.5	102.6
8.	50.9	88.1	100.4	104.1	104.1
9.	35.4	66.0	92.5	102.2	102.4
10.	46.2	80.5	98.6	102.4	102.4
11.	40.5	76.4	97.3	103.8	103.9
12.	42.4	78.5	98.0	103.6	103.5
Average	**45.2**	**80.9**	**98.2**	**102.7**	**102.8**
SD	4.1	5.6	2.0	0.8	0.7
CV (%)	9.0	6.9	2.1	0.7	0.7

Table 2.1.P.2.2.3-10
Dissolution of Hydroxychloroquine from the test product (batch number: HI12003) at pH 4.5 (dissolved amount in %)

	5 min	10 min	15 min	30 min	45 min
1.	48.8	85.7	97.9	101.1	101.8
2.	49.6	83.9	98.7	102.6	101.6
3.	54.7	91.0	102.6	103.9	104.7
4.	37.6	67.8	86.5	100.0	102.4
5.	51.7	87.2	99.8	103.0	102.4
6.	44.8	80.4	98.2	100.2	100.6
7.	41.5	77.1	96.4	101.9	102.3
8.	45.2	82.6	98.9	102.3	102.3
9.	41.2	76.8	96.4	101.5	101.7
10.	33.1	62.8	83.6	100.9	101.6
11.	46.7	83.3	97.8	101.6	102.2
12.	43.5	75.9	94.9	101.5	101.6
Average	**44.9**	**79.5**	**96.0**	**101.7**	**102.1**
SD	6.0	8.1	5.5	1.1	1.0
CV (%)	13.5	10.2	5.7	1.1	0.9

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

Table 2.1.P.2.2.3-11
Dissolution of Hydroxychloroquine from the reference and the test product at pH 4.5 (average of dissolved amount in %)

Minutes	Reference product	Test product		
	OR161	HI12001	HI12002	HI12003
5	55.1	45.2	47.8	44.9
10	80.0	80.9	83.3	79.5
15	90.1	98.2	98.8	96.0
30	94.1	102.7	103.0	101.7
45	96.2	102.8	102.7	102.1

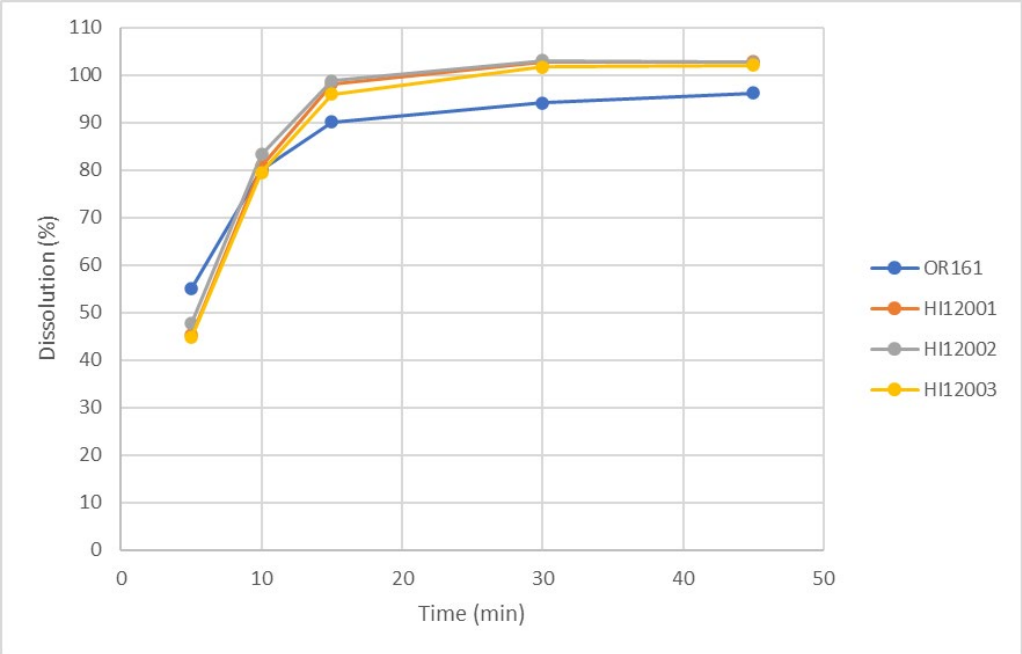


Figure 2
Dissolution of Hydroxychloroquine from the reference and the test product at pH 4.5 (average of dissolved amount in %)

It can be concluded, that more than 85% of the active agent is dissolved within 15 minutes for all the samples, consequently according to *Guideline on the Investigation of Bioequivalence CPMP/QWP/EWP/1401/98 Rev. 1.* all of these products have not to be compared by using of similarity factor. The dissolution profiles may be accepted as similar without further mathematical evaluation.

