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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 March 2016 (31.03.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/046189 A1

(51) **International Patent Classification**:
A61K 9/16 (2006.01) *A61K 31/4178* (2006.01)
A61K 9/20 (2006.01) *A61K 31/433* (2006.01)
A61K 9/48 (2006.01) *A61K 45/06* (2006.01)
A61K 31/192 (2006.01) *A61K 9/24* (2006.01)

(21) **International Application Number**:
PCT/EP2015/071694

(22) **International Filing Date**:
22 September 2015 (22.09.2015)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
2014/11290 24 September 2014 (24.09.2014) TR

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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).

Published:

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

WO 2016/046189 A1

(54) **Title**: LOXOPROFEN AND ANTISPASTIC DRUG COMBINATIONS

(57) **Abstract**: This invention is a novel pharmaceutical composition comprising loxoprofen or a pharmaceutically acceptable salt thereof in combination with antispastic drugs or pharmaceutically acceptable salts thereof with anti-inflammatory, analgesic and myorelaxant activity.

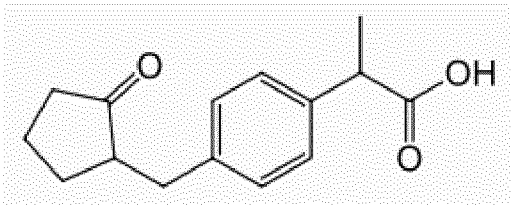
LOXOPROFEN AND ANTISPASTIC DRUG COMBINATIONS

Technical Field of the Invention

This invention is a novel pharmaceutical composition comprising loxoprofen or a pharmaceutically acceptable salt thereof in combination with antispastic drugs or pharmaceutically acceptable salts thereof with anti-inflammatory, analgesic and myorelaxant activity.

Background of the Invention

Loxoprofen is a non-steroidal anti-inflammatory drug in the propionic acid derivatives group. It is a prodrug and it is quickly converted to its active trans-alcohol metabolite following oral administration. It is a non-selective cyclooxygenase inhibitor and works by reducing the synthesis of prostaglandins from arachidonic acid. Its chemical name is (RS)-2-{4-[(2-oxocyclopentyl)methyl]phenyl}propanoic acid and its chemical structure is shown in the Formula I.



Formula I

The patent application US4161538 (A) discloses the loxoprofen molecule.

The patent EP0947584 (B1) discloses an anti-inflammatory analgesic patch comprising loxoprofen or pharmaceutically acceptable salt thereof, water, crotamiton and a water soluble polymer.

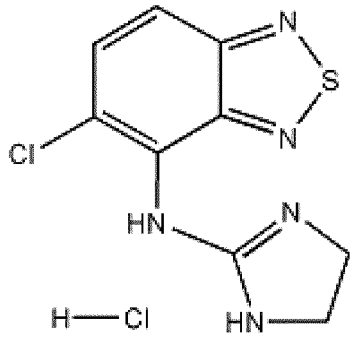
The patent application WO0247661 (A1) discloses pharmaceutical composition for intramuscular injection containing loxoprofen or a pharmaceutically acceptable salt thereof, as an active ingredient.

The patent EP1806152 (B1) discloses an external preparation containing a pharmacologically active component that is loxoprofen and a lipophilic polyglycerin fatty acid ester.

Spasticity is defined as an upper motor neuron disorder, possibly caused by a conduction interruption in the nerve pathway. Antispastic drugs are primarily used to treat neurological disorders, such as cerebral palsy.

Tizanidine, dantrolene, baclofen, diazepam, methocarbamol, succinylcholine, quinine are known as antispastic drugs used in the treatment of painful muscle spasms and spasticity occurring in musculoskeletal and neuromuscular disorders and for treating contractures and inflammatory conditions that affect the muscular system.

Tizanidine is an example for antispastic drugs. Its chemical structure is shown in Formula II.

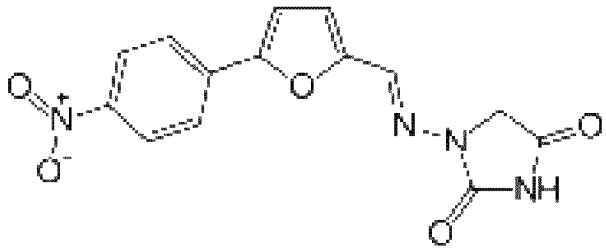


Formula II

Tizanidine is a α_2-adrenergic agonist and acts mainly at spinal and supraspinal levels to inhibit excitatory interneurones. It is used for the symptomatic relief of spasticity associated with multiple sclerosis or with spinal cord injury or disease. The recommended dose of tizanidin is 2 mg, 4mg or 6 mg.

