"Pharmaceutical oral dosage form comprising a non-steroidal anti-inflammatory drug, and having good palatability"

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The present invention relates to a pharmaceutical oral dosage form comprising a non-steroidal anti-inflammatory drug (NSAID), and having good palatability.

More particularly, the present invention relates to an oral dosage form comprising

- a NSAID selected from the group comprising ibuprofen, naproxen and flurbiprofen,
- tromethamine, and
- a compound selected from the group comprising glycine, vitamine B6, and mixtures thereof.

In the present description and in the claims, both the terms "NSAID" and "non-steroidal anti-inflammatory drug" mean ibuprofen, naproxen and flurbiprofen as racemate mixtures or as pure or enriched enantiomer forms as well as pharmaceutically acceptable salts.

It is known that a number of non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, have a "chemesthetic effect" (irritant effect) on the oral cavity, throat and pharynx (Breslin et *al.* "Ibuprofen as a chemesthetic stimulus: evidence of a novel mechanism of throat irritation", Chem. Sens. 26:55-65, 2001).

This makes irritant and unpleasant the pharmaceutical dosage forms for oral use containing ibuprofen, naproxen, flurbiprofen or enantiomers and/or salts thereof, when such pharmaceutical forms are, for example, partially swallowable or chewable tablets, orosoluble tablets, granulates and powders to be suspended or dissolved before administration, mouthwashes, sprays, cough drops, lozenges, syrups, drops, oral gels and the like.

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In the present description and in the claims, the term "oral use" embraces both systemic oral administration and topical oral administration, and the term "oral form" means a pharmaceutical dosage form for oral use.

Many investigations have been carried out so far to improve the patient tolerability of oral forms based on ibuprofen, naproxen and fluriprofen.

However, the ingredients that have been found to be capable of reducing the irritant stimulus on the on the oral cavity, throat and pharynx have also been found to give to the oral forms taste properties, such as bitterness, saltiness and lye-taste, that resulted to be unacceptable.

Therefore, there is still a great need for ingredients capable not only of eliminating the throat-irritant stimulus, but also of giving an acceptable taste, i.e. good palatability, to the oral forms based on ibuprofen, naproxen or flurbiprofen.

Surprisingly it has now been found that this goal is achieved when a compound selected from the group comprising glycine, vitamine B6 and mixtures thereof, is added to an oral form comprising tromethamine and a NSAID selected from the group comprising ibuprofen, naproxen and flurbiprofen.

Therefore, in a first aspect the present invention relates to an oral form comprising tromethamine and a NSAID selected from the group comprising ibuprofen, naproxen and flurbiprofen, characterized in that it also comprises a compound selected from the group comprising glycine, vitamine B6 and mixtures thereof.

Preferably the amount of tromethamine ranges from 0.2 to 50 parts by weight per 1 part by weight of NSAID. More preferably the amount of tromethamine ranges from 1.4 to 2.5 parts by weight and, even more

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preferably, from 1.4 to 2.2 parts by weight per 1 part by weight of NSAID.

Preferably, the amount of glycine ranges from 0.01 to 20 parts by weight per 1 part by weight of NSAID. More preferably, the amount of glycine ranges from 0.0125 to 10 parts by weight per 1 part by weight of NSAID.

In turn, also the amount of vitamin B6 ranges from 0.01 to 20 parts and, more preferably, from 0.0125 to 10 parts by weight per 1 part by weight of NSAID.

Tolerability and palatability of the oral form of the present invention have been investigated *in vivo* in man by means of the comparison tests described hereinbelow.

The following examples are intended to further illustrate the invention, without, however, limiting it in any way.

