

<b>Meditop Pharmaceutical Ltd.</b>	<b>Research &amp; Development Department</b>
Pilisborosjenő	Development Report

## **Hydroxychloroquine MEDITOP 200 mg film-coated tablets**

### **Pharmaceutical Development in Laboratory scale**

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**A kiadványt 2020-2.1.1-ED-2020-00023 projekt támogatja.  
A Projekt az Innovációs és Technológiai Minisztérium Nemzeti Kutatási, Fejlesztési és  
Innovációs Alapból nyújtott támogatásával, a Nemzeti Kutatási, Fejlesztési és  
Innovációs Hivatallal kötött támogatási szerződés alapján valósult meg.**

## 1 Products description and composition

### The product is presented as follows:

Hydroxychloroquine MEDITP 200 mg film-coated tablets are white, round, biconvex tablets with plain surfaces on both sides.

### Composition

The composition of film-coated tablets, the quality standard and the role of ingredients are shown in the following tables:

Component	Quantity (mg/tablet)	Percentage (%)	Function	Quality
Hydroxychloroquine sulfate	200.0	64.5	active ingredient	Ph. Eur.
Lactose monohydrate	30.0	9.7	diluent, binder	Ph. Eur.
Maize starch	57.0	18.4	disintegrant	Ph. Eur.
Povidone	7.0	2.3	binder	Ph. Eur.
Magnesium stearate	6.0	1.9	lubricant	Ph. Eur.
Opadry OY-L-28900	10.0	3.2	film-coating	Colorcon Ltd. in Haus
Nominal weight of a film-coated tablet	310.0			

Quantitative formula of Opadry OY-L-28900:

Ingredient	Quantity % w/w	Grade	E Number	Quality
Lactose monohydrate	36.0	-	-	Ph. Eur.
HPMC 2910/ Hypromellose	28.0	15 mPas	E464	Ph. Eur.
Titanium dioxide	26.0	-	E171	Ph. Eur.
Macrogol	10.0	MW 4000	E1521	Ph. Eur.

## 2 Pharmaceutical Development

### Abbreviations

AS	Active substance
BCS	Biopharmaceutical Classification System
BE	Bioequivalence
BID	Twice daily (bis in die)
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
L-HPC	Low Substituted Hydroxypropyl Cellulose
MCC	Microcrystalline Cellulose
QTPP	Quality target product profile

### Development Summary

The pharmaceutical development report summarizes the development of Hydroxychloroquine HU 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 aventis 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 has three basic functional groups with pKa values of 4.0, 8.3 and 9.7, two of which would be protonated at pH 7.4 (2)

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 HU 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 HU 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.

## 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-Aventis Ltd.
Legal basis	Complete application
Authorization date	07. April 2020

The product is manufactured by Sanofi Aventis S.A., 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**

<b>Components</b>	<b>In one tablet</b>
Hydroxychloroquine sulfate (Hydroxychloroquine)	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 adherent 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:

<b>Component</b>	<b>Quantity (mg)</b>
Hydroxychloroquine sulfate	200
Lactose monohydrate	30
Maize starch	55-65
Povidone	3-10
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 HU 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](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).

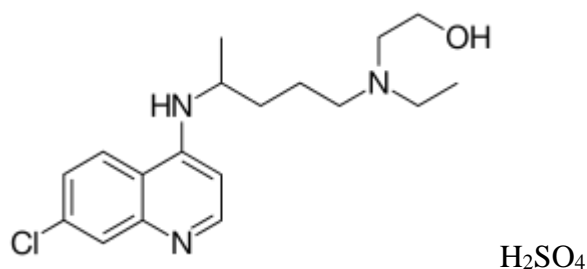
[https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf)

## 2.1 Components of the Drug Product Drug substance

### 2.1.1 Drug Substance

(CoA and AR are attached)

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



General formula:	$\text{C}_{18}\text{H}_{28}\text{ClN}_3\text{O}_5\text{S}$
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)
BCS classification:	Class III.
Solubility	

Hydroxychloroquine sulfate is freely soluble in water

Solubility in buffers of different pH values (1):

<b>Solvent</b>	<b>Solubility (mg/mL)</b>	<b>Solubility (mg/250 mL)</b>	<b>BCS* classification</b>
pH 1.2 buffer	4.83	1207.5	Class I. or Class III.
pH 4.5 buffer	4.91	1227.5	Class I. or Class III.
pH 6.8 buffer	4.91	1227.5	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 90 % of the material consists of particles of 63-250 µm that is appropriate for tablet manufacture.

