

Pharmaceutical composition comprising ibuprofen

Description of the invention

The present invention refers to pharmaceutical compositions comprising ibuprofen or
5 a pharmaceutically acceptable derivative thereof and one or more solubilizing agents
in the form of

A) aqueous solution for use in intravenous administration comprising ibuprofen of
either the sodium or lysinate salt, paracetamol and preferably one or more
cyclodextrins or

10 B) aqueous solution for use in intravenous administration wherein the one or more
solubilizing agents are one or more essential amino acids and optionally one or more
cyclodextrins or

C) composition for use in oral administration, which comprises paracetamol and
cyclodextrin, wherein said composition is in the form of either i) effervescent tablets
15 or effervescent granules or ii) oral suspension or syrup or oral solution or iii) soft
capsules.

Ibuprofen is a non-steroidal anti-inflammatory drug with anti-inflammatory, analgesic
and antipyretic properties, which is indicated for the treatment of fever and pain,
20 especially when associated with inflammation [Irvine J., Afrose A., Islam N.
Formulation and delivery strategies of ibuprofen: challenges and opportunities. Drug
Dev Ind Pharm. 2018;44(2):173-183]. The combination of ibuprofen with
paracetamol is used to enhance the analgesic effect, as for example in
musculoskeletal pain [Bettioli A., Marconi E., Vannacci A., Simonetti M., Magni A.,
25 Cricelli C., Lapi F. Effectiveness of ibuprofen plus paracetamol combination on
persistence of acute musculoskeletal disorders in primary care patients. Int J Clin
Pharm. 2021;43(4):1045-1054].

The low solubility of ibuprofen provokes dissolution problems in the cases of the
injectable forms, either with paracetamol or without paracetamol.

30 Document CN101991540A refers to an ibuprofen injection, comprising ibuprofen as a
main drug and pharmaceutically acceptable auxiliary materials, wherein said

pharmaceutically acceptable auxiliary materials include cyclodextrins or cyclodextrin derivatives and water-soluble excipients. The content is 0,5% to 20% by weight of ibuprofen, 10% to 60% of cyclodextrins or cyclodextrin derivatives, 1% to 40% of water-soluble excipients, and the rest is water. However, it does not mention the use
5 of specific solubilizing agents, such as basic amino acids, for example histidine or arginine.

Document TW201617066A relates to a method for preparing a combination product of ibuprofen and paracetamol, comprising the step of dissolving 2,8 to 3,2 mg ibuprofen and 9,8 to 10,2 mg paracetamol expressed as per ml of said composition
10 in an aqueous solvent of pH 6,3-7,3, without however referring to the dissolution of even higher concentrations of ibuprofen, for example of 100 mg/mL of the present invention, due to the presence of solubilizing agents.

Document EP2635269A1 refers to an intravenous composition, which comprises ibuprofen and paracetamol in a dose of: a) about 125 mg to about 175 mg ibuprofen
15 in combination with about 475 mg to about 525 mg paracetamol or b) about 275 mg to about 325 mg ibuprofen in combination with about 975 mg to about 1025 mg paracetamol. The above amounts are dissolved in 100 mL of water. However, it does not mention the dissolution of even higher concentrations of ibuprofen, for example of 100 mg/mL of the present invention, due to the presence of solubilizing agents.

20 Documents EP2389923B1 & EP2277546B1 refer to injectable paracetamol compositions comprising cyclodextrins as stabilizing agents. However, it does not mention the simultaneous dissolution of ibuprofen other than paracetamol.

Document EP3169307B1 relates to compositions of paracetamol and ibuprofen suitable for injectable administration, wherein the pH of the composition is from 6,3
25 to 7,3 and said compositions comprise from 2,8 to 3,2 mg of ibuprofen and from 9,8 to 10,2 mg of paracetamol expressed per ml of said composition. However, it does not refer solubilizing agents that could contribute to the dissolution of even higher concentrations of ibuprofen, for example of 100 mg/mL of the present invention, due to the presence of solubilizing agents.