COMPARISON EXAMPLE 1

Solution A

Ingredients	Amount (g)
Ibuprofen sodium	0.400
Demineralized water	qs 100 ml

pH 7.0-7.5

COMPARISON EXAMPLE 2

Solution B

Ingredients	Amount (g)
Flurbiprofen sodium	0.250
Demineralized water	qs 100 ml

pH 7.0-7.5

COMPARISON EXAMPLE 3

Solution C

Ingredients	Amount (g)
Naproxen sodium	0.220
Demineralized water	qs 100 ml

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COMPARISON EXAMPLE 4

Solution D

Ingredients	Amount (g)
Ibuprofen sodium	0.400
Tromethamine	0,600
Demineralized water	qs 100 ml

COMPARISON EXAMPLE 5

Solution E

Ingredients	Amount (g)
Flurbiprofen sodium	0.250
Tromethamine	0,500
Demineralized water	qs 100 ml

COMPARISON EXAMPLE 6

Solution F

Ingredients	Amount (g)
Naproxen sodium	0.220
Tromethamine	0.400
Demineralized water	qs 100 ml

INVENTION EXAMPLE 1

Solution G

Ingredients	Amount (g)
Ibuprofen	0.400
Tromethamine	0.600
Glycin	0.200
Demineralized water	qs 100 ml

INVENTION EXAMPLE 2

Solution H

Ingredients	Amount (g)
Flurbiprofen	0.250
Tromethamine	0.500
Glycin	0.010
Demineralized water	qs 100 ml

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INVENTION EXAMPLE 3

Solution I

Ingredients	Amount (g)
Naproxen sodium	0.220
Tromethamine	0.400
Glycin	0.145
Demineralized water	qs 100 ml

INVENTION EXAMPLE 4

Water-soluble Granulate (L)

Ingredients	Amount (g)
Ibuprofen 80 BP	0.400
Sodium saccharine	0.030
Tromethamine	0.600
Lemon flavouring Givaudan 96833-51	0.100
Acesulfame K	0.030
Vitamin B6	0.150
Sugar for tabletting	3.000
Sucrose monopalmitate	0.020

INVENTION EXAMPLE 5

Oral spray (M)

Ingredients	Amount (g)
Flurbiprofen	0.250
Glycerol FU IX	10.000
95° ethyl alcohol	10.000
Sorbitol 70	7.000
Sodium saccharine	0.150
Tromethamine	0.500
Sodium benzoate	0.150
Tween 20	1.000
Mint cool flavour	0.195
Blu patent	0.0006
Glycin	0.010

Demineralized water	qs 100 ml

INVENTION EXAMPLE 6

Water-soluble Granulate (N)

Ingredients	Amount (g)
Naproxen sodium	0.220
Sodium saccharine	0.032
Peppermint flavouring Givaudan	0.093
Acesulfame K	0.030
Maltitol	1.500
Glycin	0.145
Sucrose	1.500
Tromethamine	0.400

PALATABILITY TEST

The panel of individuals for the palatability (taste masking) test of the oral forms under evaluation has been properly selected because the irritation of the oral mucosae by the NSAIDs shows great individual variability. Indeed, whereas for some individuals the irritation may be "slightly noticeable", others define it as "strong" or "very strong" (Breslin et *al.* "Ibuprofen as a chemesthetic stimulus: evidence of a novel mechanism of throat irritation", Chem. Sens. 26:55-65, 2001).

There were therefore selected individuals who proved to be clearly sensitive to the irritant action of the NSAIDs in the test disclosed hereinafter.

Solutions A to C were administered to 40 individuals between 20 and 40 years old, and indications were given for correctly defining the perceived irritant stimulus, as follows:

Stimulus	Description
Burning	Sensation generated by abrasion of the skin or by exposure to high temperature, or to the irritant action of alcohol
Stinging	Brief sensation produced as from an insect bite or from thorns

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Prickling	Sensation similar to that caused by the action of small penetrating needles
Numbness	Diffuse sensation similar to the start of action of an anaesthetic (not an absence of sensation)

In addition, the 40 individuals were given instructions regarding the following operating procedures:

- how to define the sensation perceived according to the terminology defined in the preceding table,
- how to perform the operations of rinsing, swallowing and spraying of the preparations and also how to recognize the background sensation caused the preparations free of active principle.

Each of the 40 individuals was also requested to follow the standard procedure hereinbelow when taking the preparations:

- sip 10 ml of demineralized water, hold it in the mouth for 10 seconds and then swallow it,
- sip 10 ml of Solution, hold it in the mouth for 10 seconds and then swallow it.

Next, the 40 individuals were asked to evaluate the intensity of the irritation in the oral cavity and the perceived taste at time 0, at 30 seconds, 1 minute and 5 minutes after the administration, and 3 points were assigned to those who defined the sensation as "strong", 2 points to those who define defined the sensation as "moderate", 1 point to those who defined the sensation as "mild" and 0 points to those who defined the preparation as having no sensation.

