Provided is water-soluble hair growth compositions for treating alopecia and stimulating hair regrowth, comprising a hair growth stimulant and a multifunctional compound, preferably L-oxothiazolidine-4-carboxylic acid.
WATER SOLUBLE COMPOSITIONS FOR TREATING HAIR LOSS & PROMOTING HAIR GROWTH

Field of the Invention
The present invention relates, in general, to a hair growth composition for the treatment of alopecia, or stimulating hair regrowth. More particularly, the present invention relates to a water-soluble composition for hair regrowth, or for the treatment of hair loss, comprising a hair growth stimulant and a multifunctional compound.

Background of the Invention
In human beings, hair growth and shedding is random and not seasonal or cyclical. At any given time, a random number of hairs will be in one of three stages of growth and shedding: anagen, catagen, and telogen. The anagen phase or growth phase, during which the hair lengthens, lasts several years. The catagen phase, which succeeds the anagen phase, is very short and lasts only a few weeks. The telogen phase, which lasts several months, corresponds to a period of rest of the follicle, where the hair finishes by falling out.

The natural loss of the hair can be estimated, on average, at a few hundred hairs per day for a normal physiological state. However, it happens that the hair cycle can go wrong and that hair loss accelerates and results in a temporary or definitive loss of the hair known as alopecia.

Hair loss, particularly in men, mainly after middle age, can be attributed to several factors or a combination of them. The factors can be medication, genetics, stress, malnutrition, hormonal imbalance, reduced blood flow to hair follicles etc.

Even though several active ingredients are known for hair loss treatment, minoxidil is the only active chemical ingredient that is approved by FDA for generating new hair growth.

A major disadvantage of minoxidil is that it is practically insoluble in water, which limits its use to such formulations having relatively low proportion of water. Formulations containing high concentrations of alcohol or polyalcohol are in general not well tolerated and alcohol present in topical preparation may dry the scalp resulting in dandruff, rash and itchiness.
When the vehicle evaporates, formation of crystalline Minoxidil occurs. But the water-soluble formulation enhances the transdermal delivery or penetration of Minoxidil in comparison with solvent based.

Therefore, although numerous compositions for stimulation of hair growth are known and taught in the art, there is still a need to develop a hair growth composition, which is water-soluble and have superior effects without side effects.

Summary of the Invention

The present invention aims to disclose and provide a hair growth composition that is capable of providing required nutrients to hair follicles to stimulate hair growth and prevent hair loss. The composition of the present invention comprises a hair growth stimulant and a multifunctional compound.

The present invention also provides a water-soluble composition comprising a hair growth stimulant and a multifunctional compound. The composition of the present invention is intended for topical administration.

The present invention further provides a water-soluble salt, which is prepared by combination of a hair growth stimulant and a multifunctional compound. The hair growth stimulant used in the present invention is pyrimidine-3-oxide derivative whereas the multifunctional compound of the present invention is L-2-oxothiazolidine-4-carboxylic acid.

The present invention further provides a method for preparing water-soluble salt by reacting a pyrimidine-3-oxide derivative with L-2-oxothiazolidine-4-carboxylic acid in a stoichiometric ratio. In another aspect of the present invention, the water-soluble salt is prepared using solvents and isolated using conventional techniques such as evaporation of solvent, precipitation with non-solvents etc.

The present invention further provides a method for preventing hair loss and stimulating hair regrowth by topically administering a water-soluble composition comprising a hair growth stimulant and a multifunctional compound. In one aspect of the present invention, a water-soluble composition comprises a pyrimidine-3-oxide derivative and a cyclic amino acid, preferably L-2-oxothiazolidine-4-carboxylic acid.
These and other aspects of the present invention will be explained and understood when considered in conjunction with the following detailed description and the accompanying drawings. It should be understood, however, that the following descriptions, while indicating preferred embodiments and numerous specific details thereof, are given by way of illustration and not of limitation.

**Brief Description of Accompanied Figures**

FIG 1. Hair density and hair growth results on Minoxidil 5% (market sample) on subjects tested.

FIG 2. Hair density and hair growth results of water-soluble salt of L-2-oxothiazolidine-4-carboxylic acid with 2,4-Diamino-6-piperidinopyrimidine-3-oxide (Minoxidil) on subjects tested.

FIG 3. Hair density and hair growth results of water-soluble salt of L-2-oxothiazolidine-4-carboxylic acid with 2,4-Diamino-6-pyrrolidinoyrimidine-3-oxide on subjects tested.

FIG 4. Hair density and hair growth results of water-soluble salt of L-2-Oxothiazolidine-4-carboxylic acid with 2,4-Diamino pyrimidine-3-oxide on subjects tested.