United Kingdom patent application GB 2 197 198 A1 (Sandoz Ltd.) 03.11.1986, describes novel pharmaceutical preparations comprising ibuprofen and tizanidine with analgesic and myotonolytic activity as well as to methods of inducing analgesia and of treating conditions associated with increased muscle tone. The composition is preferably formulated as a tablet and desirably the weight ratio of tizanidine to ibuprofen is from 1:50 to 1:200, especially 1:100.

Dantrolene is also an antispastic drug indicated in controlling the manifestations of clinical spasticity resulting from upper motor neuron disorders (e.g., spinal cord injury, stroke, cerebral palsy, or multiple sclerosis). Its chemical structure is shown in Formula III.



Formula III

The recommended dose of dantrolene is 25 mg to 100 mg four times a day and at bedtime.

It is well known that drugs used in the same therapeutic area or even for treating the same indication cannot always be combined *a priori* with the expectation of at least additive therapeutic effects. The scientific literature is full of examples wherein compounds of different classes, which are used to treat the same indications, cannot be combined into safe and efficacious dosage forms thereby resulting in incompatible drug combinations. The reasons for this unexpected lack of compatibility are varied; however, it is often found that the incompatible drug combinations result in increased side effects, unwanted drug interactions or new side effects. More specifically, in the area of analgesia there are drug combinations that are contraindicated for some or all of these very same reasons.

Antispastic drugs have been evaluated alone or in combination with conventional analgesics for the treatment of pain. Mixed and unpredictable results have been obtained in a pharmaceutical composition. But loxoprofen has not previously been combined with antispastic drugs, in particular with tizanidine or dantrolone in a pharmaceutical composition for the treatment of inflammatory, pain and musculoskeletal diseases.

Detailed Description of the invention

The present invention relates to a pharmaceutical composition comprising loxoprofen or a pharmaceutically acceptable salt thereof in combination with antispastic drugs or pharmaceutically acceptable salts thereof with anti-inflammatory, analgesic and myorelaxant activity.

According to one embodiment pharmaceutical composition is administrated orally, parenterally, intramuscularly and topicaly in tablet, bilayer tablet, multi layer tablet, capsule, sachet, injectable preparat, suspension, syrup, ointment, cream or gel form.

According to one embodiment, the present composition is in the form of a tablet, bilayer tablet or a capsule.

Novel pharmaceutical composition in the form of a tablet or a capsule administrated orally may provide a significant advance in the available treatments. Such combination therapy may also provide therapeutic improvements owing to the potential synergistic effect provided by the combination.

As mentioned above, this invention comprises active ingredient, loxoprofen or a pharmaceutically acceptable salt thereof in combination with antispastic drugs or pharmaceutically acceptable salts thereof.

According to this embodiment, antispastic drugs are selected from the group comprising, tizanidine, dantrolene, baclofen, diazapem, methocarbamol, succinylcholine, quinine. Preferably they are tizanidine or dantrolene or pharmaceutically acceptable salts thereof.

According to one embodiment, this invention comprises **loxoprofen** or a pharmaceutically acceptable salt thereof in combination with **tizanidine** or a pharmaceutically acceptable salt thereof wherein the loxoprofen is present in an amount of between 10.0% and 45.0% and the **tizanidine** is present in an amount of 0.5% and 10.0% (w/w), preferred amount of the loxoprofen is between 20.0% and 35.0% and the **tizanidine** is between 1.0 % and 5.0% (w/w).

According to another embodiment, this invention comprises **loxoprofen** or a pharmaceutically acceptable salt thereof in combination with **dantrolene** or a pharmaceutically acceptable salt thereof wherein the loxoprofen is present in an amount of between 10.0% and 45.0% and the **dantrolene** is present in an amount of 1.0% and 50.0% (w/w), preferred amount of the loxoprofen is between 20.0% and 35.0% and the **dantrolene** is between 5.0 % and 30.0 % (w/w).

