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(54) Title: HIGH DRUG LOAD IBUPROFEN SUSTAINED RELEASE COMPOSITION

(57) Abstract: The present invention relates to invention relates to a sustained release composition of ibuprofen or pharmaceutically acceptable salt thereof, comprising high drug load of active ingredient and its method of preparation. The sustained release pharmaceutical composition comprising ibuprofen or a pharmaceutically acceptable salt thereof in an amount of about 80% or more, preferably about 85% in the weight of the active ingredient based on the total weight of the composition.

HIGH DRUG LOAD IBUPROFEN SUSTAINED RELEASE COMPOSITION

Field of the Invention

The present invention relates to a sustained release composition of ibuprofen or pharmaceutically acceptable salt thereof, comprising high drug load of active ingredient and its method of preparation.

Background of the Invention

Ibuprofen is 2-(4-isobutylphenyl) propionic acid known as ibuprofen, is a non-steroidal anti-inflammatory compound (NSAID), which exhibits high levels of anti-inflammatory, analgesic and antipyretic activities necessary for the effective treatment of rheumatoid arthritis and osteo-arthritis and other inflammatory conditions. It is available in both prescription and OTC dosages. Compared with other non-steroidal anti-inflammatory products, ibuprofen is distinguished by inter alia, being well tolerated by the stomach.

Most dosage forms of ibuprofen are immediate release dosage forms that provide rapid onset of therapeutic action, then rapidly declining levels of active ingredient, necessitating repeated dosing. They do not maintain therapeutic levels from one treatment over an extended period of time. Repeat dosing is thus required at intervals of four to six hours.

The recommended dose for the treatment of, in particular, rheumatoid arthritis and osteoarthritis is 1200 mg-3200 mg daily (400 mg, 600 mg or 800 mg tid or qid). Likewise a dose of 400 mg of ibuprofen in every 4 to 6 hours is necessary for relief of pain and a dose of 400 mg every 4 hours is necessary for the treatment of dysmenorrhea.

With more frequency of intake of immediate release dosage form, the patient may in time become exasperated with or antipathetic to the medicament and make the treatment unsuccessful. In addition, the frequent intake of amounts of active compound which again and again exceed definitely the effective blood level raises a risk of side effects, especially in the gastro-intestinal tract.

For this reason, it would be desirable to have available a pharmaceutical form which would release the contents over a longer period of time. It would be possible in this way to reduce the frequency of intake and the number of dose units per day, and simultaneously also be almost suppress the fluctuations of the blood level, which hitherto were unavoidable, between a very high and a very low concentration of ibuprofen (fluctuating index).

There have been, in fact, many suggestions in the above mentioned sense. Nevertheless, controlled-release products have also appeared, such as, inter alia, the products are sustained-release capsules of ibuprofen (Fenbid Spansules®) by Smith Kline and Beecham; and ibuprofen sustained-release tablets (Balkaprofen SR®) by APM Co. and Brufen® by Abbott Laboratories.

US patent application No. 20060068009 describes a solid dosage form for modified oral administration of ibuprofen comprising a hydrophilic polymer, 10% to 35% by weight of the ibuprofen and a dissolution additive.

European Patent application No. 061217 describes a product with delayed release of the active compound, which is composed of hard gelatin capsules containing 300 mg of ibuprofen. The production is carried out in a coating pan. Ibuprofen in the form of a powder is bound, by means of low-viscosity polyvinylpyrrolidone, over a spherical core composed of sugar and starch, the spheroids are then coated with a high-viscosity polyvinylpyrrolidone and the final spheroids are encapsulated.

Ibuprofen has a low melting point (75^0-77^0C) which is reduced further on mixing with customary excipients. As a consequence, the pressure during tabletting is sufficient partially to melt the active compound. This makes the solid composition sticking and caking, which considerably impedes the preparation of tablets. In order to prevent such problems, a relatively high amount of excipient needs to be used. Again to sustain the release of active ingredient from the composition, large quantity of release retard excipients are required. As the dose of ibuprofen is very high, higher quantity of excipients in the composition leads to higher dosage size. As is generally known, the

biggest capsules which are available on the market - standard size 0 to 00, there is limitation in preparation of sustained release capsules with desired strengths.