Only the 18 individuals who received more than 40 points, and who therefore had greater sensitivity of perception of the unpleasant sensations generated by the NSAIDs, were thus selected.

These 18 individuals were requested to evaluate the palatability of the solutions D to F as well as the aqueous solutions of the granulates L and N and the oral spay M.

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The procedure followed and the points assigned were as for those described above, except that, in the case of the spray, the patients sprayed in the mouth two puffs of 200 µl and then swallowed the sprayed spray, whereas in the case of the granulate, each patient was administered the content (average weight = 4.33 g) of a sachet dissolved in 100 ml of water and stirred for 30 seconds.

In addition, the evaluation times were longer, since the 18 individuals were requested to evaluate the intensity of the irritation in the mouth and the perceived taste at time 0, at 30 seconds, 1 minute, 2 minutes, 3 minutes, 5 minutes, 10 minutes and 15 minutes after the administration.

The sum of the evaluations (0-15 minutes) for, respectively, the burning, the stinging, the prickling and the numbness etc. was calculated for each individual, along with the sum of the evaluations (0-15 minutes) for all the sensations. These parameters were analysed by the Wilcoxon "signed rank" method to compare the solutions and oral forms containing the same active ingredient. The final scores are shown in the following Table.

TABLE

Composition	Active Ingredient	Score
Solution A	Ibuprofen	21
Solution D	"	16
Solution G	"	11
Granulate L	"	8
Solution B	Flurbiprofen	15
Solution E	"	12
Solution H	"	9
Oral Spray M	"	6
Solution C	Naproxen	20
Solution F	"	17
Solution I	"	10

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Granulate N	"	7

The evaluation of the compositions containing ibuprofen showed that Solution G and the solution of Granulate L of the invention were less irritant and unpleasant and had a better palatability than the comparison Solutions A and D, not only for each individual sensation considered, but also for the sum of the evaluations obtained for all the sensations.

The evaluation of the compositions containing flurbiprofen showed that Solution H and the Oral Spray M of the invention were less irritant and unpleasant and had a better palatability than the comparison Solutions B and E, not only for each individual sensation considered, but also for the sum of the evaluations obtained for all the sensations.

The evaluation of the compositions containing naproxen showed that Solution I and the solution of Granulate N of the invention were less irritant and unpleasant and had a better palatability than the comparison Solutions C and F, not only for each individual sensation considered, but also for the sum of the evaluations obtained for all the sensations.

CLAIMS

1. A pharmaceutical oral dosage form comprising tromethamine and a NSAID selected from the group comprising ibuprofen, naproxen and flurbiprofen, characterized in that it also comprises a compound selected from the group comprising glycine, vitamine B6 and mixtures thereof.
2. A pharmaceutical oral dosage form according to Claim 1, characterized in that it comprises from 0.2 to 50 parts by weight of tromethamine per one part by weight of NSAID.
3. A pharmaceutical oral dosage form according to Claim 1, characterized in that it comprises from 1.4 to 2.5 parts by weight of tromethamine per one part by weight of NSAID.
4. A pharmaceutical oral dosage form according to Claim 1, characterized in that it comprises from 1.4 to 2.2 parts by weight of tromethamine per one part by weight of NSAID.
5. A pharmaceutical oral dosage form according any one of Claims 1 to 4, characterized in that it comprises from 0.01 to 20 parts by weight of glycine per one part by weight of NSAID.
6. A pharmaceutical oral dosage form according to Claim 5, characterized in that it comprises from 0.0125 to 10 parts by weight of glycine per one part by weight of NSAID.
7. A pharmaceutical oral dosage form according to any one of Claims 1 to 6, characterized in that it comprises from 0.01 to 20 parts by weight of vitamine B6 per one part by weight of NSAID.
8. A pharmaceutical oral dosage form according to Claim 7, characterized in that it comprises from 0.0125 to 10 parts by weight of vitamine B6 per one part by weight of NSAID.
9. A pharmaceutical oral dosage form according to any one of Claims 1 to 8, characterized in that it is a water-soluble granulate.

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10. A pharmaceutical oral dosage form according to any one of Claims 1 to 8, characterized in that it is a spray.

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