SPECIFICATION
COMBILAC®

SAP-Nr./No. 10000000160	Version: 4	Gültig ab/effective from: 07.06.2020	1 / 6

DEFINITION/CHARACTERS/PRODUCTION
COMBILAC is MEGGLE's brand name for a co-processed, directly compressible spray agglomerate comprising 70 % Lactose Monohydrate (Ph. Eur., USP-NF, JP), 20 % Microcrystalline Cellulose (Ph. Eur., USP-NF, JP) and 10 % GMO free, white, native Maize Starch (Ph. Eur., USP-NF, JP). The monographs "Lactose Monohydrate", "Microcrystalline Cellulose" and "Maize Starch" have undergone pharmacopoeial harmonisation.
COMBILAC is a white or almost white, odourless powder; partly soluble in cold water.

Production and release site: Molkerei MEGGLE Wasserburg GmbH & Co. KG (effective July 1st 2020 renamed to MEGGLE GmbH & Co. KG), Megglestr. 6-12, 83512 Wasserburg, Germany

The management system of Molkerei MEGGLE Wasserburg GmbH & Co. KG (effective July 1st 2020 renamed to MEGGLE GmbH & Co. KG), Megglestr. 6-12, 83512 Wasserburg, Germany has been certified meeting the requirements of GMP and GDP according to EXCiPACT™.

Additional regulatory information is available under https://www.meggle-pharma.com.

IDENTIFICATION

Method	Specification
Identification COMBILAC/Ph. Eur. 2.2.24 Infrared absorption spectrophotometry (Annex methods in specification)	conforms
Identification Lactose Monohydrate/Ph. Eur. Lactose Monohydrate identification C colour reaction, modified (Annex methods in specification)	conforms
Identification Microcrystalline Cellulose/Ph. Eur. Microcrystalline Cellulose identification B colour reaction, modified (Annex methods in specification)	conforms
Identification Maize Starch/Ph. Eur. Maize Starch identification B mucilage formation, modified (Annex methods in specification)	conforms
Identification Maize Starch/Ph. Eur. Maize Starch identification C colour reaction, modified (Annex methods in specification)	conforms

TESTS

	Method	Specification
Loss on drying	Ph. Eur. 2.2.32 (Annex methods in specification)	max 3.0 %
Sulfated ash	Ph. Eur. 2.4.14 (Annex methods in specification)	max 0.2 %
Lactose Monohydrate calculated on the dried basis	HPLC (Annex methods in specification)	68 - 72 %
Microcrystalline Cellulose calculated on the dried basis	Gravimetry (Annex methods in specification)	18 - 22 %
Maize Starch calculated on the dried basis	Polarimetry (Annex methods in specification)	8 - 12 %
Particle size distribution < 32 µm	Ph. Eur. 2.9.38/Air-entrainment method (air-jet sieving); 10 g; + 0.1 g Al_2O_3; p = 1500 - 2500 Pa; 2 min	max 15 %
Particle size distribution < 160 µm	Ph. Eur. 2.9.38/Air-entrainment method (air-jet sieving); 10 g; + 0.1 g Al_2O_3; p = 1500 - 2500 Pa; 2 min	35 - 65 %
Particle size distribution < 250 µm	Ph. Eur. 2.9.38/Air-entrainment method (air-jet sieving); 10 g; + 0.1 g Al_2O_3; p = 1500 - 2500 Pa; 2 min	min 85 %

MICROBIAL CONTAMINATION

	Method	Specification
Total aerobic microbial count (TAMC)	Ph. Eur. 2.6.12/USP-NF <61>/JP <4.05>	max 1000 cfu/g
Total combined yeasts/moulds count (TYMC)	Ph. Eur. 2.6.12/USP-NF <61>/JP <4.05>	max 100 cfu/g
Escherichia coli	Ph. Eur. 2.6.13/USP-NF <62>/JP <4.05>	absence /10 g
Salmonella spp.	Ph. Eur. 2.6.13/USP-NF <62>/JP <4.05>	absence /10 g

STORAGE

Well-closed container. Storage in an unopened, originally packed MEGGLE container at room temperature under dry and odour-free conditions.

This specification was electronically released.

ANNEX METHODS IN SPECIFICATION

IDENTIFICATION

Identification COMBILAC (Ph. Eur. 2.2.24 Infrared absorption spectro-photometry)
The identification is carried out by infrared absorption (Ph. Eur. 2.2.24). The absorption maxima in the spectrum obtained with the sample correspond in position and relative size to those in the spectrum with the physical mixture of 70 parts Lactose Monohydrate (Ph. Eur.), 20 parts Microcrystalline Cellulose (Ph. Eur.) and 10 parts Maize Starch (Ph. Eur.). Prepare the sample according to your equipment requirements and measure the spectra between 4000 and 650 cm^{-1} (2.5 and 15.4 µm).

