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(73) Proprietor: AMERICAN HOME PRODUCTS CORPORATION
Five Giralda Farms
Madison, New Jersey 07940-0874/US

(72) Inventor: Motola, Solomon
40 Majestic Way
Marlton, New Jersey (US)
Inventor: Mogavero, Annabelle
190 Taunton Blvd.
Medford, New Jersey (US)
Inventor: Aglsim, Gary Robert
17 Crofton Commons
Cherry Hill, New Jersey (US)
Inventor: Panopoulos, Pamela N.
10 McGeary Place
Mayslanding, New Jersey (US)

(74) Representative: Wileman, David Francis Dr. et al
c/o Wyeth Laboratories Huntercombe Lane South
Taplow Maidenhead Berkshire SL6 OPH (GB)

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(73) Proprietor : **AMERICAN HOME PRODUCTS CORPORATION**
685, Third Avenue
New York, New York 10017 (US)

(72) Inventor : **Motola, Solomon**
40 Majestic Way
Marlton, New Jersey (US)
Inventor : **Mogavero, Annabelle**
190 Taunton Blvd.
Medford, New Jersey (US)
Inventor : **Agisim, Gary Robert**
17 Crofton Commons
Cherry Hill, New Jersey (US)
Inventor : **Panopoulos, Pamela N.**
10 McGeary Place
Maysianding, New Jersey (US)

(74) Representative : **Wileman, David Francis Dr. et al**
c/o Wyeth Laboratories Huntercombe Lane South
Taplow Maidenhead Berkshire SL6 OPH (GB)

EP 0 390 369 B1

Description

This invention relates to a water base ibuprofen composition wherein the ibuprofen remains in suspension and wherein the bitter taste of ibuprofen is masked. More particularly the invention relates to an improved ibuprofen composition wherein the ibuprofen is maintained in suspension by primary suspending agents such as xanthan gum, microcrystalline cellulose, sodium carboxymethyl cellulose and polysorbate 80, and wherein the ibuprofen is taste-masked with taste masking agents such as sucrose and sorbitol solution, by maintaining the pH of the suspension between 1.5 and up to less than 3.5.

Liquid ibuprofen compositions for oral administration are known in the art. One such composition is described in US Patent 4,684,666 as a stabilized liquid ibuprofen syrup suitable for oral administration comprising from 50 to 400 mg of ibuprofen per 5 ml of syrup, the ibuprofen being suspended in an aqueous liquid having more than 50% by weight of a polyhydric alcohol bodying agent, a sweetening agent and a pH of higher than 7.0 and below 7.7. Another such composition is described in US Patent 4,788,220 wherein the ibuprofen is maintained in suspension by the primary suspending agents xanthan gum, microcrystalline cellulose, sodium carboxymethyl cellulose and polysorbate 80, wherein the ibuprofen is taste-masked with sucrose and sorbitol solution and the pH is maintained at about 3.5 to 5.

It has now been found that improved taste neutral aqueous base compositions suitable for oral administration can be formulated from ibuprofen maintained in suspension by a combination of suspending agents and also including taste masking agents by adjusting the pH of the suspension between 1.5 to less than 3.5 and providing a buffering capacity within the range of 0.03 to 0.05 between the initial pH of the formulation and a pH which is 1.0 pH unit higher than the initial pH.

Since ibuprofen has essentially no aqueous solubility within a pH range of 1 and 4 with a dramatic increase in solubility at pH 5, the buffering capacity of the formulation inhibits dissolution of the ibuprofen content of the suspension in the human saliva upon administration. Human saliva normally has a pH of 5.6 to 7.6 and dissolution of the ibuprofen in the saliva would contribute a bitter after taste and throat bite.

The ibuprofen compositions of the invention suitable for oral administration contain 0.8% to 4% ibuprofen weight by volume of the total composition, and 0.1% to 2% weight by volume of the total composition, of suspension stabilizing agents, 20% to 70% weight by volume of the total composition of a combination of taste masking agents, the composition also containing a buffer acid e.g citric acid or phosphoric acid or a mixture thereof in an amount sufficient to adjust the pH from 1.5 to less than 3.5, preferably 3, and to provide a buffer capacity within the range of 0.03 to 0.05 between the initial pH and a pH which is 1.0 pH unit higher than the initial pH, and water qs to 100% by volume of the composition.

The amount of citric acid or phosphoric acid or mixture thereof may be for example from 0.1% to 2.0% weight by volume. The amount of water may be for example 25% to 70% weight by volume of the total composition.

Preferably the suspending agents include xanthan gum, microcrystalline cellulose, sodium carboxymethyl cellulose and polysorbate 80. Also, preferably the taste masking agents include sucrose and sorbitol solution, although other pharmaceutically acceptable polyols can be used such as glycerin. The buffer acids are preferably citric acid and phosphoric acid although other pharmaceutically acceptable buffer acids can be used.

The ibuprofen composition is formulated to contain 40 mg to 200 mg of ibuprofen per teaspoon (5ml) of formulation, eg 50 mg to 100 mg/5ml preferably 100 mg/5ml.

Xanthan gum is an article of commerce and is marketed by R T Vanderbilt Company, Inc of Los Angeles, California under the tradename Rhodigel 23. (**RHODIGEL** is a Registered Trade Mark). It is a food grade thickener in powder form of about 80 mesh.