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

Batch No.:	C63-200405
on 500 µm	0.03 %
on 315 µm	0.45 %
on 250 µm	4.74 %
on 180 µm	17.15 %
on 125 µm	38.82 %
on 63 µm	35.04 %
on 45 µm	1.79 %
Through	0.41 %

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.

### 2.1.2 Excipients

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

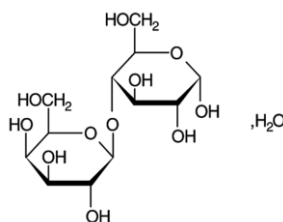
The tablet core has the following excipients:

- 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.

### Lactose monohydrate

Ph. Eur:	Lactose ( <i>Ph Eur monograph 0187</i> )
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 <sub>12</sub> H <sub>22</sub> O <sub>11</sub> · H <sub>2</sub> O
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.

**Polyvidonpyrrolidone**

Ph.Eur:

Povidonum

Synonyms:

Kollidon;

Plasdone;

polyvidone;

polyvinylpyrrolidone

Chemical Name:

1-Ethenyl-2-pyrrolidinone homopolymer

CAS Registry No.:

[9003-39-8]

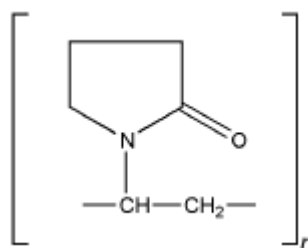
Empirical Formula:

(C<sub>6</sub>H<sub>9</sub>NO)<sub>n</sub>

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/cm<sup>3</sup> for Plasdone.

Density (true): 1.180 g/cm<sup>3</sup>  
Melting point: softens at 150°C.  
Moisture content: povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidity.  
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.

#### Maize (Corn) Starch

Ph. Eur: *Maydis amyllum* (maize starch)

Chemical Name and CAS Registry Number: Starch [9005-25-8]

Empirical Formula: (C<sub>6</sub>H<sub>10</sub>O<sub>5</sub>)<sub>n</sub>

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/cm<sup>3</sup> for corn starch.

Density (tapped): 0.658 g/cm<sup>3</sup> for corn starch.

Density (true): 1.478 g/cm<sup>3</sup> for corn starch.

Flowability: Corn starch is cohesive and has poor flow characteristics.

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

Particle size distribution: 2–32 μm

Solubility: practically insoluble in cold ethanol (95%) and in cold water.

Starch swells instantaneously in water by about 5–10% at 37°C

Specific surface area: 0.41–0.43 m<sup>2</sup>/g

#### Stability and Storage Conditions:

Dry, unheated starch is stable if protected from high humidity.

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

### **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 <sub>36</sub> H <sub>70</sub> MgO <sub>4</sub>
Molecular Weight:	591.34
Structural Formula:	[CH <sub>3</sub> (CH <sub>2</sub> ) <sub>16</sub> COO] <sub>2</sub> Mg

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 odor 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/cm <sup>3</sup>
Density (tapped):	0.286 g/cm <sup>3</sup>
Density (true):	1.092 g/cm <sup>3</sup>
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 m <sup>2</sup> /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 m<sup>2</sup>/g.

The branded type is a guarantee for the proper specific surface area.

**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:

<b>Ingredient</b>	<b>Quantity % w/w</b>	<b>Grade</b>	<b>E Number</b>	<b>Quality</b>
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

## 2.2 Drug Product Development

### Drug Product Development Strategy

At the development of the Hydroxychloroquine HU 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.

### 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 1.0 % 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 pharmacopeial acceptance criteria for uniformity of dosage units.

