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(54) Title: PHARMACEUTICAL PREPARATION CONTAINING NIMESULIDE FOR TOPICAL USE

(57) Abrégé/Abstract:
The subject matter of this invention is a pharmaceutical preparation for topical use containing as active principle nimesulide (CAS No. 51 803-78-2) or one of its active derivatives. The invention is characterized by the fact that the preparation's base contains at least one phospholipid and at least one substance with acid reaction, specifically an acid. The figure reports the results of an ex vivo nimesulide absorption test performed with topical formulations including those which are the subject matter of this invention.

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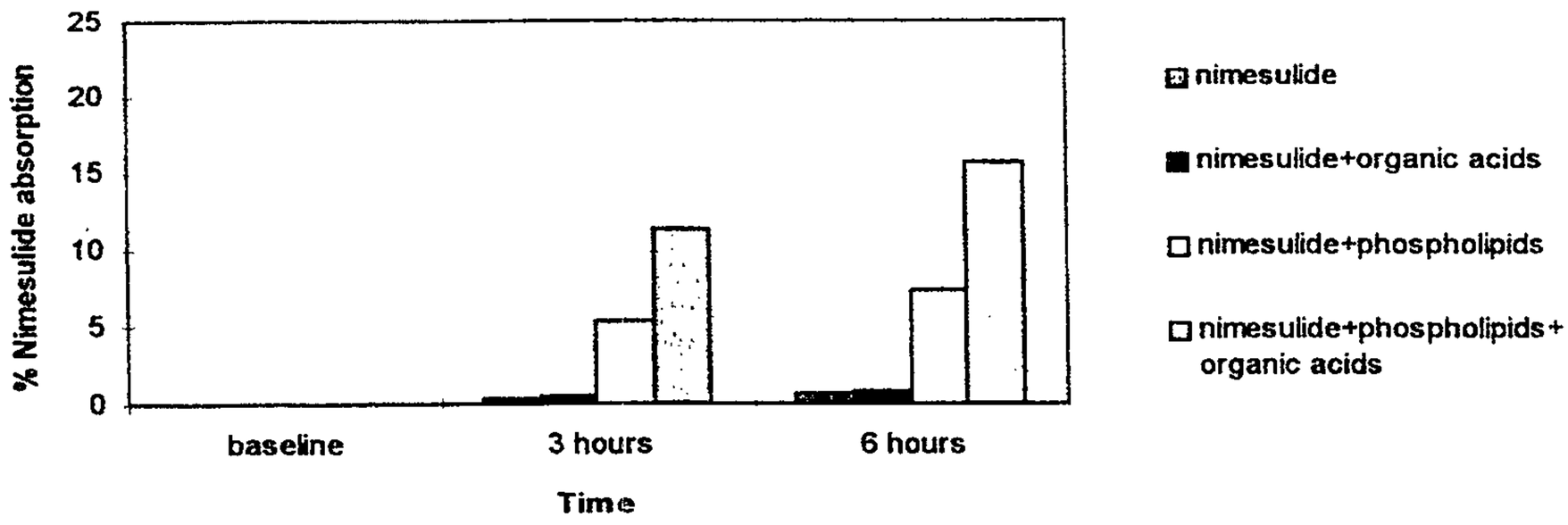

(57) Abstract

The subject matter of this invention is a pharmaceutical preparation for topical use containing as active principle nimesulide (CAS No. 51 803-78-2) or one of its active derivatives. The invention is characterized by the fact that the preparation's base contains at least one phospholipid and at least one substance with acid reaction, specifically an acid. The figure reports the results of an ex vivo nimesulide absorption test performed with topical formulations including those which are the subject matter of this invention.

"PHARMACEUTICAL PREPARATION CONTAINING NIMESULIDE FOR TOPICAL USE"

DESCRIPTION

The subject matter of this invention are topical preparations based on nimesulide containing phospholipids and organic or inorganic acids.

