(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 May 2017 (18.05.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/080566 Al

(51) International Patent Classification:
A61K 9/20 (2006.01) *A61K 31/192* (2006.01)
A61K 9/50 (2006.01) *A61K 31/46* (2006.01)

(21) International Application Number:
PCT/EP2015/002239

(22) International Filing Date:
9 November 2015 (09.11.2015)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2017/080566 A1

(54) **Title:** STABLE ANALGESIC PHARMACEUTICAL COMPOSITION AND PROCESS FOR THE PREPARATION THEREOF

(57) **Abstract:** The present invention relates to a stable pharmaceutical composition comprising a therapeutically effective quantity of Ibuprofen or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and Hyoscine Butylbromide or a pharmaceutically acceptable salt, prodrug, or derivative thereof in a fixed dosage combination, and a process for the preparation thereof.

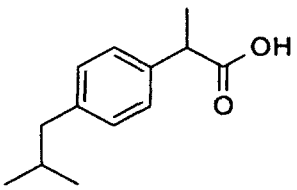
STABLE ANALGESIC PHARMACEUTICAL COMPOSITION AND PROCESS FOR THE PREPARATION THEREOF

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a stable pharmaceutical composition comprising a therapeutically effective quantity of Ibuprofen or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and Hyoscine Butylbromide or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and a process for the preparation thereof. The stable pharmaceutical composition of the present invention is useful as an analgesic agent and in the treatment of spasmodic pain in diseases of the stomach and intestines, cramping pain and dysfunction in the biliary tract, urinary tract and female genital organs, such as dysmenorrhea.

BACKGROUND OF THE INVENTION

Ibuprofen' s chemical name is (±)-2-(p-isobutylphenyl) propionic acid, and its chemical structure is presented by the following Formula I.



Formula I

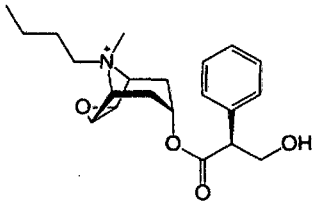
Ibuprofen is a commonly prescribed Non-Steroidal Anti-inflammatory Drug (NSAID). Ibuprofen is indicated for its analgesic and anti-inflammatory effects in the treatment of rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's disease), ankylosing spondylitis, osteoarthritis and other non-rheumatoid (seronegative) arthropathies. In the treatment of non-articular rheumatic conditions, is indicated in periarticular conditions such as frozen shoulder (capsulitis), bursitis, tendonitis, tenosynovitis and low back pain. Ibuprofen is also indicated for its analgesic effect in the relief of mild to moderate pain such as dysmenorrhoea, dental and post¬ operative pain and for symptomatic relief of headache, including migraine headache, while it can also be used in soft tissue injuries such as sprains and strains.

Ibuprofen works by blocking enzyme cyclo-oxygenase, which produces prostaglandins that are involved in inflammation and pain. The recommended dose of Ibuprofen in adults is 1200-1800 mg daily in divided doses. Some patients can be maintained on 600-1200 mg daily. In severe or acute conditions, it can be advantageous to increase the dosage until the acute phase is brought under control, provided that the total daily dose does not exceed 2400 mg in divided doses.

Ibuprofen is rapidly absorbed from the gastrointestinal tract and metabolized in the liver in two inactive metabolites and said metabolites together with unchanged ibuprofen are excreted by the kidney either as such or as conjugates. Excretion by the kidney is both rapid and complete.

Although, Ibuprofen has highly effective pain relieving properties, it may cause abnormal stomach or intestinal bleeding that may sometimes even prove fatal, especially when administered in high dose.

Hyoscine Butylbromide also known as Scopolamine butylbromide is an antispasmodic drug indicated for the relief of spasm of the genito-urinary tract or gastro- intestinal tract and for the symptomatic relief of irritable bowel syndrome (IBS). Its chemical name is 7(S)-(la,2p,4p,5a,7p)]-9-butyl-7-(3-hydroxy-l-oxo-2-phenylpropoxy)-9-methyl-3-oxa-9-azo nitricyclo[3.3.1.0(2,4)]nonanebromide and its chemical structure is presented by the following Formula II.