The particle size of the ibuprofen should be suitable for providing a suspension, ie not too fine which might cause the ibuprofen to float and not too coarse which would cause it to sink. Typical average particle sizes may be in the range 30 to 250 μm with the preferred average particle size being 40 μm.

Ibuprofen is available commercially from Ethyl Corporation, Baton Rouge, Louisiana in an average particle size of 40 μm.

Microcrystalline cellulose and sodium carboxymethylcellulose are available from FMC Corporation, Newark, Delaware, the former under the brand name Avicel CL 611. (**AVICEL** is a Registered Trade Mark).

Colouring and flavouring agents can be added as desired. The other ingredients can be any national formulary or USP grades.

Other suitable ingredients including other stabilizing agents are described in US Patent 4,684,666.

The invention is further described by reference to the following examples.

EXAMPLE 1

A pediatric ibuprofen formulation was prepared having the following composition:

Ingredient	Percent Wt/vol.	Grams per 15 liters
Xanthan Gum	0.15	22.5
Microcrystalline Cellulose	0.75	112.5
Sodium Benzoate, NF	0.25	37.5
Citric Acid, Hydrous, USP	0.95	142.5
Sucrose, NF	50.00	7500.0
Glycerin, USP	10.00	1500.0
Sorbitol Solution, USP	10.00	1500.0
Ibuprofen USP	2.0	300.0
Sodium Carboxymethylcellulose, USP	0.10	15.0
Polysorbate 80, NF	0.30	45.0
Red FDC 40	0.015	2.25
Disodium Edetate, USP	0.05	7.5
Artificial flavour oils	0.16	24.0
Purified Water Deionized, USP	qs. to 100 ml	qs to 15000 ml.

The procedure for preparation of the above pediatric formulation is first to prepare an ibuprofen slurry. The sorbitol solution and glycerin were weighed into a jacketed kettle equipped with a stirrer. The sodium carboxymethyl cellulose was sprinkled onto the solution and mixed for 10 minutes until all of the particles were completely wet. The mixture was then heated to about 70°C and mixed until the gum was completely hydrated. The mixture was then cooled to 45°C and the polysorbate 80 was added. Mixing was continued while cooling the mixture to 30°C. The ibuprofen was then sprinkled slowly into the mixture and mixing was continued for 15 minutes.

The xanthan gum solution was prepared first in the form of a 1% by weight solution in water. The required amount of water was placed into a mixing bowl equipped with a Lightnin mixer and the xanthan gum slowly added and hydrated by mixing at high shear for approximately 25 minutes. Into a separate mixing vessel, equipped with a Lightnin mixer was placed a quantity of water equivalent to 30% to 40% weight by volume of the total batch (4500 to 6000 ml). The microcrystalline cellulose was sprinkled onto the water and mixing at medium shear for 30 minutes was continued in order to completely suspended the microcrystalline cellulose. The required amount of the xanthan gum solution was added to the microcrystalline cellulose suspension with mixing for 15 minutes or until a uniform suspension was obtained.

The sucrose was then added slowly with mixing for 15 minutes, or until no sucrose particles are observed, and the colouring was added. The required amount of the ibuprofen slurry was slowly added from the first step and mixed for 15 minutes. The sodium benzoate, disodium edetate and citric acid were sequentially added and mixed for 5 minutes. The citric acid and the flavouring agents were sequentially added with mixing for 5 minutes after each addition. The remainder of the water was then added with mixing until the formulation was homogeneous.

The initial viscosity of the final formulation at 25°C was 2800 mPa.s (2800 cps) with a #2 spindle at 4 r.p.m. and standing the viscosity increased to 4800 mPa.s (4800 cps) which on shaking for 5 seconds decreased to 2000 mPa.s (2000 cps). The initial pH of the formulation was 3.05 and the specific gravity was 1.24 gram/milliliter. The ibuprofen solubility was 0.009% weight by volume.

The formulation had a sweet, pleasant. fruity taste with no discernible unpleasant after taste or throat bite characteristic of ibuprofen.

The buffer capacity of the formulation between pH 3.0 and pH 3.5 was 0.044 and the buffer capacity between pH 3.0 and pH 4.1 was 0.044.

With this formulation the quantity of 1 Normal sodium hydroxide solution necessary to increase the pH of 5 milliliters of the formulation to the normal pH of human saliva, i.e. pH 5.6 to pH 7.6, is 0.63ml to a pH of 5.6 and 1.13 ml to a pH of 7.5.

EXAMPLE 2

A pediatric ibuprofen formulation was prepared having the following composition:

Ingredient	Percent Wt/vol.	Grams per 15 liters
Xanthan Gum	0.15	22.5
Microcrystalline Cellulose	0.75	112.5
Sodium Benzoate, NF	0.25	37.5
Phosphoric Acid, USP	1.0	150.0
Sucrose, NF	50.00	7500.0
Glycerin, USP	10.00	1500.0
Sorbitol Solution, USP	10.00	1500.0
Ibuprofen, USP	2.0	300.0
Sodium Carboxymethylcellulose, USP	0.10	15.0
Polysorbate 80, NF	0.30	45.0
Red FDC 40	0.015	2.25
Disodium Edetate, USP	0.05	7.5
Artificial flavor oils	0.16	24.0
Purified Water, Deionized, USP	qs. to 100 ml	qs to 15000 ml.