As ibuprofen is having very low melting point, there is a particularly disadvantageous effect in the preparation of controlled-release products which frequently contain fatty compositions or similar low melting auxiliaries like lipids such as hydrogenated oils or paraffins according to JP No. 84-122,425 A.

As melting point of ibuprofen is very low, increase of temperature during the process of preparation of dosage form may lead to degradation of active ingredient. Hence, any process of preparation of ibuprofen dosage form using temperature higher than the melting point of active ingredient causes instability of the active ingredient.

Moreover, the processes of preparation of sustained release compositions known in the art, need a considerable expenditure of work for coating and evaporating the solvent in time-consuming and repeated operations.

Though sustained release composition of ibuprofen is the most suitable dosage form considering its pharmacokinetic profile, the known sustained release dosage forms in the art are having so many drawbacks like higher dosage size; complex, time consuming and costly method of preparation; stability problem. So there is a need to develop a sustained release composition which will solve most of the problems of the current composition.

To reduce these problems, it is desirable to minimize the inclusion of pharmaceutical excipients with the active agent to have high drug load. Also it is desirable to prepare the composition in a simple process without use of solvents especially organic solvents and at a temperature below the melting point of the active ingredient.

Summary of the Invention

Accordingly, one of the objects of the present invention to provide a sustained release pharmaceutical composition with high drug loading comprising ibuprofen or a pharmaceutically acceptable salt thereof in an amount of about 80% or more, preferably about 85% in the weight of the active ingredient based on the total weight of the composition.

Accordingly, another object of the present invention to provide a sustained release pharmaceutical composition comprising ibuprofen or a pharmaceutically acceptable salt thereof prepared by hot melt extrusion method using processing temperature below the melting point of active ingredient.

Accordingly, another object of the present invention to provide a sustained release pharmaceutical composition comprising ibuprofen or a pharmaceutically acceptable salt thereof in an amount of 80% or more in the weight of the active ingredient based on the total weight of the composition prepared by hot melt extrusion method.

Accordingly, another object of the present invention to provide a sustained release pharmaceutical composition comprising ibuprofen or a pharmaceutically acceptable salt thereof prepared by hot melt extrusion method using processing temperature below 70°C.

Accordingly, another object of the present invention to provide a sustained release pharmaceutical composition comprising ibuprofen or a pharmaceutically acceptable salt thereof in an amount of 80% or more in the weight of the active ingredient based on the total weight of the composition prepared by hot melt extrusion method using processing temperature below the melting point of active ingredient.

Accordingly, another object of the present invention to provide a sustained release pharmaceutical composition comprising ibuprofen or a pharmaceutically acceptable salt thereof in an amount of 80% or more in the weight of the active ingredient based on the

total weight of the composition prepared by hot melt extrusion method using processing temperature below 70°C.

Accordingly, another object of the present invention to provide a process of preparation of a pharmaceutical composition comprising ibuprofen or a pharmaceutically acceptable salt thereof in an amount of 80% or more in the weight of the active ingredient based on the total weight of the composition.

Accordingly, another object of the present invention to provide to a process of preparation of a pharmaceutical composition comprising ibuprofen or a pharmaceutically acceptable salt thereof in an amount of 80% or more in the weight of the active ingredient based on the total weight of the composition by hot melt extrusion method.

Accordingly, another object of the present invention to provide a process of preparation of a pharmaceutical composition comprising ibuprofen or a pharmaceutically acceptable salt thereof by hot melt extrusion method using processing temperature below the melting point of active ingredient.

Accordingly, another object of the present invention to provide a process of preparation of a pharmaceutical composition comprising ibuprofen or a pharmaceutically acceptable salt thereof by hot melt extrusion method using processing temperature below 70°C.

Detailed Description of the Invention

The present invention relates to a sustained release composition of ibuprofen or pharmaceutically acceptable salt thereof. In one of the embodiment, the present invention relates to a sustained release composition of ibuprofen or pharmaceutically acceptable salt thereof, comprising high drug load of active ingredient. The sustained release pharmaceutical composition with high drug loading comprising ibuprofen or a pharmaceutically acceptable salt thereof in an amount of about 80% or more, preferably about 85% in the weight of the active ingredient based on the total weight of the composition.