**Detailed Description of the Invention**

The present invention is directed to water-soluble compositions for the treatment of alopecia and stimulating hair regrowth. The composition is intended for topical administration and significantly enhances the transdermal delivery of the hair growth stimulant and the multifunctional compound.

According to an embodiment of the present invention, the multifunctional compound is a cysteine source and a simulator of intracellular glutathione. Cysteine is the major acid component of hair, which plays an important role by contributing to hair growth and hair loss prevention.

In an embodiment of the present invention, a water soluble hair growth salt suitable for treating alopecia and stimulate hair growth is provided. The water soluble salt having a cyclic amino acid and a hair growth stimulant, wherein the cyclic amino acid is preferably
L-2-Oxothiazolidine-4-carboxylic acid formula (a), wherein the hair growth stimulant is 2,4-Diamino pyrimidine-3-oxide derivatives of the formula (b).

\[
\begin{align*}
    &\quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \ quad
In yet another embodiment of the present invention, a water-soluble salt having formula (III) is prepared by combination of L-2-oxothiazolidine-4-carboxylic acid and 2, 4-diamine pyrimidine-3-oxide.

The multifunctional compound used in the present invention is L-2-oxothiazolidine-4-carboxylic acid, which considerably enhances the properties of hair growth stimulant in treating hair loss and stimulating hair regrowth.

It has been observed that L-2-oxothiazolidine-4-carboxylic acid added to the present invention provides necessary ingredients for the healthy growth of hair. Further, L-2-oxothiazolidine-4-carboxylic acid can provide necessary nutrients to increase the strength and stability of hair-scalp bond. Additionally, L-2-oxothiazolidine-4-carboxylic acid being an excellent antioxidant, it can prevent and limit toxic alopecia also.

Moreover, L-2-oxothiazolidine-4-carboxylic acid blocks the formation of dihydro testosterone (DHT), which is the main cause of destruction of hair follicles, by preventing reaction of 5-alpha reductase on the male hormone testosterone.

In yet another embodiment of the present invention, water-soluble composition of the present invention contains high percentage of water and enhance the transdermal delivery of the hair growth stimulant and multifunctional compound. Further, it has been observed that the water-soluble composition can also be used in the treatment of alopecia resulting
from oxidative stress as L-2-oxothiazolidine-4-carboxylic acid is excellent antioxidant. Moreover, L-2-oxothiazolidine-4-carboxylic acid has been proved to be an excellent radical scavenger and hence the water-soluble composition can also be used in the treatment of alopecia induced by the use of chemotherapeutic agents.

In another embodiment, the water-soluble composition of the present invention is intended for topical use and can be administered as gel, cream, lotion, ointment, solution or spray. The water-soluble composition may further contain other therapeutic agents and conventionally used vehicles and excipients such as fragrances, stabilizers, colors etc.

It has been found that the water-soluble compositions of the present invention are therapeutically superior to the compositions containing hair growth stimulants alone. This showed marked synergism between the hair growth stimulant and multifunctional compound.

The examples used herein are intended merely to facilitate an understanding of ways in which the embodiments herein may be practiced and to further enable those skilled in the art, to practice the embodiments herein. Accordingly, the examples should not be construed as limiting the scope of the embodiments herein.

Example 1
20 gm of L-2-Oxothiazolidine-4-carboxylic acid was added to a suspension of 30 gm of 2,4-Diamino-6-piperidinopyrimidine-3-oxide in 450 gm water. The solution becomes clear after stirring for 1 hr. The resulting solution can be used directly for the preparation of compositions suitable for topical applications. The solution was analyzed for the contents present.

Example 2
20 gm of L-2-Oxothiazolidine-4-carboxylic acid and 30 gm of 2,4-Diamino-6-piperidinopyrimidine-3-oxide was dissolved in 1.0 ltr of 95% alcohol. The solvent was evaporated to give the desired solid. Alternatively the solid can also be obtained by partial distillation of the solvent and precipitation of the same with a suitable solvent. The solid can be analyzed using techniques known in the art.

Example 3
21.5 gm of L-2-Oxothiazolidine-4-carboxylic acid was added to a suspension of 28.5 gm of 2,4-Diamino-6-pyrrolidinopyrimidine 3-oxide in 450 gm water. The solution becomes clear after stirring for 1 hr. The resulting solution can be used directly for the preparation of compositions suitable for topical applications. The solution was analyzed for the contents present.

Example 4
21.5 gm of L-2-Oxothiazolidine-4-carboxylic acid and 28.5 gm of 2,4-Diamino-6-pyrrolidinopyrimidine-3-oxide was dissolved in 1.0 ltr of 95% alcohol. The solvent was evaporated to give the desired solid. Alternatively the solid can also be obtained by partial distillation of the solvent and precipitation of the same with a suitable solvent. The solid can be analyzed using techniques known in the art.