The procedure for preparation of the above pediatric formulation is first to prepare an ibuprofen slurry. The sorbitol solution was weighed into a jacketed kettle equipped with a stirrer. The sodium carboxymethyl cellulose was sprinkled onto the solution and mixed for 10 minutes until all of the particles were completely wet. The glycerin was added with mixing for 5 minutes and the mixture was then heated to about 70°C the temperature held for at least 30 minutes to make sure the gum is completely hydrated and then the temperature was reduced to 45°C. The polysorbate 80 was added. Mixing was continued while cooling the mixture to 30°C. The ibuprofen was then sprinkled slowly into the mixture and mixing was continued for 15 minutes.

The xanthan gum solution was prepared first in the form of a 1% by weight solution in water. The required amount of water, 2475 grams, was placed into a mixing bowl equipped with a Lightnin mixer and 25 grams of the xanthan gum slowly added and hydrated by mixing at high shear for 25 minutes. Into a separate mixing vessel, equipped with a Lightnin mixer having a large propeller was placed a quantity of water equivalent to 30% to 40% of the total batch (4500-6000 ml). The microcrystalline cellulose was sprinkled onto the water and mixing at medium shear for 30 minutes was continued in order to completely suspend the microcrystalline cellulose. The required amount of the xanthan gum solution was added to the microcrystalline cellulose solution with mixing for 15 minutes or until a uniform solution was obtained.

The sucrose was then added slowly with mixing for 15 minutes, or until no sucrose particles are observed, and the colouring was added. The sodium benzoate and disodium edetate were sequentially added and mixed for 5 minutes. The required amount of the ibuprofen slurry was slowly added from the first step and mixed for 15 minutes. The phosphoric acid and the flavouring agents were sequentially added with mixing for 5 minutes after each addition. The remainder of the water then added with mixing until the formulation was homogeneous.

The initial viscosity of the final formulation at 25°C was 2400 mPa.s (2400 cps) with a #2 spindle at 4 r.p.m.

the initial pH of the formulation was 1.84 and the specific gravity was 1.241 gram/milliliter. On standing the viscosity increased to 4800 mPa.s (4800 cps) which on shaking for 5 seconds decreased to 2200 mPa.s (2200 cps). The ibuprofen solubility was 0.007% weight by volume.

The formulation had a sweet, fruity taste with no discernible after taste or throat bite characteristic of ibuprofen.

The buffer capacity of the formulation between pH 1.7 and pH 2.2 was 0.059 and the buffer capacity between pH 1.7 and 2.7 was 0.046.

With this formulation the quantity of 1 Normal sodium hydroxide solution necessary to increase the pH of 5 milliliters of the formulation to the normal pH of human saliva, i.e. pH 5.6 to pH 7.6, is 0.50ml to a pH of 5.6 and 0.70 ml to a pH of 6.4.

EXAMPLE 3

A formulation similar to that of Example 1 of Mody et al patent 4,788,220 was prepared as described in the patent containing 0.25% weight by volume of citric acid, 2% weight by volume of ibuprofen, 0.15% weight by volume of xanthan gum and having a pH of 4.10.

A 100 ml sample of this product was titrated with 1 Normal sodium hydroxide with pH measurements being made at each milliliter increment of sodium hydroxide up to 7.0 ml.

A 100 ml sample of Example 1 of this application was also titrated with 1 Normal sodium hydroxide with pH measurements being made at each milliliter increment of sodium hydroxide up to 7.0 ml.

The results are set forth in Table I below.

TABLE I

Milliliters	Example 1 4,788,220		Example 1 Application	
1 N NaOH	pH	Buffer* capacity	pH	Buffer* capacity
0.00	4.16	0.0268	3.01	0.0413
1.0	4.53	0.0216	3.25	0.0462
2.0	4.98	0.0158	3.46	0.0432
3.0	5.58	0.0165	3.68	0.0427
4.0	6.15	0.0276	3.90	0.0455
5.0	6.48	0.0562	4.10	0.0500
6.0	6.64	0.0518	4.28	0.0489
7.0	6.81		4.46	

*Buffer capacity calculated in accordance with method described in Physical Pharmacy, Alfred Martin et al., 3rd Edition, Lea & Febiger, Philadelphia, Pa., page 227.

Referring to Table I above, it can be seen from the data with respect to Example 1 of patent 4,788,220, that buffer capacity remained fairly constant within a range of 0.02 and 0.03 up to a pH of 5.58 (approximately the lower limit of the pH of human saliva pH 5.6) and still below 0.03 up to a pH of 6.48. Above a pH of about 6.5, the buffer capacity of above 0.05 is due to conversion of ibuprofen to the more soluble sodium salt form. Ibuprofen throat bite is least observed when ibuprofen is insoluble. With respect to Example 1 of this application, however, it can be seen that the buffer capacity remained fairly constant within a range of 0.04 to 0.05 up to a pH of 4.46.

Accordingly, the aqueous base ibuprofen compositions of this invention contain citric or phosphoric acid in an amount of 0.1% to 2.0% sufficient to adjust the pH to 1.5 up to less than 3.5 and to provide a buffer capacity within the range of 0.03 to 0.05 between the initial pH and a pH which is 1.0 pH unit higher than the initial pH.