Table 2.1.P.2.2-1

Target Product Profile of Hydroxychloroquine HU 200 mg film-coated tablets

Description	White/white capsules of sizes #0
Identification	Positive
Assay	Labelled amount $\pm$ 5 %
Uniformity of dose units	Meets pharmacopoeia acceptance criteria
Total impurities	Not more than 1.0 %
Dissolution	Very rapid dissolution (Q=80 % in 15 minutes)
Microbiological limits	Meet pharmacopeial acceptance criteria

### Quality Attributes of the Drug Product

Table 2.1.P.2.2-2 summarizes the quality attributes of the Hydroxychloroquine HU 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 HU 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 buffer of pH 4.5. volume 900 ml. rpm 50	Yes	Variability in the dissolution rate can impact the efficacy. Both formulation and process variables affect the dissolution profile.
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

Quality Attributes of the Drug Product	Target	Is this CQA?	Justification
Residual Solvents	Conform to ICH	Yes*	Formulation and process variables applied do not impact the residual solvent.
Loss on drying	NMT 3.0% 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.

### **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.



Table 2.2-1 Preliminary Hazard Analysis (PHA) of development of Hydroxychloroquine HU 200 mg film-coated tablets

CQA	CMA					Working conditions	CPP			
	AS assay	AS impurities	AS particle size	AS sensitivity	Type and rate of excipients		Wet granulation	Final blending	Tableting	Coating
Appearance	N	N	M	L	L	L	N	N	M	L
Assay	H	L	N	N	N	L	N	L	M	N
CU	N	N	L	N	N	N	L	L	M	N
Dissolution	N	N	L	N	H	N	L	N	M	L
Impurities	N	H	L	L	L	L	N	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 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. 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 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 rate 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 and stability test.
	Dissolution	H		
	Impurities	L		

Table 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
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 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, CU values and the dissolution rate of the AS	With proper control of the tableting process the required appearance, Assay, CU and dissolution can be ensured.
	Assay	M		
	CU	M		
	Dissolution	M		
Coating	Appearance	L	The coating may affect the appearance of the product.	With proper control of the coating process the required appearance can be ensured.

Therefore, in the case of the development of Hydroxychloroquine HU 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.

## 2.2.1 Formulation Development

### 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 Liter pot
- ProCept 4m8 fluid bed dryer with 1 Liter capacity
- IKA mill with 2 mm screen
- Korsch EK 0 eccentric tablet machine.

### Manufacturing process

The materials to be granulated were sifted through a sieve of 0.8 mm and filled into the pot of the ProCept equipment (with 1 Liter 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.

The results were the followings:

Table 2.2.1-1 Tablet core compositions and blend parameters

Components (g)	Number of experiments		
	VAXVIII172	VAXIX040	VAXIX046
Hydroxychloroquine sulfate	200	200	200
Lactose monohydrate	30	30	30
Povidon	7	7	7
Maize starch	60	57	54
Magnesium stearate	3	6	9
Purified water	28	28	28
<i>Blend parameters</i>			
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 ration (-)	1.17	1.22	1.25

Table 2.2.1-2 Parameters Hydroxychloroquine MEDITOP 200 mg tablets

<i>Tablet parameters/Nr. of exp.</i>	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

The data show that the 3 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 6 mg and 9 mg of magnesium stearate the lubrication was good however, the 9 mg magnesium stearate decreased the dissolution rate. The quantity of povidon and maize starch seems to be good from the point of the tablet-hardness. the disintegration time and the dissolution rate as well. therefore, these quantities were chosen for the manufacturing process optimization and scale up.

### **Revised risk assessment after formulation development**

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

Table 2.2.1-3 Hazard Analysis (HA) of manufacture of Hydroxychloroquine HU 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 2.2.1-4 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



### **2.2.2 Overages**

Overages were not applied in this preparation.

### **2.2.3 Physicochemical and Biological Properties**

#### ***In vitro* dissolution**

Because the QC method is the same as the dissolution method at pH 4.5 separates tests weren't made.

Scientific databases, official monographs and guidelines (issued by EMA, FDA, ICH) as well as the data presented by the manufacturer of reference product (Plaque 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.

Dissolution method was chosen based on USP Monograph of Hydroxychloroquine Sulfate tablets for the evaluation of the profiles.