Example 5
8.67 gm of L-2-Oxothiazolidine-4-carboxylic acid was added to a suspension of 7.33 gm of 2,4-Diamino pyrimidine-3-oxide in 484 gm water. The solution becomes clear after stirring for 1 hr. The resulting solution can be used directly for the preparation of compositions suitable for topical applications. The solution was analyzed for the contents present.

Example 6
8.67 gm of L-2-Oxothiazolidine-4-carboxylic acid and 7.33 gm of 2,4-Diamino pyrimidine-3-oxide was dissolved in 1.0 ltr of 95% alcohol. The solvent was evaporated to give the desired solid. Alternatively the solid can also be obtained by partial distillation of the solvent and precipitation of the same with a suitable solvent. The solid can be analyzed using techniques known in the art.

IR and NMR analysis of all the above salts confirmed their desired structures.

Example 7
Composition containing water-soluble salt prepared in Example 1 and 2 is shown in Table 1

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
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<tr>
<td>Salt</td>
<td>5 gm</td>
</tr>
<tr>
<td>Tween 20</td>
<td>0.5 gm</td>
</tr>
<tr>
<td>Alcohol</td>
<td>10.0 gm</td>
</tr>
</tbody>
</table>
Example 8
Composition containing water-soluble salt prepared in Example 3 and 4 is shown in Table 2

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
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<tr>
<td>Salt</td>
<td>5.27gm</td>
</tr>
<tr>
<td>Tween 20</td>
<td>0.5 gm</td>
</tr>
<tr>
<td>Alcohol</td>
<td>10.0 gm</td>
</tr>
<tr>
<td>Fragrance</td>
<td>q.s</td>
</tr>
<tr>
<td>Colour</td>
<td>q.s</td>
</tr>
<tr>
<td>Water</td>
<td>q.s to 100</td>
</tr>
</tbody>
</table>

Table 2

Example 9
Composition containing water-soluble salt prepared in Example 5 and 6 is shown in Table 3

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
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<tbody>
<tr>
<td>Salt</td>
<td>3.26 gm</td>
</tr>
<tr>
<td>Tween 20</td>
<td>0.5 gm</td>
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<tr>
<td>Alcohol</td>
<td>10.0 gm</td>
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<tr>
<td>Fragrance</td>
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<tr>
<td>Colour</td>
<td>q.s</td>
</tr>
<tr>
<td>Water</td>
<td>q.s to 100</td>
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</table>

Table 3

pH of all the above water soluble compositions were adjusted to 4.5 - 5.5 using mild bases (organic / inorganic) known in the art.
Open label, phase II, clinical study was carried out, to evaluate the safety and efficacy of topical application of the above 3 compositions and conventional 5% solution of 2,4-Diamino-6-piperidinopyrimidine-3-oxide (Minoxidil) available in market, for the treatment of mild to moderate androgenic alopecia in male patients.

Few research papers disclosed that mRNA levels have been co-related to hair growth. More the mRNA value, better is the effectiveness of the formulation in hair growth. According to above clinical study, the water soluble salts showed increased mRNA values. Particularly, the water soluble composition of 2,4-Diamino-6-piperidinopyrimidine-3-oxide (Minoxidil) with L-2-Oxothiazolidine-4-carboxylic acid showed almost 3 times mRNA value when compared with 5% solution of 2,4-Diamino-6-piperidinopyrimidine-3-oxide (Minoxidil) available in market as shown in Table 4.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Composition (mRNA levels)</th>
<th>Figure</th>
<th>% Improvement after month 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5% Minoxidil (market)</td>
<td>FIG.1</td>
<td>6.3%</td>
</tr>
<tr>
<td>2</td>
<td>Salt of L-2-Oxothiazolidine-4-carboxylic acid with 2,4-Diamino-6-piperidinopyrimidine-3-oxide</td>
<td>FIG 2</td>
<td>18%</td>
</tr>
<tr>
<td>3</td>
<td>Salt of L-2-Oxothiazolidine-4-carboxylic acid with 2,4-Diamino-6-pyrrolidinopyrimidine-3-oxide</td>
<td>FIG 3</td>
<td>13.5%</td>
</tr>
<tr>
<td>4</td>
<td>Salt of L-2-Oxothiazolidine-4-carboxylic acid with 2,4-Diamino pyrimidine-3-oxide</td>
<td>FIG 4</td>
<td>12.6%</td>
</tr>
</tbody>
</table>