In another embodiment, the present invention relates to a sustained release pharmaceutical composition comprising ibuprofen or a pharmaceutically acceptable salt thereof prepared by hot melt extrusion method using processing temperature below the melting point of active ingredient.

The term “ibuprofen” includes various forms of ibuprofen such as hydrates, solvates, polymorphs, isomers, stereoisomers, enantiomers, racemates, esters, prodrugs, complexes or mixture thereof and all other forms known in the art. Ibuprofen can be present in different physical forms, e.g. in an amorphous form, in one or several crystal form (s) (e.g. anhydrous, solvated or hydrated forms), in the form of mixture of different crystal forms (e.g. anhydrous, solvated or hydrated forms) or as a mixture of an amorphous form and crystal form (s) (e.g. anhydrous, solvated or hydrated forms). Each of these forms is included in the term "ibuprofen" as used in the present invention.

The term "pharmaceutical composition" as used herein refers to a solid dosage form suitable for administration, such as a tablet, capsule, caplets, powders, pellets, beads, microspheres, granules, pill, etc.

The term "pharmaceutically acceptable salt" means a salt which is acceptable for administration to a patient, such as a mammal (e.g., salts having acceptable mammalian safety for a given dosage regime). Such salts can be derived from pharmaceutically acceptable inorganic or organic bases and from pharmaceutically acceptable inorganic or organic acids.

The active ingredient, active agent and drug herein can be interchangeably used.

As used herein, "%" refers to the weight percent of a substance as it relates to the overall composition unless otherwise indicated.

The term "comprising", which is synonymous with "including", "containing", or "characterized by" here is defined as being inclusive or open-ended, and does not exclude

additional, unrecited elements or method steps, unless the context clearly requires otherwise.

Sustained release rate of an active agent is the rate of release of the active agent other than that of an immediate release formulation as per USP. Examples of sustained release includes but not limited to slow release, controlled release, prolonged release, extended release, timed release etc., which terms are generally known in the art and to the extent they mean a release other than an immediate release.

The sustained release composition of ibuprofen or pharmaceutically acceptable salt thereof comprising high drug load of active ingredient is relatively small size and accommodate more drug in the dosage form. The sustained release pharmaceutical composition with high drug loading comprises ibuprofen or a pharmaceutically acceptable salt thereof in an amount of about 80% or more, preferably about 85% in the weight of the active ingredient based on the total weight of the composition. The remaining of the dosage form is release rate controlling agents and optionally one or more excipients required for the dosage form preparation.

Release rate controlling agents are defined as hydrophilic or hydrophobic agents, which can be polymeric or non-polymeric and which are capable of controlling the release rate of an active agent, preferably the rate controlling agent is a hydrophilic agent. The release controlling agents may be natural, semi-synthetic and synthetic agents or mixtures thereof. The release controlling agent can be used in the concentration ranges from about 1 to about 20 % w/w of the total composition, preferably from about 1 to about 15 % w/w of the total composition.

In one embodiment of the present invention, a sustained release composition comprises ibuprofen or a pharmaceutically acceptable salt thereof in an amount of about 80% or more in the weight of the active ingredient based on the total weight of the composition, mixed with at least one hydrophilic release rate controlling agent. The hydrophilic release rate controlling agents preferably, hydrophilic polymers gel and dissolve slowly in

gastrointestinal track thereby allowing ibuprofen to diffuse from the gel for sustained action.

