Abstract:

The present invention relates to a stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1.1 to about 3.4:1, having pH of about 6.5 to about 8.7, wherein the said aqueous solution is lyophilized.

Declarations under Rule 4.17:

— of inventorship (Rule 4.1 7(iv))

Published:

— with international search report (Art. 21(3))
A STABLE INJECTABLE PHARMACEUTICAL COMPOSITION OF ACECLOFENAC AND PROCESS FOR PREPARING THEREOF

FIELD OF THE INVENTION

The present invention relates to a stable injectable pharmaceutical composition of aceclofenac and process for its preparation.

BACKGROUND OF THE INVENTION

Aceclofenac is a non-steroidal anti-inflammatory drug which in the form of white or almost white, crystalline powder. Chemically aceclofenac is $2\{-2\{-2\{-((2,6$-dichlorophenyl)amino$)$phenyl$\}$acetyl$\}$oxyacetic acid with molecular formula of $\text{C}_{16}\text{H}_{13}\text{Cl}_2\text{NO}_4$ and molecular weight of 354.18472 g/mol. The mode of action of aceclofenac is largely based on the inhibition of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase, which is involved in the production of prostaglandins. It inhibits synthesis of the inflammatory cytokines interleukin (IL)-1, tumor necrosis factor and prostaglandin $\text{E}_2$ (PGE2) production. Its effects on cell-adhesion molecular from neutrophils have also been noted. In vitro data indicate inhibition of cyclooxygenase (Cox)-1 and 2 by aceclofenac in whole bipod assays, with selectivity for Cox-2 being evident. Aceclofenac is used for the relief of pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The dose is 100mg twice daily. However, aceclofenac is practically insoluble in water, freely soluble in acetone and soluble in alcohol. It is manufactured by Intas Biopharmaceuticals, under the tradename Hifenac® in various forms (tablets, gel, injection etc.).

U.S. Patent No. 4548952 specifically claims aceclofenac compound;

U.S. Patent Application No. 20090156670A1 relates to a nonaqueous liquid parenteral aceclofenac formulation, capable of pharmaceutical application,
comprising an aceclofenac component in a form of a non-water-soluble aceclofenac salt, in a solubilized or dissolved form in a solvent liquid wherein said solvent liquid comprises: a) a nonaqueous solubilizer component effective to stabilize aceclofenac and diclofenac that forms by conversion of the aceclofenac component thereto, said nonaqueous solubilizer component being substantially inert with respect to said conversion; and b) an aceclofenac salt stabilizer component effective to inhibit precipitation of aceclofenac free acid. It also discloses that the presented pharmaceutical compositions are stable upon storage at room temperature and at refrigerated temperatures.

Nisharani S. Ranpise et al., Pharmaceutical Development and Technology, June 2009 describe the inclusion complexation of aceclofenac with β-cyclodextrin by grinding, microwave and spray-drying techniques & provide an improvement of water solubility and in vitro dissolution rate of aceclofenac by complexation with β-cyclodextrin and hydroxypropyl-β-cyclodextrin.

U.S. Patent No. 6727286 provides a pharmaceutical composition comprising an aqueous solution of arginine and ibuprofen with a molar ratio of arginine to ibuprofen, which is less than 1:1, as well as a method of making the same. It also discloses a method of treating a condition chosen from pain, inflammation, fever, and/or other conditions alleviated by ibuprofen comprising administering the above said pharmaceutical composition.

The above cited prior arts generally relate to non aqueous aceclofenac compositions or inclusion complexation of aceclofenac with β-cyclodextrin. Non aqueous injectable pharmaceutical compositions of lipophilic water-insoluble drugs like aceclofenac frequently consist of mixtures of water, organic cosolvents and surfactants. Limitations in using non aqueous solvents for injectable compositions include possible drug precipitation, pain, inflammation and hemolysis upon injection. As such no aqueous injectable preparation of aceclofenac is commercially available. As aqueous solution is readily adaptable for formulating & also because of instability of aceclofenac, there is a need to provide industrially applicable process to prepare a stable injectable aceclofenac pharmaceutical composition which uses aqueous solution of aceclofenac.
Prior art also discloses pharmaceutical composition of an aqueous solution of arginine and ibuprofen comprising a molar ratio of arginine to ibuprofen, which is less than 1:1. However, ibuprofen is very slightly soluble in water and readily soluble in ethanol. Also it is readily soluble and stable in alkaline pH. Unlike ibuprofen, aceclofenac is practically insoluble in water & its solubility in alkaline medium is less than 10 mg/ml. Moreover, aceclofenac is instable in alkaline medium as it gets converted to diclofenac by hydrolysis. So making a formulation of aceclofenac by solubilizing aceclofenac instead of ibuprofen with arginine in line with the teachings of US6727286 would run into several problems. Firstly, Aceclofenac is less soluble in aqueous medium as compared to ibuprofen. Additionally a formulation of aceclofenac with arginine would give rise to a formulation with alkaline pH in which the aceclofenac would be instable unlike ibuprofen which is stable at alkaline pH. Moreover, we have observed that solution preparations of aceclofenac are highly unstable unlike ibuprofen solution preparations which are stable. Additionally solutions of aceclofenac are prone to degradation even at acidic or neutral pH.

