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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING LOXOPROFEN, GLUCOSAMINE, CHONDROITIN, HYALURONIC ACID FOR JOINT AND CARTILAGE DISORDERS

(57) Abstract: The present invention, relates to a new pharmaceutical composition comprising loxoprofen sodium, glucosamine sulfate, chondroitin sulfate and hyaluronic acid which has therapeutic effect against pain and inflammatory symptoms associated with joint and cartilage disorders, especially with osteoarthritis and rheumatoid arthritis.

Description

PHARMACEUTICAL COMPOSITION COMPRISING LOXOPROFEN, GLUCOSAMINE, CHONDROITIN, HYALURONIC ACID FOR JOINT AND CARTILAGE DISORDERS

Field of Invention

The present invention, relates to a new pharmaceutical composition comprising loxoprofen, glucosamine, chondroitin and hyaluronic acid which has therapeutic effect against pain and inflammatory symptoms associated with joint and cartilage disorders, especially with osteoarthritis and rheumatoid arthritis.

Background of Invention

Joint and cartilage disorders, is a painful degenerative condition that results in the deterioration of cartilage tissues that support the weight-bearing joints in the body. Once the cartilage is thinned or lost, the constant grinding of bones against each other causes pain and stiffness around the joint. Abnormal and excess bone formations called spurs grow from the damaged bones, causing further pain and stiffness. It is believed that degenerative joint disorders affect 80% of people over the age of 60. Degenerative joint disorders include, for example, osteoarthritis, rheumatoid arthritis, other rheumatic disorders with cartilage breakdown, chondrolysis after joint trauma, for example, after meniscus or patella injuries or torn ligaments, or chondrolysis associated with prolonged immobilization of joints.

Osteoarthritis is the most prevalent form of arthritis which is a painful, degenerative joint disease that often involves the hips, knees, neck, lower back, or the small joints of the hands. It is characterized by pain and progressive degeneration of cartilage in synovial joints and vertebrae, leading to significant reduction of mobility and quality of life. Osteoarthritis usually develops in joints that are injured by repeated overuse in the performance of a particular job or a favorite sport or from carrying around excess body weight. Eventually this injury or repeated impact thins or wears away the cartilage that cushions the ends of the bones in the joint so that the bones rub together, causing a grating sensation. Joint flexibility is reduced, bony spurs develop, and the joint swells. Usually, the first symptom a person has with osteoarthritis is pain that worsens following exercise or immobility.

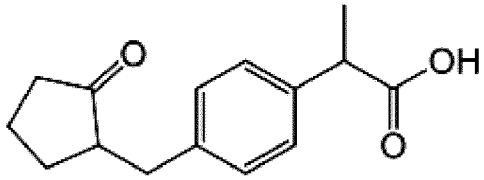
Rheumatoid arthritis is an autoimmune inflammatory disease in which the body releases enzymes that attack its own healthy tissues. In rheumatoid arthritis, these enzymes destroy

the linings of joints causing pain, swelling, stiffness, deformity, and reduced movement and function. Rheumatoid arthritis also may include systemic symptoms.

Hence, pharmacological treatment of arthritis involves two therapeutic goals:

- Analgesic & anti-inflammatory treatment: Relief from pain and inflammation of the soft tissue surrounding the joint.
- Disease-modifying treatment to treat the underlying pathology.

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.



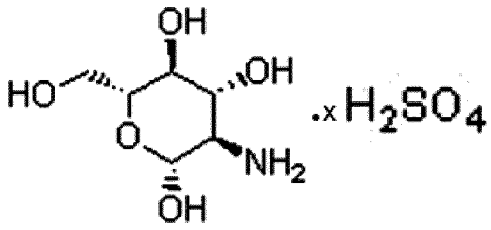
Formula I

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

The patent application JP2010270140 (A) discloses an oral pharmaceutical composition which alleviates gastric mucosa disorders caused by loxoprofen, comprises one or more sugars and sugar alcohols selected from the group consisting of sucrose, maltitol, fructose, xylitol, trehalose, lactose and lactitol; and loxoprofen. A tablet, subtle granule (powder is included), capsule, solution (syrup is included), etc., may be cited as a concrete dosage form of the oral pharmaceutical composition.