The non limiting examples of hydrophilic release rate controlling agents suitable for use in the sustained release pharmaceutical composition include: one or more natural or partially or totally synthetic hydrophilic gums such as acacia, gum tragacanth, locust bean gum, guar gum, or karaya gum, celluloses and cellulose derivatives such as methylecllulose, hydroxymethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, carboxyethylcellulose, hydroxybutylmethyl cellulose, sodium carboxymethyl cellulose, polycarbonates, polyalkylenes, polyalkylene glycols such as poly(ethylene glycol), polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols (PVA), polyvinyl phenol, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone (PVP), polyglycolides, polysiloxanes, polyurethanes, polystyrene, polylactides, poly (butyric acid), poly (valeric acid), poly(lactide-co-glycolide), poly (ethyleneterephthalate), poly (lactide-co-caprolactone), polyanhydrides (e.g., poly (adipic anhydride)), polyorthoesters, poly(fumaric acid), poly(maleic acid), polyvinyl acetate, polystyrene; polymers of acrylic and methacrylic esters; carbomer, carbopol®; proteinaceous substances such as agar, pectin, carrageen, gluten, serum albumin, or collagen, chitosan, oligosaccharides and alginates; and other hydrophilic polymers such as carboxypolymethylene, gelatin, casein, bentonite, magnesium aluminum silicate, polysaccharides, modified starch derivatives, and other hydrophilic polymers known to those of skill in the art or a combination of such polymers, preferably hydrophilic release rate controlling agents are hydroxymethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, polyvinylpyrrolidone (PVP) and polyvinyl alcohols (PVA); more preferably hydroxypropyl methylcellulose and polyvinylpyrrolidone (PVP).

In one embodiment of the present invention, a sustained release composition comprises ibuprofen or a pharmaceutically acceptable salt thereof in an amount of about 80% or more in the weight of the active ingredient based on the total weight of the composition, mixed with at least one hydrophobic release rate controlling agent.

The non limiting examples of hydrophobic release rate controlling agents includes but are not limited to hydrogenated vegetable oil, but other suitable agents include purified grades of beeswax; fatty acids; long chain fatty alcohols, such as cetyl alcohol, myristyl alcohol, and stearyl alcohol; glycerides such as glyceryl esters of fatty acids like glyceryl monostearate, glyceryl distearate, glyceryl esters of hydrogenated castor oil and the like; oils such as mineral oil and the like, or acetylated glycerides; ethyl cellulose, stearic acid, paraffin, carnauba wax, talc; and the stearate salt(s) such as calcium, magnesium, zinc, cellulose derivatives like ethylcellulose and other materials known to the person skilled in the art; preferably ethylcellulose and stearic acid.

A type of low viscosity polyvinylpyrrolidone is for instance that available on the market under the trademark Kollidon® 30 and a high viscosity polyvinylpyrrolidone is for instance that available on the market under the trademark Kollidon® 90 and Kollidon® SR of the company BASF AKTIENGESELL-SCHAFT of Ludwigshafen, Federal Republic of Germany. Ethylcellulose is for instance that available on the market under the trademark Ethocel® of Dow Chemicals Ltd is used in the composition.

In one embodiment of the present invention, a sustained release composition comprises ibuprofen or a pharmaceutically acceptable salt thereof in an amount of about 80% or more in the weight of the active ingredient based on the total weight of the composition, mixed with at least one hydrophilic release rate controlling agent and at least one hydrophobic release rate controlling agent.

In one embodiment of the present invention, a sustained release composition comprises ibuprofen or a pharmaceutically acceptable salt thereof prepared by hot melt extrusion method using processing temperature below the melting point of the active ingredient (i.e. below 75°C), preferably below 70°C.

In one embodiment of the present invention, a sustained release composition comprises ibuprofen or a pharmaceutically acceptable salt thereof in an amount of about 80% or more in the weight of the active ingredient based on the total weight of the composition

prepared by hot melt extrusion method using processing temperature below the melting point of the active ingredient (i.e. below 75°C), preferably below 70°C.

In one embodiment of the present invention, a sustained release composition comprises ibuprofen or a pharmaceutically acceptable salt thereof in an amount of about 80% or more in the weight of the active ingredient based on the total weight of the composition, mixed with at least one hydrophilic release rate controlling agent, prepared by hot melt extrusion method using processing temperature below the melting point of the active ingredient (i.e. below 75°C), preferably below 70°C.