The increased buffering capacity provided by the orally administrable ibuprofen formulations of this invention inhibit ibuprofen dissolution in the mouth during administration and hence the formulations exhibit negli-

gible throat bite and a pleasant taste.

The data from Example 3 are plotted on the graph shown in FIGURE 1 of the accompanying drawing wherein milliliters of 1 Normal sodium hydroxide is the absissa and pH is the ordinate. Although the experimental work was done with 100 milliliters of ibuprofen formulation, the graph represents the amount of 1 Normal sodium hydroxide required to titrate a 5 milliliter (1 teaspoon) dose. The horizontal lines at pH 5.6 and 7.6 reflect the pH range of normal human saliva.

As can be seen from an examination of Figure 1, the formulation of Example 1 of this application required more than 4 times the quantity of 1 Normal sodium hydroxide (0.646 ml) than did the formulation of Example 1 of patent 4,788,220 to reach the saliva pH range (0.154 ml) due to the higher buffering capacity of the formulations of this invention.

Claims

Claims for the following Contracting States: DE, GB, FR, IT, NL, SE, LI, CH, BE, AT, LU, DK

1. A taste neutral aqueous base ibuprofen composition suitable for oral administration containing ibuprofen, a primary suspension stabilizing combination of ingredients, a primary taste masking combination of ingredients and water, characterised in that the ibuprofen comprises 0.8% to 4% weight by volume of the total composition, the suspension stabilizing combination of ingredients comprises 0.1% to 2% weight suspension stabilizing combination by volume of the total composition, the taste masking combination comprises 20% to 70% weight taste masking combination by volume of the total composition, the composition also containing one or more pharmaceutically acceptable buffer acids in an amount sufficient to adjust the pH from 1.5 to less than 3.5 and to provide a buffer capacity within the range of 0.03 to 0.05 between the initial pH and a pH which is 1.0 pH unit higher than the initial pH, and water qs to 100% by volume of the composition.

2. An ibuprofen composition as claimed in Claim 1 in which the buffer acid is selected from citric acid and phosphoric acid or a mixture thereof.

3. An ibuprofen composition as claimed in Claim 1 containing citric acid or phosphoric acid in an amount of 0.1% to 2.0% weight by volume.

4. An ibuprofen composition as claimed in any one of Claims 2 to 3 in which the initial pH is 3.

5. An ibuprofen composition as claimed in any one of Claims 1 to 4 having an ibuprofen concentration of 50mg to 100mg per 5ml of composition.

6. An ibuprofen composition as claimed in anyone of Claims 1 to 4 having an ibuprofen concentration of 100mg per 5ml.

7. An ibuprofen composition as claimed in any one of Claims 1 to 6 wherein the primary suspension stabilizing combination of ingredients consists essentially of xanthan gum, microcrystalline cellulose, sodium carboxymethyl cellulose and polysorbate 80.

8. An ibuprofen composition as claimed in anyone of Claims 1 to 7 wherein the primary taste masking combination of ingredients comprises sucrose and sorbitol solution.

9. An ibuprofen composition as claimed in any one of Claims 1 to 7 wherein the primary taste masking combination of ingredients consists essentially of sucrose, sorbitol solution and glycerin.

10. An ibuprofen composition as claimed in any one of Claims 1 to 9 in which the ibuprofen has an average particle size of 40 μm.

11. An ibuprofen composition as claimed in any one of Claims 1 to 9 containing one or more flavouring agents.

12. A process for preparing a taste neutral aqueous base ibuprofen composition suitable for oral administration containing ibuprofen, a primary suspension stabilising combination of ingredients, a primary taste masking combination of ingredients and water, characterised in that 0.8% to 4% weight ibuprofen by volume of total

composition is suspended in 0.1% to 2% weight suspension stabilizing combination of ingredients by volume of total composition, 20% to 70% weight taste masking combination of ingredients by volume of the total composition, one or more pharmaceutically acceptable buffer acids in an amount sufficient to adjust the pH from 1.5 to less than 3.5 and to provide a buffer capacity within the range of 0.03 to 0.05 between the initial pH and a pH which is 1.0 pH unit higher than the initial pH and water qs to 100% by volume of the composition.

Claims for the following Contracting States: GR, ES

1. A process for preparing a taste neutral aqueous base ibuprofen composition suitable for oral administration comprising ibuprofen, a primary suspension stabilizing combination of ingredients, a primary taste masking combination of ingredients and water characterised in that 0.8% to 4% weight ibuprofen by volume of total composition is suspended in 0.1% to 2% weight suspension stabilizing combination of ingredients by volume of the total composition, 20% to 70% weight taste masking combination by volume of the total composition, one or more buffer acids in an amount sufficient to adjust the pH from 1.5 to less than 3.5 and to provide a buffer capacity within the range of 0.03 to 0.05 between the initial pH and a pH which is 1.0 pH unit higher than the initial pH, and water qs to 100% by volume of the composition.

2. A process as claimed in Claim 1 in which the buffer acid is selected from citric acid and phosporic acid or a mixture thereof.

3. A process as claimed in Claim 2 in which the amount of citric acid or phosphoric acid is 0.1% to 2.0% weight by volume.

4. A process as claimed in any one of Claims 1 to 3 in which the initial pH is 3.

5. A process as claimed in any one of Claims 1 to 4 having an ibuprofen concentration of 50mg to 100mg per 5ml of composition.