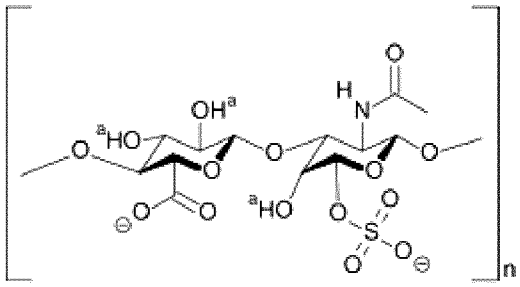
Glucosamine is an amino sugar and a prominent precursor in the biochemical synthesis of glycosylated proteins and lipids. Glucosamine is part of the structure of the polysaccharides chitosan and chitin and it is naturally present in the shells of shellfish, animal bones and bone marrow. It is also present in some fungi and can be also synthetically derived. Glucosamine is used for the treatment of osteoarthritis. Its chemical name is (3R,4R,5S)-3-Amino-6-(hydroxymethyl)oxane-2,4,5-triol. Chemical structure of glucosamine sulfate (GS) is shown in the formula II. Recent studies indicate that it also slows the deterioration of cartilage and

relieves pain. Tablet form of glucosamine sulfate is authorized in the strength of 500 and 750mg. Daily recommended dose is between 500 to 2500 mg.



Formula II. Glucosamine sulfate

Chondroitin sulfate (CS) is a sulfated glycosaminoglycan (GAG) composed of a chain of alternating sugars. Chondroitin sulfate is an important structural component of cartilage and provides much of its resistance to compression. Chondroitin sulfate is mostly administrated orally. Tablet form is authorized in the strength of 120, 250 and 400mg and daily recommended dose is 1200mg. Chemical structure of chondroitin sulfate is shown in the formula III.



Formula III. Chondroitin sulfate

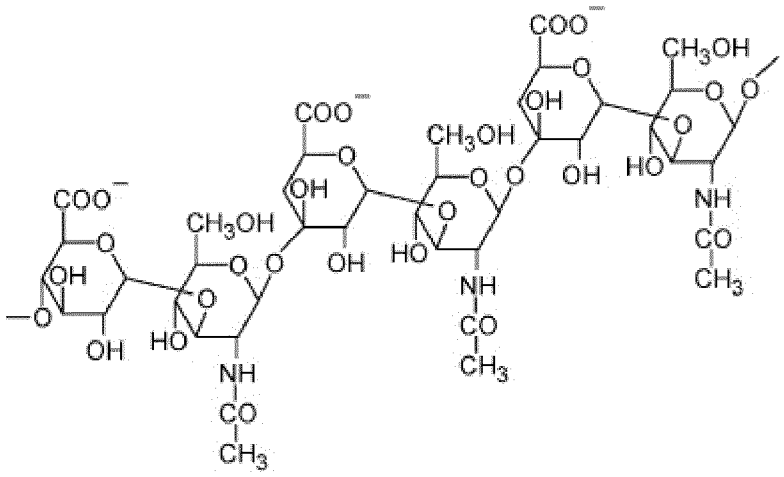
In the state of art, there are capsule and tablet forms of glucosamine and chondroitin combination authorized in U.S. The main benefit of glucosamine and chondroitin combination is prevention of cartilage degeneration in the joints, especially in those affected by osteoarthritis. It also helps to reduce the pain associated with overuse conditions, such as knee tendonitis and other sports-related injuries and helps to reduce inflammation while increasing the health of the muscle and other tissue. US 2008/0227747 A1 discloses a therapeutic composition and methods for the treatment and prevention of a degenerative joint disorder and/or cardiovascular disease comprising polycosanols, glucosamine and chondroitin. Composition further may comprise NSAIDs, but neither an example nor loxoprofen as one of the NSAIDs is disclosed in the patent application in combination with glucosamine.

Hyaluronic acid (HA) exists as a naturally-occurring polysaccharide (also known as a mucoid polysaccharide) that can be extracted from such diverse sources as rooster comb, umbilical cord, vitreous humor, synovial fluid, pathologic joints, skin and group A and C hemolytic Streptococci. The hyaluronic acid is also defined as a high viscosity naturally occurring glycosaminoglycan having a polymeric structure containing alternating N-acetyl-D-glucosamine and D-glucuronic acid monosaccharide units linked with [beta] 1-4 bonds and the disaccharide units linked with [beta] 1-3 glycoside bonds

Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan. It is ubiquitous in the organism, with the highest concentration found in soft connective tissue and joint fluid. It is a constituent of the intercellular matrix of connective tissue that exists in almost all vertebrates. It plays an important role in a number of physiological functions, including protection and lubrication of cells, maintenance of the structural integrity of tissues, transport of molecules and cells, cell migration, cell function and differentiation, and fluid retention and regulation.

