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(54) Title: NOVEL INJECTABLE COMPOSITION OF DICLOFENAC SODIUM

(57) Abstract: The present invention relates to injectable preparations containing 75 mg to 100 mg of water soluble salts of diclofenac in about 1ml injection solution, wherein the pH of the solution is maintained at 8-9 using alkali. The composition is suitable for parenteral administration through intramuscular, intravenous, subcutaneous, intradeltoid, intragluteal route of administration. More specifically, the injectable preparations comprise 75 mg/ml of diclofenac sodium in a solvent system containing water and two or more solubilizers along with antioxidants and buffering agents. The invention also provides a method of preparing the injectable preparations.

NOVEL INJECTABLE COMPOSITION OF DICLOFENAC SODIUM

FIELD OF THE INVENTION:

The present invention relates to injectable preparation of diclofenac and water solubles salts thereof which can be administered via intradeltoid route along with intragluteal, subcutaneous and slow intravenous route. The invention further provides a process of preparing said preparation and its use in treatment of acute or chronic pain & inflammatory conditions.

BACKGROUND OF THE INVENTION:

Diclofenac belongs to a class of non-steroidal anti-inflammatory drugs (NSAIDs) with antipyretic and analgesic properties. NSAIDs are usually indicated for the treatment of acute or chronic pain and inflammatory conditions. Similar to other NSAIDS, diclofenac is generally indicated for rheumatoid arthritis, osteoarthritis, Dysmenorrhea (menstrual pain), Headache and migraine, Postoperative pain and also for mild to moderate pain after tissue injury. It has also been used in some countries for the management of actinic keratosis and fever. Eye drops of Diclofenac Sodium are used for the prevention of intra-operative miosis during cataract extraction, for the treatment of inflammation after surgery or accidental trauma, and for the relief of ocular signs and symptoms of seasonal allergic conjunctivitis.

Diclofenac can be administered by oral as well as by parenteral route. Oral doses of diclofenac range from 100-200mg/day while parenteral doses range from 75 to 150mg/day.

Modified-release preparations of Diclofenac Sodium are available for oral use. Diclofenac has also been given in equivalent oral doses as the free acid in tablet forms as dispersible preparations for short-term treatment up to 3 months period. Diclofenac is also given orally as the potassium salt.

Diclofenac Sodium may also be given by deep intramuscular injection into the gluteal muscle in a dose of 75 mg once daily or, if required in severe conditions, 75 mg twice daily. Diclofenac Sodium may also be given as a continuous or intermittent intravenous infusion in glucose. 5% or sodium chloride 0.9% (both previously buffered with sodium bicarbonate) or as a bolus intravenous injection. For the treatment of postoperative pain a dose of 75 mg may be given over 30 to 120 minutes or as a bolus injection. The dose may be repeated once after 4 to 6 hours if necessary. To prevent postoperative pain, as initial dose of 25 to 50 mg Diclofenac sodium may be given after surgery over 15 to 60 minutes followed by 5 mg / hour to a maximum of 150 mg daily. Alternatively, the initial dose may be given as a bolus injection over 5 to 60 seconds followed by additional injections up to the maximum daily dosage; this may be repeated after 4 to 6 hours if necessary although the total dose should not exceed the maximum daily dose of 150 mg. The maximum period recommended for parenteral use is 2 days. Diclofenac Sodium is also used intramuscularly in renal colic in a dose of 75 mg repeated once after 30 minutes if necessary.

Diclofenac injections have to be administered deep intramuscularly and are generally administered intraguluteally as the injection causes substantial pain at the site of injection and its administration in the deltoid (upper arm) region is generally avoided.

Pain at the site of injection is due to relatively large volume of the injection (3 mL) and the fact that the injection solution contains relatively high volumes of propylene glycol, which is a known irritant upon parenteral administration. As mentioned in Applied Nursing Research, Vol. 16, No. 2, August, 2002 empirical data from published research reports, recommendations of established advisory panels and

generally accepted scientific principals conclude that only small volumes of medication (2 ml or less) should be given in the deltoid site.

