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(54) Titre : L-(-)-MOPROLOL L-(+)-TARTRATE
(54) Title: L-(-)-MOPROLOL L-(+)-TARTRATE

(57) **Abrégé/Abstract:**

The disclosed invention relates to L-(-)-moprolol L-(+)-tartrate salt (2:1) for ophthalmic use, for example, in the treatment of pathological conditions such as ocular hypertension and glaucoma. The disclosed invention also relates to a method for preparing the L-(-)-moprolol L-(+)-tartrate salt (2:1) and a pharmaceutical composition which comprises the salt.

ABSTRACT

The disclosed invention relates to L-(-)-moprolol L-(+)-tartrate salt (2:1) for ophthalmic use, for example, in the treatment of pathological conditions such as ocular hypertension and glaucoma. The disclosed invention also relates to a method for preparing the L-(-)-moprolol L-(+)-tartrate salt (2:1) and a pharmaceutical composition which comprises the salt.

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"L-(-)-moprolol L-(+)-tartrate"

DESCRIPTION

5 The present invention relates to L-(-)-moprolol L-(+)-tartrate (2:1),
to a method for preparing it and to a pharmaceutical composition for
ophthalmic use comprising it.

IT 1 113 029 describes a process for separating the two optical
isomers of moprolol.

10 EP-A-0 118 940 describes the use of L-(-)-moprolol or a
pharmaceutically acceptable acid-addition salt thereof to produce a fluid
ophthalmic composition for treating glaucoma. The pharmaceutical
acceptable acid-addition salt specifically illustrated and tested in the said
document is the hydrochloride.

15 It has now been found that the L-(+)-tartrate shows better local
tolerability than the hydrochloride.

In a first aspect, the present invention thus relates to L-(-)-moprolol
L-(+)-tartrate (2:1).

20 The salt L-(-)-moprolol L-(+)-tartrate (2:1) is readily prepared via
known techniques, for instance the addition of L-(+)-tartaric acid,
dissolved in a suitable organic solvent, to L-(-)-moprolol base, also
dissolved in a suitable organic solvent, in a 1:2 molar ratio. The salt thus
formed (L-(-)-moprolol L-(+)-tartrate (2:1)) is then isolated via known
techniques including the precipitation of the salt and its filtration or via
25 removal of the solvents by evaporation.

In one preferred embodiment, the abovementioned organic solvent
is ethyl alcohol and the salt is precipitated from the acetone solution via
addition of ethyl ether.

30 In a second aspect, the present invention thus relates to a method
for preparing L-(-)-moprolol L-(+)-tartrate (2:1), characterized in that it
includes the addition of L-(+)-tartaric acid, dissolved in a suitable organic

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solvent, to L-(-)-moprolol, also dissolved in a suitable organic solvent, in a 1:2 molar ratio.

5 By virtue of its better local tolerability, L-(-)-moprolol L-(+)-tartrate is found to be particularly useful for ophthalmic use.

In a third aspect, the present invention thus relates to a pharmaceutical composition for ophthalmic use, characterized in that it comprises L-(-)-moprolol L-(+)-tartrate (2:1) together with at least one pharmaceutically acceptable vehicle.

10 Typical examples of pathological conditions that may find benefit from treatment with a pharmaceutical composition according to the present invention are ocular hypertension and glaucoma.

Preferably, the pharmaceutical composition according to the present invention will be in the form of a gel, an ointment or eyedrops and
15 may also include other vehicles suitable for ophthalmic use, for instance ethylene glycol, PEG, carboxymethylcellulose, mannitol, sorbitol, poloxamers, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and the like.

The composition may also comprise other conventional ingredients
20 such as: preserving agents, stabilizers, surfactants, buffers, salts for controlling the osmotic pressure, emulsifiers and the like.

If required for particular therapeutic uses, the pharmaceutical composition according to the present invention may comprise other pharmacologically active ingredients whose simultaneous administration
25 is useful.

The amount of L-(-)-moprolol L-(+)-tartrate in the pharmaceutical composition of the present invention may vary within a wide range depending on known factors, for instance the particular type of disease to be treated, the seriousness of the disease and the number of daily
30 administrations. However, a person skilled in the art may easily and routinely determine the optimum amount.