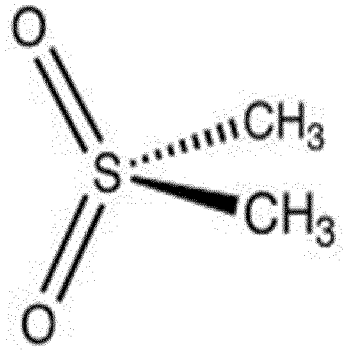
Natural Hyaluronic acid is polydisperse in respect of molecular weight and is known to show excellent biocompatibility even when implanted or injected into the body by virtue of the absence of species and organ specificity. However, because of the relatively short in vivo residence time of Hyaluronic acid solution in biological applications, improvements in the persistency of Hyaluronic acid by chemical crosslinking with various chemical modifiers has been attempted to broaden its use for medical materials.

Hyaluronic acid is an important component of the intercellular matrix. Specifically, the highest levels are found in the eye and synovial fluid of joints. In joints, its primary role is that of lubrication, reducing pain, and inflammation. In arthritic joints HA is deficient. In regards to the joints, synovial fluid supplies nutrition to the articular cartilage and has incomparable functions as a lubricant and a shock absorber. It is clarified that its excellent viscoelastisity heavily owes to one of the main components, Hyaluronic acid. Concentration and molecular weight analyses of Hyaluronic acid demonstrated the concentration and molecular weight of Hyaluronic acid in the synovial fluid from patients with arthritis such as osteoarthritis and chronic articular rheumatism generally tended to be lower than in normal synovial fluid, and the lower concentration and molecular weight of Hyaluronic acid were closely associated with development of locomotor dysfunction and pain attributable to the weaker lubricating action and the weaker protecting action on the surface of the articular cartilage of synovial fluid. Chemical structure Hyaluronic acid is shown in the formula IV.



Formula IV. Hyaluronic acid

Methylsulfonylmethane (MSM) is an organosulfur compound with the formula (CH 3) 2SO 2. It occurs naturally in some primitive plants, is present in small amounts in many foods and beverages, and is marketed as a dietary supplement. MSM is sold as a dietary supplement and marketed with a variety of combinations, often in combination with glucosamine and/or chondroitin for helping to treat or prevent osteoarthritis. Small-scale studies of possible treatments with MSM have been conducted on both animals and humans. These studies of MSM have suggested some benefits, particularly for treatment of osteoarthritis. A review by Brien, et al., (Systematic review of the nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis, Osteoarthritis and Cartilage, 2008; 16:1277) of the two small randomized controlled trials of methylsulfonylmethane in osteoarthritis knee pain relief reported significant improvement in pain outcomes in the treatment group compared to comparator treatments. After several reports that MSM helped arthritis in animal models, one study by Usha et al. (Double- blind, parallel, placebo- controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis, Clinical Drug Investigation, 2004; 24:353-63) had confirmed that 1.5 g per day MSM (alone or in combination with glucosamine sulfate) was helpful in relieving symptoms of knee osteoarthritis. Chemical structure methylsulfonylmethane is shown in the formula V.



Formula V. Methylsulfonylmethane (MSM)

The combination of chondroitin sulfate with glucosamine, with or without the presence of other materials, was described by Towheed, T. E. et al., in JAMA 283(11):1483-1484 (2000). The same combination was reported by Canapp, S. O. et al., in Am. J. Vet. Res., 60(12):1552-7 (1999), who believed that orally administered glucosamine hydrochloride and chondroitin sulfate had a protective effect against chemically induced synovitis and associated bone remodeling in dogs. U.S. Pat. Nos. 6,162,787; 6,136,795; 5,929,050; 5,916,565; 5,888,514; 5,840,715; 4,772,591; and 4,473,551, also report glucosamine combinations with chondroitin sulfate. Henderson, R. W., in WO 9827988 described an aminosugar and glycosaminoglycan composition for the treatment and repair of connective tissue. A commercial dietary supplement, Flex-A-Min(R), is reported to provide a combination of glucosamine, chondroitin sulfate and methylsulfonylmethane, and is directed at subjects with arthritis and joint pain.

There are various patent applications in prior art in relation to separately or combinations of 2 or 3 active agents but not all 4 or 5 active agents in combination, therefore none of them are specifically comprises loxoprofen sodium, glucosamine sulfate, chondroitin sulfate and hyaluronic acid in oral administration as tablet dosage form.

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.

However, no orally-administrable pharmaceutical composition has been produced until today, which contains a combination of loxoprofen, glucosamine, chondroitin and hyaluronic acid. Even if some medicaments comprising either of these active agents have been administered concomitantly in practice, this fact requires the patients to carry more than one drug and causes application-related difficulties. Additionally, administering and formulating a combination, in place of the individual use of each active agent, may provide improved treatment features.