*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 Plaquenil 200 mg film-coated tablets – Sanofi-Aventis Co., Ltd.) and the one batch of the test product Hydroxychloroquine HU 200 mg film-coated tablets produced in laboratory scale were compared to evaluate the similarity.

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

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 purified water
Method:	paddle
Agitation rate:	50 rpm
Temperature:	37 ± 0.5°C
Sample amount:	1 tablet per vessel
Time points:	10, 15, 20, 25, 30 and 45 min
Detection:	226 nm
Type of cuvette:	1 cm quartz

#### *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*

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

A<sub>s</sub>: absorbance of the sample solution

$A_{std}$ :	absorbance of the standard solution
$W_{std}$ :	dose weight of the reference material. mg
$St$ :	strength. mg
$X_{dilat}$ :	dilution ratio
$P_{std}$ :	potency of the reference material. %

### 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.

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

where  $f_2$  is similarity factor.  $n$  is the number of observations.  $R_i$  is percentage drug dissolved from reference formulation, and  $T_i$  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.

### Tested products

Reference product:

- Plaquenil 200 mg tablets – Sanofi-Aventis Co. Ltd.
  - batch numbers: 8R208

Test product:

- Hydroxychloroquine 200 mg tablets
  - batch numbers: VAXVIII040

## Results

*In vitro* dissolution test results of 12 tablets of reference product (Plaquenil 200 mg tablets) and 12 capsules of test product (Hydroxychloroquine MEDITOP 200 mg film-coated tablets) are summarized in the following tables.

2.2.3-1 Table Dissolution of Hydroxychloroquine from the reference product (batch number: 8R208). in purified water (dissolved amount in %)

	<b>10 min</b>	<b>15 min</b>	<b>20 min</b>	<b>30 min</b>	<b>45 min</b>	<b>60 min</b>
1.	75.5	88.1	93.8	95.2	95.7	96.2
2.	73.1	90.0	95.3	95.1	95.3	95.3
3.	79.6	95.5	98.0	98.3	98.3	98.6
4.	65.5	83.7	92.9	95.3	95.7	95.8
5.	67.9	85.9	93.8	96.5	97.3	97.7
6.	60.1	78.0	88.2	92.7	93.7	94.5
7.	80.5	93.8	98.0	98.8	98.5	99.0
8.	72.0	87.4	93.9	95.3	95.4	95.6
9.	58.9	79.3	89.3	93.3	94.9	95.3
10.	73.2	91.0	93.9	94.5	94.9	96.0
11.	63.6	83.5	92.6	96.3	97.5	98.0
12.	71.3	89.6	97.0	99.0	99.6	99.8
<b>Average</b>	70.1	87.2	93.9	95.9	96.4	96.8
<i>SD</i>	7.0	5.4	3.0	2.0	1.8	1.7
<i>CV (%)</i>	10.0	6.1	3.2	2.1	1.9	1.8

2.2.3-2 Table Dissolution of Hydroxychloroquine from the test product (batch number: VAXIX040) in purified water (dissolved amount in %)

	10 min	15 min	20 min	25 min	30 min	45 min	60 min
1.	89.7	98.7	101.9	103.3	103.9	104.7	104.7
2.	83.5	97.7	100.6	101.3	101.9	102.2	103.0
3.	91.4	99.3	101.7	102.6	103.5	104.5	105.6
4.	88.6	98.1	102.0	103.1	103.9	104.6	105.3
5.	85.1	99.5	101.4	101.6	102.4	102.4	103.5
6.	87.8	98.2	101.4	102.8	103.8	105.3	105.8
<b>Average</b>	87.7	98.6	101.5	102.5	103.2	103.9	104.7
<i>SD</i>	2.9	0.7	0.5	0.8	0.9	1.3	1.1
<i>CV (%)</i>	3.3	0.7	0.5	0.8	0.8	1.3	1.1

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

2.2.3-3 Table Dissolution of Hydroxychloroquine from the reference and the test product at pH 1.2 (average of dissolved amount in %)