Formula II

In adults, the recommended dosage is 20 mg of Hyoscine Butylbromide four times daily, while in case of IBS the recommended starting dose is 10 mg three times daily, which can be increased up to 20 mg four times daily if necessary. Hyoscine Butylbromide works by relaxing some of the muscles in the gastrointestinal and urinary systems and exerts a spasmolytic action on the smooth muscle of the gastrointestinal, biliary and genito-urinary tracts. As a quaternary ammonium derivative, hyoscine butylbromide does not enter the central nervous system. Therefore, anticholinergic side effects at the central nervous system do not occur. Peripheral anticholinergic action results from a ganglion-blocking action within the visceral wall as well as from an anti-muscarinic activity.

It is well known that combination of an antispasmodic with a potent analgesic drug offers higher efficacy and safety than analgesic alone for e.g. Spasmofen® i.e. combination of Ketoprofen and Hyoscine Butylbromide is useful to provide relief in severe colicky pain in the renal system, hepatobiliary system, or gastrointestinal tract. Moreover, medicaments comprising combination of Hyoscine Butylbromide and Ibuprofen in suppository dosage form are also known for treatment of severe pain associated with smooth muscle spasms.

Various methods are also known for the industrial preparation of oral dosage forms comprising Ibuprofen or a pharmaceutically acceptable salt, prodrug or derivative thereof, in combination with Hyoscine Butylbromide. However, the prior art has encountered substantial difficulties in the production of stable pharmaceutical compositions, in particular comprising Hyoscine Butylbromide and Ibuprofen for oral administration.

EP-A-2702989 discloses a stable pharmaceutical composition comprising ibuprofen and scopolamine butylbromide with one or more species selected from the group consisting of a xanthine derivative, tranexamic acid or a salt thereof, acetaminophen and an isovaleryl urea derivative.

EP-A-2659889 discloses a pharmaceutical composition comprising ibuprofen and butylscopolamine bromide and a moisture-absorbing polymer, wherein ibuprofen and butylscopolamine bromide are substantially free of contact with each other in order to avoid the interaction between the active ingredients.

Although each of the above patents represents an attempt to overcome the stability problems associated with pharmaceutical compositions comprising ibuprofen and hyoscine butylbromide, there still exists a need for improving the stability of such pharmaceutical compositions in a less complicated production approach.

SUMMARY OF THE INVENTION

It is, therefore, an object of the present invention to provide a pharmaceutical composition for oral administration comprising Ibuprofen or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and Hyoscine Butylbromide or a pharmaceutically acceptable salt, prodrug, or derivative thereof, with enhanced stability which overcomes the deficiencies of the prior art.

Still, it is another object of the present invention to provide a pharmaceutical composition for oral administration comprising Ibuprofen or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and Hyoscine Butylbromide or a pharmaceutically acceptable salt, prodrug, or derivative thereof, with better dose and patience compliance.

Moreover, it is another object of the present invention to provide a suitable process for the preparation of a stable pharmaceutical composition for oral administration comprising a therapeutically effective quantity of Ibuprofen or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and Hyoscine Butylbromide or a pharmaceutically acceptable salt, prodrug, or derivative thereof, which is cost effective and reproducible.

In accordance with the above objects of the present invention, a pharmaceutical composition for oral administration is provided comprising a therapeutically effective quantity of Ibuprofen or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and Hyoscine Butylbromide or a pharmaceutically acceptable salt, prodrug, or derivative thereof, wherein the weight ratio of Hyoscine butylbromide to Ibuprofen is about 1:20 in order to improve the stability of the composition and provide better dose and patience compliance.

Still, according to another embodiment of the present invention, the pharmaceutical composition for oral administration further comprises a pharmaceutically acceptable acidifying agent, such as anhydrous citric acid, citric acid hydrate, sodium citrate hydrate, ascorbic acid, tartaric acid, malic acid, succinic acid, gallic acid, acetic acid, lactic acid etc. and/or mixture thereof, from about 0.01 to 50% by weight of the finished dosage form.