Table 4

The foregoing description of the specific embodiments will so fully reveal the general nature of the embodiments herein that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without departing from the generic concept, and therefore, such adaptations and modifications are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the phraseology or terminology employed herein is for the purpose of description and not of limitation. Therefore, while the embodiments herein have been described in terms of preferred embodiments, those skilled in the art will recognize that the embodiments herein can be practiced with modifications within the spirit and scope of the appended claims.
Claims

1. A water soluble hair growth salt suitable for treating alopecia and stimulate hair growth, wherein the water soluble salt having a cyclic amino acid and a hair growth stimulant, wherein the cyclic amino acid is preferably L-2-Oxothiazolidine-4-carboxylic acid formula (a), wherein the hair growth stimulant is 2,4-Diamino pyrimidine-3-oxide derivatives of the formula (b).

   \[
   \text{(a)} \quad \begin{array}{c}
   \text{H}_2\text{C} \quad \text{H} \quad \text{COOH} \\
   \text{S} \quad \text{NH} \\
   \text{O}
   \end{array}
   \quad \text{(b)} \quad \begin{array}{c}
   \text{H}_2\text{N} \quad \text{N} \\
   \text{O} \quad \text{NH}_2 \quad \text{N}
   \end{array}
   \]

2. The water soluble hair growth salt as claimed in claim 1, wherein R is either Hydrogen or Alkyl of from 1 to 8 carbon atoms or heterocyclic moieties containing either Nitrogen or Nitrogen and Oxygen.

3. The water soluble hair growth salt as claimed in claim 2, wherein the heterocyclic moieties is selected from a group comprising pyrrolidine, piperidine, piperazine, morpholine.

4. The water soluble hair growth salt as claimed in claim 1, wherein 2,4-Diamino pyrimidine-3-oxide derivatives of the formula (b) is selected from a group comprising 2,4-Diamino-6-piperidinopyrimidine, 2,4-Diamino-6-pyrrolidinopyrimidine, 2,4-Diamino pyrimidine N-oxides.

5. A composition suitable for topical application for treating alopecia and stimulate hair growth, wherein the composition comprising a water soluble salt as claimed in claim 1.

6. The composition as claimed in claim 5, wherein the composition can be administered in the form of lotion, cream, spray, gel, solution or ointment.

7. The composition as claimed in claim 5, wherein the salt is in the range from 0.1 to 15% of the composition.

8. The composition as claimed in claim 5, wherein the composition contains water up to 95% of the composition.

9. The composition as claimed in claim 5, further comprises pharmaceutically acceptable vehicles or pharmaceutically acceptable excipients.
10. A process for preparing water soluble salt suitable for treating alopecia and stimulate hair growth, wherein the salt is prepared by reacting stoichiometric quantities of formula (a) and formula (b) in water or organic solvents or in a suitable vehicle.

(a)

(b)
Hair density for 5% Minoxidil (Market sample)

% improvement in hair density for 5% Minoxidil (Market sample)

Hair growth for 5% Minoxidil (Market sample)

% Improvement of Hair growth for 5% Minoxidil (Market sample)

FIG. 1
FIG. 2
Hair density for salt of 1,2-Oxothiazolidine-4-carboxylic acid with 2,4-Diamino-6-pyrolidinopyrimidine-3-oxide

% Improvement of Hair density for salt of 1,2-Oxothiazolidine-4-carboxylic acid with 2,4-Diamino-6-pyrolidinopyrimidine-3-oxide

Hair growth for salt of 1,2-Oxothiazolidine-4-carboxylic acid with 2,4-Diamino-6-pyrolidinopyrimidine-3-oxide

% Improvement of Hair growth for salt of 1,2-Oxothiazolidine-4-carboxylic acid with 2,4-Diamino-6-pyrolidinopyrimidine-3-oxide

FIG. 3
INTERNATIONAL SEARCH REPORT

Internati onal application No.
PCT/IB2014/062353

A. CLASSIFICATION OF SUBJECT MATTER
C07D23 9/50, A61Q7/02, C12P13/12 Version=2014.01

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)
C07D, A61Q, C12P

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)
ORBIT, IPO INTERNAL DATABASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C. See patent family annex.

- **A** Special categories of cited documents:
  - Document defining the general state of the art which is not considered to be of particular relevance
  - Earlier application or patent but published on or after the international filing date
  - 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)
  - Document referring to an oral disclosure, use, exhibition or other means
  - Document published prior to the international filing date but later than the priority date claimed

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- **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
29-10-2014

Date of mailing of the international search report
29-10-2014

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B. Ramamuni
Telephone No. +91-H25300200

Form PCT/ISA/210 (second sheet) (July 2009)
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