Minutes	Reference product	Test product
	8R208	VAXVIII040
10	70.2	87.7
15	87.4	98.6
20	95.2	101.5
25	97.3	102.5
30	97.9	103.2
45	98.4	103.9
60	99.0	104.7

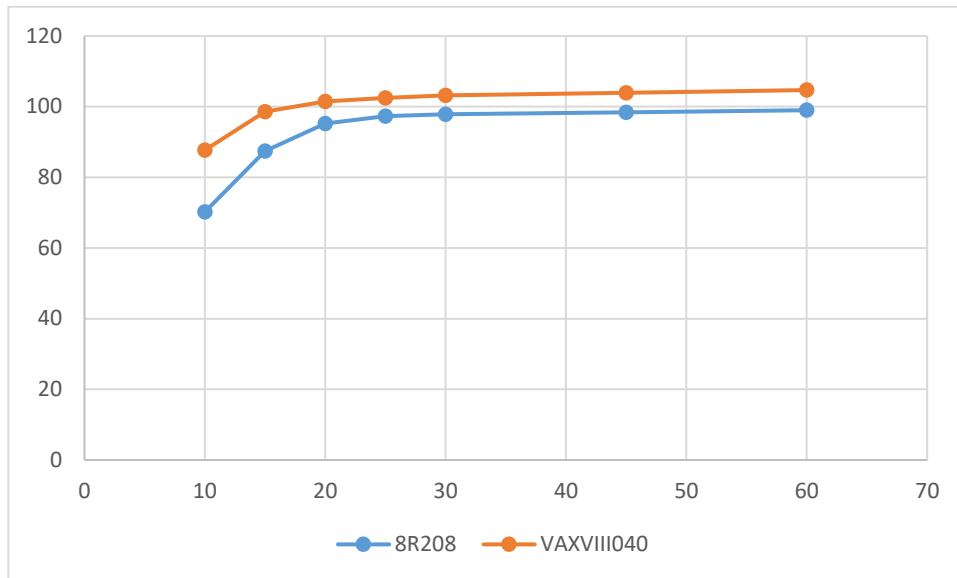


Figure 1 Dissolution of Hydroxychloroquine from the reference and test product in purified water (average of dissolved amount in %)

It can be concluded. that more than 85% of the active agent is dissolved within 15 minutes for all the samples therefore, the dissolution profiles may be accepted as similar without further mathematical evaluation.

## 2.3 Manufacturing Process Development

Predetermined target product profile and the related preliminary risk assessment are presented in the part *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 capsules 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

<b>Unit operation</b>	<b>Process parameter</b>	<b>Critical Quality Attributes</b>
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

### **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.

### **Evaluation of effect of the particle size of the excipients**

Among the excipients of Hydroxychloroquine 200 mg tablets 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  $\mu\text{m}$  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  $\text{m}^2/\text{g}$  and another which has 5-12  $\text{m}^2/\text{g}$ . 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 2.3-1 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
<i>Blend parameters</i>		
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 2.3-2 Parameters Hydroxychloroquine MEDITOP 200 mg tablets

<i>Tablet parameters/Nr. of exp.</i>	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.

### **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

## **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 2.3-3.

### 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 2.3-4.

## 2.3-3 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
<i>Blend parameters</i>					
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
<i>Tablet parameters</i>					
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

2.3-4 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
<i>Blend parameters</i>	
Loss on drying (%)	2.33
Flowability (100 g) (s)	16
Bulk density (g/mL)	0.79
Hausner ration (-)	1.26

*Tablet parameter*

<i>Compression force</i>	15kN	20kN	25kN	30kN	20kN
<i>Compression speed</i>	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 2.3-5 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 °C
Product temperature	49-51°C
Spraying rate	2.0 g/min
Atomization air volume speed	20 l/h
Air volume	1 m <sup>3</sup> /min

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

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

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Table 2.3-6  
Hazard Analysis (HA) of manufacture of Hydroxychloroquine HU 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 2.3-7 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
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.
	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. No investigation was needed.
	Dissolution	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.
	CU	L		
Tableting	Appearance	L	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.
	Assay	L		
	CU	L		
	Dissolution	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.

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.