30 Document EP3612157A1 relates to compositions comprising ibuprofen and paracetamol, suitable for injectable administration, which additionally comprise dissolved oxygen at a maximum concentration of 1,0 ppm in a closed container, pH

from 6,3 to 7,3, one or more antioxidants, one or more isotonic agents and one or more buffering agents, wherein the concentration of paracetamol is 10 mg/mL and the concentration of ibuprofen is 2 to 4 mg/mL. However, it does not refer to solubilizing agents that could contribute to the dissolution of even higher concentrations of ibuprofen, for example of 100 mg/mL of the present invention, due to the presence of solubilizing agents.

Moreover, the low solubility of ibuprofen, which affects its dissolution and absorption, and therefore its bioavailability, is a major problem during the development of effective formulations for the oral administration of the ibuprofen-paracetamol combination.

Document EP2089013A1 refers to analgesic, antipyretic compositions, for oral dosage, comprising ibuprofen and paracetamol in ratios from 5:19 to 81:95.

Document CN102389423A relates to formulations of ibuprofen sodium in combinations with other active substances, including ibuprofen-paracetamol combination, which are formulated into oral forms such as tablets, dispersible tablets, extended-release tablets, capsules, granules, dry suspensions, suspensions and others similar. The amount of ibuprofen ranges from 12,5 to 1000 mg, preferably from 50 to 500 mg and the amount of paracetamol ranges from 25 to 1000 mg, preferably from 100 to 500 mg.

Document WO2009083759A1 refers to an oral pharmaceutical suspension composition comprising 40-80 mg/ 5 mL ibuprofen, 100-500 mg/ 5 mL paracetamol and one or more pharmaceutically acceptable excipients.

Document EP0109281A1 relates to compositions of flubiprofen or ibuprofen or derivatives thereof, paracetamol and a pharmaceutically acceptable carrier, which are formulated into powder or liquid.

Document CN103751158A refers to a pharmaceutical oral suspension composition comprising 40-80 mg/5 mL ibuprofen, 100-500 mg/5 mL paracetamol and one or more pharmaceutically acceptable excipients.

Document EP1129709A2 refers to an effervescent composition comprising ibuprofen and cyclodextrin, but no paracetamol.

Document CN100404025C refers to an effervescent composition comprising paracetamol and cyclodextrin, but no ibuprofen.

However, none of the above documents about formulations for oral administration mentions the triple combination of ibuprofen, paracetamol and cyclodextrin in the
5 composition.

Despite of the achievements already mentioned in the state of the art, due to the increased requirements of quality and safety, there is a continuous need to further improve the stability of the aqueous solution of ibuprofen in the form of either
10 sodium salt or lysinate and paracetamol for use in IV administration, even in high temperatures, for a long time, without the need to keep it in a completely airtight bottle.

However, the combination of ibuprofen in the form of sodium salt or lysinate and paracetamol and preferably cyclodextrin as a solubilizing agent for the preparation of
15 compositions of injectable solutions suitable for intravenous administration has not yet been reported in the state of the art.

Notably, if the skilled person, starting with the product comprising the two active ingredients paracetamol and ibuprofen, wanted to improve the solubility, he would start with the more difficult to be dissolved, which is ibuprofen. Although the state of
20 the art mentions the use of solubilizing agents e.g. cyclodextrins, for the least insoluble, i.e. paracetamol, there is no technical information on how the solubility of a pharmaceutical composition comprising ibuprofen and paracetamol, could be improved.

Despite of the achievements already mentioned in the state of the art, due to the increased requirements of quality and safety, there is a continuous need to further improve the stability of the aqueous solution of ibuprofen for use in IV infusion, even
25 at high temperatures, for a long time, without the need to keep it in a completely airtight bottle.

However, the combination of ibuprofen with histidine and optionally with cyclodextrin
30 for the preparation of compositions of injectable ibuprofen solutions, suitable for intravenous administration, has not been reported in the prior art yet.

Despite of the achievements already mentioned in the state of the art, there is a continuous need for further improvement of pharmaceutical products of ibuprofen in combination with paracetamol for use in oral administration, with an emphasis on pharmaceutical forms other than classic tablets, in order to improve the compliance
5 of patient, by facilitating swallowing.