Table 2.1.P.2.2.3-12
Dissolution of Hydroxychloroquine from the reference product (batch number: OR161) at pH 6.8 (dissolved amount in %)

	5 min	10 min	15 min	30 min	45 min
1.	59.9	81.9	92.9	98.3	98.4
2.	59.9	84.7	93.0	96.4	96.9
3.	62.3	87.1	94.6	96.8	97.6
4.	55.4	81.2	94.2	97.2	98.3
5.	63.4	87.9	94.1	95.6	96.8
6.	53.3	83.7	94.4	97.6	96.7
7.	54.8	84.0	95.1	97.8	97.5
8.	51.9	80.7	92.4	95.9	96.3
9.	60.0	88.1	94.4	95.0	94.8
10.	47.8	76.9	88.9	96.0	95.6
11.	57.0	84.4	93.7	95.1	95.0
12.	52.8	82.6	93.1	95.1	94.8
Average	**56.5**	**83.6**	**93.4**	**96.4**	**96.6**
SD	4.7	3.2	1.6	1.1	1.3
CV (%)	8.3	3.9	1.7	1.2	1.3

Table 2.1.P.2.2.3-13
Dissolution of Hydroxychloroquine from the test product (batch number: HI12001) at pH 6.8 (dissolved amount in %)

	5 min	10 min	15 min	30 min	45 min
1.	47.7	81.6	93.2	103.2	101.0
2.	47.8	83.4	96.3	103.4	102.8
3.	42.9	76.1	92.8	98.6	99.7
4.	34.5	66.6	88.5	99.8	100.9
5.	35.4	77.8	95.1	101.3	103.1
6.	43.6	66.5	87.9	99.6	99.1
7.	42.0	75.3	92.3	101.0	101.1
8.	43.9	79.2	98.2	102.9	103.3
9.	43.5	79.6	98.1	102.7	102.9
10.	50.2	85.4	95.2	99.9	100.5
11.	39.8	74.8	94.3	101.2	101.4
12.	31.3	62.5	83.2	101.0	101.5
Average	**41.9**	**75.7**	**92.9**	**101.2**	**101.4**
SD	5.7	7.1	4.5	1.6	1.4
CV (%)	13.7	9.4	4.8	1.5	1.3

Table 2.1.P.2.2.3-14
Dissolution of Hydroxychloroquine from the test product (batch number: HI12002) at pH 6.8 (dissolved amount in %)

	5 min	10 min	15 min	30 min	45 min
1.	43.5	78.4	97.5	102.8	103.3
2.	44.7	79.4	97.4	102.8	103.3
3.	40.3	74.1	94.9	102.0	102.9
4.	43.5	76.9	94.9	102.5	103.1
5.	43.3	79.5	98.9	103.5	104.0
6.	39.8	74.6	95.1	101.7	102.8
7.	37.4	70.4	90.7	102.7	103.0
8.	45.1	82.0	96.1	100.7	101.6
9.	46.1	82.9	98.5	102.9	103.3
10.	39.4	72.3	91.9	102.5	103.0
11.	50.9	85.2	95.8	101.6	102.7
12.	43.4	79.0	96.7	103.0	103.4
Average	**43.1**	**77.9**	**95.7**	**102.4**	**103.0**
SD	3.6	4.4	2.5	0.8	0.6
CV (%)	8.3	5.7	2.6	0.7	0.5

Table 2.1.P.2.2.3-15
Dissolution of Hydroxychloroquine from the test product (batch number: HI12003) at pH 6.8 (dissolved amount in %)