### **3 Manufacture at laboratory scale**

#### **3.1 Batch formula**

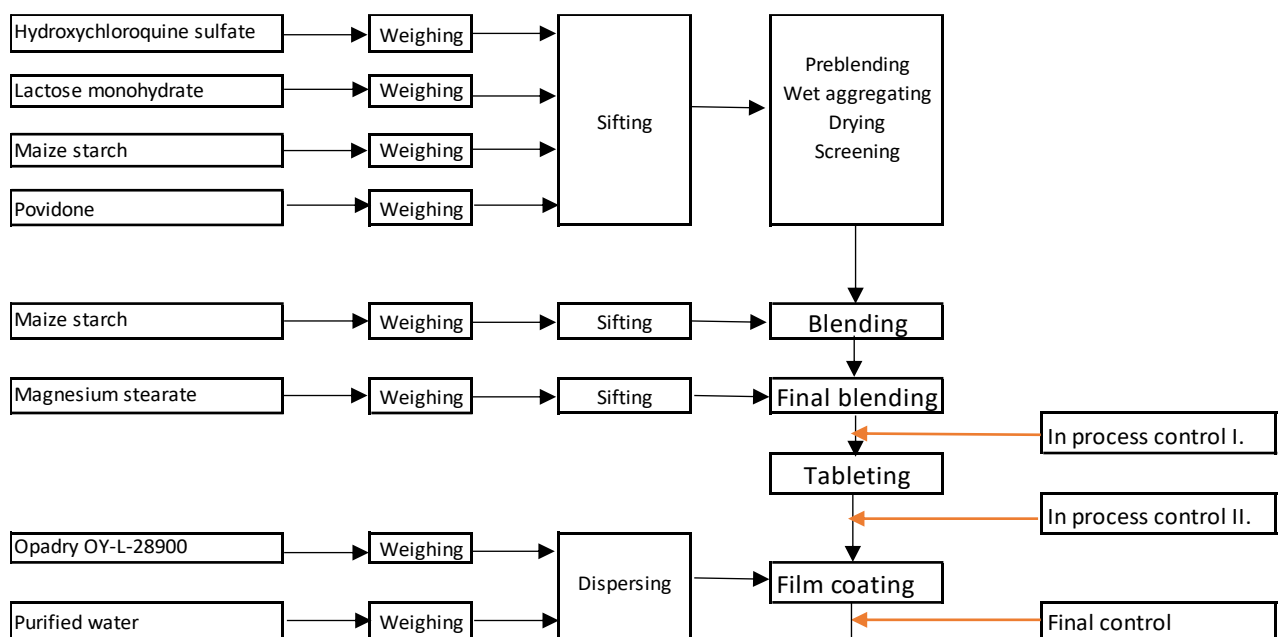
Laboratory batch size of Hydroxychloroquine MEDITOP 200 mg film-coated tablets is 1500 pieces, which means mass of final blending of 450 g

<b>Component</b>	<b>Quantity (mg/FP)</b>	<b>Quantity (mg/batch)</b>
Hydroxychloroquine sulfate	200.0	300.0
Lactose monohydrate	30.0	45.0
Maize starch	57.0	85.5
Povidone	7.0	10.5
Magnesium stearate	6.0	9
Opadry OY-L-28900	10.0	15
Nominal weight of a film-coated tablet/batch	310.0	465

### 3.3 Description of Manufacturing Process and Process Control

The manufacturing of film-coated tablets consists of weighing, shifting, wet granulating, drying, screening, tableting and coating steps. A description of the manufacturing process is provided below along with a flow chart of the process.

#### Flow chart



## **Preparation of the materials, weighing**

### Inner phase

Hydroxychloroquine sulfate	300.0 g
Lactose monohydrate	45.0 g
Maize starch I.	45.0 g
Povidone I.	5.25 g

### Granulating liquid

Povidone II	5.25 g
Purified water	18.0 g

### Outer phase

Maize starch II.	40.5 g
Magnesium stearate	9.0 g

## **High shear granulation**

Equipment: ProCept 4M8 high shear mixer  
ProCept 4M8 high fluid bed dryer  
IKA mill with a screen of 3 mm

### *Manufacture of the granulating liquid*

The Povidone dissolved in the purified water in a proper vessel at room temperature.