Another problem is related to combine these four active ingredients in one dosage form such as tablet or capsule, it would require a dosage form having approximately or more than 1000 mg active ingredients in total without any further tablet or capsule excipients. This is an amount that would create a very large tablet or capsule size that would not be swallowable or it would require composition that would require ingesting multiple tablets to achieve the desired effect.

Accordingly, based on said drawbacks, a novelty is required in the art of pharmaceutical combinations having therapeutic effects against pain and inflammatory symptoms associated with joint and cartilage disorders, especially with osteoarthritis and rheumatoid arthritis. In this present invention, the object is to provide a new pharmaceutical composition comprising loxoprofen sodium, glucosamine sulfate, chondroitin sulfate and hyaluronic acid. In further, the present invention also provides loxoprofen sodium, glucosamine sulfate, chondroitin sulfate, hyaluronic acid and MSM as a dietary supplement.

Detailed description of the invention

In the main embodiment of this present invention is to provide a pharmaceutical composition comprising loxoprofen, glucosamine, chondroitin and hyaluronic acid or their pharmaceutically acceptable salts thereof and at least one pharmaceutically acceptable excipient.

The pharmaceutical composition of this present invention is to treat, reduce or prevent the degenerative joint and cartilage disorders by administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising loxoprofen, glucosamine , chondroitin and hyaluronic acid or their pharmaceutically acceptable salts thereof and at least one pharmaceutically acceptable excipient which overcomes the above described problems in prior art and have additional advantages over them.

An embodiment of this present invention is to eliminate the GI adverse effects of loxoprofen when it is administered orally in high terapeutic effective amounts for a long time. It is known that the treatment of the degenerative joint and cartilage disorders, especially osteoarthritis and rheumatoid arthritis needs a long treatment period. Therefore to use of loxoprofen for a long time with high terapeutic effective amounts may increase the possibility of GI adverse effects of loxoprofen. As a rule, after a long-term administration of a drug, drug addiction develops and as a consequence its dosage should be increased. This certainly affects the occurrence of side effects.

According to one embodiment, salt of loxoprofen is loxoprofen sodium.

The present invention provides the solution to this problem by using the amount of loxoprofen sodium is not more than 15 % by weight of the total composition by combining it with glucosamine sulfate, chondroitin sulfate, hyaluronic acid, methylsulfonylmethane. It has been found surprisingly that this ratios have an increased/synergistic effect over analgesic and antiinflammatory activity of loxoprofen even with low doses.

In one embodiment, salt of glucosamine used in this present invention is selected from the group comprising glucosamine sulfate, N-acetyl-glucosamine, glucosamine hydrochloride, glucosamine sodium hydrochloride, glucosamine potassium chloride, glucosamine sulfate sodium and mixtures thereof. Preferably, salt of glucosamine is glucosamine sulfate.

The role which glucosamine sulfate plays in the treatment or prevention of the degenerative joint and cartilage disorders is most likely associated directly its ability to act as the most important substrate for glycosaminoglycans and a basis of hyaluronic acid. A successful treatment of osteoarthritis and rheumatoid arthritis must control pain effectively as well as slow down or ensure the reverse development of joint degeneration process. It has been found that the introduction of the amount of glucosamine sulfate is not more than 45 % by weight of the total composition makes it possible to ensure a chondroprotective and anti-inflammatory effect of the composition and prevents destructive effect of glucocorticoids on chondrocytes and to reduce a need for NSAID (i.e.loxoprofen) in high dosage for patients suffering from osteoarthritis and rheumatoid arthritis which in turn makes it possible to decrease side effect risks.

According to one embodiment, salt of chondroitin is chondroitin sulfate.

In this embodiment, the amount of chondroitin sulfate is not more than 25 % by weight of the total composition.

According to this embodiment, the amount of hyaluronic acid is not more than 15 % by weight of the total composition.

Accordingly, when loxoprofen sodium is used for a long period of time, it may have a desensitizing effect. It has been also found that when loxoprofen sodium is used by combination with glucosamine, chondroitin and hyaluronic acid makes it possible to ensure increased analgesic and anti-inflammatory effect of the composition, whilst reducing the pain and inflammation syndrome in degenerative joint and cartilage disorders synergistically. Thus this qualify to use loxoprofen in low dosage for patients also reduces the risk of the GI side effects.