On the other hand intramuscular injection volumes above 2 ml and up to 5 ml must be administered into the gluteal muscle. This is because; the gluteal muscle is larger as compared to the deltoid muscle and hence can accommodate the relatively larger injected volume (3-5 ml). On the other hand if this relatively larger volume is injected into the deltoid muscle, which has relatively lesser muscle mass, the injected solution will cause excessive stretching of the muscle fiber, thereby damaging the local muscle tissue and hence cause pain and discomfort to the patient.

Commercially available VOLTAROL® ampoules comprise 75mg/3ml solution of Diclofenac sodium which is used as Intra muscular injection. The formulation must be diluted with 100-500ml of either sodium chloride solution (0.9%) or glucose solution (5%) buffered with sodium bicarbonate solution (0.5ml 8.4% or 1ml 4.2%) so that only clear solutions are used as intravenous infusion. The sodium metabisulphite present in solution for injection can also lead to isolated severe hypersensitivity reactions and bronchospasm.

Similarly, another marketed product DYLOJECT® is 75mg/2ml solution for injection of diclofenac sodium. It can be given as intravenous bolus injection for the treatment or prevention of post-operative pain in supervised healthcare system or as an intramuscular injection for the treatment of acute pain and inflammatory conditions. It cannot be given as IV infusion. It is HP-beta-cyclodextrin complex and

contains monothioglycerol as antioxidant. These products Dyloject and Voltarol cause thrombophlebitis in 5.4% and 4.9% patients respectively.

Further, the high pH of the marketed Diclofenac product requires rendering Diclofenac sodium soluble and the hyper-osmolar nature of the formulation contribute to the discomfort which is frequently experienced at the site of the injection when administered intramuscularly.

Further, injectable Diclofenac preparations contain relatively high amounts (18-40%) of propylene glycol, which is known irritant.

US Patent No.3558690 discloses injectable preparations comprising water soluble salts of substituted phenyl acetic acid derivatives (diclofenac being one such compound) in concentrations of 0.5 to 5 %.

PCT application number WO 9603121 A1 describes a antiphlogistic, analgesic, antipyretic parenteral preparation comprising diclofenac, its salt, or both, a surfactant, co-surfactant, water, at pH of 3-10 and optionally comprising an oily component, that can exhibit sustained therapeutic levels of diclofenac in plasma and which does not cause pain at site of injection.

US5389681 discloses to a pharmaceutical composition in the form of a sterilizable parenteral solution comprising a diclofenac salt and stabilizers, such as ethyl lactate combined with glutathione or N-acetylcysteine. The invention describes a method for treating pain, inflammation or rheumatic diseases.

US555465 discloses an antiphlogistic, analgesic, antipyretic parenteral preparation comprising diclofenac, its salt, or both, a surfactant, and co-surfactant, and water, and having a pH of 3-10 is provided.

EP0658347A2 covers a method of preparing an injectable pharmaceutical or veterinary composition which comprises either diclofenac or a salt thereof and 2-hydroxypropyl beta-cyclodextrin, or an inclusion complex of diclofenac or a salt thereof and 2-hydroxypropyl beta-cyclodextrin, includes the step of dissolving either the diclofenac or salt thereof and the 2-hydroxypropyl beta-cyclodextrin, or the inclusion complex, in water to form a solution, the water having been acidified to a pH such that the pH of the solution is from 6.0 to 8.5 inclusive, in the absence of a phosphate buffer.

US2005/0238674 relates to a stable parenteral aqueous solutions comprising either (a) diclofenac or a pharmaceutically acceptable diclofenac salt and a cyclodextrin, or (b) an inclusion complex of diclofenac or a pharmaceutically acceptable diclofenac salt and a cyclodextrin, or a mixture of (a) and (b), which are suitable for intramuscular and intravenous administration. The solutions contain diclofenac or diclofenac salt, cyclodextrin, and an antioxidant selected from monothioglycerol, or a combination of ethylene-diamine tetra-acetic acid and N-acetyl-cysteine. According to the invention, the parenteral solution is in the form of a unit dose that does not exceed 2 milliliters. The stabilized injectable solution of the invention may be intravenously administered by admixture with non-dextrose infusion fluids.