According to another embodiment, the present invention provides a process for the preparation of a stable pharmaceutical composition for oral administration comprising a therapeutically

effective quantity of Ibuprofen or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and Hyoscine Butylbromide or a pharmaceutically acceptable salt, prodrug, or derivative thereof, wherein the weight ratio of Hyoscine butylbromide to Ibuprofen is about 1:20 in order to improve the stability of the composition and provide better dose and patience compliance, which process comprises:

a) Forming a homogenous mixture by mixing the total quantity of both said active ingredients with an effective amount of an acidifying agent as stabilizer and the total quantity of at least one pharmaceutically acceptable excipient such as binder, filler or diluent, disintegrant, glidant or mixtures thereof; **b)** Kneading the above mixture of step a) with a suitable aqueous solvent such as purified water and mixing until uniformity is achieved; **c)** Milling the wet mass through suitable mill; **d)** Drying the obtained granules from step c) and sieving through a suitable sieve to achieve the desired granule size; **e)** Adding to the obtained granules from step d) the total quantities of at least one optional excipient such as a lubricant and/or a glidant and mixing until uniform; **f)** Formulating the resulting mixture from step e) in a solid dosage form either by compressing it into a desired tablet form or by filling capsules or sachets; and g) Optionally apply a film coating on the tablet.

Alternative process for the preparation of the pharmaceutical composition according to the present invention is also defined in independent claim 7.

Further preferred embodiments of the present invention are defined in dependent claims 2 to 5, 8 and 9.

Other objects and advantages of the present invention will become apparent to those skilled in the art in view of the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of the present invention, the term "pharmaceutically acceptable salt" refers to a salt that is not toxic at the specific therapeutic dosage and a salt that does not independently possess significant pharmacological activity.

Although the pharmaceutical composition may be in various forms, the preferred solid dosage forms are tablets, capsules and caplets.

The improved solid pharmaceutical composition of the present invention is characterized by physicochemical properties suitable for the tablet formulation by wet granulation, dry granulation or dry mixing (compaction), having adequate release rate of the active ingredients and storage stability.

As already mentioned the combination of Ibuprofen and Hyoscine Butylbromide in a fixed composition encounters stability issues and said tendency gets stronger when they are formulated and mixed with excipients or other active substances.

It has been surprisingly found that the object of the present invention is achieved by employing a therapeutically effective quantity of Ibuprofen or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and Hyoscine Butylbromide or a pharmaceutically acceptable salt, prodrug, or

derivative thereof, wherein the weight ratio between Hyoscine butylbromide and Ibuprofen is about 1:20 in order to improve the stability of the composition.

Further, it has been found that the stability of the pharmaceutical composition containing Hyoscine Butylbromide and Ibuprofen in weight ratio of 1:20 can be significantly improved when an effective quantity of an acidifying agent is employed as a stabilizer.

An acidifying agent has a property of increasing the concentration of hydrogen ion more than hydroxide ion when present in aqueous solution, and thus, represents an excipient that lowers pH of a substance or a solution by increasing the acidity thereof. Specifically, an acidifying agent according to the present invention may be an excipient which has acidifying effect or increases its acidity, resulting in a pH value of about 7 or lower in an aqueous solution or dispersion. Examples of acidifying agent may include, but not limited to, anhydrous citric acid, citric acid hydrate, sodium citrate hydrate, ascorbic acid, tartaric acid, malic acid, succinic acid, gallic acid, acetic acid and lactic acid and mixtures thereof.

The acidifying agent is comprised in the pharmaceutical composition of the present invention in an amount from about 0.01 to 50% by weight of the finished dosage form. Said acidifying agent is able to effectively inhibit the chemical and physico-chemical instability of the finished dosage form.

Moreover, an acidifying agent, when incorporated in the pharmaceutical composition of the present invention in an amount form about 0.01 to 50% by weight of the finished dosage form, results in a highly stable composition with improved blending, flowing and compression characteristics.

The composition of the present invention in addition to being highly stable, it demonstrates better dose and patience compliance, as well.

Therefore, in a first embodiment, the present invention provides a stable pharmaceutical composition for oral administration comprising a therapeutically effective quantity of 400mg Ibuprofen or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and 20mg Hyoscine Butylbromide or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and an effective quantity of an acidifying agent in a quantity from about 0.01 to 50% by weight.