However, the combination of ibuprofen-paracetamol in orally administered forms including effervescent forms, by using solubilizing agents and specifically cyclodextrin in an appropriate amount, in order to achieve sufficient dissolution and/or suspension of the active substances, has not been referred in the prior art yet.

10

More specifically, the present invention is defined by the following:

Definition 1. Pharmaceutical composition comprising ibuprofen or a pharmaceutically acceptable derivative thereof and one or more solubilizing agents in the form of

15 A) aqueous solution for use in intravenous administration comprising ibuprofen of either the sodium or lysinate salt, paracetamol and preferably one or more cyclodextrins or

B) aqueous solution for use in intravenous administration wherein the one or more solubilizing agents are one or more essential amino acids and optionally one or more
20 cyclodextrins or

C) composition for use in oral administration, which comprises paracetamol and cyclodextrin, wherein said composition is in the form of either i) effervescent tablets or effervescent granules or ii) oral suspension or syrup or oral solution or iii) soft capsules.

25

Definition 2. Pharmaceutical composition according to definition 1, wherein the ibuprofen is preferably in the form of the sodium salt.

Definition 3. Pharmaceutical composition according to any of the definitions 1 to 2, wherein the amount of ibuprofen ranges from 1 to 1000 mg, preferably from 150 to 600 mg or 200 to 500 mg or 300 to 400 mg.

5 Definition 4. Pharmaceutical composition according to any of the definitions 1 to 3, wherein in the form of aqueous solution A or B, the concentration of equivalent free ibuprofen ranges from 1 to 400 mg/mL, preferably from 2 to 100 mg/mL, more preferably from 3 to 50 mg/mL and even more preferably 3 mg/mL.

10 Definition 5. Pharmaceutical composition according to any one of definitions 1 to 4, which comprises paracetamol preferably in a ratio of ibuprofen: paracetamol 600mg:1000mg or 500mg:1000mg or 500mg:500mg or 400mg:1000mg or 400mg:500mg or 300mg:1000mg or 300mg:500mg or 200mg :1000mg or 200mg:500mg or 200mg:200mg or 200mg:100mg or 150mg:1000mg or
15 150mg:500mg or 150mg:200mg or 150mg:100mg.

Definition 6. Pharmaceutical composition according to any of the definitions 1 to 5, wherein when in the form of aqueous solution A, the concentration of paracetamol ranges from 0,20% to 10% m/v, preferably from 0,5% to 1,5% m/v.

20

Definition 7. Pharmaceutical composition according to any of the definitions 1 to 6, wherein when in the form of aqueous solution A or B, said composition comprises one or more cyclodextrins, preferably hydroxyalkyl- β -cyclodextrins, more preferably 2-hydroxypropyl- β -cyclodextrin, wherein the concentration of the cyclodextrin ranges
25 from 0,2% m/v to 19% m/v, preferably from 0,2% m/v to 6% m/v, more preferably from 0,5% m/v to 3% m/v.

Definition 8. Pharmaceutical composition according to any of the definitions 1 to 6, wherein when in the form of aqueous solution A or B, said composition comprises
30 one or more cyclodextrins, preferably hydroxyalkyl- β -cyclodextrins, more preferably 2-hydroxypropyl- β -cyclodextrin, wherein the concentration of the cyclodextrin ranges

from 10 to 2000 mg/mL, preferably from 200 to 1500 mg/mL, more preferably from 350 to 750 mg/mL.

5 Definition 9. Pharmaceutical composition according to any of the definitions 1 to 8, which comprises one or more essential amino acids, preferably histidine or arginine, more preferably histidine, wherein when said composition is in the form of aqueous solution A or B the concentration of the essential amino acid ranges from 1 to 400 mg/L, preferably from 20 to 300 mg/L, more preferably from 50 to 200 mg/L and even more preferably from 70 to 100 mg/L.