US2011/0275717 discloses a pharmaceutical formulation comprising a pharmaceutically acceptable salt of Diclofenac, at least one polyoxyalkylene ester of a hydroxyl fatty acid, water, and, optionally, a co-solvent. This composition has a limitation with use of fatty acid derivative and requires special carriers.

US5679660 teaches about the method of preparing an injectable pharmaceutical or veterinary composition which comprises either Diclofenac or a salt thereof and 2-hydroxypropyl beta-cyclodextrin, or an inclusion complex of Diclofenac or a salt thereof and 2-hydroxypropyl beta-cyclodextrin with preferred' concentration of Diclofenac of 25 mg/ml. The volume of injection prepared by this method contains 75mg/3ml Diclofenac which can be painful as IM dosage form. The use of beta cyclodextrin has also toxicity problem which is always questioned for IV administration.

US20080153914 discloses injectable formulations of water-soluble salts of diclofenac in Glycofurol. However, Glycofurol is known as a tissue irritant.

US 4,614,741 teaches about the depot injectable containing anti-inflammatory agents like Diclofenac or Diclofenac Sodium, which was prepared in 10-60% of suspending agents selected from the group consisting of biscoleo, isopropyl myristate, ethyl oleate, castor oil, sesame oil, arachis oil, cottonseed oil, almond oil, olive oil, neats foot oil, neutral oil and maize oil, for intramuscular administration. However, use of such suspending agent provides painful and viscous injection that causes swelling or pain at the site of injection.

US 4,711,906 discloses an aqueous, stable, relatively concentrated solution of Diclofenac, which contain a mixture of propylene glycol and polyethylene glycol in defined quantitative proportions. The solutions preferably contain a local anesthetic such as lidocaine and a reducing agent as stabilizer. However, use of propylene glycol makes the injection painful and lignocaine is added to alleviate such painful administration.

The present invention attempts to provide preparations comprising 75mg of water soluble salt of diclofenac & reducing the volume of injection to 1ml resulting in the minimization of pain at site of injection. Further, smaller volume enables administration in the deltoid muscle.
Further, inventors find out simple & economical process for the preparation, using cheaper excipients.

OBJECTS OF THE INVENTION:

It is an objective of invention to provide an injectable composition comprising therapeutically effective amount of diclofenac or water soluble salts thereof, in a solvent system comprising two or more solubilizers and water.

Another objective of invention is to provide a therapeutic effective dose of 75mg of water soluble salts of diclofenac in just one ml, without significantly raising the viscosity of the injection preparation.

Another objective of invention is to provide a composition comprising diclofenac suitable to be given through multiple routes viz., intramuscular or intravenous or subcutaneous, intradeltoid or intragluteal route of administration.

Another objective of invention is to provide patient compliant aqueous composition of diclofenac which is not irritating or painful.

Another objective of invention is to provide simple & economical process for the preparation.

Still another object of the invention is to provide an economical and physiologically effective composition comprising diclofenac or water soluble salts thereof.

SUMMARY OF THE INVENTION:

In an embodiment, the present invention provides an injectable preparation comprising 75mg/ml to 100 mg/ml of diclofenac sodium or therapeutically equivalent amounts of water soluble salts of diclofenac in a solvent system comprising two or more solublizers in an amount ranging from 0.01 to 40% w/v and water and optionally, one or more antioxidant (s) in an amount ranging from 0.01 to 0.5% w/v and/or one or more buffering agent (s) in an amount ranging from 0.05 to 1.0% w/v, wherein the pH of the preparation is maintained at 8-9.

In one embodiment, the invention provides an injectable preparation comprising 75 mg/ml of diclofenac sodium in a solvent system comprising hydroxypropyl-beta-cyclodextrin and polysorbate 80 as solublizers and water.

In another embodiment, the water soluble salts of diclofenac are selected from the group consisting of diclofenac potassium, diclofenac diethyllamine, diclofenac diethanolamine and diclofenac beta-dimethyl aminoethanol.

In another embodiment, the amount of two or more solublizers in the preparation is between 0.01 to 40% w/v. The solublizers may be selected from, but not limited to hydroxypropyl-beta-cyclodextrin, polysorbate 80, Cremophor EL, glycofurol, benzyl alcohol, polyethylene glycol, Cremophor RH 40 and hydrogenated soy phosphatidylcholine.