According to another preferred embodiment, the present invention provides a process for the preparation of a stable pharmaceutical composition for oral administration comprising Hyoscine Butylbromide and Ibuprofen in weight ratio of 1:20, wherein Hyoscine Butylbromide may be incorporated in the composition in intra-granular or extra-granular phase.

The pharmaceutical composition of the present invention is an immediate release solid dosage form for oral administration that may be administered four times daily.

The pharmaceutical composition of the present invention may be manufactured by wet granulation or dry granulation or dry mixing (compaction) process.

All percentages stated herein are weight percentages based on total composition weight, unless otherwise stated.

Another embodiment of the present invention is the use of wet granulation process for the preparation of solid dosage forms for oral administration such as tablets, capsules and sachets containing Ibuprofen and Hyoscine Butylbromide as active ingredients, which comprises the following steps:

a) granulating both active pharmaceutical ingredients (both together or individually) with suitable granulation liquid and at least one pharmaceutically acceptable excipient such as binder, filler or diluent, disintegrant, glidant and/or mixtures thereof, by performing wet or fluid bed granulation; **b)** drying the obtained granules and sizing through appropriate sieve; **c)** mixing the granules of step b) for appropriate time with extra-granular excipients; **d)** lubricating the granules of step c) with suitable lubricants; **e)** compressing the blend resulting from step d) into tablets, and optionally, coating the tablets.

Still, another embodiment of the present invention is the use of dry granulation process for the preparation of solid dosage forms for oral administration containing Ibuprofen and Hyoscine Butylbromide as active ingredients, which comprises the following steps:

a) granulating both active pharmaceutical ingredients (both together or individually) with at least one pharmaceutically acceptable excipient such as binder, filler or diluent, disintegrant, glidant and/or mixtures thereof by performing roller compaction or by preparing suitable slugs; **b)** sizing through appropriate sieve; **c)** mixing the granules of step b) for appropriate time with at least one extra-granular excipient such as binder, filler or diluent, disintegrant, glidant and/or mixtures thereof; **d)** lubricating the granules of step c) with suitable lubricants; **e)** compressing the blend resulting from step d) into tablets, and optionally, coating the tablets.

Moreover, another embodiment of the present invention is the use of direct compression process for the preparation of solid dosage forms for oral administration containing Ibuprofen and Hyoscine Butylbromide as active ingredients, which comprises the following steps:

a) forming a homogenous blend by mixing the total quantity of both active ingredients with at least one pharmaceutical acceptable excipient such as binder, filler or diluent, disintegrant, glidant and/or mixtures thereof for appropriate time; **b)** lubricating the above blend with suitable lubricants; and **c)** compressing the blend resulting from step b) into tablets, and optionally, coating the tablets.

The pharmaceutical compositions of the present invention may also contain one or more additional formulation ingredients selected from a wide variety of excipients.
According to the desired properties of the composition, any number of ingredients may be selected, alone or in combination, based upon their known uses in preparation of solid oral dosage form compositions.

Such ingredients include, but are not limited to, fillers or diluents, binders, compression aids, disintegrants, surfactants, wetting agents, glidants, lubricants, flavours, water scavengers, colorants, sweetener, coating agents and preservatives.

Pharmaceutically acceptable fillers or diluents may be selected from starch, microcrystalline cellulose, dicalcium phosphate, lactose monohydrate, calcium carbonate, magnesium carbonate, sorbitol, mannitol, sucrose, dextrine, kaolin, magnesium oxide, calcium sulfate, xylitol, isomalt, glucose, fructose, maltose, acids like citric acid, tartaric acid, fumaric acid, co-polymers such as those from vinyl pyrrolidone and vinyl acetate or those of polyethylene glycol, and mixtures thereof. Preferred diluents are lactose monohydrate and microcrystalline cellulose.
Pharmaceutically acceptable binders may be selected povidone, hydroxypropyl methylcellulose, dihydroxy propylcellulose, sodium carboxyl methylcellulose, and mixtures thereof.

Pharmaceutically acceptable disintegrants may be selected from sodium starch glycolate, crospovidone, croscarmellose sodium, and/or mixtures thereof. Preferred disintegrant is croscarmellose.