6. A process as claimed in anyone of Claims 1 to 4 having an ibuprofen concentration 100mg per 5ml.

7. A process as claimed in any one of Claims 1 to 6 wherein the primary suspension stabilizing combination of ingredients consists essentially of xanthan gum, microcrystalline cellulose, sodium carboxymethyl cellulose and polysorbate 80.

8. A process as claimed in anyone of Claims 1 to 7 wherein the primary taste masking combination of ingredients comprises sucrose and sorbitol solution.

9. A process as claimed in any one of Claims 1 to 7 wherein the primary taste masking combination of ingredients consists essentially of sucrose, sorbitol solution and glycerin.

10. A process as claimed in any one of Claims 1 to 9 in which the ibuprofen has an average particle size of 40 µm.

11. A process as claimed in any one of Claims 1 to 9 in which the composition contains one or more flavouring agents.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten: DE, GB, FR, IT, NL, SE, LI, CH, BE, AT, LU, DK

1. Geschmacksneutrale Ibuprofenzusammensetzung auf wässeriger Basis, die für orale Verabreichung geeignet ist, und die Ibuprofen, eine primäre suspensions-stabilisierende Kombination von Bestandteilen, eine primäre geschmacksmaskierende Kombination von Bestandteilen und Wasser enthält, dadurch gekennzeichnet, daß das Ibuprofen 0,8 % bis 4 % Masse bezogen auf das Volumen der Gesamtzusammensetzung umfaßt, die suspensionsstabilisierende Kombination von Bestandteilen 0,1 % bis 2 % Masse suspensions-stabilisierende Kombination bezogen auf das Volumen der Gesamtzusammensetzung umfaßt, und die geschmacksmaskierende Kombination 20 % bis 70 % Masse geschmacksmaskierende Kom-

bination bezogen auf das Volumen der Gesamtzusammensetzung umfaßt, wobei die Zusammensetzung auch eine oder mehrere pharmazeutisch annehmbare Puffersäuren in einer Menge, die ausreicht, um einen pH von 1,5 bis weniger als 3,5 einzustellen, und um eine Pufferkapazität im Bereich von 0,03 bis 0,05 zwischen dem anfänglichen pH und einem pH, der 1,0 pH-Einheit höher ist als der anfängliche pH, vorzusehen, und Wasser q.s. auf 100 % bezogen auf das Volumen der Zusammensetzung enthält.

2. Ibuprofenzusammensetzung nach Anspruch 1, bei welcher die Puffersäure aus Zitronensäure und Phosphorsäure oder einer Mischung hievon ausgewählt ist.

3. Ibuprofenzusammensetzung nach Anspruch 1, welche Zitronensäure oder Phosphorsäure in einer Menge von 0,1 % bis 2,0 % M/V enthält.

4. Ibuprofenzusammensetzung nach Anspruch 2 oder 3, bei welcher der anfängliche pH 3 beträgt.

5. Ibuprofenzusammensetzung nach einem der Ansprüche 1 bis 4, welche eine Ibuprofenkonzentration von 50 mg bis 100 mg pro 5 ml Zusammensetzung aufweist.

6. Ibuprofenzusammensetzung nach einem der Ansprüche 1 bis 4, welche eine Ibuprofenkonzentration von 100 mg pro 5 ml aufweist.

7. Ibuprofenzusammensetzung nach einem der Ansprüche 1 bis 6, bei welcher die primäre suspensionsstabilisierende Kombination von Bestandteilen im wesentlichen aus Xanthan-Gummi, mikrokristalliner Cellulose, Natriumcarboxymethylcellulose und Polysorbat 80 besteht.

8. Ibuprofenzusammensetzung nach einem der Ansprüche 1 bis 7, bei welcher die primäre geschmacksmaskierende Kombination von Bestandteilen Saccharose und Sorbit-Lösung umfaßt.

9. Ibuprofenzusammensetzung nach einem der Ansprüche 1 bis 7, bei welcher die primäre geschmacksmaskierende Kombination von Bestandteilen im wesentlichen aus Saccharose, Sorbit-Lösung und Glycerin besteht.

10. Ibuprofenzusammensetzung nach einem der Ansprüche 1 bis 9, bei welcher das Ibuprofen eine mittlere Teilchengröße von 40 µm aufweist.

11. Ibuprofenzusammensetzung nach einem der Ansprüche 1 bis 9, welche einen oder mehrere Geschmacksstoffe enthält.

12. Verfahren zur Herstellung einer geschmacksneutralen Ibuprofenzusammensetzung auf wässeriger Basis, die für orale Verabreichung geeignet ist, und die Ibuprofen, eine primäre suspensions-stabilisierende Kombination von Bestandteilen, eine primäre geschmacksmaskierende Kombination von Bestandteilen und Wasser enthält, dadurch gekennzeichnet, daß 0,8 % bis 4 % Masse Ibuprofen bezogen auf das Volumen der Gesamtzusammensetzung in 0,1 % bis 2 % Masse suspensionsstabilisierender Kombination von Bestandteilen bezogen auf das Volumen der Gesamtzusammensetzung, 20 % bis 70 % Masse geschmacksmaskierender Kombination von Bestandteilen bezogen auf das Volumen der Gesamtzusammensetzung, einer oder mehreren pharmazeutisch annehmbaren Puffersäuren in einer Menge, die ausreicht, um einen pH von 1,5 bis weniger als 3,5 einzustellen, und um eine Pufferkapazität im Bereich von 0,03 bis 0,05 zwischen dem anfänglichen pH und einem pH, der 1,0 pH-Einheit höher ist als der anfängliche pH, vorzusehen, und Wasser q.s. auf 100 Vol.% der Zusammensetzung suspendiert werden.