10

Definition 10. Pharmaceutical composition according to definition 9, wherein when in the form of aqueous solution A or B, said composition comprises one or more essential amino acids, wherein the concentration of said essential amino acid ranges from 0,5 to 200 mg/L, preferably from 10 to 150 mg/L, more preferably from 25 to 100 mg/L and even more preferably from 35 to 50 mg/L and one or more cyclodextrins, wherein the concentration of the cyclodextrin is from 10 to 2000 mg/mL, preferably from 200 to 1500 mg/mL, more preferably from 350 to 750 mg/mL.

20 Definition 11. Pharmaceutical composition according to any of the definitions 1 to 10, wherein when in the form of aqueous solution A or B, said composition comprises additionally a derivative bearing at least one thiol functional group, which is selected from thioglycerols, cysteine, acetylcysteine, thioglycolic acid and/or salts thereof, dithiothreitol, reduced glutathione, thiolactic acid and/or salts thereof and 25 mercaptoethanesulfonic acid, preferably thioglycerol and particularly preferably monothioglycerol, wherein the concentration of the derivative bearing at least one thiol functional group ranges from 0,001% to 0,5% m/v either from 1,5% to 3% m/v or from 2% to 2,5% m/v.

30 Definition 12. Pharmaceutical composition according to any of the definitions 1 to 11, wherein when in the form of aqueous solution A or B, said composition comprises a

chelating agent selected from EDTA, nitrilotriacetic acid, ethylenediamine-N,N'-dipropionic acid, ethylenediamine-tetra-(methylene phosphoric acid)), 2,2'(ethylenediamino)-dibutyl acid, bis(2-aminoethyl ether)-N,N'ethylene glycol, N'-tetraacetic acid and/or their salts, preferably EDTA, wherein the concentration of the
5 chelating agent ranges from 0,001% to 0,5% m/v either from 1,5% to 3% m/v or from 2% to 2,5% m/v.

Definition 13. Pharmaceutical composition according to any of the definitions 1 to 12, wherein when in the form of aqueous solution A or B, said composition comprises
10 one or more derivatives selected from thiamine salts, preferably thiamine hydrochloride, wherein the concentration of the thiamine salt ranges from 0,001% m/v to 0,2 % m/v.

Definition 14. Pharmaceutical composition according to any of the definitions 1 to 13,
15 wherein when in the form of aqueous solution A or B, pH is between 4 and 8, preferably from 6 to 8, more preferably from 7 to 8, such as pH=7,6, said pH is adjusted by using a suitable alkalinizing agent, preferably sodium carbonate and/or by at least one acid and its ionized form, said acid is selected from citric, malic, acetate, sorbic, phosphoric, fumaric, lactic, gluconic and tartaric acid or mixtures thereof.

20

Definition 15. Pharmaceutical composition according to any of the definitions 1 to 14, wherein when in the form of A or B, said composition additionally comprises one or more pharmaceutically acceptable excipients.

25 Definition 16. Pharmaceutical composition according to any of the definitions 1 to 5, wherein when in the form of C suitable for effervescent tablets or effervescent granules, said composition comprises one or more effervescent agents, preferably ascorbic acid and/or anhydrous citric acid and/or anhydrous sodium bicarbonate and/or sodium bicarbonate and/or sodium tartrate and/or sodium bitartrate.

30

Definition 17. Pharmaceutical composition according to definition 16, wherein when in the form of C, said composition additionally comprises one or more excipients, preferably one or more diluents and/or one or more lubricants and/or one or more binders and/or one or more sweeteners and/or one or more flavor enhancers.

5

Definition 18. Pharmaceutical composition according to any of the definitions 1 to 17, which additionally comprises one or more active substances other than ibuprofen or paracetamol or a pharmaceutically acceptable derivative thereof, for example other non-steroidal anti-inflammatory drugs for example acetylsalicylic acid and/or opioids for example codeine and/or anticonvulsants for example hyoscine and/or antihistamines for example chlorphenamine, orphenadrine and/or mucolytics for example acetylcysteine and/or sympathomimetics for example pseudoephedrine and/or vitamin C and/or caffeine.

15 It was surprisingly found that the composition of the aqueous solution of ibuprofen in the form of either sodium salt or lysinate and paracetamol comprising one or more solubilizing agents, preferably one or more cyclodextrins, was stable even at high temperatures for a long time.