In further embodiment, pharmaceutical composition of this present invention further comprises a dietary supplement. The dietary supplement may be used in the composition is selected from the group comprising methylsulfonylmethane (dimethyl sulfone), dimethyl sulfoxide, carbonate salts, probiotics, saccharides, vitamins, carotenoids, xanthophylls, minerals,electrolytes, preferably it is methylsulfonylmethane.

According to this embodiment, dietary supplement used in this present invention is methylsulfonylmethane.

In this embodiment, the amount of methylsulfonylmethane is not more than 15 % by weight of the total composition.

According to this embodiment of the present invention, it has been found that when the pharmaceutical composition of the present invention comprises in certain ratios of;

a) loxoprofen sodium to glucosamine sulfate is in the range of 0.01 to 10.0, preferably 0.01 to 5.0, and more preferably 0.10 to 2.0;
b) loxoprofen sodium to chondroitin sulfate is in the range of 0.1 to 15.0, preferably 0.1 to 10.0, and more preferably 0.1 to 5.0;
c) loxoprofen sodium to hyaluronic acid is in the range of 0.1 to 15.0, preferably 0.5 to 10.0, and more preferably 0.5 to 5.0;
d) loxoprofen sodium to methylsulfonylmethane (MSM) is in the range of 0.1 to 15.0, preferably 0.5 to 10.0, and more preferably 0.5 to 5.0;

e) hyaluronic acid to methylsulfonylmethane (MSM) is in the range of 0.1 to 15.0, preferably 0.5 to 10.0, and more preferably 0.5 to 5.0;

f) chondroitin sulfate to glucosamine sulfate is in the range of 0.01 to 15.0, preferably 0.1 to 10.0, and more preferably 0.1 to 5.0;

helps the composition to be easily processed into a tablet form, in desired weight which can easily be swallowed by the patients, whilst maintaining or increasing the therapeutic effective doses for the joint and cartilage disorders, especially with osteoarthritis and rheumatoid arthritis.

In an embodiment, said pharmaceutical composition is for oral administration.

In this embodiment, the pharmaceutical form of said composition is solid dosage form. The solid dosage form is selected from the group comprising tablets, bilayer tablets, multilayer tablets, buccal tablets, sublingual tablets, tablet in tablets, in-lay tablets, effervescent compositions, effervescent tablets, immediate release tablets, modified release tablets, ODT-ER (orally disintegrating tablets-extended release), orally disintegrating tablets, gastric disintegrating tablets, mini tablets; pills, capsules, hard or soft gelatin capsules, powders, pellets, coated bead systems, granules, microspheres, ion exchange resin systems, dragees, sachets; orally administrable thin films, solutions or solids.

In this embodiment, pharmaceutical combination of this present invention is in the form of a tablet.

In this present invention, the pharmaceutical composition is for use in the treatment of pain and inflammatory symptoms associated with joint and cartilage disorders, especially with osteoarthritis and rheumatoid arthritis

The pharmaceutical composition comprising;

a) loxoprofen sodium at 3-15% by weight,

b) glucosamin sulfate at 30-45% by weight,

c) chondroitin sulfate at 15-25% by weight,

d) hyaluranic asit at 5-15% by weight,

e) methylsulfonylmethane (MSM) at 5-15% by weight,

f) lactose monohydrate at 5-20% by weight,

g) hydroxypropyl cellulose (low substituted) at 15-25% by weight,

h) colloidal silicon dioxide at 0.1-5% by weight,

i) magnesium stearate at 0.1-5% by weight,

j) film coating (PVA based) at 1-5% by weight.

According to the challenges mentioned above the selection of the excipients thus very important. According to this embodiment, one or more pharmaceutically acceptable the excipient is selected from the group comprising buffering agents, stabilizers, binders, diluents, dispersing agents, lubricants, glidants, disintegrants, plasticizers, preservatives, sweeteners, flavoring agents, coloring agents, coating agents or mixtures thereof.

Suitable buffering agents may comprise but not limited to alkali metal citrate, citric acid/sodium citrate, tartaric acid, fumaric acid, sorbic acid, citric acid, succinic acid, adipic acid, ascorbic acid, glutaric acid, potassium hydrogen tartrate, sodium hydrogen tartrate, potassium hydrogen phthalate, sodium hydrogen phthalate, potassium dihydrogen phosphate, sodium dihydrogen phosphate, disodium hydrogen phosphate, hydrochloric acid/sodium hydroxide or mixtures thereof, and preferably citric acid, fumaric acid, ascorbic acid, sodium dihydrogen phosphate or mixtures thereof.