Patentansprüche für folgende Vertragsstaaten: GR, ES

1. Verfahren zur Herstellung einer geschmacksneutralen Ibuprofenzusammensetzung auf wässeriger Basis, die für orale Verabreichung geeignet ist, und die Ibuprofen, eine primäre suspensions-stabilisierende Kombination von Bestandteilen, eine primäre geschmacksstabilisierende Kombination von Bestandteilen und Wasser enthält, dadurch gekennzeichnet, daß 0,8 % bis 4 % Masse in 0,1 % bis 2 % Masse suspensionsstabilisierender Kombination von Bestandteilen bezogen auf das Volumen der Gesamtzusammensetzung, 20 % bis 70 % Masse geschmacksmaskierender Kombination von Bestandteilen bezogen auf das Volumen der Gesamtzusammensetzung, einer oder mehreren Puffersäuren in einer Menge, die ausreicht, um einen pH von 1,5 bis weniger als 3,5 einzustellen, und um eine Pufferkapazität im Bereich von 0,03

bis 0,05 zwischen dem anfänglichen pH und einem pH, der 1,0 pH-Einheit höher ist als der anfängliche pH, vorzusehen, und Wasser q.s. auf 100 % bezogen auf das Volumen der Zusammensetzung suspendiert werden.

2. Verfahren nach Anspruch 1, bei welchem die Puffersäure aus Zitronensäure und Phosphorsäure oder einer Mischung hievon ausgewählt wird.

3. Verfahren nach Anspruch 2, bei welchem die Menge an Zitronensäure oder Phosphorsäure 0,1 % bis 2,0 % M/V beträgt.

4. Verfahren nach einem der Ansprüche 1 bis 3, bei welchem der anfängliche pH 3 beträgt.

5. Verfahren nach einem der Ansprüche 1 bis 4, bei welchem die Zusammensetzung eine Ibuprofenkonzentration von 50 mg bis 100 mg pro 5 ml Zusammensetzung aufweist.

6. Verfahren nach einem der Ansprüche 1 bis 4, bei welchem die Zusammensetzung eine Ibuprofenkonzentration von 100 mg pro 5 ml aufweist.

7. Verfahren nach einem der Ansprüche 1 bis 6, bei welchem die primäre suspensions-stabilisierende Kombination von Bestandteilen im wesentlichen aus Xanthan-Gummi, mikrokristalliner Cellulose, Natriumcarboxymethylcellulose und Polysorbat 80 besteht.

8. Verfahren nach einem der Ansprüche 1 bis 7, bei welcher die primäre geschmacksmaskierende Kombination von Bestandteilen Saccharose und Sorbit-Lösung umfaßt.

9. Verfahren nach einem der Ansprüche 1 bis 7, bei welcher die primäre geschmacksmaskierende Kombination von Bestandteilen im wesentlichen aus Saccharose, Sorbit-Lösung und Glycerin besteht.

10. Verfahren nach einem der Ansprüche 1 bis 9, bei welcher das Ibuprofen eine mittlere Teilchengröße von 40 µm aufweist.

11. Verfahren nach einem der Ansprüche 1 bis 9, bei welchem die Zusammensetzung einen oder mehrere Geschmacksstoffe enthält.

Revendications

Revendications pour les Etats contractants suivants : DE, GB, FR, IT, NL, SE, LI, CH, BE, AT, LU, DK

1. Composition d'ibuprofène à base aqueuse à goût neutre, appropriée pour l'administration orale contenant de l'ibuprofène, un mélange d'ingrédients de stabilisation de suspension primaires, un mélange d'ingrédients de masquage du goût primaires, et de l'eau, caractérisée en ce que l'ibuprofène compose 0,8% à 4% en poids par volume de la composition totale, le mélange des ingrédients de stabilisation de suspension compose 0,1% à 2% en poids du mélange de stabilisants de suspension par volume de la composition totale, le mélange de masquage de goût compose 20% à 70% en poids du mélange de masquage de goût par volume de la composition totale, la composition contient aussi un ou plusieurs acides tampons pharmaceutiquement acceptables en une quantité suffisante pour ajuster le pH de 1,5 à moins de 3,5 et pour fournir une capacité tampon dans l'intervalle de 0,03 à 0,05 entre le pH initial et un pH qui est de 1,0 unité de pH supérieure au pH initial, et de l'eau pour faire 100% en volume de la composition.

2. Composition d'ibuprofène suivant la revendication 1, dans laquelle l'acide tampon est choisi parmi l'acide citrique et l'acide phosphorique ou un mélange de ceux-ci.

3. Composition d'ibuprofène suivant la revendication 1, contenant de l'acide citrique ou de l'acide phosphorique en une quantité de 0,1% à 2,0% poids par volume.

4. Composition d'ibuprofène suivant l'une quelconque des revendications 2 et 3, dans laquelle le pH initial est 3.

5. Composition d'ibuprofène suivant l'une quelconque des revendications 1 à 4, ayant une concentration en ibuprofène de 50 mg à 100 mg par 5 ml de composition.