20 It was surprisingly found that the composition of an aqueous solution of ibuprofen in the form of either sodium salt or lysinate and paracetamol comprising one or more solubilizing agents, preferably one or more cyclodextrins, exhibited even more increased solubilization of ibuprofen.

25 This new proposed combination of ibuprofen in the form of either sodium salt or lysinate and paracetamol and preferably cyclodextrin exhibits all the advantages of the prior art and indeed with unexpectedly improved stability and in particular improved solubility.

30 It was surprisingly found that the composition of an aqueous solution of ibuprofen comprising one or more solubilizing agents, especially one or more basic amino acids and optionally one or more cyclodextrins, was stable even at high temperatures for a long time.

It was surprisingly found that the composition of an aqueous solution of ibuprofen comprising one or more solubilizing agents, especially one or more basic amino acids and optionally one or more cyclodextrins, showed even more increased solubilization of ibuprofen.

- 5 This new proposed combination of ibuprofen with histidine and optionally with cyclodextrin of the present invention exhibits all the advantages of the prior art with unexpectedly improved stability and especially improved solubility.

In addition to the strong improvement in the solubility and non-immediate precipitation of the active substances of the composition, in the form of orally
10 administrated forms, it was surprisingly found that the absorption of said active substances is improved on the one hand, and on the other hand the onset of their action is accelerated.

It was also surprisingly found that the ibuprofen, paracetamol and additionally cyclodextrin compositions of the present invention in the form of orally administrated
15 forms, showed an unexpected improvement in the unpleasant taste, resulting not only from ibuprofen but also from the combination of ibuprofen and paracetamol.

This new proposed combination of ibuprofen-paracetamol with cyclodextrin of the present invention solves all the above problems of the state of the art, and in fact with unexpected, surprising results in term of improved solubility.

- 20 Furthermore, it was surprisingly found that the more is restricted the scope of the claims, the more intense are the effects and the advantages of the present invention.

In particular, the more intense are the effects and the advantages of the present invention were observed when ibuprofen was combined with paracetamol.

25

By the expression equivalent free ibuprofen we mean the free form of ibuprofen, i.e. not the salt form e.g. sodium or other complex e.g. with lysine.

The stable aqueous solution composition for use in intravenous infusion according to the present invention may further comprise isotonic agents, preferably sodium
30 chloride.

The stable aqueous solution formulation for use in intravenous infusion according to the present invention can be sterilized by heat or by filtration.

The aqueous medium of the stable aqueous solution composition for use in intravenous infusion according to the present invention may be deoxygenated by a water-insoluble inert gas (N2).

The compositions of the present invention will be administered intravenously and are stable when stored for more than 24 months at room temperature, saving refrigeration costs during transport and storage and alleviating patient discomfort during administration. Furthermore, the compositions may even be stable when stored for more than 30 days at elevated temperatures, for example 70°C.

The compositions of the present invention may be prepared in solution and stored in transparent glass containers, for example glass ampoules, vials, cartridges, glass sealed vials or in stoppered glass vials or bottles of polymeric material such as polyethylene or in bags of soft polyethylene material, polyvinyl chloride or polypropylene. The glass should preferably be transparent to facilitate use.

The amounts of cyclodextrin may be of the same order of magnitude as those reported in CN101991540A, the entire contents of which are incorporated into the description of the present invention. For example, the cyclodextrin may be in an amount of from 100 to 600 mg per dose, e.g. 120, 200, 300, 400, 500 mg per dose.

The compositions of the present invention can be prepared by methods already known in the state of art.

The present invention is further described by the following indicative, but non-limiting examples.