In another embodiment, the amount of antioxidant (s) in the composition is between 0.01 to 0.5% w/v. The antioxidant (s) may be selected from, but not limited to monothioglycerol, sodium bisulphate and sodium metabisulphate.

In another embodiment, the amount of the buffering agent is between 0.05 to 1.0% w/v. The buffering agent (s) may be selected from, but not limited to potassium dihydrogen phosphate, phosphate buffer and bicarbonate buffer.

In another embodiment, the solvent system comprises hydroxypropyl-beta-cyclodextrin in an amount ranging from 0.01 to 40% w/v, polysorbate 80 in an amount ranging from 0.10 to 0.5% w/v and water, and potassium dihydrogen phosphate in an amount ranging from 0.05 to 1.0 % w/v.

In another embodiment, the invention provides a method for preparation of injectable preparation comprises suspending 75mg diclofenac sodium or water soluble salt of diclofenac in the solvent system comprising two or more solubilizers in water for injection, with stirring under constant nitrogen purging, optionally, adding one or more buffering agent (s) and/or antioxidant (s), adjusting pH between 8-9 using an alkali, further diluting with water for injection to achieve concentration of 75mg in 1 ml, sterilizing by sterile filtration and filling in 1 ml ampoules flushed with inert gas prior to sealing.

In still another embodiment, the invention provides use of composition comprising 75 mg/ml of diclofenac sodium or water soluble salts of diclofenac in a solvent system comprising two or more solublizers 0.01 to 40% w/v and water and optionally, one or more antioxidant (s) 0.10 to 0.5% w/v and/or buffering agent 0.05 to 1.0 % w/v for treatment or prevention of acute or chronic pain and inflammatory conditions selected from rheumatoid arthritis, osteoarthritis, dysmenorrhea (menstrual pain), headache and migraine, postoperative pain and also for mild to moderate pain after tissue injury, ankylosing spondylitis, pain control of total hip replacement arthroplasty, actinic keratosis and fever, accidental trauma.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

DETAILED DESCRIPTION OF THE INVENTION:

The "composition" or “formulation” as used herein refers to parenteral preparations include injections, intravenous infusions, powders for injections or intravenous infusions, concentrates for injections or intravenous infusions, implants.

The “buffering agent” as used herein refers to either a weak acid or weak base. Buffering agents are usually added to water to form a buffer solution, which only slightly changes its pH in response to other acids and bases being combined with it, particularly a strong acid or a strong base.

The “antioxidant” as used herein refers to substance that inhibits the oxidation of other substances. They are widely used to prevent the oxidative degradation of product.

"pharmaceutically acceptable" is meant those salts and esters which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use.

The invention provides a composition comprising Diclofenac or salt thereof. Diclofenac salt is selected from Diclofenac sodium, Diclofenac potassium, Diclofenac diethylamine, Diclofenac diethanolamine or Diclofenac beta-dimethyl aminoethanol.

Poor aqueous solubility of the Sodium salt of Diclofenac has a particularly high tendency to crystallize from aqueous and organic solutions. The invention provides therapeutically effective amount of Diclofenac or salts thereof in an aqueous composition suitable to be administered by multiple routes.

In some embodiments, the invention provides compositions comprising additional excipients e.g. buffering agents, solubilizers and antioxidants.

In another embodiment, the composition comprises solubilizers at a concentration in the range of 0.01 to 40%.

Preferably, the Solubilizers include but not limited to hydroxypropylbetadex (Hydroxypropyl-beta-cyclodextrin), polysorbate 80 (Tween 80), Cremophor EL, glycofurol, acetic acid, N[3-hydroxyethyllactamide, benzyl alcohol, polyethylene glycol, Cremophor RH 40, d-alpha-tocopherol polyethylene glycol 1000 succinate, sulfobutylether-beta-cyclodextrin,L-alpha-dimyristoylphosphatidylglycerol, hydrogenated soy phosphatidylcholine.