We have surprisingly found that a stable injectable pharmaceutical composition of aceclofenac can be prepared by solubilizing aceclofenac in arginine at a pH of about 6:5 to about 8.7 & subsequently lyophilizing the prepared aceclofenac solution. The aqueous solubility of aceclofenac can be enhanced by mixing it with arginine in a specified molar ratio, which can be used to prepare the said pharmaceutical composition of aceclofenac.

OBJECT OF THE INVENTION

It is an object of the present invention to provide a stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1.1:1 to about 3.4:1, having pH of about 6.5 to about 8.7, wherein the said aqueous solution is lyophilized.

It is an object of the present invention to provide a stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac in the molar
ratio of arginine to aceclofenac in the range of about 1.1:1 to about 3.4:1, having pH of about 6.5 to about 7.5, wherein the said aqueous solution is lyophilized.

It is another object of the present invention to provide a process to prepare a stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1.1:1 to about 3.4:1, having pH of about 6.5 to about 8.7, wherein the said aqueous solution is lyophilized.

It is yet another object of the present invention to provide a process to prepare a stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1.1:1 to about 3.4:1, having pH of about 6.5 to about 7.5, wherein the said aqueous solution is lyophilized.

Accordingly, it is an object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

SUMMARY OF THE INVENTION

The present invention relates to a stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1.1:1 to about 3.4:1, having pH of about 6.5 to about 8.7, wherein the said aqueous solution is lyophilized.

The present invention relates to a stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1.1:1 to about 3.4:1, having pH of about 6.5 to about 7.5, wherein the said aqueous solution is lyophilized.

The present invention also relates to a process for preparing a stable injectable pharmaceutical composition comprising an aqueous solution of arginine and
aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1:1 to about 3.4:1, having pH of about 6.5 to about 8.7 comprising:

(a) dissolving arginine in water to form an arginine solution & optionally mixing one or more pharmaceutically acceptable excipients,

(b) dissolving aceclofenac in the arginine solution of (a) to form an aqueous solution of arginine and aceclofenac,

(c) adjusting pH of the solution of (b),

(d) lyophilizing the solution of (c),

and wherein the said aqueous solution is lyophilized.

The present invention also relates to a process for preparing a stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1:1 to about 3.4:1, having pH of about 6.5 to about 7.5 comprising:

(a) dissolving arginine in water to form an arginine solution & optionally mixing one or more pharmaceutically acceptable excipients,

(b) dissolving aceclofenac in the arginine solution of (a) to form an aqueous solution of arginine and aceclofenac,

(c) adjusting pH of the solution of (b),

(d) lyophilizing the solution of (c),

and wherein the said aqueous solution is lyophilized.

DETAILED DESCRIPTION OF THE INVENTION

Before the present process and methods are described, it is to be understood that this invention is not limited to particular compounds, formulas or steps described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise,
between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the invention.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

It must be noted that as used herein and in the appended claims, the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" includes a plurality of such compounds and reference to "the step" includes reference to one or more step and equivalents thereof known to those skilled in the art, and so forth.

The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

The term "stable" as used herein refers to chemical stability of aceclofenac in pharmaceutical composition wherein there is no change in assay values of aceclofenac when kept at 40°C/75%RH or 30°C/75%RH or 25°C/60%RH for 1 month.

We have surprisingly found that a stable injectable pharmaceutical composition of aceclofenac can be prepared by solubilizing aceclofenac in arginine at a pH of about 6.5 to about 8.7 & subsequently lyophilizing the prepared aceclofenac solution. The
aqueous solubility of aceclofenac can be enhanced by mixing it with arginine in a specified molar ratio, which can be used to prepare the said pharmaceutical composition of aceclofenac.