Example 1: In a preferred embodiment the composition of the present invention comprises the following per 100 mL

Ibuprofen sodium	331,97 mg
Paracetamol	1000 mg

2-hydroxypropyl-β-cyclodextrin	666 mg
EDTA	10 mg
Monothioglycerol	10 mg
Sodium chloride	600 mg
Sodium hydrogen phosphate	35,6 mg
Water suitable for injection	100 mL
Final pH (HCl or NaOH) 1M	5,5-6,5

Suitable for intravenous injection

Example 2: In a preferred embodiment the composition of the present invention comprises the following per 100 mL

Ibuprofen lysinate	512,7 mg
Paracetamol	1000 mg
2-hydroxypropyl-β-cyclodextrin	666 mg
EDTA	10 mg
Monothioglycerol	10 mg
Sodium chloride	600 mg
Sodium hydrogen phosphate	35,6 mg
Water suitable for injection	100 mL
Final pH (HCl or NaOH) 1M	5,5-6,5

5 Suitable for intravenous injection

Example 3: In a preferred embodiment the composition of the present invention comprises the following per 100 mL

Ibuprofen sodium	331,97 mg
Paracetamol	1000 mg

2-hydroxypropyl- β -cyclodextrin	666 mg
EDTA	10 mg
Monothioglycerol	10 mg
Thiamine hydrochloride	10 mg
Sodium chloride	600 mg
Sodium hydrogen phosphate	35,6 mg
Water suitable for injection	100 mL
Final pH (HCl or NaOH) 1M	5,5-6,5

Suitable for intravenous injection

Example 4: In a preferred embodiment the composition of the present invention comprises the following per mL

Ibuprofen	100 mg/mL
Histidine	74 mg/mL
Water suitable for injection	1 mL
Sodium carbonate	Qs to pH=7.4 $\pm$ 0,5

5 Suitable for intravenous injection

Example 5: In a preferred embodiment the composition of the present invention comprises the following per mL

Ibuprofen	100 mg/mL
Histidine	74 mg/mL
2-hydroxypropyl- β -cyclodextrin	712 mg/mL
Water suitable for injection	1 mL
Sodium carbonate	Qs to pH=7.6 $\pm$ 0,5

--	--

Suitable for intravenous injection

Example 6: In a preferred embodiment the composition of the present invention comprises the following per mL

Ibuprofen	100 mg/mL
Histidine	74 mg/mL
2-hydroxypropyl-β-cyclodextrin	712 mg/mL
monothioglycerol	10 mg/mL
EDTA	10 mg/mL
Water suitable for injection	1 mL
Sodium carbonate	Qs to pH=7.6±0,5

5 Suitable for intravenous injection

Example 7: In a preferred embodiment the composition of the present invention comprises the following per mL

Ibuprofen	3 mg/mL
Histidine	74 mg/mL
Paracetamol	10 mg/mL
2-hydroxypropyl-β-cyclodextrin	712 mg/mL
Water suitable for injection	1 mL
Sodium carbonate	Qs to pH=7.6±0,5

Suitable for intravenous injection with infusion

Example 8: In an embodiment the composition of the present invention comprises the following per effervescent tablet

ibuprofen	400 mg
paracetamol	500 mg
2-hydroxypropyl-β-cyclodextrin	500 mg
arginine	250 mg
sodium bicarbonate	1000 mg
sodium bitartrate	1200 mg
sodium saccharin	40 mg
polyvidone	90 mg
flavor (powder)	200 mg

The compositions of Example 1 are formulated into effervescent tablets.

- 5 **Example 9:** In an embodiment the composition of the present invention comprises the following per sachet

ibuprofen	200 mg
paracetamol	500 mg
2-hydroxypropyl-β-cyclodextrin	300 mg
sodium bicarbonate	1000 mg
sodium bitartrate	1200 mg
Vitamin C	500 mg
sodium saccharin	40 mg
polyvidone	90 mg
flavor (powder)	200 mg

The compositions of Example 1 are formulated into effervescent granules.