Preferably, the antioxidant includes but not limited to monothioglycerol,thioglycerols, acetyl cysteine, sodium bisulphate, sodium metabisulphate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ascorbates, ascorbylpalmitate, methylparaben, propylparaben, thiomersal and mixed Tocopheryl ingredient.

In another embodiment, the invention provides composition comprising the solvent system consisting of hydroxypropyl-beta-cyclodextrin, 0.01 to 40% w/v, polysorbate 80,0.10 to 0.5% w/v and water, and potassium dihydrogen phosphate, 0.05 to 1.0 % w/v.

In another embodiment, the invention provides method of use of an injectable composition comprising Diclofenac or water soluble salts thereof 75mg for treatment or prevention of various musculoskeletal and joint disorders like rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, peri-articular disorders like bursitis and tendinitis, soft tissue disorders like sprains and strains, painful condition such as renal colic, acute gout, dysmenorrhoea, migraine and some surgical procedures, in management of actinic keratosis and fever, postoperative pain, juvenile idiopathic arthritis, acute postoperative pain, intra-operative miosis, for treatment of inflammation after surgery, pain control of total hip replacement arthroplasty.

The pH is critical for maintaining stability of the Diclofenac injection hence pH is maintained at 8 to 9 using suitable buffering agents and alkalizer. The buffering agents may be selected from, but not limited to alkali metal hydroxides like sodium hydroxide, potassium hydroxide, tri sodium citrate, sodium phosphate salts like monosodium phosphate salt or disodium phosphate salt, potassium phosphate salts like mono or di potassium phosphate salt, sodium acetate, potassium dihydrogen phosphate, phosphate buffer, bicarbonate buffer, Tris buffers or other alkaliser are used for adjusting pH in the desired range.

Water is added in the composition in quantity sufficient (q.s.) to make it 0.5 ml or 1 ml or to give different volumes for different strength. The injectable composition may be filled in ampoule and vials after aseptic filtration and flushed under nitrogen blanket. The injections so formed are stable and may

diluted further in infusion liquid to obtain the desired strength of drug or without diluting further by intramuscular and as slow bolus intravenous or suitably adding to infusion liquid as per physician need.

In another embodiment, the invention provides a process for preparing composition comprising 75mg of diclofenac sodium or therapeutically equivalent amounts of water soluble salts of diclofenac comprising suspending diclofenac sodium or water soluble salt of diclofenac in the solvent system comprising two or more solubilizers in water for injection, with stirring under constant nitrogen purging, optionally, adding said one or more buffering agent (s) and/or antioxidant (s); adjusting pH between 8-9 using an alkali; further diluting with water for injection to achieve concentration of 75mg in 1 ml; sterilizing by sterile filtration and filling in 1 ml ampoules flushed with inert gas prior to sealing.

Preferably, the invention provides a process for preparing composition comprising 75mg of diclofenac sodium or therapeutically equivalent amounts of water soluble salts of diclofenac comprising suspending diclofenac sodium or water soluble salt of diclofenacin the solvent system comprising hydroxypropyl-beta-cyclodextrin and polysorbate 80 in water for injection, with stirring under constant nitrogen purging, adding potassium dihydrogen phosphate, adjusting pH between 8-9 using an alkali, further diluting with water for injection to achieve concentration of 75mg in 1 ml, sterilizing by sterile filtration and filling in 1 ml ampoules flushed with inert gas prior to sealing.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

Example 1

Formula	mg/ml	% w/v
Diclofenac sodium	75	7.50
Hydroxypropylbetadex (Hydroxypropyl-Beta-Cyclodextrin)	333	33.30
Polysorbate 80 (Tween 80)	0.3	0.03
1% Sodium hydroxide Solution	q.s.	-
Water for Injection	q.s. to 1 ml	upto 100.00

Manufacturing Procedure:

Dissolve polysorbate 80 about 0.03%w/v in water for injection (about 50%) under stirring and nitrogen purging, stir till it dissolved in water for injection. Add hydroxypropyl-beta-cyclodextrin about 33.30% w/v to it under stirring and continue stirring till it dissolved. Add diclofenac sodium about 7.50% w/v to polysorbate 80 and hydroxypropyl-β-cyclodextrin solution under stirring and continue stirring for about 30 minutes. Add 1% Sodium hydroxide solution to diclofenac sodium dispersion under stirring and continue stirring till clear solution is formed. Check the pH of solution and adjust it to 8-9 if required with 1% Sodium hydroxide solution. Record the quantity of sodium hydroxide solution used for pH adjustment. Make up the volume to 1 mL with water for injection and stir it. Filter the solution through 0.45 micron membrane filter and then through 0.22 micron membrane filter and again check the pH of filtered solution. Carry out filling of the solutions in clear glass ampoules followed by sealing.