The present invention relates to a stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1.1:1 to about 3.4:1, having pH of about 6.5 to about 8.7, wherein the said aqueous solution is lyophilized.

The present invention relates to a stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1.1:1 to about 3.4:1, having pH of about 6.5 to about 7.5, wherein the said aqueous solution is lyophilized.

The present invention also relates to a process for preparing a stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1.1:1 to about 3.4:1, having pH of about 6.5 to about 8.7 comprising:

(a) dissolving arginine in water to form an arginine solution & optionally mixing one or more pharmaceutically acceptable excipients,
(b) dissolving aceclofenac in the arginine solution of (a) to form an aqueous solution of arginine and aceclofenac,
(c) adjusting pH of the solution of (b),
(d) lyophilizing the solution of (c),

and wherein the said aqueous solution is lyophilized.

The present invention also relates to a process for preparing a stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1.1:1 to about 3.4:1, having pH of about 6.5 to about 7.5 comprising:

(a) dissolving arginine in water to form an arginine solution & optionally mixing one or more pharmaceutically acceptable excipients,
(b) dissolving aceclofenac in the arginine solution of (a) to form an aqueous solution of arginine and aceclofenac,
(c) adjusting pH of the solution of (b),
(d) lyophilizing the solution of (c),
and wherein the said aqueous solution is lyophilized.

In the present invention for pharmaceutical composition of aceclofenac and process for its preparation, the therapeutic effective amount of aceclofenac that may be used is in the range from about 100 mg to about 300 mg per day.

Arginine is a conditionally nonessential amino acid, meaning most of the time it can be manufactured by the human body, and does not need to be obtained directly through the diet. The L-form is one of the 20 most common natural amino acids. The present invention utilizes arginine or its pharmaceutically acceptable salt forms, preferably L-arginine or arginine hydrochloride, more preferably L-arginine for solubilization. In the present invention for pharmaceutical composition of aceclofenac and process for its preparation, the therapeutic effective amount of arginine that may be used is in the range from about 2 gm to about 8 gm per day.

One embodiment of the present invention relates to provide a stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac, wherein a molar ratio of arginine to aceclofenac is from about 1.1:1 to about 3.40:1, more preferably about 1.22:1 to about 2.04:1. The said molar ratio of arginine to aceclofenac ensures the solubility of aceclofenac in the aqueous solution. When the molar ratio of arginine to aceclofenac is below the said limit, aceclofenac is insoluble form and when it is above the said limit, arginine would in insoluble form after reconstitution. Accordingly, for the purpose of the present invention the molar ratio of arginine to aceclofenac is from about 1.1:1 to about 3.40:1, more preferably about 1.22:1 to about 2.04:1.

Another embodiment of the present invention relates to adjusting pH of the aqueous solution of arginine and aceclofenac to about 6.5 to about 8.7, preferably about 6.5 to about 7.5. At a pH of less than 6.5, aceclofenac does not form solution with arginine due to its insolubility at pH of less than 6.5 and in alkaline medium at pH greater than about 8.7, aceclofenac is unstable due to its hydrolysis. The solution stability study of the solution of arginine and aceclofenac before lyophilization by adjusting the pH in
between about 6.5 to about 8.7, shows degradation of aceclofenac and unstable formulation. So, additionally lyophilization is a dehydration process and is typically used to preserve a perishable material or make the material more convenient for transport. We have found that adjusting the pH of the solution of arginine and aceclofenac in between about 6.5 to about 8.7 and subsequently lyophilizing it, results in minimum degradation of aceclofenac during lyophilization process as well as upon reconstitution of the lyophilized pharmaceutical composition. In general, the present invention relates to provide a stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1.1:1 to about 3.4:1, having pH of about 6.5 to about 8.7, wherein the said aqueous solution is lyophilized.

The present pharmaceutical composition of aceclofenac may include one or more pharmaceutically acceptable excipients such as buffers like disodium hydrogen phosphate, sodium dihydrogen phosphate or mixtures thereof, solubilizers, stabilizers, antioxidants which will be apparent to the skilled person.

The pharmaceutical composition as described herein may be prepared by different techniques. For example, one embodiment of the present invention may relate to dissolving L-arginine in water for injection. Optionally mixing disodium hydrogen phosphate dihydrate, sodium dihydrogen phosphate monohydrate or mixtures thereof, with L-arginine solution. Adding aceclofenac to this mixture and dissolving it with stirring. Then required volume was made up by water for injection and adjusting the pH of about 6.5 to about 8.7. The filling of the above solution in the vial of amber colored tubular glass & finally lyophilizing it. Such methods provide the present stable injectable pharmaceutical compositions of aceclofenac.