### *Granulating*

The components of the inner phase are filled into the ProCept mixer and blended for 10 minutes at an impeller speed of 100 rpm. After it the granulating liquid is added during 2 minutes at an impeller speed of 300 rpm and chopper speed 500 rpm. Then the wet mixture is granulated by an impeller speed of 500 rpm and a chopper speed of 700 rpm for 2 minutes.

### *Drying*

The granules are filled into the vessel of the ProCept fluid dryer. The drying is made at an inlet air temperature of 60°C±5°C until the outlet air temperature increased to 40°C.

### **Sizing (regranulation)**

The dried granules are screened in the Ikamill by the bar rotor at 3000 rpm through a screen of 2 mm.

### **In process control I.**

The process might be continued if the loss on drying value is less than 2.0 %.

### **Mixing**

Equipment: ProCept 4M8 high shear mixer

The sized granules and the shifted maize starch II are fed into the ProCept 4M8 high shear mixer and blended for 10 minutes by 100 rpm. Then the shifted magnesium stearate is added to it and blended for 2 minutes by 100 rpm.

### **In process control II.**

The blend is controlled according to the prescription.  
The process might be continued if the specifications are fulfilled.

### **Compression**

Equipment: Wynka Kompressor Developer  
Tools: 9 mm round, biconvex punches of plain surfaces

The compression is done with the Wynka press assembled with the proper punches and dies. The blend is filled into the hopper, the feeder is started and the tablet mass and hardness are adjusted.

The tablet mass is adjusted cc. 300 mg (the mass of ten tablets should be between 2.85-3.15 g) and the hardness is adjusted above 70 N (the optimum 80N-120N).

### **In-process control III.**

Before the continuous compression the quality of the tablets has to be controlled according to the in-process control prescription.  
The compression can be started if the specifications are fulfilled.

During compression the mass, hardness and height of the tablets have to be controlled in every 15 minutes by the machine operator and recorded into the batch record.

The tablets are gathered into plastic boxes lined with PE sacks.

### **Film coating**

The actual amount of coating material is calculated from the actual weight of the tablets to be coated by the following formula (5% excess is used to compensate the loss during the coating):

$$X = 0.05 \times M \times 1.05$$

Where:  $X$  - is the weighing amount of coating materials (kg)  
Opadry Blue OY-4492 for 15 mg strength  
 $M$  - is the actual weight of the tablet cores (kg)

The actual amount of purified water ( $Y$ ) is calculated from the actual weight of the coating material by the following formula:

$$Y = 5.67 \times X$$

### Preparation of coating liquid

*Equipment:* magnetic stirrer

The calculated amount of purified water is weighted into a plastic vessel and at continuous stirring the weighed amount of the coating materials is added to it. After 60 minutes stirring the liquid is ready for coating.

The coating liquid should be used within 24 hours after preparation.

### Coating

*Equipment:* ProCept 4M8 coater with 14 Schlick nozzle

Coating steps:

- Preheating of pan (FB1)
- Filling, preheating of tablets (FB2)
- Coating (FB3)
- Cooling, unloading (FB4)

Film coating parameters

Parameter	FB1	FB2	FB3	FB4
Inlet air temperature (°C)	55-65	55-65	55-65*	25
Inlet air flow rate (m <sup>3</sup> /h)	1	1	1	1
Exhaust air temperature (°C)	min 45	min 45	42-44	-
Pan speed (ford/min)	3	3	25	3
Liquid feeding rate (g/min)	0	0	2-3	0
Atomizing pressure (bar)	0	0	1	0
Time (min)	5-10	5-10	40-60	5-10

\* The inlet air temperature must be so adjusted that the exhaust temperature be kept in the interval.

The prepared film coated tablets are placed into plastic boxes trimmed with plastic sacks and kept open at room temperature to reach the room temperature.

**In process control III.**

The samples are taken for in process control of film-coated tablets according to Sampling instruction.

**Final product control**

Hydroxychloroquine film-coated film coated tablets are tested according to drug product specifications.