Example 2

Formula	mg/ml	% w/v
Diclofenac sodium	75	7.50
Hydroxypropylbetadex (Hydroxypropyl-β-cyclodextrin)	333	33.30
Polysorbate 80 (Tween 80)	3	0.30
Monothioglycerol	5	0.50
0.1 N Hydrochloric acid	q.s.	-
1% Sodium hydroxide Solution	q.s.	-
Water for Injection	q.s. to 1 ml	upto 100.00

Manufacturing Procedure:

Dissolve hydroxypropylbeta-cyclodextrin about 33.30% w/v in water for injection (about 50%) under stirring and nitrogen purging, stir till it dissolved in water for injection, followed by addition of Monothioglycerol about 0.50% w/v and continue stirring. Adjust the pH of the solution to 4.6 (± 0.5) with 0.1N Hydrochloric acid. Add diclofenac sodium about 7.50% w/v to hydroxypropylbeta-cyclodextrin and monothioglycerol solution under stirring and continue stirring for about 30 minutes.

Add polysorbate 80 (Tween 80) about 0.30% w/v in water for injection (about 1%) under stirring and nitrogen purging, stir till it dissolved in water for injection and then add to above diclofenac sodium dispersion. Check the pH of solution and adjust it to 8-9 with 1% Sodium hydroxide solution. Record the quantity of sodium hydroxide solution used for pH adjustment.

Make up the volume to 1 mL with water for injection and stir it. Filter the solution through 0.45 micron membrane filter and then through 0.22 micron membrane filter and again check the pH of filtered solution. Carry out filling of the solutions in clear glass ampoules followed by sealing.

Example 3

Formula	mg/ml	% w/v
Diclofenac sodium	75	7.50
Hydroxypropylbetadex (Hydroxypropylβ-cyclodextrin)	350	35.00
Polysorbate 80 (Tween 80)	0.3	0.03
Potassium dihydrogen phosphate	3.4	0.34
Sodium hydroxidepellets	q.s.	--
Water for Injection	q.s. to 1 ml	upto 100.00

Manufacturing Procedure:

Dissolve polysorbate 80 about 0.03% w/v in water for injection (about 50%) under stirring and nitrogen purging, stir till it dissolved in water for injection. Add hydroxypropyl beta-cyclodextrin about 35.00% w/v to it under stirring and continue stirring till it dissolved. Add diclofenac sodium about 7.50% w/v to hydroxypropyl beta-cyclodextrin and polysorbate 80 solution under stirring and continue stirring for about 30 minutes. Take water for injection (about 20%) and dissolve sodium hydroxide pellets in it under stirring. Then add potassium dihydrogenphosphate about 0.34% w/v under stirring and continue stirring till it dissolved. Check the pH of the solution (limit 8-9).Add buffer solution to diclofenac sodium dispersion under stirring. Continue stirring till all the drug particles get dissolved. Check the pH of solution and adjust it to 8-9 if required with 1% Sodium hydroxide solution. Record the quantity of sodium hydroxide solution used for pH adjustment. Make up the volume to 1 mL with water for injection and stir it. Filter the solution through 0.45 micron membrane filter and then through 0.22 micron membrane filter and again check the pH of filtered solution. Carry out filling of the solutions in clear glass ampoules followed by sealing.