As is known, nimesulide (4-nitro-2-phenoxy-methan-sulfanilide) is a non steroidal anti-inflammatory drug, that has been well-known for some time, with analgesic and antipyretic activity (BE 801812). This molecule is used in the treatment of articular and extra-articular inflammatory conditions with pain related to rheumatoid arthritis, as well as cataract (EP 0 532900 A). Nimesulide has demonstrated as having a better therapeutical ratio, less gastrolesivity and, in general, better tolerability with respect to other non steroidal anti-inflammatories such as for example, arylalkaloid acids such as acetylsalicylic acid, Ketoprofen, Diclofenac, Naproxen, thanks to the presence of a sulfanilide group in its molecule. Nimesulide appears to be very sparingly soluble in water (about 0.01 mg/ml at room temperature). Nimesulide's scarce water solubility

and "wettability" can cause problems with drug release and constant bioavailability in various pharmaceutical forms.

In order to overcome such disadvantages, caused by nimesulide's low and variable bioavailability due to its scarce absorption properties (correlated with the very low solubility and bad "wetting" properties), it is possible to employ differing techniques.

Since nimesulide, a weak acid from the chemical viewpoint, is scarcely absorbed at low pH values (for example in the gastric tract), a possible initial step is salification with alkaline or alkaline-earth bases. This technique is not usually adopted, however, due to the very high pH of the salt solutions obtained.

A further method of increasing and achieving constant nimesulide bioavailability is complexation with cyclodextrins, above all β-cyclodextrins (as described in PCT/IT91/00043, DE 4116659 and PCT/HU94/00014) which enables better solubility and quicker absorption.

Another method, whose widest field of application is topical administration, is to vehicle the compound by using liposomal systems consisting of phospholipids.

In this specific sector there is, therefore, a demand for preparations based on nimesulide with better active principle bioavailability and absorption in the form of pharmaceutical presentations for topical application.

This invention is able to satisfy such requirement by also providing other advantages that will become evident further on.

The subject matter of this invention is a pharmaceutical preparation containing as active ingredient nimesulide (CAS-No. 51 803-78-2) or one of its active derivatives, characterized by the fact that the base of the preparation contains at least one phospholipid and at least one substance with an acid reaction, specifically an acid.

In the preparation according to this invention, nimesulide can be present at concentrations from 0.1 to 15%, the phospholipid from 0.1 to 10% and the acid from 0.1 to 10% of the preparation's weight.

In the preparation according to this invention, nimesulide can be present in dispersed form, the phospholipid can be a phosphatidyl acid ester, phosphatidylcholine in particular, and the acid can be an organic or an inorganic acid, preferably chosen from the group that comprises lactic acid, salicylic acid, glycol acid, citric acid, aqueous hydrochloric acid.

The pH of the preparation according to this invention can preferably be between 1 and 7.

The preparation according to this invention can contain other substances acceptable by pharmaceutical carriers.

The preparation according to this invention can be in the form of a gel, lipogel, cream, ointment, lotion, foam, with and without propellants or pressurized gas.

This invention is not limited to the pharmaceutical preparation containing nimesulide as active ingredient according to the preceding description. It is instead extended also to the use of the above mentioned preparation for formulation of drugs for topical use in the treatment of painful articular and

extra-articular inflammation, rheumatoid arthritis, inflammation of soft tissues, whether accompanied by pain or not, and for the treatment of psoriasis and cataract.

The only figure attached shows - in an ex vivo test using a model that involves the use of Franz cells - the active ingredient concentration in the collection medium, at the beginning of the test, after 3 hours and after 6 hours, assayed by calculating the percentage of nimesulide which passes through the membrane that separates the donor compartment from the receptor compartment.

The manufacture of the pharmaceutical preparations according to this invention was carried out with techniques, apparatus and excipients that are traditionally used on a routine basis in the pharmaceutical industry such as, for example, those described in "Remington's Pharmaceutical Science Handbook", Mack Pub. Co., N.Y., U.S.A.

In vitro and ex vivo tests have been performed using the model that involves the use of Franz cells consisting of two compartments, a donor and a receptor, separated by an artificial or natural membrane on which a thin layer of test product is distributed. Rat skin was used as membrane for the tests, whilst pH 8 phosphate buffer solution was used as medium in the receptor compartment. The active principle concentration in the collection medium was assayed, using suitable techniques (HPLC), at the beginning of the test, after 3 and after 6 hours, with determination of the percentage of nimesulide which passed through the membrane.

