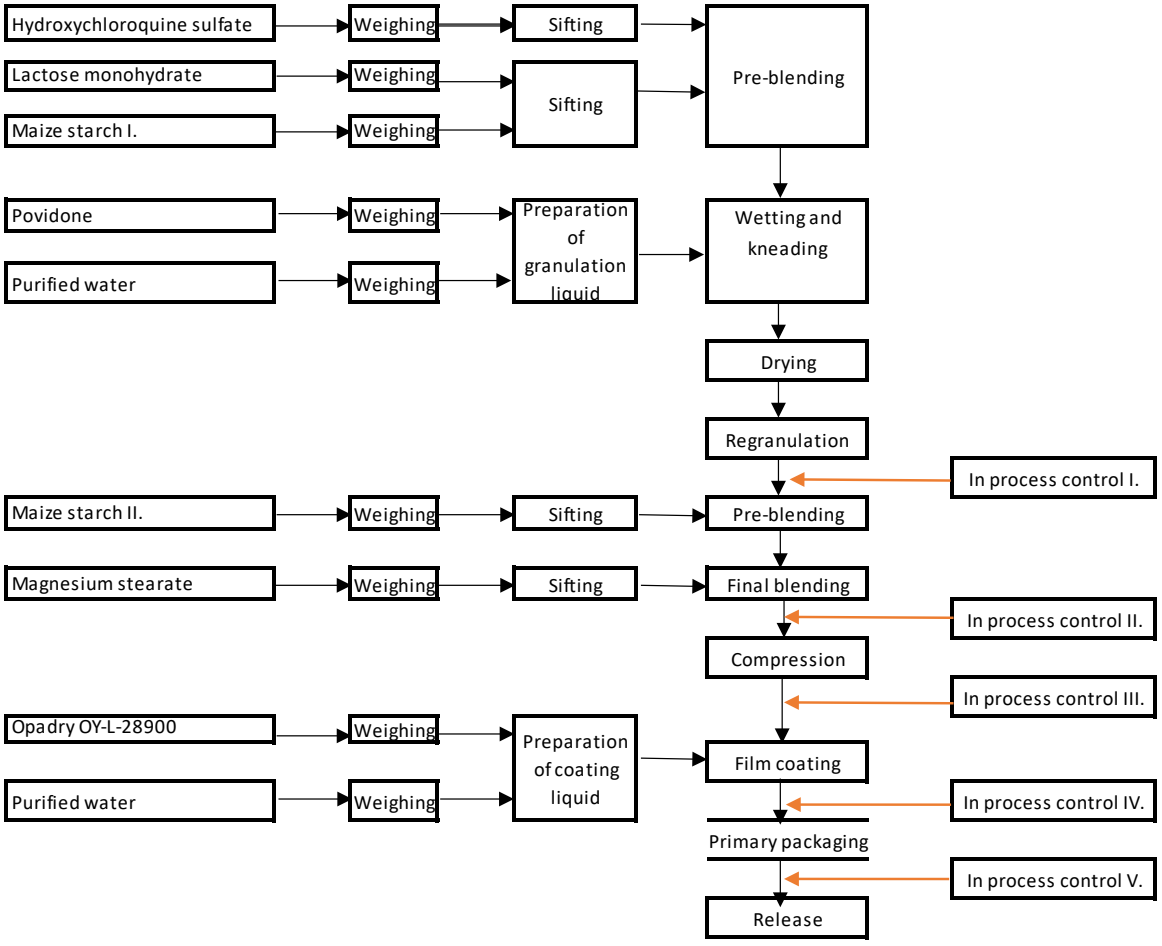
2.1.P.3.3 Description of Manufacturing Process and Process Control

The manufacturing of the bulk film-coated tablets consists of weighing, shifting, wet granulating, sieving, blending and compression and film-coating steps. Film-coated tablets prepared by this process are packaged in a subsequent step. A description of the manufacturing process is provided below along with a flow chart of the process.

1 Flow chart



2 Weighing of materials

Machines, equipment: Mettler Toledo PUA579 scale
Mettler SG 32001 scale
Mettler Toledo KA32 S scale or equivalent equipment

The prescribed amount of core materials of a batch is weighed on the above-mentioned scales into plastic containers lined with polyethylene bags and signed in accordance with the GMP prescriptions.

Industrial batch size of Hydroxychloroquine MEDITOP 200 mg film-coated tablets was 100 000 pieces, which means the mass of final blending is 31 500 g.

Component	Quantity (mg/tablet)	Quantity (g/batch)	Function	Quality
Hydroxychloroquine sulfate	200.0	20 000	active ingredient	Ph. Eur.
Lactose monohydrate	30.0	3 000	diluent, binder	Ph. Eur.
Maize starch	69.5	6 950	disintegrant	Ph. Eur.
Povidone	3.5	350	binder	Ph. Eur.
Magnesium stearate	3.0	300	lubricant	Ph. Eur.
Purified water*	14.0	1 400	solvent	Ph. Eur.
Opadry OY-L-28900	9.0	900	film-coating	Colorcon Ltd. in Haus
Purified water*	51.0	5 100	solvent	Ph. Eur.