In one embodiment of the present invention, a sustained release composition comprises ibuprofen or a pharmaceutically acceptable salt thereof in an amount of about 80% or more in the weight of the active ingredient based on the total weight of the composition, mixed with at least one hydrophobic release rate controlling agent, prepared by hot melt extrusion method using processing temperature below the melting point of the active ingredient (i.e. below 75°C), preferably below 70°C.

In one embodiment of the present invention, a sustained release composition comprises ibuprofen or a pharmaceutically acceptable salt thereof in an amount of about 80% or more in the weight of the active ingredient based on the total weight of the composition, mixed with at least one hydrophilic release rate controlling agent and at least one hydrophobic release rate controlling agent, prepared by hot melt extrusion method using processing temperature below the melting point of the active ingredient (i.e. below 75°C), preferably below 70°C.

Another embodiment of the invention relates to a process for preparing a sustained release composition comprises ibuprofen or a pharmaceutically acceptable salt thereof in an amount of about 80% or more in the weight of the active ingredient based on the total weight of the composition by employing to the following steps,

a) sieving and mixing active ingredient and a release rate controlling agent,
b) heating the mixture in a hot melt extrusion to prepare a solid dispersion,

c) cooling the solid dispersion to room temperature, milling to achieve suitable size
d) optionally filling into a capsule or compressing into a tablet.

Another embodiment of the invention relates to a process for preparing a sustained release composition comprises ibuprofen or a pharmaceutically acceptable salt thereof in an amount of about 80% or more in the weight of the active ingredient based on the total weight of the composition by employing to the following steps,

a) sieving and mixing active ingredient and a release rate controlling agent,
b) heating the mixture at a temperature below the melting point of the active ingredient in a hot melt extrusion to prepare a solid dispersion,
c) cooling the solid dispersion to room temperature, milling to achieve suitable size,
d) optionally filling into a capsule or compressing into a tablet.

Another embodiment of the invention relates to a process for preparing a sustained release composition comprises ibuprofen or a pharmaceutically acceptable salt thereof in an amount of about 80% or more in the weight of the active ingredient based on the total weight of the composition by employing to the following steps,

a) sieving and mixing active ingredient and a release rate controlling agent,
b) heating the mixture at a temperature below 70°C in a hot melt extrusion to prepare a solid dispersion,
c) cooling the solid dispersion to room temperature, milling to achieve suitable size
d) optionally filling into a capsule or compressing into a tablet.

In one embodiment, the compositions can be in the form of a tablet, capsule, caplets, powders, pellets, beads, microspheres, granules, pill, etc. The preferred dosage form is capsule and tablet. The dosage form is preferably suitable for oral application.

In another embodiment of the invention relates to a sustained release pharmaceutical composition with high drug loading comprising ibuprofen or a pharmaceutically acceptable salt thereof in an amount of about 80% or more in the weight of the active ingredient based on the total weight of the composition and one or more excipients such

as binders, diluents, lubricants/glidants, disintegrating agents, surfactants, solvents, and coloring agents.

Excipients such as diluents, lubricants and glidants commonly used in pharmaceutical composition may be used and reference is made to the extensive literature on suitable substances [see in particular "Handbook of Pharmaceutical Excipients" edited by Raymond C Rowe, Paul J Sheskey & Sian C Owen (2006)] the content of which is incorporated herein by reference.

Other excipients are also used in the preparation of the pharmaceutical composition like diluents such as microcrystalline cellulose, powdered cellulose, lactose (anhydrous or monohydrate), compressible sugar, fructose, dextranes, other sugars such as mannitol, sorbitol, lactitol, saccharose or a mixture thereof, siliconised microcrystalline cellulose, calcium hydrogen phosphate, calcium carbonate, calcium lactate or mixtures thereof. A further preferred diluent that also causes reduced sticking properties of tablets to the equipment used for tabletting is silica, preferably colloidal or fumed silica. Preferably, the excipients include at least one diluent selected from microcrystalline cellulose and lactose monohydrate.