Suitable stabilizers may comprise but not limited to citric acid, fumaric acid, tartaric acid, sodium citrate, sodium benzoate, sodium dihydrogen phosphate, calcium carbonate, magnesium carbonate, arginine, lysine, meglamine, tocopherol, butylhydroxyanisole (BHA), butylhydroxytoluene (BHT), ascorbic acid, gallic acid esters or the mixtures thereof, and preferably, citric acid, fumaric acid, arginine or mixtures thereof.

Suitable binders may include but not limited to hydroxypropyl methyl cellulose, polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohol, starch, pregelatinized starch, glucose, glucose syrup, natural gums, sucrose, sodium alginate, hydroxypropyl cellulose, carboxy methyl cellulose, methyl cellulose, gelatin, carrageenan, guar gum, carbomer, polymethacrylates, methacrylate polymers, collagens gelatin, agar, alginate, alginic acid, xanthan gum, hyaluronic acid, pectin, polysaccharides, carbomer, poloxamer, polyacrylamide, aluminium hydroxide, laponit, bentonit, polyoxyethylene-alkyl ether, polydextrose, polyethylene oxide or mixtures thereof.

Suitable diluents may comprise but not limited to lactose monohydrate, spray dried, microcrystalline cellulose, mannitol, spray-dried mannitol, starch, dextrose, sucrose, fructose, maltose, sorbitol, xylitol, inositol, kaolin, inorganic salts, calcium salts, polysaccharides, dicalcium phosphate, sodium chloride, dextrates, lactitol, maltodextrin, sucrose-maltodextrin mixture, trehalose, sodium carbonate, sodium bicarbonate, calcium carbonate or mixtures thereof.

Suitable dispersing agents may comprise but not limited to calcium silicate, magnesium aluminum silicate or mixtures thereof.

Suitable lubricants may comprise but not limited to magnesium stearate, calcium stearate, zinc stearate, talc, waxes, boric acid, hydrogenated vegetable oil, sodium chlorate, magnesium lauryl sulfate, sodium oleate, sodium acetate, sodium benzoate, polyethylene glycol, stearic acid, fatty acid, fumaric acid, glyseryl palmito sulphate, sodium stearyl fumarate, sodium lauryl sulphate or mixtures thereof.

Suitable glidants may comprise but not limited to colloidal silicon dioxide, talc, aluminium silicate, colloidal silica, starch or mixtures thereof.

Suitable disintegrants may comprise but not limited to hydroxypropyl cellulose (low substituted), croscarmellose sodium, cross-linked polyvinil pyrrolidone (crospovidone), povidone, cross-linked carboxymethyl cellulose (croscarmellose sodium), , pregelatinized starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, carboxymethyl cellulose, docusate sodium, guar gum, , polyacryline potassium, sodium alginate, corn starch, sodium starch glycolate, alginic acid, alginates, ion-exchange resins, magnesium aluminium silica, sodium dodesyl sulphate, poloxamer, sodium glycine carbonate, sodium lauryl sulphate or mixtures thereof.

Suitable plasticizers may comprise but not limited to polyethylene glycols of different molecular weights, propylene glycol, glycerine, triethyl citrate (TEC), triacetin, diethyl phthalate (DEP), dibutyl phthalate (DBP), tributhyl citrate (TBC), castor oil, dibutyl sebacate (DBS), diacetylated monogglycerides or mixtures thereof.

Suitable preservatives may comprise but not limited to methyl paraben, propyl paraben and their salts (such as sodium, potassium), sodium benzoate, citric acid, benzoic acid, butylated hydroxytoluene, boric acid, sorbic acid, benzyl alcohol, benzalconium chloride, parahydroxybenzoic acids or butylated hydroxyanisole or mixtures thereof.

Suitable sweeteners may comprise but not limited to aspartame, potassium acesulfame, sodium saccharinate, neohesperidine dihydrochalcone, sucralose, saccharin, sugars such as sucrose, glucose, lactose, fructose or sugar alcohols such as mannitol, sorbitol, xylitol, erythritol or mixtures thereof.

Suitable flavoring agents may comprise but not limited to menthol, peppermint, cinnamon, chocolate, vanillin or fruit essences such as cherry, orange, strawberry, grape, black currant, raspberry, banana, red fruits, wild berries or mixtures thereof.

Suitable coloring agents may comprise but not limited to ferric oxide, titanium dioxide, Food, Drug & Cosmetic (FD&C) dyes (such as; FD&C blue, FD&C green, FD&C red, FD&C yellow, FD&C lakes), poncau, indigo Drug & Cosmetic (D&C) blue, indigotine FD&C blue, carmoisine indigotine (indigo Carmine); iron oxides (such as; iron oxide red, yellow, black), quinoline yellow, flaming red, carmine, carmoisine, sunset yellow or mixtures thereof.