The following examples are intended to illustrate the scope of the present invention in all its aspects but not to limit it thereto.

**EXAMPLE 1-3**

The stable injectable pharmaceutical composition of aceclofenac may be prepared as given in table 1.
Manufacturing Formula of Aceclofenac for Injection 150 mg

Batch Size: 200 ml

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Ingredients</th>
<th>Quantity in gm per 200 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>With Molar ratio (Arginine : Aceclofenac)</td>
</tr>
<tr>
<td>1</td>
<td>Aceclofenac</td>
<td>15.00</td>
</tr>
<tr>
<td>2</td>
<td>L-arginine</td>
<td>9.00</td>
</tr>
<tr>
<td>3</td>
<td>Disodium hydrogen phosphate dihydrate</td>
<td>0.205</td>
</tr>
<tr>
<td>4</td>
<td>Sodium dihydrogen phosphate monohydrate</td>
<td>1.828</td>
</tr>
<tr>
<td>5</td>
<td>Water for Injection</td>
<td>q. s. to 200 ml</td>
</tr>
</tbody>
</table>

Procedure:

130 ml of water for injection was taken and L-Arginine was added and dissolved in it under stirring. Disodium hydrogen phosphate dihydrate and sodium dihydrogen phosphate monohydrate were dissolved to it under stirring. Aceclofenac was mixed to it under stirring and dissolved to obtain clear solution. The final volume was made up to 200 ml with water for injection. The pH of the final injection was 7.00 ± 0.50. The solution was filtered through 0.22 micron nylon membrane filter. Then it was filled in 2 ml vial of amber colored tubular glass and lyophilized.

EXAMPLE 4

The stable injectable pharmaceutical composition of the present invention as prepared in example 2 (with some variations in the pH before lyophilization) was subjected to stability studies and the results are shown in table 2.
Table 2

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Tests</th>
<th>Condition</th>
<th>Specification</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Description</td>
<td>Initial</td>
<td>White color powder in amber color glass vial with flip off seal</td>
<td>Complies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1M (40°C/75%RH)</td>
<td>Complies</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1M (30°C/75%RH)</td>
<td>Complies</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1M (25°C/60%RH)</td>
<td>Complies</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Assay FDB-061-05A</td>
<td>Initial</td>
<td>90% - 110% of L.A.</td>
<td>98.59 %</td>
</tr>
<tr>
<td></td>
<td>(Lyophilized with pH 8.68 without Buffer)</td>
<td>1M (40°C/75%RH)</td>
<td>95.41 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1M (30°C/75%RH)</td>
<td>98.51 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1M (25°C/60%RH)</td>
<td>99.09 %</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Assay FDB-061-06B</td>
<td>Initial</td>
<td>90% - 110% of L.A.</td>
<td>98.47%</td>
</tr>
<tr>
<td></td>
<td>(Lyophilized with pH 7.4 with phosphate buffer)</td>
<td>1M (40°C/75%RH)</td>
<td>92.47 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2M (40°C/75%RH)</td>
<td>93.00 %</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Assay FDB-061-06C</td>
<td>Initial</td>
<td>90% - 110% of L.A.</td>
<td>95.28%</td>
</tr>
<tr>
<td></td>
<td>(Lyophilized with pH 6.5 with phosphate buffer)</td>
<td>1M (40°C/75%RH)</td>
<td>92.00 %</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Market Sample - Hifenac®</td>
<td>Initial</td>
<td>90% - 110% of L.A.</td>
<td>96.37%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1M (40°C/75%RH)</td>
<td>98.1 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1M (30°C/65%RH)</td>
<td>98.16%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1M (25°C/60%RH)</td>
<td>98.92%</td>
<td></td>
</tr>
</tbody>
</table>

* - Hifenac® is marketed by Intas Pharma in India & is available in 1 ml ampoule containing 150 mg Aceclofenac/ml and is meant for intramuscular administration in a ready to use form.

The above results show the stability of the pharmaceutical composition of the present invention at different pH range of the invention.

**EXAMPLE 5**

The stable injectable pharmaceutical composition of the present invention as prepared in example 2 was subjected to stability studies before lyophilization and the results are shown in table 3.