6. Composition d'ibuprofène suivant l'une quelconque des revendications 1 à 4, ayant une concentration en ibuprofène de 100 mg par 5 ml.

7. Composition d'ibuprofène suivant l'une quelconque des revendications 1 à 6, où le mélange d'ingrédients stabilisants de suspension primaires consiste essentiellement en gomme de xanthane, en cellulose microcristalline, en carboxyméthylcellulose sodique et en polysorbate 80.

8. Composition d'ibuprofène suivant l'une quelconque des revendications 1 à 7, où la combinaison d'ingrédients de masquage de goût primaires comprend le sucrose et une solution de sorbitol.

9. Composition d'ibuprofène suivant l'une quelconque des revendications 1 à 7, où le mélange d'ingrédients de masquage de goût primaires consiste essentiellement en sucrose, solution de sorbitol et glycérine.

10. Composition d'ibuprofène suivant l'une quelconque des revendications 1 à 9, dans laquelle l'ibuprofène a une granulométrie moyenne de 40 µm.

11. Composition d'ibuprofène suivant l'une quelconque des revendications 1 à 9, contenant un ou plusieurs agents aromatisants.

12. Procédé pour la préparation d'une composition d'ibuprofène à base aqueuse et à goût neutre appropriée pour l'administration par voie orale contenant de l'ibuprofène, un mélange d'ingrédients de stabilisation de suspension primaires, un mélange d'ingrédients de masquage de goût primaires et de l'eau, caractérisé en ce que 0,8% à 4% en poids d'ibuprofène par volume de la composition totale sont mis en suspension dans 0,1% à 2% en poids du mélange d'ingrédients stabilisant la suspension par volume de composition totale; 20% à 70% en poids du mélange des ingrédients de masquage de goût par volume de la composition totale, un ou plusieurs acides tampons pharmaceutiquement acceptables en une quantité suffisante pour ajuster le pH de 1,5 à moins que 3,5 et pour fournir une capacité tampon dans l'intervalle de 0,03 à 0,05 entre le pH initial et un pH qui est de 1,0 unité de pH supérieure au pH initial et de l'eau pour faire 100% en volume de la composition.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour la préparation d'une composition d'ibuprofène à base aqueuse et à goût neutre appropriée pour l'administration par voie orale contenant de l'ibuprofène, un mélange d'ingrédients de stabilisation de suspension primaires, un mélange d'ingrédients de masquage de goût primaires et de l'eau, caractérisé en ce que 0,8% à 4% en poids d'ibuprofène par volume de la composition totale sont mis en suspension dans 0,1% à 2% en poids du mélange d'ingrédients stabilisant la suspension par volume de composition totale; 20% à 70% en poids du mélange des ingrédients de masquage de goût par volume de la composition totale, un ou plusieurs acides tampons pharmaceutiquement acceptables en une quantité suffisante pour ajuster le pH de 1,5 à moins que 3,5 et pour fournir une capacité tampon dans l'intervalle de 0,03 à 0,05 entre le pH initial et un pH qui est de 1,0 unité de pH supérieure au pH initial et de l'eau pour faire 100% en volume de la composition.

2. Procédé suivant la revendication 1, dans lequel l'acide tampon est choisi parmi l'acide citrique et l'acide phosphorique ou un mélange de ceux-ci.

3. Procédé suivant la revendication 2, dans lequel la quantité d'acide citrique ou d'acide phosphorique est 0,1% à 2,0% en poids par volume.

4. Procédé suivant l'une quelconque des revendications 1 à 3, dans lequel le pH initial est 3.

5. Procédé suivant l'une quelconque des revendications 1 à 4, ayant une concentration en ibuprofène de 50 mg à 100 mg par 5 ml de composition.

6. Procédé suivant l'une quelconque des revendications 1 à 4, ayant une concentration en ibuprofène de 100 mg par 5 ml.

7. Procédé suivant l'une quelconque des revendications 1 à 6, où le mélange d'ingrédients de stabilisation de suspension primaires consiste essentiellement en la gomme de xanthane, la cellulose microcristalline, la carboxyméthylcellulose sodique et le polysorbate 80.