Coating agents may comprise but not limited polyvinyl alcohol based coating agents, OpadryTM derivatives (such as opadry yellow (20A22418) and opadry II), aminoalkyl metacrylate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, carnauba wax, cellulose acetate, cellulose acetate phthalate, ceresin, cetyl alcohol, chitosan, ethylcellulose, fructose, gelatin, glycerin, glyceryl behenate, glyceryl palmitostearate, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, hypromellose, hypromellose phthalate, isomalt, liquid glucose, maltitol, maltodextrin, methylcellulose, microcrystalline wax, paraffin, poloxamer, polydextrose, polyethylene oxide, poly-DL-(lactic acid), polyvinyl acetate phthalate, potassium chloride, shellac, shellac with stearic acid, sucrose, surface color agents, titanium oxide, tributyl citrate, triethyl citrate, vanillin, white wax, xylitol, yellow wax, zein, dimethylaminoethyl methacrylate, butyl methacrylate and methyl methacrylate (Eudragit E 100) (Poly(butyl methacrylate-co-(2- demethylaminoeethyl)methacrylate-co-methyl methacrylate)) or mixture of polyethylene glycol and polyvinyl alcohol (Kollicoat IR) and their copolymers, hydroxypropyl methyl cellulose (HPMC), polyethyleneglycol (PEG), polivinylpyrrolidon (PVP), polyvinyl alcohol (PVA), vinylpyrrolidone-vinyl acetate copolymer (PVP- PVAc) and pigments, titanium dioxide, dyes and iron oxide and talc or mixtures thereof.

Example 1: Film coated tablet

Ingredients	Amount (%)
Loxoprofen sodium dihydrate	4.29
Glucosamin sulfate sodium	35.71
Chondroitin sulfate sodium	16.07
Hyaluranic acid	7.14
Lactose monohydrate	17.04
Hydroxypropyl cellulose (low substituted)	18.35
Colloidal Silicon Dioxide	0.80
Magnesium Stearate	0.60

Ethyl alcohol	**q.s.***

Film Coating (PVA base)	**3.21**

*q.s.:quantity sufficient

Production process of the composition: Loxoprofen sodium, Lactose monohydrate and a part of Hydroxypropyl cellulose (low substituted) are mixed. Then, the mixture is granulated with ethyl alcohol. Granules are sieved and dried, then sieved. Glucosamin sulfate sodium, chondroitin sulfate sodium, hyaluranic acid and other part of hydroxypropyl cellulose (low substituted) are added to this mixture and mixed together. This mixture is mixed with colloidal silicon dioxide. Then, magnesium stearate is added and mixed. This total homogenous mixture is compressed into tablets. Tablets are coated with water solution of polyvinyl alcohol based coating agent.

Example 2: Film coated tablet

Ingredients	Amount (%)
Loxoprofen sodium dihydrate	4.29
Glucosamin sulfate sodium	35.71
Chondroitin sulfate sodium	16.07
Hyaluranic acid	7.14

Mehylsulfonylmethane (MSM)	7.14
Lactose monohydrate	9.90
Hydroxypropyl cellulose (low substituted)	18.35
Colloidal Silicon Dioxide	0.80
Magnesium Stearate	0.60

Ethyl alcohol	**q.s.***

Film Coating (PVA base)	**3.21**

*q.s.:quantity sufficient

Production process of the composition: Loxoprofen sodium, Lactose monohydrate and a part of Hydroxypropyl cellulose (low substituted) are mixed. Then, the mixture is granulated with ethyl alcohol. Granules are sieved and dried, then sieved. Glucosamin sulfate sodium, chondroitin sulfate sodium, hyaluranic acid, mehylsulfonylmethane and other part of hydroxypropyl cellulose (low substituted) are added to this mixture and mixed together. This mixture is mixed with colloidal silicon dioxide. Then, magnesium stearate is added and mixed. this total homogenous mixture is compressed into tablets. Tablets are coated with water solution of polyvinyl alcohol based coating agent.

CLAIMS

1) A pharmaceutical composition comprising loxoprofen, glucosamine, chondroitin and hyaluronic acid and at least one pharmaceutically acceptable excipient.

2) The pharmaceutical composition according to claim 1 or 2, wherein the salt of loxoprofen is loxoprofen sodium.

3) The pharmaceutical composition according to claim 1, wherein the amount of loxoprofen sodium is not more than 15 % by weight of the total composition.