Table 3

<table>
<thead>
<tr>
<th>Batch Number</th>
<th>Condition</th>
<th>Assay</th>
<th>Physical observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDB-061-009A</td>
<td>Initial</td>
<td>106.43 %</td>
<td>Clear solution</td>
</tr>
</tbody>
</table>
The results as shown in table 3 indicate that the aqueous solution of arginine and aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1.1:1 to about 3.4:1, having pH of about 6.5 to about 8.7, is unstable before lyophilization. It shows degradation of aceclofenac, when kept at 2°C to 8°C, 25°C/60%RH, 30°C/65%RH and 40°C/75%RH for 15 days without lyophilization.

**EXAMPLE 6**

The stable injectable pharmaceutical composition may also be prepared by using different molar ratios of arginine to aceclofenac as shown in table 4.

<table>
<thead>
<tr>
<th>Table 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>with molar ratio</strong></td>
</tr>
<tr>
<td>(Arginine : Aceclofenac)</td>
</tr>
<tr>
<td>Sr. No.</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

| Result                  | Insoluble | Soluble | Soluble (Insoluble after reconstitution) |

**Trial 1**: Solution is not clear. Aceclofenac is in insoluble form.

**Trial 2**: Solution is clear. Both aceclofenac and arginine are soluble.

**Trial 3**: Solution is clear. But arginine is in insoluble form after reconstitution.

The results as shown in Table 4 indicate that when the molar ratio of arginine to aceclofenac is 0.95:1, solution is not clear as aceclofenac is in insoluble form. When the molar ratio of arginine to aceclofenac is 4.07:1, solution is clear but arginine is in insoluble form after reconstitution. And when the molar ratio of arginine to aceclofenac is used within the specified limit of the present invention i.e. 1.36:1, solution is clear as both aceclofenac and arginine are soluble.

Although the invention has been described in terms of particular embodiments and applications, one of ordinary skill in the art, in light of this teaching, can generate additional embodiments and modifications without departing from the spirit of or exceeding the scope of the claimed invention. It should be emphasized that the above-described embodiments of the present invention, particularly any "preferred" embodiments, are merely possible examples of the invention of implementations, merely set forth for a clear understanding of the principles of the invention. Accordingly, it is to be understood that the drawings and descriptions herein are preferred by Way of example to facilitate comprehension of the invention and should not be construed to limit the scope thereof.
Claims:

1. A stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1.1:1 to about 3.4:1, having pH of about 6.5 to about 8.7, wherein the said aqueous solution is lyophilized.

2. A stable injectable pharmaceutical composition as in claim 1, wherein the aqueous solution of arginine and aceclofenac having pH of about 6.5 to about 7.5, and wherein the said aqueous solution is lyophilized.

3. A process for preparing a stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1.1:1 to about 3.4:1, having pH of about 6.5 to about 8.7 comprising:
   (a) dissolving arginine in water to form an arginine solution & optionally mixing one or more pharmaceutically acceptable excipients,
   (b) dissolving aceclofenac in the arginine solution of (a) to form an aqueous solution of arginine and aceclofenac,
   (c) adjusting pH of the solution of (b),
   (d) lyophilizing the solution of (c),
and wherein the said aqueous solution is lyophilized.

4. A process as in claim 3, wherein the stable injectable pharmaceutical composition comprising an aqueous solution of arginine and aceclofenac in the molar ratio of arginine to aceclofenac in the range of about 1.1:1 to about 3.4:1, having pH of about 6.5 to about 7.5, and wherein the said aqueous solution is lyophilized.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 2010/000310

A. CLASSIFICATION OF SUBJECT MATTER
IPC*: A61K 31/216 (2006.01); A61K 31/136 (2006.01); A61K 31/155 (2006.01);
A61K9/19 (2006.01)

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)
IPC*: A61K

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

Electronic database consulted during the international search (name of data base and, where practicable, search terms used)
WPI, EPODOC, TXTE, TXTG, TXTWOT, TXTJPS, TXTJPT, embase, medline, xpesp

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 2006/000228 A2 (NYCOMED DANMARK APS) 05 January 2006 (05.01.2006) page 11, lines 34-40; claims 1,2,4-6 and 9</td>
<td>1-2</td>
</tr>
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<td>WO 2004/024186 A2 (NITROMED, INC.) 25 March 2004 (25.03.2004) page 29, line 17; page 38, line 13-page 39, line 3; page 42, lines 3-4; claims 1,8,9,13</td>
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Further documents are listed in the continuation of Box C.

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Date of the actual completion of the international search 03 November 2010 (03.11.2010)
Date of mailing of the international search report 19 November 2010 (19.11.2010)

Name and mailing address of the ISA/ AT

Austrian Patent Office
Dresdner Straße 87, A-1200 Vienna

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