Measured amount are the followings:

		Industrial scale
Component	**Quantity (mg/tablet)**	**Quantity (g/batch)**
Inner phase		
Hydroxychloroquine sulfate	200.00	20 000
Lactose monohydrate	30.00	3 000
Maize starch I.	36.50	3 650
Granulating liquid		
Povidone	3.50	350
Purified water*	14.00	1 400
External phase		
Maize starch II.	33.00	3 300
Magnesium stearate	3.00	300
Nominal weight of tablets	**306.00**	**30 600**
Coating material		
Opadry OY-L-28900	9.0	900
Purified water*	51.0	5 100
Nominal weight of film-coated tablets	**315.0**	**31 500**

* Total volume of solvent purified water removed after granulation and coating process by drying.

3 Manufacturing

3.1 Preparation of granulating liquid

Povidone is dispersed in purified water, in an appropriate vessel for 10 minutes.

3.2 Preparation of powder mixture

Equipment: Vibrating sieve
Zanchetta Roto P200 granulator or equivalent equipment

The total amount of hydroxychloroquine sulfate is sifted by the vibrating sieve through 0.8 mm diameter galvanized steel wire. Then this shifted material is added into the vessel of Zanchetta Roto P200 granulator or of equivalent equipment.
Lactose monohydrate and maize starch I. are sifted by the vibrating sieve through 0.8 mm diameter galvanized steel wire. This shifted mixture is added to hydroxychloroquine sulfate and the materials are blended by using of the following parameters:

Blending time:	10 minutes
Impeller speed:	80-120 rpm
Chopper speed:	-

3.3 Wetting

Equipment: Zanchetta Roto P200 granulator or equivalent equipment

During a constant mixing add the granulation liquid in about 2 minutes to the blend prepared in step 3.2.

Wetting time:	1-2 minutes
Impeller speed:	80-120 rpm
Chopper speed:	-

3.4 Kneading

Equipment: Zanchetta Roto P200 granulator or equivalent equipment

Knead the wet blend with using of chopper to produce a homogenous granular mixture.

Kneading time:	1-2 minutes
Impeller speed:	80-120 rpm
Chopper speed:	I.

3.5 Drying

Equipment: Glatt WSG-30 fluid dryer or equivalent equipment

The granules are filled into the vessel of the Glatt WSG-30 fluid dryer. Dry the wet granules in fluidized bed dryer until between 1.0% - 2.0% loss on drying (LOD) value is reached (at 80 °C until weight equilibrium).

Inlet air temperature: 60 ± 2 ºC.

3.6 Regranulation (sizing)

Equipment: Fitzmill M5A type mill or equivalent equipment

The appropriately dried granules are re-granulated through 0.5 mm diameter galvanized steel wire by comminuting machine. After regranulation the water content is measured and if it is required, the granule is further dried.

The finished granules are collected into a plastic barrel lined with plastic bag, are labelled and weighed.

4 In process control (IPC) I. - Granules

Sample is taken from the re-granulated granules by QC for testing, based on sampling instruction.

5 Sifting and blending

5.1 Pre-blending

Equipment: Vibrating sieve
Double Cone mixer
Pharmatech Multiblender (MB100) powder blender
or equivalent equipment

A weighed amount of external phase material, maize starch II. is sifted with a vibrating sieve with 0.8 mm diameter galvanized steel wire. The granules and the sifted amount of maize starch II. filled into the mixer, and blended by using the following parameters:

Blending time: 10 minutes
Blending speed: 16 rpm

5.2 Final blending

Equipment: Vibrating sieve
Double Cone mixer
Pharmatech Multiblender (MB100) powder blender
or equivalent equipment

Weighted amount of Magnesium-stearate is sifted by the vibrating sieve through 0.8 mm diameter galvanized steel wire. This shifted material is added to the 6. powder mix into the tank of the homogenizing equipment, and blended by using of the following parameters:

Blending time: 2 minutes
Blending speed: 16 rpm

The final blend is filled into plastic containers lined with double polyethylene bags, signed in accordance with the GMP prescriptions and weighted.

6 In process control (IPC) II. – Final blend

Samples are taken from blended batch by quality control department for the in the process control and tested according to testing instruction.

Holding time:

The final blend can be stored pending the next processing step for 30 days. After that the bulk product has to be retested.

7 Compression

Equipment: Courtoy R 190 Tablet Press
Courtoy Performa P Tablet Press
Wynka Kompressor Developer Tablet Press or
equivalent equipment

The released blend is compressed on a rotary tablet press. The blend is sucked by powder intake system into the cone feeder and compressed on Courtoy R 190 Rotary Tablet Press, Courtoy Performa P Tablet Press or Wynka Kompressor Developer Tablet Press. Adequate operation of the metal detector is checked before the tablet making.