	5 min	10 min	15 min	30 min	45 min
1.	43.2	73.9	94.1	101.2	102.1
2.	41.6	71.4	92.3	101.7	102.8
3.	43.6	75.2	92.8	98.5	102.8
4.	49.5	81.2	94.2	101.2	101.9
5.	47.2	82.1	93.9	100.1	101.4
6.	35.7	63.4	93.3	99.6	101.4
7.	47.9	85.4	100.4	104.3	104.8
8.	47.9	83.2	98.1	102.1	103.1
9.	45.6	81.9	98.4	102.0	103.0
10.	44.6	80.2	95.3	102.4	103.0
11.	43.5	79.6	97.0	104.0	104.5
12.	35.2	67.9	88.6	103.3	103.9
Average	**43.8**	**77.1**	**94.9**	**101.7**	**102.9**
SD	4.5	6.8	3.2	1.7	1.1
CV (%)	10.4	8.8	3.4	1.7	1.1

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

Table 2.1.P.2.2.3-16
Dissolution of Hydroxychloroquine from the reference and the test product at pH 6.8 (average of dissolved amount in %)

Minutes	Reference product	Test product		
	OR161	HI12001	HI12002	HI12003
5	56.5	41.9	43.1	43.8
10	83.6	75.7	77.9	77.1
15	93.4	92.9	95.7	94.9
30	96.4	101.2	102.4	101.7
45	96.6	101.4	103.0	102.9

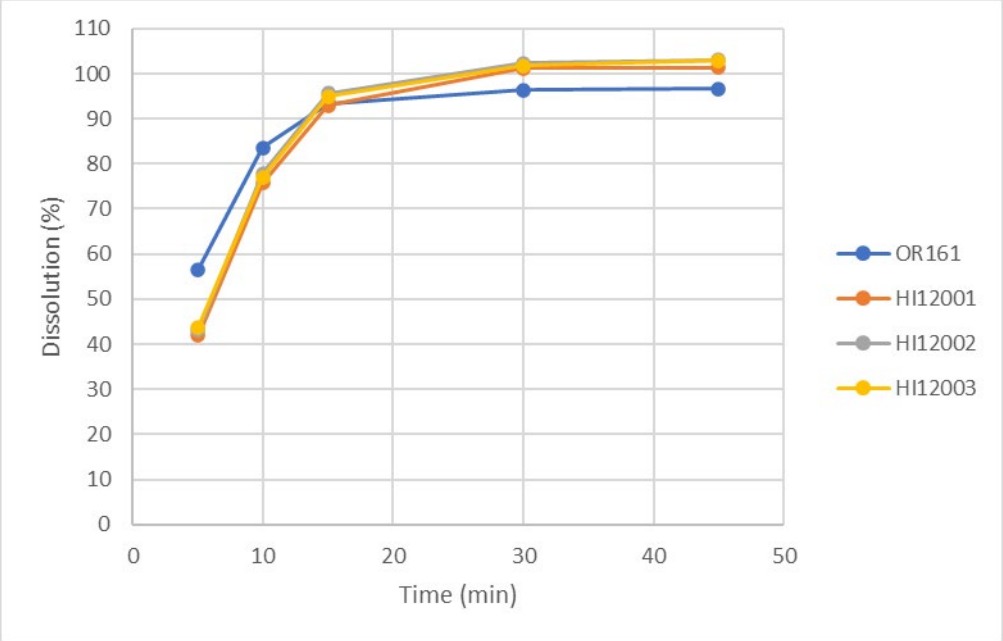


Figure 3 Dissolution of Hydroxychloroquine from the reference and the test product at pH 6.8 (average of dissolved amount in %)

It can be concluded, that more than 85% of the active agent is dissolved within 15 minutes for all the samples, consequently according to *Guideline on the Investigation of Bioequivalence CPMP/QWP/EWP/1401/98 Rev. 1.* all of these products have not to be compared by using of similarity factor. The dissolution profiles may be accepted as similar without further mathematical evaluation.

1.5 Summary of *in vitro* dissolution tests

Method development for the in vitro dissolution method was carried out by using of principles recommended by Ph. Eur. (5.17.1 Recommendations on dissolution testing), EMA/CHMP /CVMP/QWP/336031/2017 reflection paper and the *Guideline on the Investigation of Bioequivalence CPMP/QWP/EWP/1401/98 Rev. 1*
The above-mentioned data demonstrate that over the physiological range, the three batches of the test product Hydroxychloroquine MEDITOP 200 mg film-coated tablets manufactured by Meditop Pharmaceutical Ltd. display the same *in vitro* dissolution characters as the commercial batch of reference product, Plaquenil 200 mg film-coated tablets manufactured by Sanofi Co., Ltd. The data exhibit that the dissolution is very rapid in 0.1 M hydrochloric acid an in buffers of pH 4.5 and pH 6.8. The batches of the developed test product have the same dissolution profile at all the tested pH-s, consequently the robustness of the manufacturing is also supported by these results.