Pharmaceutically acceptable lubricants may be selected from magnesium stearate, calcium stearate, stearic acid, stearic acid, glyceryl behenate, hexanedioic acid, hygrogenated vegetable oil sodium stearyl fumarate and glycerine fumarate. Preferred lubricant is magnesium stearate.

Pharmaceutical compositions according to the present invention may also comprise glidants such as colloidal silicon dioxide.

The following examples illustrate preferred embodiments in accordance with the present invention without limiting the scope or spirit of the invention.

EXAMPLES

Example 1: Preparation of Ibuprofen/HyoscineButylbromide 400mg/20mg Tablets

A preferred composition 1 according to the present invention is illustrated in Table 1 below.

TABLE 1: Quantitative and qualitative composition 1 according to the present invention

s. no	Ingredients	Percentage by weight (% w/w) in tablet
Intragranular		
1	API Ibuprofen	40.0
2	Microcrystalline Cellulose 101	20.0
3	Lactose Monohydrate	29.3
4	Croscarmellose Sodium	5.0
5	Colloidal Silicon Dioxide	1.0
6	API HyoscineButylbromide	2.0
7	SLS	0.5
8	Tartaric Acid	1.2
9	Purified Water	40.0
Extragranular		
10	Magnesium Stearate	1.0
	TOTAL	100

Tablets of composition of Example 1 of the present invention were prepared according to the following manufacturing process:

a) Pre-Mixing: Weight individually 400mg Ibuprofen, 20mg Hyoscine Butylbromide and all remaining ingredients 2 to 5, 7 and 8 and pass through appropriate sieve and pre-mix;

b) Granulation/Kneading: the blend resulting from step a) is kneaded with purified water until a homogenous mass is produced. The wet mass is passed through appropriate mill;

c) Drying: the above granules are dried to appropriate loss of drying (LOD);

d) Sizing/Mixing: the dried granules are passed through appropriate sieve to achieve the desired granule size, and further mixed for appropriate time;

e) Lubrication: weigh individually ingredient 10 and mix with the obtained granules from step d) for appropriate time.

Finally, the blend resulting from step e) is formulated in a solid dosage form by compression into tablets. Subsequently, the tablets may be coated with appropriate coating material.

The produced tablets were tested for content uniformity, disintegration, water content and dissolution proving that they are meeting the specifications.

Tablets of Composition 1 were exposed to normal (25°C±2°C/60%±5% RH), intermediate (30°C±2°C/65%±5% RH) and accelerated (40°C±2°C/75%±5% RH) stability studies according to the current ICH guidelines.

The results have shown a good stability of the product and compatibility between the active ingredients and the excipients proposed by the present invention. The excellent results regarding the physicochemical characteristics, the excellent stability of the product as well as the simple and economic manufacturing process indicate the advantages of the present invention relative to the prior art used methods.

Example 2: Preparation of Ibuprofen/HyoscineButylbromide 400mg/20mg Tablets

A preferred composition 2 according to the present invention is illustrated in Table 2 below.

Tablets of composition of Example 2 according to the present invention were prepared according to the following manufacturing process:

a) Pre-Mixing: Weight individually 400mg Ibuprofen, 20mg Hyoscine Butylbromide and all the ingredients 2 to 6 and 9 to 14 and pass through appropriate sieve; Subsequently, forming a first homogenous blend by mixing the total quantity of Ibuprofen with the total quantity of ingredients 2 to 6; **b)** Granulation/Kneading: Kneading the first blend obtained form step a) with purified water and wet granulating by passing the wet mass through appropriate mill; c) Drying: Drying the obtained granules to appropriate Loss of Drying (LOD) and sizing by passing through appropriate sieve; **d)** Mixing: Mixing for appropriate time the granules from step c) with the total quantity of Hyoscine butylbromide and the extra-granular ingredients 9 to 13; **e)** Lubrication: mix the blend from step d) for appropriate time with extra-granular ingredient 14; **f)** Compression: Compress the blend resulting from step e) into tablets; and g) Optionally Coating: Coat the resulting tablets from step f), with appropriate coating material.