The details of the tableting process are the following:

Tableting parameter	Set value
Punch diameter	9 mm biconvex, round tablets
Punch sign	Upper punch: without sign Lower punch: without sign
Average mass	306.0 mg ± 5 %
Minimum hardness	70 N

After setting the compressing machine tablet sample is taken and it is controlled by the quality control department. If the results fulfil the specifications the tableting process is permitted.

During the tableting process the weight and hardness of tablets are controlled with half hour periodicity by the machine operator and with one-hour periodicity by the Quality Control.

The tablets are filled into plastic containers lined with double polyethylene bags, signed in accordance with the GMP prescriptions and weighted. The net weight of the tablets is calculated.

8 In-process control III. - Tablets

After tableting tablet sample is taken by QC department for the in-process control and tested according to testing instruction and related specification.

Holding time:

The tablet bulk can be stored pending the next processing step for 30 days. After that the bulk product has to be retested.

9 Film-coating

Equipment: O'Hara FCC 75 coater
Mettler SG 32001 balance or equivalent

The actual amount of coating material is calculated from the actual weight of the tablets to be coated by the following formula:

X = 0.0294 x M x 1.10

Where: X - is the weighing amount of coating materials (kg),
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 = 5.667*X

Where: X - is the weighing amount of coating materials (kg)

In the case of O'Hara FCC 75 coater due to the special character and reservoir function of the liquid dosing system, additional coating liquid must be prepared. Ratio of the Opadry OY-L-28900 and purified water is 1:5.667 in this additional liquid as well.

After 60 minutes stirring the liquid is ready for coating.
The coating liquid should be used within 24 hours after preparation.

Coating steps:

Preheating	FB1
Filling, preheating	FB2
Startup coating	FB3*
Continuous coating	FB4*
Shutdown coating	FB5*
Unloading	FB6

* Phases can be merged for batch coating in sub-batches (7-12 kg pan load), in this case the exact amount of coating liquid can be calculated by the following formula for the given sub-batch.

X=0.0294 x M x 1.10 x 6.667

Where M = mass of uncoated tablet (g)

X = Mass of coating liquid (g)

Film-coating parameters:

Parameter	FB1	FB2	FB3	FB4	FB5	FB6
Tablet feeding rate (kg/min)	-	0.8-1.5	-	0.8-1.5	-	-
Inlet air temperature (°C)	55-70	55-70	55-70*	55-70*	55-60*	25
Inlet air flow rate (m^3/h)	3000-4000	3000-4000	3000-4000	3000-4000	3000-4000	3000-4000
Exhaust air temperature (°C)	min 46	40-60	40-60	40-60	40-60	-
Pan speed (ford/min)	4-10	4-20	10-25	10-25	10-25	4-30
Differential pressure (bar)	-0.1--0.3	-0.1--0.3	-0.1--0.3	-0.1--0.3	-0.1--0.3	-0.1--0.3
Liquid feeding rate (ml/min)	0	0	110-210**	110-210**	110-210**	0
Atomizing pressure (bar)	0	0	0.6-1.6	0.6-1.6	0.6-1.6	0

* The inlet air temperature must be so adjusted that the exhaust temperature be kept in the interval.
**Spray guns close and open according to the program and the excess of coating liquid is recirculated.

10 In-process Control IV. - Film-coated tablet

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

11 Finished product control

Samples are taken for finished product control of tablets according to Sampling instruction.

12 Primary packaging

Equipment: Counter machine
Capping machine or equivalent equipment

Preparation of primer packaging

Primer packaging materials are inspected by QC. It must not be used any packaging materials if the foil package is torn or the foil is damaged.

100 tablets in a labelled PE container closed by PP closure in carton box with leaflet.

Primary Packaging Materials:

- 40 ml HDPE container
- PP cap

For detailed information, see in part *2.2.1.P.7 Container Closure System*.

13 In-process control V. – Primary packaging

Package I.

Samples are taken for in process control under packaging procedure for testing bottle closing.

Pressure to close the vial:
The bottles should be closed with sufficient pressure to close the cap properly. The cap closes properly if it cannot be opened without damaging the safety plastic strip.

14 Cartoning
(On demand)

Equipment: Promatic AS100 cartoning machine or equivalent equipment

This manufacturing step is also executed manually.

Package I.

Secondary packaging materials:
- Hydroxychloroquine MEDITOP 200 mg film-coated tablet 100 x folding box
- Hydroxychloroquine MEDITOP 200 mg film-coated tablet leaflet
- Gathering box
- Label for gathering box

Container and patient information leaflet are packed into the related folding box and it is marked with the expiry date and batch number.

Preparation of secondary packaging
Secondary packaging materials are inspected by QC. It must not be used any packaging materials if the box is torn or the box is damaged.
The expiry date of the product calculates from the first step of manufacturing process performed involving combining the active ingredient with other ingredients in accordance with CPMP/QWP/072/96 EMEA/CVMP/453/01 guideline.

15 In-process control VI. – Finished product control

The samples are taken for in-process control of packaged product according to Packaging control of finished products.