Based on the data the proposed specification limit is Q = 80% at 15 minutes in 0.1 M hydrochloric acid and the applied dissolution method (Apparatus 2; rpm 50)

2.1.P.2.3 Manufacturing Process Development

Predetermined target product profile and the related preliminary risk assessment are presented in the part *2.1.2.2 Drug Product*. 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 film-coating tablets produced by wet granulation, the following matrix with the most relevant relationship can be compiled.

Table 2.1.P.2.3-1
CPP of the manufacturing process and CQAs of the intermediates and of the products

Unit operation	Process parameter	Critical Quality Attributes
Wet granulation Wet mixing Drying Milling	Blending speed Blending time Drying temperature and time Screen hole size Milling speed	Particle size Bulk density Flowability Loss of drying
Final blending	Blending speed Blending time	Blend uniformity
Tableting	Filling position	Average weight Assay
	Filling speed	Weight uniformity Uniformity of dose unit
	Compression force	Tablet parameters: hardness. disintegration time. dissolution rate
Coating	Atomization rate Drying temperature and time Drying air volume speed	Appearance of the film-coated tablets

Based 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 granulating process
Testing of the blending process
Testing the tableting process
Testing the coating process

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

It is well-known that the particle size of the active substances has only small effect at wet granulation because the primer particles form granules that ensure good flowability and compactibility. From the point of dissolution in the case of hydroxychloroquine sulfate due to the its high solubility the particle size of the active substance has only small effect as well.

As the active substance content of the Hydroxychloroquine 200 mg tablets is relatively high. 2/3 part of the tablet weight therefore the particle size has no risk from the point of the homogeneity too.

Consequently. the particle size of Hydroxychloroquine sulfate batch no. C63-200405 considered good for manufacture of the clinical sample.

2 Evaluation of effect of the particle size of the excipients

Among the excipients the particle size of lactose and magnesium stearate is considered as functionality related characteristics.

In the case of lactose. the type that is used is a milled one under brand name Granulac 200 which is a standard crystalline and milled lactose monohydrate for wet granulation process. More than 90 % of the particles are smaller than 100 µm by air-jet-sieving.
The branded type is a guarantee for the proper particle size.

In the case of magnesium stearate there are two main types a normal one which has specific surface area of 1-4 m^2/g and another which has 5-12 m^2/g. The second one has better lubricating properties however it could decrease the dissolution rate as well.
At development both types were tested and it was found that the lubricating effect of the normal type is enough in the case of Hydroxychloroquine 200 mg tablets.

The results were the followings:

Table 2.1.P.2.3-2
Tablet core compositions and blend parameters

Components (g)	Number of experiments	
	VAXIX040	VAXIX048
Hydroxychloroquine sulfate	200	200
Lactose monohydrate	30	30
Povidon	7	7
Maize starch	57	57
Magnesium stearate	6*	6**
Purified water	24	24
Blend parameters		
Loss on drying (%)	2.9	2.1
Flowability (100 g) (s)	19	30
Bulk density (g/mL)	0.83	0.77
Hausner ration (-)	1.22	1.27

*normal magnesium stearate (Magnesia)
** Merck: Emprove Essential lub MST of high specific surface area

Table 2.1.P.2.3-4
Parameters Hydroxychloroquine MEDITOP 200 mg tablets

Tablet parameters/Nr. of exp.	**VAXIX040**	**VAXIX048**
Average weight (mg)	299.6	307
Weight variation (%)	1.7	0.83
Height of the tablets (mm)	4.15	4.26
Hardness (N)	128	107
Friability (%)	0.08	0.15
Disintegration time (min)	6.5	9.5
Appearance	Suitable	Suitable

The data show that due to the better lubrication effect of the magnesium stearate of high specific surface area the weight variation and the hardness of the tablets decreased. while the value of friability and disintegration time increased. Because the normal magnesium stearate gave acceptable results as well it was chosen for the product.