We claim:

1. An injectable preparation comprising 75mg/ml to 100 mg/ml of diclofenac sodium or therapeutically equivalent amounts of water soluble salts of diclofenac in a solvent system comprising two or more solubilizers in an amount ranging from 0.01 to 40% w/v and water and optionally one or more antioxidant(s) in an amount ranging from 0.10 to 0.5% w/v and/or one or more buffering agent (s) in an amount ranging from 0.05 to 1.0% w/v, wherein the pH of the preparation is maintained at 8-9.
2. An injectable preparation comprising 75 mg/ml of diclofenac sodium or therapeutically equivalent amounts of water soluble salts of diclofenac in a solvent system comprising two or more solublizers in an amount ranging from 0.01 to 40% w/v and water and optionally, one or more antioxidant (s) in an amount ranging from 0.01 to 0.5% w/v and/or one or more buffering agent (s) in an amount ranging from 0.05 to 1.0% w/v, wherein the pH of the preparation is maintained at 8-9.
3. The injectable preparation according to claims 1-2, wherein the water soluble salts of diclofenac are selected from the group consisting of diclofenac potassium, diclofenac diethyllamine, diclofenac diethanolamine and diclofenac beta-dimethyl aminoethanol.
4. The injectable preparation according to claims 1-2, wherein the solubilizers are selected from the group consisting of hydroxypropyl-beta-cyclodextrin, polysorbate 80, Cremophor EL, glycofurol, benzyl alcohol, polyethylene glycol, Cremophor RH 40 and hydrogenated soy phosphatidylcholine.
5. The injectable preparation according to claim 4, wherein the solubilizers are selected from the group consisting of hydroxypropyl-beta-cyclodextrin and polysorbate 80.
6. The injectable preparation according to claims 1-2, wherein the antioxidant is selected from the group consisting of monothioglycerol, sodium bisulphate and sodium metabisulphate.

7. The injectable preparation according to claims 1-2, wherein the buffering agent is selected from the group consisting of potassium dihydrogen phosphate, phosphate buffer and bicarbonate buffer.

8. The injectable preparation according to claims 1-2, wherein the solvent system comprises hydroxypropyl-beta-cyclodextrin in an amount ranging from 0.01 to 40% w/v, polysorbate 80 in an amount ranging from 0.10 to 0.5% w/v and water and optionally monothioglycerol in an amount ranging from 0.10 to 0.5% w/v and/or potassium dihydrogen phosphate in an amount ranging from 0.05 to 1.0% w/v, wherein the pH of the preparation is maintained at 8-9.

9. The injectable preparation according to claims 1-2, wherein the preparation is administered in a route selected from the group consisting of intramuscular, intravenous, intradeltoid and intragluteal route.

10. The injectable preparation according to claims 1-2, wherein the solvent system comprises hydroxypropyl-beta-cyclodextrin in an amount ranging from 0.01 to 40% w/v, polysorbate 80 in an amount ranging from 0.10 to 0.5% w/v, water, and potassium dihydrogen phosphate in an amount ranging from 0.05 to 1.0 % w/v, wherein the pH of the preparation is maintained at 8-9.

11. The injectable preparation according to claims 1-2, wherein total volume of the preparation comprises about 1 ml.

12. A process for the preparation of 1 ml injectable preparation consisting of 75mg of diclofenac sodium or therapeutically equivalent amounts of water soluble salts of diclofenac according to claim 11, comprising the steps of :

a) suspending said diclofenac sodium or said water soluble salt of diclofenac in the solvent system comprising said two or more solubilizers in water for injection, with stirring under constant nitrogen purging,

b) optionally adding said one or more buffering agent (s) and/or antioxidant (s),

c) adjusting pH between 8-9 using an alkali,

d) further diluting with water for injection to achieve concentration of 75mg in 1 ml,

e) sterilizing by sterile filtration and filling in 1 ml ampoules flushed with inert gas prior to sealing.

13. A process for the preparation of 1 ml injectable preparation consisting of 75mg of diclofenac sodium or therapeutically equivalent amounts of water soluble salts of diclofenac according to claim 11, comprising the steps of:

a) suspending said diclofenac sodium or said water soluble diclofenac in the solvent system comprising hydroxypropyl-beta-cyclodextrin and polysorbate 80 in water for injection, with stirring under constant nitrogen purging,

b) optionally, adding potassium dihydrogen phosphate and/or monothioglycerol,

c) adjusting pH between 8-9 using an alkali,

d) further diluting with water for injection to achieve concentration of 75mg in 1 ml,

e) sterilizing by sterile filtration and filling in 1 ml ampoules flushed with inert gas prior to sealing.