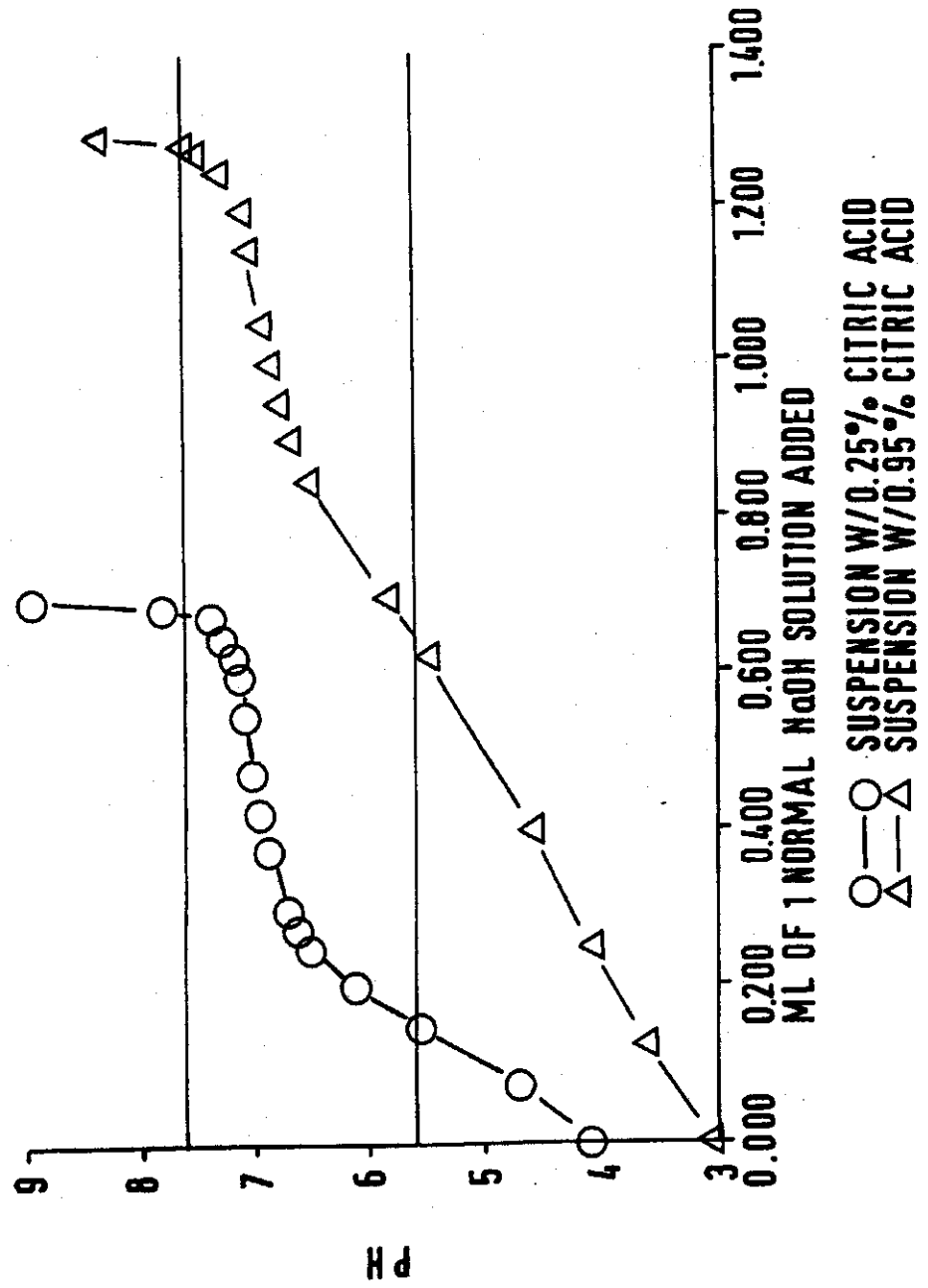
8. Procédé suivant l'une quelconque des revendications 1 à 7, où le mélange d'ingrédients de masquage de goût primaires comprend le sucrose et une solution sorbitol.

9. Procédé suivant l'une quelconque des revendications 1 à 7, où le mélange des ingrédients de masquage de goût primaires consiste essentiellement en le sucrose, une solution de sorbitol et la glycérine.

10. Procédé suivant l'une quelconque des revendications 1 à 9, dans lequel l'ibuprofène a une granulométrie moyenne de 40 µm.

11. Procédé suivant l'une quelconque des revendications 1 à 9, dans lequel la composition comprend un ou plusieurs agents aromatisants.

FIG.1 TITRATION OF IBUPROFEN SUSPENSIONS (5ML) WITH 1 NORMAL SODIUM HYDROXIDE SOLUTION



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Applicant/Proprietor
AMERICAN HOME PRODUCTS CORPORATION, 685, Third Avenue, New York, New York 10017, United States of America [ADP No. 50692508001]

Inventors
SOLOMON MOTOLA, 40 Majestic Way, Marlton, New Jersey, United States of America [ADP No. 57856965001]

ANNABELLE MOGAVERO, 190 Taunton Blvd., Medford, New Jersey, United States of America [ADP No. 57856973001]

GARY ROBERT AGISIM, 17 Crofton Commons, Cherry Hill, New Jersey, United States of America [ADP No. 57856981001]

PAMELA N. PANOPOULOS, 10 McGeary Place, Mayslanding, New Jersey, United States of America [ADP No. 57856999001]

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Address for Service
WYETH LABORATORIES, Huntercombe Lane South, Taplow, MAIDENHEAD, Berkshire, SL6 0PH, United Kingdom [ADP No. 00041004001]

EPO Representative
DAVID FRANCIS DR. WILEMAN, c/o Wyeth Laboratories Huntercombe Lane South, Taplow Maidenhead Berkshire SL6 OPH, United Kingdom [ADP No. 50656156001]

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AMERICAN HOME PRODUCTS CORPORATION, 685, Third Avenue, New York,
New York 10017, United States of America [ADP No. 50692508001]
to
AMERICAN HOME PRODUCTS CORPORATION, Incorporated in USA - Delaware,
Five Giralda Farms, Madison, New Jersey07940-0874, United States of
America [ADP No. 00307579002]
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American Home Products Corporation, Incorporated in USA - Delaware, Five Giralda Farms, Madison, New Jersey07940-0874, United States of America

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