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. granulation parameters
   - granulation binder
   - composition of inner phase
   - granulation liquid – solid phase ratio
   - kneading time
2. mixing time. at addition of magnesium-stearate
3. effect of compression force
4. 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
- ProCepT 4m8 fluid drier with 1 Litre capacity
- Korsch EK0 single punch tablet press
- Wynka Kompressor Developer tablet press

4 Development of granulation process

Manufacturing process

Materials to be granulated (inner phase) were sifted through a sieve of 0.8 mm mesh size and filled into the pot of the ProCepT equipment (with 1 Litre capacity) and mixed for 2 minutes with an impeller speed of 100 rpm without chopper.
The maize starch was divided between the inner and the outer phase. The inner phase contains maize starch in equal quantity of lactose.
Granulating liquid was added to the mixture during continuous mixing (300 rpm impeller. 500 rpm chopper speed). The wetting time was 2 minutes. kneading time was 2 minutes or 4 minutes with impeller speed of 500 and chopper speed of 700 rpm. or 1000/1500 rpm.
The granulated blend was dried in the ProCepT 4m8 fluid drier to reach less than 2 % water content. Loss on drying testing is performed at 80 °C.
Materials of external phase were sifted through a screen of 0.8 mm sieve and it was added to the internal phase and mixed for 10 minutes with an impeller speed of 100 rpm. without chopper. Finally. the magnesium stearate was blended for 2 minutes by the same way.

The effect of CPP on the quality of the blend and tablets are summarizes in table 2.1.P.2.3-3.

5 Tableting process

The final blend was compressed into tablets of 300 mg and 9 mm diameter by Wynka Kompressor Developer tablet press.

The compression force was varied from 5 kN to 20 kN by 5 KN the applied compression speeds were 10 or 20 rpm.

The effect of CPP on the quality of the blend and tablets are summarizes in table 2.1.P.2.3-4.

Table 2.1.P.2.3-5
Final blend and tablet parameters - effect of CPP of granulation

Components/CPP/CQA	Number of experiments				
	VAXVIII178	**VAXVIII184**	**VAXIX044**	**VAXIX052**	**VAXIX054**
Hydroxychloroquine sul.(g)	200	200	200	200	200
Lactose monohydrate (g)	30	30	30	30	30
Povidon (g)	7	3+3	3+3	3+3	3+3
Maize starch (g)	30+27=57	30+27=57	30+27=57	30+27=57	30+27=57
Magnesium stearate (g)	6	6	6	6	6
Purified water (g)	24	12	12	12	12
Wet mixing time (min)	2	2	4	4	4
Mixing time (min)		10	10	10	10*
Final mixing time (min)		2	2	-	2
Blend parameters					
Loss on drying (%)		2.1	2.02	2.29	2.20
Flowability (100 g) (s)		17	25	23	28
Bulk density (g/mL)		0.86	0.79	0.82	0.78
Hausner ration (-)		1.22	1.26	1.27	1.23
Tablet parameters					
Average weight (mg)		295.5	304.8	301.2	305.6
Weight variation (%)		1.03	1.23	1.3	1.6
Height of the tablets (mm)		4.18	4.15	4.2	4.21
Hardness (N)		92	114	100	119
Friability (%)		0.38	0.1	0.28	0.06
Disintegration time (min)		6.5	7.0	7.0	7.0
Appearance	Drying is too long	Suitable	Suitable	Suitable	Suitable

*Mixing speed is 1000/1500 rpm for impeller and chopper

Table 2.1.P.2.3-6
Tablet parameters - effect of CPP of tableting

Components (g)	**Number of experiments**				
	VAXIX040				
Hydroxychloroquine sulfate	200				
Lactose monohydrate	30				
Povidon	3.5+3.5				
Maize starch	30+27				
Magnesium stearate	6				
Purified water	12				
Blend parameters					
Loss on drying (%)	2.33				
Flowability (100 g) (s)	16				
Bulk density (g/mL)	0.79				
Hausner ration (-)	1.26				
Tablet parameter					
Compression force	15kN	20kN	25kN	30kN	20kN
Compression speed	10	10	10	10	20
Average weight (mg)	302.9	307	305.1	307	307.3
Weight variation (%)	1.45	1.04	1.37	1.15	1.45
Height of the tablets (mm)	4.23	4.26	4.23	4.24	4.27
Hardness (N)	127	134	141	145	121
Friability (%)	0.08	0.08	0.08	0.11	0.06
Disintegration time (min)	6	6	6	6	6
Appearance	Suitable	Suitable	Suitable	Suitable	Suitable