Example 10: In an embodiment the composition of the present invention comprises the following per dose of 5 mL

ibuprofen	150 mg
paracetamol	100 mg
2-hydroxypropyl-β-cyclodextrin	120 mg
xanthan gum	7,5 mg
glycerol	500 mg
sodium benzoate	12,5 mg
citric acid	10 mg
sodium saccharin	2,5 mg
polysorbate 80	15 mg
microcrystalline cellulose	60 mg
water	qs to 5 mL
strawberry flavor	12,5 mg
colouring agent	0,5 mg
sorbitol solution 70%	2000 mg
Carmellose sodium	7,5 mg
EDTA	2,5 mg

The compositions of Example 1 are formulated into syrup

- 5
- The compositions of the present examples 1-10 exhibit all the advantages of the present invention mentioned above, e.g. solubility, improved taste (in the cases of the orally administrated examples 8-10), improved absorption and faster onset of action.
- In addition, we prepared the compositions of the above examples 1-3 and 5-10 in the absence of cyclodextrin and found clearly lower solubility with almost immediate precipitation of the active substances.
- 10

Claims

1. Pharmaceutical composition comprising ibuprofen or a pharmaceutically acceptable derivative thereof and one or more solubilizing agents in the form of
 - 5 A) aqueous solution for use in intravenous administration comprising ibuprofen of either the sodium or lysinate salt, paracetamol and preferably one or more cyclodextrins or
 - B) aqueous solution for use in intravenous administration wherein the one or more solubilizing agents are one or more essential amino acids and optionally one or more
10 cyclodextrins or
 - C) composition for use in oral administration, which comprises paracetamol and cyclodextrin, wherein said composition is in the form of either i) effervescent tablets or effervescent granules or ii) oral suspension or syrup or oral solution or iii) soft capsules.
- 15 2. Pharmaceutical composition according to claim 1, wherein the ibuprofen is preferably in the form of the sodium salt.
3. Pharmaceutical composition according to any of the claims 1 to 2, wherein the
20 amount of ibuprofen ranges from 1 to 1000 mg, preferably from 150 to 600 mg or 200 to 500 mg or 300 to 400 mg.
4. Pharmaceutical composition according to any of the claims 1 to 3, wherein in the
25 form of aqueous solution A or B, the concentration of equivalent free ibuprofen ranges from 1 to 400 mg/mL, preferably from 2 to 100 mg/mL, more preferably from 3 to 50 mg/mL and even more preferably 3 mg/mL.
5. Pharmaceutical composition according to any one of claims 1 to 4, which
30 comprises paracetamol, preferably in a ratio of ibuprofen: paracetamol 600mg:1000mg or 500mg:1000mg or 500mg:500mg or 400mg:1000mg or

400mg:500mg or 300mg:1000mg or 300mg:500mg or 200mg:1000mg or 200mg:500mg or 200mg:200mg or 200mg:100mg or 150mg:1000mg or 150mg:500mg or 150mg:200mg or 150mg:100mg.

5 6. Pharmaceutical composition according to any of the claims 1 to 5, wherein when in the form of aqueous solution A, the concentration of paracetamol ranges from 0,20% to 10% m/v, preferably from 0,5% to 1,5% m/v.

10 7. Pharmaceutical composition according to any of the claims 1 to 6, wherein when in the form of aqueous solution A or B, said composition comprises one or more cyclodextrins, preferably hydroxyalkyl- β -cyclodextrins, more preferably 2-hydroxypropyl- β -cyclodextrin, wherein the concentration of the cyclodextrin ranges from 0,2% m/v to 19% m/v, preferably from 0,2% m/v to 6% m/v, more preferably from 0,5% m/v to 3% m/v.

15

8. Pharmaceutical composition according to any of the claims 1 to 6, wherein when in the form of aqueous solution A or B, said composition comprises one or more cyclodextrins, preferably hydroxyalkyl- β -cyclodextrins, more preferably 2-hydroxypropyl- β -cyclodextrin, wherein the concentration of the cyclodextrin ranges
20 from 10 to 2000 mg/mL, preferably from 200 to 1500 mg/mL, more preferably from 350 to 750 mg/mL.

9. Pharmaceutical composition according to any of the claims 1 to 8, which comprises one or more essential amino acids, preferably histidine or arginine, more
25 preferably histidine, wherein when said composition is in the form of aqueous solution A or B the concentration of the essential amino acid ranges from 1 to 400 mg/L, preferably from 20 to 300 mg/L, more preferably from 50 to 200 mg/L and even more preferably from 70 to 100 mg/L.