TABLE 2: Quantitative and qualitative composition 2 according to the present invention

s. no	Ingredients	Percentage by weight (% w/w) in tablet
Intragranular		
1	API Ibuprofen	31.2
2	Microcrystalline Cellulose 101	15.7
3	Lactose Monohydrate	23.6
4	Croscarmellose	3.9
5	Colloidal Silicon Dioxide	0.8
6	SLS	0.4
7	Purified Water	
Extragranular		
8	API HyoscineButylbromide	1.6
9	Calcium Hydrogen Phosphate	3.9
10	Starch maize	7.8
11	Starch 1500	7.8
12	Colloidal silicon dioxide	0.4
13	Tartaric Acid	0.8
14	Stearic Acid	2.3
	TOTAL	100

Tablets of composition 2 of the present invention may optionally be prepared by dry granulation or direct compression.

The tablets may be film coated with functional or non-functional coating.

The selection of appropriate materials (excipients, reagents etc.) should be done carefully in order to avoid any incompatibility problems or non-compliance with EMA and FDA guidelines for inactive ingredients.

Analytical procedures and tests were performed for the film-coated tablets, including tests for physical appearance, identification, average mass and mass uniformity, uniformity of dosage units, loss on drying, hardness, assay, related substances, thickness, disintegration times, dissolution rates and microbiological limit tests, in order to prove that tablets of the invention meet the current technical specifications.

While the present invention has been described with respect to the particular embodiments, it will be apparent to those skilled in the art that various changes and modifications may be made in the invention without departing from the spirit and scope thereof, as defined in the appended claims.

CLAIMS

1. A stable pharmaceutical composition for oral administration comprising a therapeutically effective quantity of Ibuprofen or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and a therapeutically effective quantity of Hyoscine Butylbromide or a pharmaceutically acceptable salt, prodrug, or derivative thereof, wherein the weight ratio of Hyoscine Butylbromide to Ibuprofen is 1:20.

2. The pharmaceutical composition according to claim 1, wherein said composition further comprises an effective amount of an acidifying agent as a stabilizer in an amount from about 0.01 to about 50% by weight of the total weight of the finished dosage form.

3. The pharmaceutical composition according to claim 2, wherein said acidifying agent is selected from anhydrous citric acid, citric acid hydrate, sodium citrate hydrate, ascorbic acid, tartaric acid, malic acid, succinic acid, gallic acid, acetic acid and lactic acid and/or mixtures thereof.

4. The pharmaceutical composition according to claim 1 or 2, wherein said composition comprises a therapeutically effective quantity of 400mg Ibuprofen or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and 20mg Hyoscine Butylbromide or a pharmaceutically acceptable salt, prodrug, or derivative thereof.

5. The pharmaceutical composition according to claim 1, wherein said pharmaceutical composition further comprises at least one pharmaceutically acceptable excipient selected from absorbents, acids, adjuvants, anticaking agents, glidants, antitacking agents, antifoamers, anticoagulants, antimicrobials, antiseptics, diluents, binders, chelating agents, sequestrants, coating agents, colorants, dyes, pigments, complexing agents, softeners, crystal growth regulators, denaturants, desiccants, dehydrating agents, dispersants, solubilizers, emollients, emulsifiers, fillers, flavor masking agents, gelling agents, humectants, lubricants, moisturizers, bufferants, pH control agents, plasticizers, retarding agents, stabilizers, suspending agents, sweeteners, disintegrants, thickening agents, surfactants, opacifiers, coloring agents, preservatives, antigellants, rheology control agents, toniciflers and their combinations thereof.

6. A process for the preparation of a stable pharmaceutical composition for oral administration comprising a therapeutically effective quantity of Ibuprofen or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and a therapeutically effective quantity of Hyoscine Butylbromide or a pharmaceutically acceptable salt, prodrug, or derivative thereof, wherein the weight ratio of Hyoscine Butylbromide to Ibuprofen is 1:20, which process comprises:

a) Forming a homogenous mixture by mixing the total quantity of both said active ingredients with an effective amount of an acidifying agent as stabilizer and the total quantity of at least one pharmaceutically acceptable excipient such as binder, filler or diluent, disintegrant, glidant or mixtures thereof;

b) Kneading the above mixture of step a) with a suitable aqueous solvent such as purified water and mixing until uniformity is achieved;

c) Milling the wet mass through suitable mill;

d) Drying the obtained granules from step c) and sieving through a suitable sieve to achieve the desired granule size;

e) Adding to the obtained granules from step d) the total quantities of at least one optional excipient such as a lubricant and/or a glidant and mixing until uniform;

f) Formulating the resulting mixture from step e) in a solid dosage form either by compressing it into a desired tablet form or by filling capsules or sachets; and

g) Optionally apply a film coating on the tablet.