14. A process for the preparation of 1 ml injectable preparation consisting of 75mg of diclofenac sodium or therapeutically equivalent amounts of water soluble salts of diclofenac according to claim 11, comprising the steps of:

a) suspending said diclofenac sodium or said water soluble salt of diclofenac in the solvent system comprising hydroxypropyl-beta-cyclodextrin and polysorbate 80 in water for injection, with stirring under constant nitrogen purging,

b) adding potassium dihydrogen phosphate,

c) adjusting pH between 8-9 using an alkali,

d) further diluting with water for injection to achieve concentration of 75mg in 1 ml,

e) sterilizing by sterile filtration and filling in 1 ml ampoules flushed with inert gas prior to sealing.

15. A method for treatment or prevention of acute or chronic pain and inflammatory conditions selected from rheumatoid arthritis, osteoarthritis, dysmenorrhea (menstrual pain), headache and migraine, postoperative pain and also for mild to moderate pain after tissue injury, ankylosing spondylitis, pain control of total hip replacement arthroplasty, actinic keratosis and fever, accidental trauma, comprising administering to a subject in need thereof a composition comprising 75 mg/ml of diclofenac sodium or therapeutically equivalent amounts of water soluble salts of diclofenac in a solvent system comprising two or more solublizers in an amount ranging from 0.01 to 40% w/v and water and optionally one or more antioxidant (s) in an amount ranging from 0.10 to 0.5% w/v and/or buffering agent (s) in an amount ranging from 0.05 to 1.0 % w/v, wherein the pH of the composition is maintained at 8-9.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/054893

A. CLASSIFICATION OF SUBJECT MATTER
A61K9/08 Version=2016.01

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)

IPO-Internal Database, Patseer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US8809393 B2 (TROIKAA PHARMACEUTICALS LTD [IN]) 19 AUGUST 2014 (19-08 2014). Abstract;Claims & Examples	1-14
Y	WO2014102824 A1 (THEMIS MEDICARE LTD [IN]) 03 JULY 2014 (03-07-2014) The whole document	1-14
Y	EP0595766 A1 (CIBA GEIGY AG [CH]) 04 MAY 1994 (04-05-1994) The whole document	1-11
A	WO2006126214 A2 (PANACEA BIOTEC LTD [IN]) 30 NOVEMBER 2006 (30-11-2006) Claims	1-14
A	CH694034 A5(MEPHA AG [CH]) 30 JUNE 2004 (30-06-2004) Abstract & Claim 1	1-14

☐ 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
08-01-2016	08-01-2016

Name and mailing address of the ISA/	Authorized officer
Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075	K Janardana
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/054893

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matter of claim 15 relates to [a method for treatment of the human or animal body by surgery or therapy for treatment of the human or animal body by surgery or therapy as well as diagnostic methods], which does not require an international search by the International Searching Authority in accordance with PCT Article

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

International application No.
PCT/IB2015/054893

Continuation of Claims found unsearchable(Box II)

17(2)(a)(i) and [Rule 39.1(iv)].

International application No.
PCT/IB2015/054893

Citation	Pub.Date	Family	Pub.Date
US 8809393 B2	19-08-2014	US 2008153914 A1	26-06-2008
		WO 2006095363 A2	14-09-2006
		EP 1848419 A2	31-10-2007
		CN 101123957 A	13-02-2008
		AU 2006221633 A1	14-09-2006
AE 2014102824 A1	03-07-2014	US 2014187635 A1	03-07-2014
		EP 2938325 A1	14-11-2015
		CN 104968331 A	07-10-2015
		AU 2013368849 A1	09-07-2015
EP 0595766 A1	04-05-1994	AU 4905293 A	05-05-1994
		US 5389681 A	14-02-1995
		CA 2108820 A1	23-04-1994
WO 2006126214 A2	30-11-2006	JP 2008542260 A	27-11-2008
		EP 1895983 A2	12-03-2008
		KR 20080016689 A	21-02-2008
		CN 101217939 A	09-07-2008