30 10. Pharmaceutical composition according to claim 9, wherein when in the form of aqueous solution A or B, said composition comprises one or more essential amino

acids, wherein the concentration of said essential amino acid ranges from 0,5 to 200 mg/L, preferably from 10 to 150 mg/L, more preferably from 25 to 100 mg/L and even more preferably from 35 to 50 mg/L and one or more cyclodextrins, wherein the concentration of the cyclodextrin is from 10 to 2000 mg/mL, preferably from 200
5 to 1500 mg/mL, more preferably from 350 to 750 mg/mL.

11. Pharmaceutical composition according to any of the claims 1 to 10, wherein when in the form of aqueous solution A or B, said composition comprises additionally a derivative bearing at least one thiol functional group, which is selected from
10 thioglycerols, cysteine, acetylcysteine, thioglycolic acid and/or salts thereof, dithiothreitol, reduced glutathione, thiolactic acid and/or salts thereof and mercaptoethanesulfonic acid, preferably thioglycerol and particularly preferably monothioglycerol, wherein the concentration of the derivative bearing at least one thiol functional group ranges from 0,001% to 0,5% m/v either from 1,5% to 3% m/v
15 or from 2% to 2,5% m/v.

12. Pharmaceutical composition according to any of the claims 1 to 11, wherein when in the form of aqueous solution A or B, said composition comprises a chelating agent selected from EDTA, nitrilotriacetic acid, ethylenediamine-N,N'-dipropionic acid,
20 ethylenediamine-tetra-(methylene phosphoric acid)), 2,2'(ethylenediamino)-dibutyl acid, bis(2-aminoethyl ether)-N,N,N'ethylene glycol, N'-tetraacetic acid and/or their salts, preferably EDTA, wherein the concentration of the chelating agent ranges from 0,001% to 0,5% m/v either from 1,5% to 3% m/v or from 2% to 2,5% m/v.

25 13. Pharmaceutical composition according to any of the claims 1 to 12, wherein when in the form of aqueous solution A or B, said composition comprises one or more derivatives selected from thiamine salts, preferably thiamine hydrochloride, wherein the concentration of the thiamine salt ranges from 0,001% m/v to 0,2 % m/v.

30

14. Pharmaceutical composition according to any of the claims 1 to 13, wherein when in the form of aqueous solution A or B, pH is between 4 and 8, preferably from 6 to 8, more preferably from 7 to 8, such as pH=7,6, said pH is adjusted by using a suitable alkalinizing agent, preferably sodium carbonate and/or by at least one acid
5 and its ionized form, said acid is selected from citric, malic, acetate, sorbic, phosphoric, fumaric, lactic, gluconic and tartaric acid or mixtures thereof.

15. Pharmaceutical composition according to any of the claims 1 to 14, wherein when in the form of A or B, said composition additionally comprises one or more
10 pharmaceutically acceptable excipients.

16. Pharmaceutical composition according to any of the claims 1 to 5, wherein when in the form of C suitable for effervescent tablets or effervescent granules, said composition comprises one or more effervescent agents, preferably ascorbic acid
15 and/or anhydrous citric acid and/or anhydrous sodium bicarbonate and/or sodium bicarbonate and/or sodium tartrate and/or sodium bitartrate.

17. Pharmaceutical composition according to claim 16, wherein when in the form of C, said composition additionally comprises one or more excipients, preferably one or
20 more diluents and/or one or more lubricants and/or one or more binders and/or one or more sweeteners and/or one or more flavor enhancers.

18. Pharmaceutical composition according to any of the claims 1 to 17, which additionally comprises one or more active substances other than ibuprofen or
25 paracetamol or a pharmaceutically acceptable derivative thereof, for example other non-steroidal anti-inflammatory drugs for example acetylsalicylic acid and/or opioids for example codeine and/or anticonvulsants for example hyoscine and/or antihistamines for example chlorphenamine, orphenadrine and/or mucolytics for example acetylcysteine and/or sympathomimetics for example pseudoephedrine
30 and/or vitamin C and/or caffeine.