Non-limiting examples of binders include one or more of gum acacia, cholesterol, tragacanth, stearic acid, gelatin, casein, lecithin (phosphatides), carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcelluloses, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose phthalates, microcrystalline celluloses, noncrystalline celluloses, polyvinylpyrrolidones (povidones or PVP), cetostearyl alcohol, cetyl alcohol, cetyl esters wax, dextrates, dextrin, lactose, dextrose, glyceryl monooleate, glyceryl monostearate, glyceryl palmitostearate, polyoxyethylene alkyl ethers, polyethylene glycols, polyoxyethylene castor oil derivatives, polyoxyethylene stearates, polyvinylalcohols, and mixtures thereof.

Non-limiting examples of disintegrants include starches, modified starches, croscarmellose sodium, crospovidones, and sodium starch glycolate.

The composition according to the invention can also comprise lubricants, such as stearic acid, magnesium stearate, calcium stearate, sodium lauryl sulphate, hydrogenated vegetable oil, hydrogenated castor oil, sodium stearyl fumarate, macrogols, or mixtures thereof. It is preferred that the excipients include at least one lubricant, selected from stearic acid, magnesium stearate, calcium stearate and sodium lauryl sulphate, more preferably from stearic acid, magnesium stearate and calcium stearate. The composition can also comprises glidants such as colloidal silica (e. g. Aerosil®), magnesium trisilicate, powdered cellulose, starch, talc, and tribasic calcium phosphate.

Useful coloring agents include FDA approved colorants and examples are iron oxides, lake of tartrazine, allura red, lake of quinoline yellow, and lake of erythrosine.

One or more of these additives may be selected and used by the skilled artisan having regard to the particular desired properties of the pharmaceutical composition by routine experimentation and without any undue burden. The absolute amounts of each additive and the amounts relative to other additives is similarly dependent on the desired properties of the pharmaceutical composition and may also be chosen by the skilled artisan by routine experimentation without undue burden.

The composition prepared can be packaged using appropriate packaging materials such as containers and closures composed of polyethylene (high density polyethylene or low density polyethylene), polypropylene, glass, stainless steel, etc. Also useful are various blisters or strips composed of aluminum or high-density polypropylene, or polyvinyl chloride, or polyvinyl chloride (PVC) coated with polyvinylidene dichloride (PVDC), generally termed PVC/PVDC.

The following experimental details are set forth to aid in an understanding of the invention, and are not intended, and should not be construed, to limit in any way the invention set forth in the claims that follow thereafter. A person skilled in the art will readily recognize the various modifications and variations that may be performed without altering the scope of the present invention. Such modifications and variations are

encompassed within the scope of the invention and the examples do not in any way limit the scope of the invention.

Examples:

Ingredients	Example 1 (%w/w)	Example 2 (%w/w)	Example 3 (%w/w)	Example 4 (%w/w)	Example 5 (%w/w)	Example 6 (%w/w)	Example 7 (%w/w)
Ibuprofen	90	85	85	88	85	85	88
Kollidon SR	6	9	7	8	-	-	-
Kollidon 30	3	5	7	3	9	5	3
Kollidon 90	-	-	-	-	-	-	-
Ethocel 4 cps	-	-	-	-	5	5	8
Aerosil 200	1	1	1	1	1	1	1

Ingredients	Example 8 (%w/w)	Example 9 (%w/w)	Example 10 (%w/w)	Example 11 (%w/w)	Example 12 (%w/w)	Example 13 (%w/w)	Example 14 (%w/w)
Ibuprofen	85	85	85	85	85	85	85
Kollidon SR	-	-	10	-	-	-	-
Kollidon 30	10	-	-	10	-	10	10
Kollidon 90	-	10	-	-	10	-	-
PEG 6000	4	4	4	4	4	3	4
Aerosil 200	1	1	1	1	1	-	-
Talc	-	-	-	-	-	2	1

Ingredients	Example 15 (%w/w)	Example 16 (%w/w)	Example 17 (%w/w)
Ibuprofen	80	80	85
Stearic acid	14	9	9
HPMC K 100 LVCR	5	10	5
Aerosil 200	1	1	1

Weighed required quantity of ibuprofen and other excipients, sifted through # 40 mesh and mixed well. The mixture was heated in a hot melt extrusion to prepare the solid dispersion. The temperature of the extruder was maintained between 60-69^{0}C throughout the heating process. The resulting dispersion was cooled to the room temperature while stirring to obtain a solid ibuprofen dispersion agglomeration. The resulting product was

either then grounded with a high-speed grinder, sieved to obtain a fused solid dispersion powder or pellets were prepared from the solid dispersion. Both powder and pellets were filled in the capsules of suitable size.