According to other preferred embodiment of this invention, the pharmaceutical composition is a bilayer tablet having the loxoprofen in one layer and antispastic drugs especially tizanidine or dantrolene in another layer. The amount of loxoprofen or a

pharmaceutically acceptable salt thereof employed in such bilayer tablets preferably ranges from 10.0% to 45.0%, and more preferably is 20.0% to 35.0% (w/w). The amount of tizanidine or a pharmaceutically acceptable salt thereof employed in such bilayer tablets preferably ranges from 0.5 % to 10.0% and more preferably is 1.0% to 5.0% (w/w). The amount of dantrolene or a pharmaceutically acceptable salt thereof employed in such bilayer tablets preferably ranges from 1.0% to 50.0% and more preferably is 5.0% to 30.0% (w/w).

In one embodiment the pharmaceutically acceptable salt of loxoprofen is sodium hydrate and the pharmaceutically acceptable salt of tizanidine is hydrochloride salt and the pharmaceutically acceptable salt of dantrolene is sodium salt.

The main challenges when combining two or more molecules in the same pharmaceutical form are (a) to guarantee the physicochemical compatibility between the different active ingredients and/or between the active ingredients and the excipients used; and (b) to insure the therapeutical compatibility between the two active ingredients regarding their pharmacokinetic and/or pharmaceutical properties in order that the posology of the combined composition allows to obtain safe and efficient plasma levels of both pharmacological agents.

According to main challenges mentioned above, the pharmaceutical composition comprising loxoprofen in combination with antispastic drugs, especialy with tizanidin or dantrolene have an additive analgesic effect in relief of postoperative pain and provide greater analgesia with the results in a lower incidence of side effects according to *priori.* These pharmaceutical combinations are administrated orally, parenterally, intramuscularly and topically.

The pharmaceutical compositions of the invention include tablets, capsules, injectables, suspensions, syrups, sachets, ointments, creams or gels can be made in accordance with methods that are standard in the art. Examples of oral dosage forms include tablets (comprising bilayer or multilayer and coated or uncoated), capsules, hard or soft gelatin capsules, pellets, pills, powders, granules, elixirs, tinctures, colloidal dispersions, dispersions, effervescent compositions, films, sterile solutions, suspensions, syrups or emulsions.

Preferably, the combination of a loxoprofen with tizanidine or dantrolene will be in the form of a conventional tablet or capsule. And it may be granulated by methods such as,

dry granulation, low- or high- shear granulation, wet granulation or fluidized-bed granulation. Low-shear granulation, high-shear granulation, wet granulation and fluidized-bed granulation generally produce harder, less friable tablets.

In one embodiment, this invention comprises, the combination of loxoprofen or a pharmaceutically acceptable salt and antispastic drugs or pharmaceutically acceptable salts with at least one pharmaceuticlly acceptable excipient.

Suitable pharmaceutically acceptable excipients comprise but are not limited to disintegrants, fillers, binders, glidants and lubricants or mixtures thereof.

In a preferred embodiment of the present invention, said disintegrants comprise, but are not limited to microcrystalline cellulose, low-substituted hydroxypropyl cellulose, alginic acid and alginates, ion-exchange resins, magnesium aluminum silica, sodium carboxy methyl cellulose, carboxy methyl cellulose calcium, polyvinylpyrrolidone, docusate sodium, guar gum, polacrilin potasium, poloxomer, sodium alginate, sodium glysin carbonate, or the mixtures thereof. Preferably, it is microcrystalline cellulose.

In a preferred embodiment of the present invention, said fillers comprise, but are not limited to lactose monohydrate, dibasic calcium phosphate, tribasic calcium phosphate, sorbitol, sucrose, trehalose, isomalt, microcrystalline cellulose, mannitol, starch, sodium carbonate, sodium bicarbonate, dextrose, maltodextrine, calcium carbonate, xylitol or the mixtures thereof. Preferably, it is lactose monohydrate.

In a preferred embodiment of the present invention, said binders comprise, but are not limited to hydroxypropyl cellulose, pregelatinised starch, sugars, glycose syrups, natural gums, guar gum, gelatins, pullulan, polymetacrylates, collagen, agar, algynate, sodium alginate, hyaluronic acid, pectin, tragacanth gum, carboxymethyl cellulose, polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohol, polyvinyl acetate and their copolymers, hydroxypropyl methyl cellulose, carboxy methyl cellulose, methyl cellulose, microcrystalline cellulose, polyvinylalcohol, carrageenan, carbomer, poloxamer, polyacrylamide, aluminum hydroxide, benthonite, laponite, setostearyl alcohol, polyoxyethylene-alkyl ethers, acacia mucilage, polydextrose, polyethylene oxide or the mixtures thereof. Preferably, it is hydroxypropyl cellulose.