The following formulations were used for the test:

INGREDIENT	NIMESULIDE	NIMESULIDE + ORGANIC ACIDS	NIMESULIDE + PHOSPHOLIPIDS	NIMESULIDE + PHOSPHOLIPIDS + ORGANIC ACIDS
Nimesulide	5.0%	5.0%	5.0%	5.0%
Phosphatidylcholine	-	-	3.0%	3.0%
Polyacrylammide-Isoparaffin Laureth-7	4.0%	4.0%	4.0%	4.0%
Methyl-p-hydroxybenzoate	0.15%	0.15%	0.15%	0.15%
Propyl-p-hydroxybenzoate	0.05%	0.05%	0.05%	0.05%
Lactic acid	-	3.0%	-	3.0%
Purified water (q.s. to)	100%	100%	100%	100%

The results of an ex vivo test are reported in the figure.

From the in vitro and ex vivo tests it was noted that there is a correlation between percentage of phospholipids present and the quantity of drug that penetrates through the skin layers. Such drug quantity increased significantly by using organic acids (above all lactic acid and glycol acid) with keratolytic activity. Nimesulide's increased penetrating action, however, cannot be attributed to the sole presence of organic acids which, in the absence of phospholipids, do not influence nimesulide absorption. The possible keratolytic activity of the organic acids is not, therefore, the primary cause of the increased absorption, but, through synergetic activity with phospholipids, it contributes towards increasing availability of a drug, such as nimesulide, that has very scarce solubility.

The following examples represent methods of achieving a pharmaceutical preparation according to this invention:

EXAMPLE 1

Nimesulide gel - 5% concentration

Nimesulide	5.0%
Phosphatidylcholine	3.0%
Carboxyvinylpolymer (Carbopol 940)	2.0%
Methyl-p-hydroxybenzoate	0.17%
Propyl-p-hydroxybenzoate	0.03%
Lactic acid	5.0%
Purified water (q.s. to:)	100%

EXAMPLE 2

Nimesulide gel - 5% concentration

Nimesulide	5.0%
Phosphatidylcholine	3.0%
Polyacrylammide Isoparaffin Laureth-7	4.0%
Methyl-p-hydroxybenzoate	0.15%
Propyl-p-hydroxybenzoate	0.05%
Lactic acid	3.0%
Purified water (q.s. to:)	100%

EXAMPLE 3

Nimesulide cream - 3% concentration

Nimesulide	3.0%
Phosphatidylcholine	1.0%
Glycerylmonostearate self-emulsion (Arlacel 165)	7.0%

Methyl-p-hydroxybenzoate	0.15%
Propyl-p-hydroxybenzoate	0.05%
Citric acid monohydrate	3.0%
Purified water (q.s. to:)	100%

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. Pharmaceutical preparation containing as active ingredient nimesulide (CAS-No. 51 803-78-2) or one of its active derivatives, characterized by the fact that the base of the preparation contains a phospholipid and at least one acid.

2. Pharmaceutical preparation according to claim above, in which nimesulide is present at concentrations from 0.1 to 15%, the phospholipid from 0.1 to 10% and the acid from 0.1 to 10% of the preparation's weight.

3. Pharmaceutical preparation according to claims 1 and 2 above, in which nimesulide is present in dispersed form, the phospholipid is a phosphatidyl acid ester, in particular phosphatidylcholine and the acid is an organic or inorganic acid, chosen specifically from the group that comprises lactic acid, salicylic acid, glycol acid, citric acid and aqueous hydrochloric acid.

4. Pharamaceutical preparation according to claims 2 and 3 above, which have a pH between 1 and 7.

5. Pharmaceutical preparation according to any one of the claims from 1 to 4 above, together with at least one pharmaceutically acceptable carrier.

6. Pharmaceutical preparation according to any of claims from 1 to 5 above, in the form of gel, lipogel, cream, ointment, lotion, foam, with and without propellants or pressurized gas.

7. Use of the pharmaceutical preparations according to claims 1 to 6 above, to formulate drugs for topical use in the treatment of painful articular and extra-articular inflammation, rheumatoid arthritis, inflammation of soft tissues with or without pain, psoriasis and cataract.