Identification Lactose Monohydrate (Ph. Eur. Lactose Monohydrate identification C colour reaction, modified)
The identification of Lactose Monohydrate is carried out according to the identification test C in the Lactose Monohydrate monograph of the Ph. Eur.. The test is carried out with 0.36 g COMBILAC (equivalent 0.25 g Lactose). A red colour develops.

Identification Microcrystalline Cellulose (Ph. Eur. Microcrystalline Cellulose identification B colour reaction, modified)
The identification of Microcrystalline Cellulose is carried out according to the identification test B in the Microcrystalline Cellulose monograph of Ph. Eur.. The test is carried out with 50 mg COMBILAC (equivalent 10 mg Microcrystalline Cellulose). A violet-blue colour develops.

Identification Maize Starch (Ph. Eur. Maize Starch identification B mucilage formation, modified)
and
Identification Maize Starch (Ph. Eur. Maize Starch identification C colour reaction, modified)
The identification of native Maize Starch is carried out according to the identification tests B and C in the maize Starch monograph of Ph. Eur.. The test is carried out with 10 g COMBILAC (equivalent 1 g Starch). A thin fluid jelly forms (Identification B) and a reddish violet to deep blue colour appears, which disappears when heated (Identification C).

TESTS

Loss on drying (Ph. Eur. 2.2.32)
Dry 1.0 - 2.0 g of the product at 80°C, 2h

Sulfated ash (Ph. Eur. 2.4.14)
Determined on 1.0 g COMBILAC

Lactose monohydrate calculated on the dried basis (HPLC)
Lactose contained in a blend of Lactose Monohydrate (Ph. Eur.), Microcrystalline Cellulose (Ph. Eur.) and Maize Starch (Ph. Eur.) is determined by high performance liquid chromatography (HPLC). An external calibration is used for quantification.

Equipment:
HPLC (High Performance Liquid Chromatograph) equipped with:

- an auto sampler (optional)
- a pump
- a column heater with a temperature control module
- a differential refractometric detector
- Analytical column packed like
  Aminex HPX-87C Biorad (Cat.No. 125-0095)
  length : 30 cm
  diameter : 7.8 mm
  particles size : 9 µm

Reagents:
• Water (HPLC quality)
• D(+)-Lactose Monohydrate

Procedure:
Chromatographic conditions:

- mobile phase: water
- stationary phase: cationic resin bonded with calcium
- oven temperature: 80 - 85 °C
- mobile phase flow rate: 0.3 ± 0.005 ml/min
- injected volume: 25 µl

Standard preparation:
A single point calibration on 100%-level is performed.
Reference solution (100 %):
Weigh accurately 350 mg of Lactose Monohydrate into a 100 ml volumetric flask. Add about 25 ml of water to soak all the material in the flask. Then fill up to the mark with water, shake the stoppered flask to ensure complete mixing and sonicate for 10 min. After a standing time of 30 min, filtrate about 10 ml of the supernatant through a 0.45 µm membrane filter. Prepare the reference solution in duplicate.

Sample preparation and analysis:
Weigh accurately 500 mg of sample into a 100 ml volumetric flask. Add about 25 ml of water to soak all the material. Then fill up to the mark with water, shake the stoppered flask to ensure complete mixing and sonicate for 10 min. After a standing time of 30 min, filtrate about 10 ml of the supernatant through a 0.45 µm syringe filter. Prepare the sample solution in duplicate.

System suitability:
Prepare a reference solution for assay (100 %) in duplicate. Inject the first reference solution 6 times and the second reference solution 2 times. The retention time has to be 17 ± 2 min. Calculate the standard deviation (RSD; n = 6) of the peak area from the first reference solution. The RSD has to be ≤ 2 %. The deviation of the first preparation

(mean, n = 6) and the second preparation (mean, n = 2) of the reference solution has to be ≤ 2 %.

Expression of results:
Determination of Lactose Monohydrate content in mg/g (P_s)

$$P_S = \frac{W_{ref} \times A_S \times D_S \times P_{ref} \times 100}{A_{ref} \times W_S \times (100 - LoD) \times 100 \times D_{ref}}$$

with:
W_{ref} = weight of the first reference [mg]
A_s = area of Lactose Monohydrate in the sample solution
D_s = dilution factor of the sample (100)
P_{ref} = potency of the reference standard [%]
A_{ref} = mean value (n=6) of the area of Lactose Monohydrate in the first reference solution
W_s = weight of sample [g]
LoD = loss on drying of the sample [%]
D_{ref} = dilution factor of the reference standard (100)

$$Content\ [\%](calculated\ on\ the\ dry\ substance) = \frac{P_S \times 100}{1000}$$