In a preferred embodiment of the present invention, said glidants comprise, but are not limited to colloidal silicon dioxide, stearic acid, talk, aluminium silicate or the mixtures thereof. Preferably, it is colloidal silicon dioxide.

In a preferred embodiment of the present invention, said lubricants comprise, but are not limited to stearic acid, magnesium stearate, sodium stearyl fumarate, sodium lauryl sulphate, magnesium lauryl sulphate, fumaric acid, glyceryl palmitostearate, hydrogenated natural oils, zinc stearate, calcium stearate, silica, talc, polyethylene glycol, paraffin or the mixtures thereof. Preferably, it is stearic acid.

Further aspects of the present invention concern the use of pharmaceutical composition comprising loxoprofen in combination with antispastic drugs, especially tizanidine or dantrolene for use in the treatment of painful muscle spasms associated with static and functional disorders of vertebra or occurred in post-operations of osteoarthritis, pain and inflammatory symptoms associated with tissue trauma, degenerative vertebra diseases as torticollis, dorsalgia, lombalgia, disk hernia, neurologic and traumatic disorders associated with spasticity.

The invention is further defined by reference to the following examples. Although the examples are not intended to limit the scope of the present invention, it should be considered in the light of the description detailed above.

Example 1

Internal phase	**(%) amount (w/w)**
Loxoprofen sodium hydrate	10.0 – 45.0
Lactose monohydrate	5.0 – 50.0
microcrystalline celluose	5.0 – 50.0
hydroxypropyl cellulose (LF)	0.5 – 20.0
External phase	
tizanidine hydrochloride	0.5 – 10.0
colloidal silicon dioxide	0.05 – 2.0
stearic acid	0.1 – 5.0
Optionally coating	0.00 – 3.0

The process of the composition is carried out as follows: loxoprofen sodium hydrate, lactose monohydrate, hydroxypropyl cellulose (LF) and microcrystalline cellulose are sieved and mixed. After obtaining the homogenous mixture, wet granulation process is applied with water and then dried in an oven at 55◦C. The obtained granul is then sieved and tizanidine hydrochloride, stearic acid and colloidal silicon dioxide are sieved and added to granules then mixed again. Total mixture is pressed into tablets. These tablets are optionally coated with conventional coating polymers of Opadry II.

In other preffered embodiment, these powder mixtures are filled in a capsule by capsule filling machine to obtain conventional capsule forms in appropriate lenght.

Example 2

Internal phase	**(%) amount (w/w)**
Loxoprofen sodium hydrate	10.0 – 45.0
Lactose monohydrate	5.0 – 50.0
microcrystalline celluose	5.0 – 50.0
hydroxypropyl cellulose (LF)	0.5 – 20.0
External phase	
Dantrolene sodium	1.0 – 50.0
colloidal silicon dioxide	0.05 – 2.0
stearic acid	0.1 – 5.0
Optionally coating	0.00 – 3.0

The process of the composition is carried out as follows: loxoprofen sodium hydrate, lactose monohydrate, hydroxypropyl cellulose (LF) and microcrystalline cellulose are sieved and mixed. After obtaining the homogenous mixture, wet granulation process is applied with water and then dried in an oven at 55◦C. The obtained granul is then sieved and dantrolene sodium, stearic acid and colloidal silicon dioxide are sieved and added to granules then mixed again. Total mixture is pressed into tablets. These tablets are optionally coated with conventional coating polymers of Opadry II.

Example 3

Loxoprofen pellets	**(%) amount (w/w)**
Loxoprofen sodium hydrate	10.0 – 45.0
Sugar Spheres	30.0 – 60.0
Polyvinylpyrrolidone	3.0 – 15.0
Water	q.s.
Tizanidine pellets	
Tizanidine hydrochloride	0.5 – 10.0
Sugar Spheres	45.0 – 75.0
Hydroxypropyl methyl cellulose	2.0 – 20.0
Triethly citrate	1.0 – 5.0
water	q.s.

q.s: Quantum Sufficiat (sufficient quantity)

The process of the composition is carried out as follows: Loxoprofen sodium hydrate and polyvinylpyrrolidone is mixed with water to prepare the solution 1 and solution 1 is sprayed on to sugar pellets to obtain loxoprofen pellets. Tizanidine hydrochloride, hydroxypropyl methyl cellulose and triethly citrate is mixed with water to prepare the solution 2 and solution 2 is sprayed on to sugar pellets to obtain tizanidine pellets. Obtained pellets are filled into capsules.