Dissolution study:

The *In vitro* dissolution test was performed at 30 rpm with USP apparatus I (Basket), using pH 6.0 phosphate buffer as a dissolution media. The dissolution medium used was 900 ml; maintained at 37 ± 0.5°C.

The dissolution profiles of various formulations tested are as below:

Time (hr)	Example 1 (Powder)	Example 2 (Powder)	Example 2 (Pellets)	Example 3 (Pellets)	Example 4 (Pellets)	Example 5 (Pellets)	Example 6 (Pellets)
	Cumulative % drug release						
1	26	20	18	20	21	13	18
2	47	41	33	36	35	25	31
4	74	69	53	57	55	41	47
7	94	81	69	75	71	57	62

Time (hr)	Example 6 (Powder)	Example 7 (Pellets)	Example 8 (Pellets)	Example 9 (Pellets)	Example 10 (Pellets)	Example 11 (Pellets)
	Cumulative % drug release					
1	21	15	20	22	15	17
2	30	27	38	41	26	35
4	45	42	68	69	42	62
7	56	57	89	86	57	89

Time (hr)	Example 12 (Pellets)	Example 13 (Pellets)	Example 14 (Pellets)	Example 15 (Powder)	Example 16 (Powder)	Example 17 (Powder)
	Cumulative % drug release					
1	25	19	21	20	18	27
2	46	37	42	35	33	36
4	71	61	71	50	46	47
7	88	81	91	75	65	55

CLAIMS:

1. A sustained release pharmaceutical composition comprising ibuprofen or a pharmaceutically acceptable salt thereof in an amount of 80% or more in the weight of the active ingredient based on the total weight of the composition.

2. The sustained release pharmaceutical composition according to claim 1 is prepared by hot melt extrusion method.

3. A sustained release pharmaceutical composition comprising ibuprofen or a pharmaceutically acceptable salt thereof is prepared by hot melt extrusion method using processing temperature below the melting point of active ingredient.

4. The sustained release pharmaceutical composition according to claim 3 is prepared by hot melt extrusion method using processing temperature below 70°C.

5. The sustained release pharmaceutical composition according to claim 2 is prepared by hot melt extrusion method using processing temperature below the melting point of active ingredient.

6. The sustained release pharmaceutical composition according to claim 5 is prepared by hot melt extrusion method using processing temperature below 70°C.

7. Process of preparation of a pharmaceutical composition comprising ibuprofen or a pharmaceutically acceptable salt thereof in an amount of 80% or more in the weight of the active ingredient based on the total weight of the composition.

8. The process of preparation of a pharmaceutical composition according to claim 7 is prepared by hot melt extrusion method.

9. The process of preparation of a pharmaceutical composition according to claim 8 is prepared by hot melt extrusion method using processing temperature below the melting point of active ingredient.

10. The process of preparation of a pharmaceutical composition according to claim 9 is prepared by hot melt extrusion method using processing temperature below 70°C.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2013/061370

A. CLASSIFICATION OF SUBJECT MATTER

A61K 9/14(2006.01)i; A61K 9/22(2006.01)i; A61K 31/167(2006.01)i

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 9/-; A61K 31/-

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)

CNPAT, CNKI, WPI ,EPODOC:melt, sustained, release, extrusion, hot, ibuprofen, ingredient, temperature, composition

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9614058A1 (EUROCELTIQUE SA. ET AL.) 17 May 1996 (1996-05-17) claim 1, page 11, paragraph 3, page 13, paragraph 4	1-10
A	US 2008311162A1 (DARMUZEY OLIVIA ET AL.) 18 December 2008 (2008-12-18) claims 1-10	1-10

☐ Further documents are listed in the continuation of Box C. ☑ 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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 April 2014	**16 May 2014**

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2013/061370

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