4) The pharmaceutical composition according to claim 1, wherein the salt of glucosamine is glucosamine sulfate.

5) The pharmaceutical composition according to claim 1 or 4, wherein the amount of glucosamine sulfate is not more than 45 % by weight of the total composition.

6) The pharmaceutical composition according to claim 1, wherein the salt of chondroitin is chondroitin sulfate.

7) The pharmaceutical composition according to claim 1 or 6, wherein the amount of chondroitin sulfate is not more than 25 % by weight of the total composition.

8) The pharmaceutical composition according to claim 1, wherein the amount of hyaluronic acid is not more than 15 % by weight of the total composition.

9) The pharmaceutical composition according to claim 1, further comprising a dietary supplement.

10) The pharmaceutical composition according to claim 10, wherein dietary supplement is selected from the group comprising methylsulfonylmethane (dimethyl sulfone), dimethyl sulfoxide, carbonate salts, probiotics, saccharides, vitamins, carotenoids, xanthophylls, minerals,electrolytes, preferably it is methylsulfonylmethane.

11) The pharmaceutical composition according to claim 12, wherein the amount of methylsulfonylmethane is not more than 15 % by weight of the total composition.

12) The pharmaceutical composition according to any of the preceding claims comprising;
   a) loxoprofen sodium at 3-15% by weight,
   b) glucosamin sulfate at 30-45% by weight,
   c) chondroitin sulfate at 15-25% by weight,
   d) hyaluranic asit at 5-15% by weight,
   e) lactose monohydrate at 5-20% by weight,
   f) hydroxypropyl cellulose at 15-25% by weight,
   g) colloidal silicon dioxide at 0.1-5% by weight,
   h) magnesium stearate at 0.1-5% by weight,
   i) film coating at 1-5% by weight.

13) The pharmaceutical composition according to any of the preceding claims comprising;
   j) loxoprofen sodium at 3-15% by weight,
   k) glucosamin sulfate at 30-45% by weight,
   l) chondroitin sulfate at 15-25% by weight,
   m) hyaluranic asit at 5-15% by weight,
   n) methylsulfonylmethane at 5-15% by weight,
   o) lactose monohydrate at 5-20% by weight,
   p) hydroxypropyl cellulose at 15-25% by weight,
   q) colloidal silicon dioxide at 0.1-5% by weight,
   r) magnesium stearate at 0.1-5% by weight,
   s) film coating at 1-5% by weight.

14) The pharmaceutical composition according to any of the preceding claims, wherein the excipient is selected from the group comprising buffering agents, stabilizers, binders, diluents, dispersing agents, lubricants, glidants, disintegrants, plasticizers, preservatives, sweeteners, flavoring agents, coloring agents or mixtures thereof.

15) The pharmaceutical composition according to claim 1, wherein said composition is for oral administration.

16) The pharmaceutical composition according to claim 15, wherein said composition is in the form of solid dosage form.

17) The pharmaceutical composition according to claim 16, wherein the solid dosage form is selected from the group comprising tablets, bilayer tablets, multilayer tablets, buccal tablets, sublingual tablets, tablet in tablets, in-lay tablets, effervescent compositions,

effervescent tablets, immediate release tablets, modified release tablets, ODT-ER (orally disintegrating tablets-extended release), film-coated tablets, orally disintegrating tablets, gastric disintegrating tablets, mini tablets; pills, capsules, hard or soft gelatin capsules, powders, pellets, coated bead systems, granules, microspheres, ion exchange resin systems, dragees, sachets; orally administrable thin films, solutions or solids.

18) The pharmaceutical composition according to claim 19, wherein the solid dosage form is in the form of a tablet.

19) The pharmaceutical composition according to any of the preceding claims, for use in the treatment of pain and inflammatory symptoms associated with joint and cartilage disorders, especially with osteoarthritis and rheumatoid arthritis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/056858

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/192 A61K31/7008 A61K31/728 A61K31/737 A61P19/02 A61K31/10
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 A61P

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, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 2008/157771 A1 (ARTHRODYNAMIC TECHNOLOGIES ANI [US]; MARCUM FRANCK D [US]; SEANOR JOHN) 24 December 2008 (2008-12-24) page 21, line 2; examples 1-4 page 22, line 7 - line 13 -----	1-19
Y	US 2013/330373 A1 (LEE MING-CHEN [TW]) 12 December 2013 (2013-12-12) Formulations E and F; paragraph [0004]; table 2 ----- -/--	1-19

[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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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 June 2016	24/06/2016

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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