Example 4

Loxoprofen pellets	**(%) amount (w/w)**
Loxoprofen sodium hydrate	10.0 – 45.0
Tizanidine hydrochloride	0.5 – 10.0
Sugar Spheres	30.0 – 60.0
Polyvinylpyrrolidone	3.0 – 15.0
Triethly citrate	1.0 – 5.0
water	q.s.

q.s: **Quantum** Sufficiat (**sufficient** quantity)

The process of the composition is carried out as follows: Loxoprofen sodium hydrate, polyvinylpyrrolidone, tizanidine hydrochloride and triethly citrate is mixed with water to prepare a solution and the solution is then sprayed on to sugar pellets to obtain loxoprofen and tizanidine pellets. Obtained pellets are filled into capsules.

Example 5

Loxoprofen pellets (solution 1)	**(%) amount (w/w)**
Loxoprofen sodium hydrate	10.0 – 45.0
Sugar Spheres	30.0 – 60.0
Polyvinylpyrrolidone	3.0 – 15.0
Water	q.s.
Dantrolene pellets (solution 2)	
Dantrolene sodium	1.0 – 50.0
Sugar Spheres	45.0 – 75.0
Hydroxypropyl methyl cellulose	2.0 – 20.0
Triethly citrate	1.0 – 5.0
water	q.s.

q.s: **Quantum** Sufficiat (**sufficient** quantity)

The process of the composition is carried out as follows: Loxoprofen sodium hydrate and polyvinylpyrrolidone is mixed with water to prepare the solution 1 and solution 1 is sprayed on to sugar pellets to obtain loxoprofen pellets. Dantrolene sodium, hydroxypropyl methyl cellulose and triethly citrate is mixed with water to prepare the solution 2 and solution 2 is sprayed on to sugar pellets to obtain dantrolene pellets. Obtained pellets are filled into capsules.

Example 6

Loxoprofen pellets	**(%) amount (w/w)**
Loxoprofen sodium hydrate	10.0 – 45.0
Dantrolene sodium	1.0 – 50.0
Sugar Spheres	30.0 – 60.0
Polyvinylpyrrolidone	3.0 – 15.0
Triethly citrate	1.0 – 5.0
water	q.s.

q.s: **Quantum** Sufficiat (**sufficient** quantity)

The process of the composition is carried out as follows: Loxoprofen sodium hydrate, polyvinylpyrrolidone, dantrolene sodium and triethly citrate is mixed with water to prepare a solution and the solution is then sprayed on to sugar pellets to obtain loxoprofen and dantrolene pellets. Obtained pellets are filled into capsules.

CLAIMS

1. A pharmaceutical composition comprising loxoprofen or a pharmaceutically acceptable salt thereof in combination with antispastic drugs or pharmaceutically acceptable salts thereof.

2. The pharmaceutical composition according to claim 1, wherein the antispastic drugs are selected from the group comprising tizanidine, dantrolene, baclofen, diazepam, methocarbamol, succinylcholine or quinine or pharmaceutically acceptable salts thereof.

3. The pharmaceutical composition according to claim 2, wherein the antispastic drug is tizanidine or dantrolene or a pharmaceutically acceptable salt thereof.

4. The pharmaceutical composition according to claim 3, wherein the loxoprofen or a pharmaceutically acceptable salt thereof is present in an amount of between 10.0 % and 45.0 % (w/w) and tizanidine or a pharmaceutically acceptable salt thereof is present in an amount of 0.5 % and 10.0 % (w/w).

5. The pharmaceutical composition according to claim 4, wherein the loxoprofen or a pharmaceutically acceptable salt thereof is present in an amount of between 20.0 % and 35.0 % (w/w) and tizanidine or a pharmaceutically acceptable salt thereof is present in an amount of 1.0 % and 5.0 % (w/w).

6. The pharmaceutical composition according to claim 3, wherein the loxoprofen or a pharmaceutically acceptable salt thereof is present in an amount of between 10.0 % and 45.0 % (w/w) and dantrolene or a pharmaceutically acceptable salt thereof is present in an amount of 1.0 % and 50.0 % (w/w).

7. The pharmaceutical composition according to claim 6, wherein the loxoprofen or a pharmaceutically acceptable salt thereof is present in an amount of between 20.0 % and 35.0 % (w/w) and dantrolene or a pharmaceutically acceptable salt thereof is present in an amount of 5.0 % and 30.0 % (w/w).