7. A process for the preparation of a stable pharmaceutical composition for oral administration comprising a therapeutically effective quantity of Ibuprofen or a pharmaceutically acceptable salt, prodrug, or derivative thereof, and a therapeutically effective quantity of Hyoscine Butylbromide or a pharmaceutically acceptable salt, prodrug, or derivative thereof, wherein the weight ratio of Hyoscine Butylbromide to Ibuprofen is 1:20, which comprises:

a) Forming a first homogenous blend by mixing the total quantity of Ibuprofen and the total quantity of at least one pharmaceutically acceptable excipient such as binder, filler or diluent, disintegrant, glidant or mixtures thereof;

b) Kneading the first blend obtained from step a) with a suitable aqueous solvent such as purified water, and mixing until uniformity is achieved, and milling the wet mass through suitable mill,

c) Drying the obtained granules from step b) to appropriate LOD and sieving through a suitable sieve to achieve the desired granule size;

d) Mixing the obtained granules from step c) with the total quantity of Hyoscine Butylbromide and an effective amount of an acidifying agent as stabilizer and at least one pharmaceutically acceptable excipient such as binder, filler or diluent, disintegrant, glidant or mixtures thereof, and mixing for appropriate time until uniform;

e) Adding to the blend of step d) at least one optional excipient of the extra-granular phase such as a lubricant and/or a glidant, and mixing for appropriate time;

f) Formulating the blend resulting from step e) in a solid dosage form either by compressing it into a desired tablet form or by filling capsules or sachets; and

g) Optionally apply a film coating on the tablet

8. The process according to claim 6 or 7, wherein said acidifying agent is comprised in an amount from about 0.01 to about 50% by weight of the total weight of the finished dosage form.

9. The process according to claim 6 or 7, wherein said therapeutically effective quantity of Ibuprofen or a pharmaceutically acceptable salt, prodrug, or derivative thereof is 400mg, and Hyoscine Butylbromide or a pharmaceutically acceptable salt, prodrug, or derivative thereof is 20mg.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/002239

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/50 A61K31/192 A61K31/46
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 2 659 889 Al (KOWA CO [JP]) 6 November 2013 (2013-11-06) cited in the application paragraph [0001] paragraph [0007] - paragraph [0016] production examples 1-12 claims 1-13 --- -/-	1,2,4,5 , 7-9 3,6

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 July 2016	11/07/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Marchand, Petra

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Anonymous : "Li stado de Especi al i dades Farmaceuti cas Regi stradas Gerenci a Sectori al Regi stro Control (excerpt) ", Insti tuto Naci onal de Hi gi ene Rafael Rangel ; Caracas , Venezuel a Internet ci tati on, 23 Apri l 2013 (2013-04-23) , XP002759410, Retri eved from the Internet: URL: http ://www. i nhrr .gob .ve/doc/rc_doc/ef 2 3042013 .pdf [retri eved on 2016-06-28] entri es wi t h generi c name "hi osci na N-buti l bromuro - i buprofeno"	1,4,5
Y	W0 02/45571 A2 (AMERICAN HOME PROD [US] ; ABU IZZA KHAWLA A [US] ; LI VINCENT H [US] ; L0) 13 June 2002 (2002-06-13) page 1, line 5 - line 8 page 13, line 18 - line 23 exampl es 2,4-7	3
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X	EP 2 702 989 Al (K0WA CO [JP]) 5 March 2014 (2014-03-05) ci ted i n the appl i cati on paragraph [0009] - paragraph [0012] exampl es cl aims	1,2,4,5 , 7-9

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Information on patent family members

International application No
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