Coating process

The coating parameters at laboratory and industrial scale selected based on previous experience.
The process parameters used at laboratory scale are summarized in the following tables:

Table 2.1.P.2.3-7
Coating parameters at laboratory scale

Equipment model	ProCept 4M8
Batch size	450 g (750 pcs tablet cores)
Drum type	Side ventilled
Rotation speed of the drum	25 rpm
Nozzle	0.8 mm
Inlet temperature	55 – 60 ºC
Product temperature	49-51ºC
Spraying rate	2.0 g/min
Atomization air volume speed	20 l/h
Air volume	1 m^3/min

According to the experiments the coating parameters above resultate film-coated tablets of a nice appearance.

Based on the results of the product and process development, the re-evaluation of the risk assessment was also executed.

Table 2.1.P2.3-8
Hazard Analysis (HA) of manufacture of Hydroxychloroquine MEDITOP 200 mg film-coated tablets from the point of Critical Quality Attributes

CQA	**CPP**				
	Working conditions	Wet granulation	Final blending	Tableting	Coating
Appearance	L	N	N	L	L
Assay	L	N	L	L	N
CU	N	L	L	L	N
Dissolution	N	L	N	L	N
Impurities	L	N	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 2.1.P.2.3-7
Revised Risk Assessment for Justification and Risk Mitigation Strategies for Risks of CPP-s

CPP	CQA	Initial risk	Description of CPP's effect on FP CQAs	Risk mitigation Strategy / Control Strategy Action points	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 was needed.	L
	Assay	L			L
	Impurities	L			L
Wet granulation	CU	L	Pre-blending/wetting/aggregation/drying/milling process affects particle size of the blend for compression. Inappropriate particle size affects flowability of the blend, and may have an influence on the content uniformity and may affect the dissolution rate of the AS.	Due to the high AS content and high solubility of the AS the inappropriate particle size has low risk for CU and dissolution rate. With standard working the required particle size can be can be ensured. No investigation was needed.	L
	Dissolution	L			L
Final blending	Assay	L	Due to the high AS content of the tablets with standard working the required Assay and CU can be ensured.	Low risk on quality attributes No investigations was needed.	L
	CU	L			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.	L
	Assay	M			L
	CU	M			L
	Dissolution	M			L
Coating	Appearance	L	The coating may affect the appearance of the product.	With standard control of the coating process the required appearance can be ensured.	L

Finally, it can be concluded that as a result of the formulation development and the related manufacture process development, the product and process understanding is suitable for the adequate control strategy, consequently, the potential risks of the non-conformance for Hydroxychloroquine MEDITOP 200 mg film-coated tablets were minimized to an acceptable level.

6 Conclusion

Based on the activities performed in the formulation and process development, the related risks of the production of Hydroxychloroquine MEDITOP 200 mg film-coated tablets could be decreased to low level. Based on the data and observations gained during the development adequate manufacturing and control strategy were developed. Supporting of its effectiveness 3 batches with 100.000 units were manufactured under cGMP condition and the robust manufacturing was proven.

The manufacturing process is given detailed in the part 2.1.P.3 Manufacture. The results of the in-process control tests and the analytical tests are given in the part of 2.1.P.5.4 Batch Analyses.
The detailed investigation of the product is given in the part of 2.1.P.3.5 Process Validation.
At process validation the effect of the compression speed was studied as well.
On the base of process validation, the scale up of the process was successful, therefore the products can be manufactured in larger volume as well.

The compression speed doesn't have significant effect on the tablet parameters. Therefore, the manufacture process can be considered as a robust one from the point of the compression speed as well.

All the parameters of the film-coated tablets fulfilled the requirements of Target Drug Product Profile and the products are adequate to be used in biowaiver approach during the regulatory process.

2.1.P.2.4 Container and closure system

Package size for clinical study
60 tablets in a labelled PE container closed by PP lid.

1 Primary Packaging material

- 40 ml HDPE container
- PP lid

1.1 Polyethylene container (HDPE) M-445

Description:	White colour, Polyethylene container
Type:	BS 501-17
Capacity	40 ml

1.2 Polypropylene lid D-161

Appearance:	Red colour, plastic polypropylene lid with induction insert.
Type:	Tatren HM 5046

2 Secondary Packaging Materials

According to the prescription of clinical study protocol.

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

This type of compatibility is not appropriate for the products.