8. The pharmaceutical composition according to any preceding claims, wherein the loxoprofen or a pharmaceutically acceptable salt thereof and tizanidine or a pharmaceutically acceptable salt thereof are combined together with at least one pharmaceuticlly acceptable excipient.

9. The pharmaceutical composition according to any preceding claims, wherein the loxoprofen or a pharmaceutically acceptable salt thereof and dantrolene or a pharmaceutically acceptable salt thereof are combined together with at least one pharmaceuticlly acceptable excipient.

10. The pharmaceutical composition according to claim 8 or 9, wherein at least one pharmaceuticlly acceptable excipient is selected from a group comprising disintegrants, fillers, binders, glidants and lubricants or mixtures thereof.

11. The pharmaceutical composition according to any preceding claims, wherein said pharmaceutical composition is administrated orally, parenterally, intramuscularly or topically.

12. The pharmaceutical composition according to any preceding claims, wherein said pharmaceutical composition is formulated as a tablet, bilayer tablet, multilayer tablet, capsule, sachet, injectable preparat, suspension, syrup, gel, cream or ointment.

13. The pharmaceutical composition according to claim 12, wherein said pharmaceutical composition is in the form of a tablet or a bilayer tablet or a capsule.

14. The pharmaceutical composition according to claim 13, wherein said pharmaceutical composition is in the form of a tablet or a capsule.

15. The pharmaceutical composition according to claim 14, comprising

i.	Loxoprofen sodium hydrate	10.0 – 45.0 %
ii.	tizanidin hydrochloride	0.5 – 10.0 %
iii.	lactose monohydrate	5.0 – 50.0 %
iv.	microcrystalline cellulose	5.0 – 50.0 %
v.	hydroxypropyl cellulose	0.5 – 20.0 %
vi.	colloidal silicon dioxide	0.05 – 2.0 %
vii.	stearic acid	0.1 – 5.0 %
viii.	optionally coating	0.00 – 3.0 %
ix.	water	q.s.

16. The pharmaceutical composition according to claim 14, comprising

i.	Loxoprofen sodium hydrate	10.0 – 45.0 %
ii.	Dantrolene sodium	1.0 – 50.0 %
iii.	lactose monohydrate	5.0 – 50.0 %
iv.	microcrystalline cellulose	5.0 – 50.0 %
v.	hydroxypropyl cellulose	0.5 – 20.0 %
vi.	colloidal silicon dioxide	0.05 – 2.0 %
vii.	stearic acid	0.1 – 5.0 %
viii.	optionally coating	0.00 – 3.0 %
ix.	water	q.s.

17. The pharmaceutical composition according to claim 13, wherein said pharmaceutical composition is in the form of a bilayer tablet.

18. The pharmaceutical composition according to claim 17, wherein said bilayer tablet having loxoprofen or a pharmaceutically acceptable salt thereof in one layer and antispastic drugs in another layer.

19. The pharmaceutical composition according to claim 18, wherein said bilayer tablet having loxoprofen in one layer and tizanidine or dantrolene in another layer.

20. The pharmaceutical composition according to any preceding claim, for use in the treatment of painful muscle spasms associated with static and functional disorders of vertebra or occurred in post-operations of osteoarthritis, pain and inflammatory symptoms associated with tissue trauma, degenerative vertebra diseases as torticollis, dorsalgy, lombalgy, disk hernia, neurologic and traumatic disorders associated with spasticity.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/071694

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/20 A61K9/48 A61K31/192 A61K31/4178
A61K31/433 A61K45/06
ADD. A61K9/24
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, WPI Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/173581 A1 (KIMYA ITHALAT IHRACAT VE SANAYII A S AK [TR]; PISAK IBRAHIM MUSTAFA IS) 20 December 2012 (2012-12-20) the whole document page 4, line 3 - line 6 page 6, line 17 page 8, line 7	1,11-14, 20
X	JP 2014 094894 A (KOWA CO) 22 May 2014 (2014-05-22)	1,20
Y	the whole document paragraph [0076]	2-10, 15-19
Y	US 2008/279933 A1 (CIFTER UMIT [TR] ET AL) 13 November 2008 (2008-11-13) the whole document	2-10, 15-19

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[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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Date of the actual completion of the international search	Date of mailing of the international search report
30 November 2015	09/12/2015

Name and mailing address of the ISA/	Authorized officer
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