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Typically, the amount of L-(-)-moprolol in the pharmaceutical composition of the present invention is between 0.01% and 20% by weight and even more preferably between 1% and 8% by weight.

5 The dosage forms of the pharmaceutical composition of the present invention may be prepared according to techniques that are well known to pharmaceutical chemists, including mixing, dissolution, sterilization and the like.

The examples that follow are given to illustrate the present invention without, however, limiting it.

10

Example 1

Preparation of L-(-)-moprolol L-(+)-tartrate (2:1)

Step a)

2N sodium hydroxide solution was added dropwise to a solution of L-(-)-moprolol hydrochloride (10 g) in water (100 ml) with stirring, until
15 no further precipitate was formed.

The precipitate was extracted with dichloromethane (100 ml). The organic phase was separated out and dried over sodium sulphate. Finally, the dichloromethane was removed by evaporation.

The solid residue thus obtained consisted of L-(-)-moprolol base
20 (9.1 g).

Step b)

A solution of L-(+)-tartaric acid (1.57 g; 0.01 mol) in absolute ethanol (15 ml) was added to a solution of L-(-)-moprolol base (5.0 g; 0.02 mol) in hot absolute ethanol (30 ml).

25 After stirring the solution at 60°C for 10 minutes, ethyl ether was added until precipitation was complete. The precipitate thus obtained (very hygroscopic) was separated out by decantation and crystallized from absolute ethanol (30 ml) to give the desired product (5.2 g).

m.p. = 135°C. $[\alpha] = -1.1$ (c = 5 in H₂O)

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Elemental Analysis

For C ₃₀ H ₄₈ N ₂ O ₁₂	C	H	N
Calculated	57.31	7.70	4.46
Found	57.16	7.79	4.38

5

Test 1

Ocular Tolerability

Two aqueous solutions were used.

The first contained 1% by weight of L-(-)-moprolol hydrochloride (corresponding to 0.87% by weight of L-(-)-moprolol). The second
10 contained 1.14% by weight of L-(-)-moprolol L-(+)-tartrate (2:1) (corresponding to 0.87% by weight of L-(-)-moprolol).

12 male rabbits (New Zealand White) with an average weight of 2 kg and an average age of ten months were used, divided into two groups of six rabbits each. The first group was treated with 0.1 ml of the first
15 test solution three times a day for fifteen days. The second group was treated with 0.1 ml of the second test solution three times a day for fifteen days.

The tolerability was evaluated according to J. Draize et al., Pharmacol. Exp. Ther., 83, 377-390 (1944). The results are shown in
20 Table 1 below.

Table 1

		Before the first application	After the last application
		L-(-)-moprolol hydrochloride	L-(-)-moprolol L-(+)-tartrate
Conjunctiva	Reddening	1	0
	Swelling	2	0
	Lachrymation	2	1
Iris		0	0

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Cornea	Opacity	0	0
	Area of the cornea affected by opacity	0	0
	Total Score	5	1

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CLAIMS

1. L-(-)-moprolol L-(+)-tartrate salt (2:1).
2. Pharmaceutical composition for ophthalmic use, comprising L-(-)-moprolol L-(+)-tartrate (2:1) together with at least one pharmaceutically acceptable vehicle.
3. Pharmaceutical composition according to Claim 2, characterized in that it is in the form of a gel, an ointment or eyedrops.
4. Pharmaceutical composition according to Claim 2 or 3, characterized in that the amount of L-(-)-moprolol is between 0.01% and 20% by weight.
5. Pharmaceutical composition according to Claim 2 or 3, characterized in that the amount of L-(-)-moprolol is between 1% and 8% by weight.
6. Process for preparing L-(-)-moprolol L-(+)-tartrate (2:1), comprising addition of L-(+)-tartaric acid, dissolved in a suitable organic solvent, to L-(-)-moprolol base, also dissolved in a suitable organic solvent, in a 1:2 molar ratio.
7. Process according to Claim 6, characterized in that the salt thus formed is isolated via precipitation and filtration.
8. Process according to Claim 6 or 7, characterized in that the organic solvent is ethyl alcohol.
9. Process according to Claim 8, characterized in that the salt is precipitated from the ethanolic solution via addition of ethyl ether.