Microcrystalline Cellulose calculated on the dried basis (Gravimetry)
Weigh, to the nearest 1 mg, 2 - 2.5 g COMBILAC into a conical 100 ml flask. Add 50 ml hydrochloric acid (1.128 % (m/m)) and stir to obtain a homogenous test sample. Dip the conical flask into a boiling water bath during stirring for exactly 15 min. Then cool down to 20 °C within 15 min (e.g. under running cold tap water). Filter the suspension by means of a G4-type glass filter crucible (pore size 10 to 16 µm) which is dried to constant weight and thoroughly tared. Dry the glass filter crucible with the residue at 102 ± 2 °C to constant weight and determine the weight of the residue after cooling in a desiccator.
The content of Microcrystalline Cellulose is calculated by following equations:

$$Content\ [\%] = \frac{(weight\ after\ [g] - blank\ weight\ [g]) \times 100}{Weight\ of\ sample\ [g]}$$

$$Content\ [\%](calculated\ on\ dry\ substance) = \frac{Content\ [\%] \times 100}{100 - loss\ on\ drying}$$

Maize starch calculated on the dried basis (Polarimetry)
The total Maize Starch content of the sample is determined by a double polarimetric measurement at 20 °C and 589 nm. In the first step the measurement of the specific rotation of both components (Lactose and Starch) is determined. In the second measurement the specific rotation of Lactose only is determined after the extraction of Starch. The content of Starch is calculated from the specific rotation of Starch only which calculated by the difference between these both measurements.

A) Determination of the total specific optical rotation (ISO method)
Weigh, to the nearest 1 mg, 5.0 g COMBILAC into a conical 100 ml flask. Add 50 ml hydrochloric acid (1.128 % (m/m)) and slew to obtain a homogeneous test sample. Dip the conical flask into a boiling water bath during stirring for exactly 15 min. Then cool down to 20 °C within 15 min (e.g. under running cold tap water) and transfer quantitatively to a 100 ml volumetric flask rinsing the walls of the conical flask with distilled water. Bring to volume, overturn and filter. 50.0 ml of the filtrate are pipetted into a 100 ml volumetric flask. Add 5 ml of the Carrez I solution* and stir for 1 minute. Then add 5 ml of the Carrez II solution** and stir again for 1 minute. Bring to volume with distilled water, overturn and filter (e.g. plaited filter MN 615 ¼ Ø 150 mm). Temperate to 20 °C, then measure the specific rotation **P** of the solution in a 100 mm tube at 589 nm (Na lamp).

B) Determination of the specific optical rotation of substances soluble in 10 % ethanol
Weigh, to the nearest 1 mg, 5.0 g COMBILAC into a conical 100 ml flask and add about 80 ml ethanol (10 % (V/V)). Allow the conical flask, which is covered with aluminium foil, to stand at room temperature for 1 h. During this time ensure complete dissolution of Lactose by stirring moderately (e.g. magnetic stirrer) all the time. Transfer quantitatively to a 100 ml volumetric flask rinsing the walls of the conical flask with ethanol (10 % (V/V)), bring to volume, overturn and filter. 50.0 ml of the filtrate are pipetted into a 200 ml conical flask, add 2.1 ml of 25 % hydrochloric acid (m/m), 5.0 ml of distilled water and stir. Dip the conical flask into a boiling water bath for exactly 15 minutes and allow ethanol to evaporate. Then cool down to 20 °C within 15 minutes (e.g. under running cold tap water). Transfer quantitatively to a 100 ml volumetric flask, rinsing the walls of the conical flask with distilled water. Add 5 ml of the Carrez I solution* and stir for 1 minute. Then add 5 ml of the Carrez II solution** and stir again for 1 minute. Bring to volume with distilled water, overturn and filter. Temperate to 20 °C, then measure the specific rotation **P'** of the solution in a 100 mm tube at 589 nm (Na lamp).

C) Method of Calculation
The Starch content of the product, expressed as a percentage by mass, is equal to:

$$Content\ [\%] = \frac{\left(P - P'\right) \times 100 \times 100}{184{,}6° \times 2{,}5} = \frac{4000\ (P - P')}{184{,}6°}$$

$$Content\ [\%](calculated\ on\ dry\ substance) = \frac{Content\ [\%] \times 100}{(100 - LOD)}$$

with:
LOD : Loss on drying [%]

* Carrez I solution: 21.9 g zinc acetate dihydrate and 3.0 g glacial acetic acid (100%) filled up with distilled water to 100 ml
** Carrez II solution: 10.6 g potassium hexacyanoferrate(II) trihydrate filled up with distilled water to 100 ml

CONTACT
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