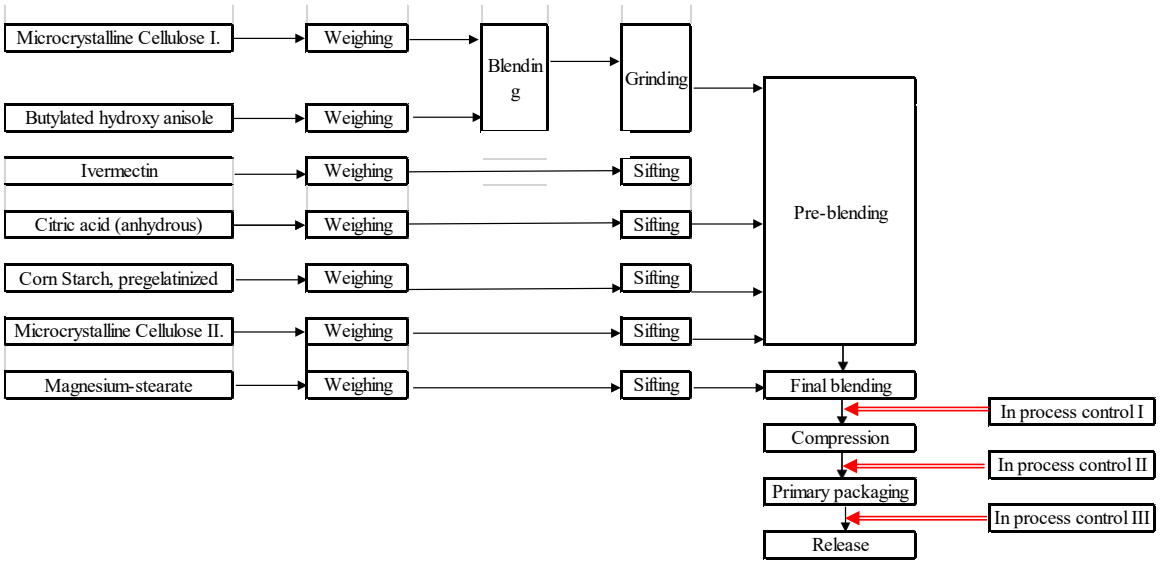
2.1.P.3.3 Description of Manufacturing Process and Process Control

The manufacturing of tablets consists of weighing, shifting, screening, tableting steps. 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 Ivermectin MEDITOP 3 mg tablets was 100 000 pieces, which means the mass of final blending is 6 000 g.

Measured amount are the followings:

	Quantity (g/batch) nominal quantity 100 000 tablets	Quantity (g/batch) +10% overages 100 000 tablets
Ivermectin*	300.0	X=300.0 / (Y/100) × 1.03
Microcrystalline cellulose II.	1 000.0	1 100
Microcrystalline cellulose II.	4 344.0	Z=4344.0-(X-300.0)
Corn Starch, pregelatinized	300.0	300.0
Citric acid anhydrous	20.0	20.0
Magnesium stearate	30.0	30.0
Butilhydroxy anisole	6.0	6.0
Total	6 000.0	6 000.0

* The amount of ivermectin must be corrected for the "as is" (Ivermecin H2B1b+H2B1) of ivermectin and 3% overages is used. The nominal weight is corrected by reducing the weight of the Microcrystalline cellulose.

Amount of ivermectin:
X = 300 / (Y / 100) × 1.03

where X is the actual amount of ivermectin to be measured, Y is the "as is" of ivermectin (%) (based on quality control measurements of MEDITOP).

Amount of MCC:
Z = 4344 - (X-300)
where Z is the amount of Microcrystalline cellulose to be measured and X is the actual amount of ivermectin to be measured.

Excipients for grinding:

	Quantity (g/batch) nominal quantity 100 000 tablets	Quantity (g/batch) +10% overages 100 000 tablets
Microcrystalline cellulose[1]	1000.0	1100.0
Butilhydroxy anisole[2]	6.0	6.6
Total	**1006.0**	**1106.6**

[1] 10% overages are used to compensate for grinding loss.
[2] 10% overages are used to compensate for grinding loss.

3 Blending

3.1 Grinding

Equipment: Fitzmill M5A comminuting machine or equivalent equipment

The microcrystalline cellulose I. and the total amount of the butylated hydroxy anisole are blended in polyethylene bag and grinded below 0.8 mm of size by comminuting machine by using of the following parameters:

Milling direction: knife-edged
Milling speed: high (3 000 rpm)

1006 g of the grist are weighed out. The remaining grist is measured and this type of grist are overwhelmed according to the prescriptions.

The grinded material is collected into plastic containers lined with double polyethylene bags signed in accordance with the GMP prescriptions and weighted.

3.2 Premixing, blending

Equipment: Vibrating sieve
Pharmatech Multiblender (MB100) powder blender 25L or equivalent equipment

Ivermectin, Corn Starch (pregelatinized), the Microcrystalline Cellulose II. and Citric acid anhydrous is sifted by the vibrating sieve through 0.8 mm diameter galvanized steel wire. Then this shifted material is added into the homogenizing tank.
The measured quantity of the grinded material is added to the same homogenizing tank and blended by using of the following parameters:

Blending time: 15 minutes
Blending speed: 25 rpm

3.3 Blending

Equipment: Vibrating sieve
Pharmatech Multiblender (MB100) powder blender 25L or equivalent equipment

The pre-blend is sifted by the vibrating sieve through 0.8 mm diameter galvanized steel wire. Then this shifted material is added into the homogenizing tank and blended by using of the following parameters:

Blending time: 10 minutes
Blending speed: 25 rpm

3.4 Final blending

Equipment: Vibrating sieve
Pharmatech Multiblender (MB100) powder blender 25L 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 3.2 powder mix into the tank of the homogenizing equipment, and blended by using of the following parameters:

Blending time: 2 minutes
Blending speed: 25 rpm

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

4 In process control I. - Blend for compression

Samples are taken from the blend by quality control department for the in process control and tested according to testing instruction and related specification.

5 Tableting

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

The released 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 released blend is poured into the cone feeder and compressed on Wynka Kompressor Developer Tablet Press. The 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	6.0 mm, round flat-faced tablet of bevelled edge on both side
Punch sign	Upper punch: marked "I" Lower punch: no sign
Average mass	60.0 mg ± 5%
Hardness	NLT 25 N
Height	1.5 – 2.2 mm

After setting the compressing machine tablet sample is taken and controlled. If the results fulfil the specifications the tableting process is permitted.
During the tableting process the appearance, weight, hardness and height of tablets are controlled with half hour periodicity by the machine operator.
The tablets are filled into plastic boxes lined by polyethylene bag of tare weight and the gross weight is weighed. The net weight of the tablets is calculated.

6 In-process Control II. - Tablets

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

7 Container closer system - Primary Packaging

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.

7.1 ALU//ALU blister

Primary packaging materials

- Soft tempered Aluminium foil for cold forming
- Aluminium foil

Specifications of Soft tempered Aluminium foil

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

Specifications of Aluminium foil for closing

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

8 In-process control III. - Blisters

Samples are taken for in-process control under blistering procedure for testing blister integrity.

For detailed information, see in part *2.1.P.7 Container Closure System.*