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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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(54) Title: HYPERBARIC INJECTION SOLUTION OF ROPIVACAINE HYDROCHLORIDE AND PROCESS FOR PREPARATION THEREOF

(57) Abstract: Disclosed herein is hyperbaric solution for injection of Ropivacaine Hydrochloride which comprises Ropivacaine Hydrochloride; a base/acid to adjust the pH and a baricity adjuster to modify Baricity of the injection solution.

"HYPERBARIC INJECTION SOLUTION OF ROPIVACAINE HYDROCHLORIDE AND PROCESS FOR PREPARATION THEREOF"

Technical field of the Invention:

The present invention relates to a hyperbaric injection solution of pharmaceutically acceptable salt of Ropivacaine. More particularly, the present invention relates to a stable hyperbaric injection solution of Ropivacaine Hydrochloride comprising; an active ingredient, a baricity adjuster, a base/acid to adjust the pH and water as a vehicle. The invention further relates to the process of preparation of a stable hyperbaric injection of Ropivacaine Hydrochloride.

Background and Prior art:

Ropivacaine Hydrochloride is a new long acting amino-amide local anaesthetic agent with Pharmacodynamics, pharmacokinetic properties, which has chemical structure resembling to Bupivacaine Hydrochloride. The name Ropivacaine refers to racemate.

Currently available (Marketed) formulation of Ropivacaine Hydrochloride injection is a sterile solution of Ropivacaine Hydrochloride in water for injections which is isobaric solution. Their duration of anaesthesia in the lumbosacral areas is prolonged significantly. The Hyperbaric solution of Bupivacaine is also available in market.

Hyperbaric solutions have a greater specific gravity than the cerebrospinal fluid often making the spread of anaesthesia more predictable with greater spread in the direction of gravity. Hyperbaric solutions gravitate to the thoracic kyphosis in the supine patient, therefore assuring an adequate level of spinal anesthesia, which is T-6 in the average patient.

Hyperbaric Ropivacaine solution gravitates to dependent areas and provides reliable spinal anaesthesia of shorter duration than bupivacaine. The recovery profile of Ropivacaine may be useful where prompt mobilization is required.

Since Bupivacaine has long duration of sensory blockade with delayed return of motor activity and prolongs postanesthesia care unit stay after delivery.

For surgical procedure performed on patients who are not in the supine position, the baricity of the local anaesthetic solution and gravity are employed to direct the local anaesthetic towards the spinal nerves innervating the surgical site.
Hyperbaric Roupivacaine solution will provide a more rapid onset and greater spread of anasthesia but a shorter duration of anaesthesia and analgesia. Thus this solution is primarily useful for abdominal surgery procedures of limited duration.

In the above context, there are few arts which state the anaesthetic effect of Ropivacaine.

J. F. Kuck, P.D.W. Fettes and J.A. Wildsmith in 'Spinal Anaesthesia for Elective surgery: A comparison of hyperbaric solution of racemic Bupivacaine, Levobupivacaine and Ropivacaine' states that, Hyperbaric Ropivacaine provides reliable spinal anaesthesia of shorter duration than Bupivacaine or Levobupivacaine, both of which are clinically indistinguishable. The recovery profile of Ropivacaine may be useful where prompt mobilization is required.

Dr. Feroz Ahmad Dar and Dr. Neelofar Jan in 'Evaluation of Hyperbaric spinal Ropivacaine in lower limb and hip surgery: A comparison with hyperbaric Bupivacaine' states that, a solution of Ropivacaine (hyperbaric) can be used for anaesthesia and is comparable with hyperbaric Bupivacaine in terms of block, but has shorter recovery profile.

CN1660094A discloses the invention related to a freeze-dried powder injection of Ropivacine hydrochloride which is prepared from Ropivacaine hydrochloride and pharmacologically supporting materials including material, lactose, glucose, and dextran. It's preparing process features use of low-tempt aseptic vacuum spray drying for shortening time.

CN1626081 discloses a freeze-dried injection of Ropivacaine which is prepared from the Ropivacaine methanesulfonate (or hydrochloride), diluent chosen from mannitol, lactose, sodium chloride, dextran, glucose, glycine, hydrolytic gelatin and povidone, isotonic regulator and pH regulator through dissolving them in the water for injection, stirring, cooling, adding the water for injection, adding activated carbon, adsorption, filtering for removing carbon, filtering by millipore filter and freeze drying.

CN102670489B discloses Ropivacaine hydrochloride and sodium chloride injection and preparation methods thereof. The process steps including carbon adsorption, coarse filter, fine filter, filling, sterilization, light inspection and packaging process steps. The prepared hydrochloric acid Ropivacaine clear efficacy of sodium chloride injection, measurement results safe; stability test of the indicators are in line with the provisions of, and to address the Ropivacaine water injections require multiple injections, inconvenient to use; freeze-dried powder tends to increase secondary pollution and other defects, particularly suitable for use in patients with analgesia pump; large capacity utilization, so that liquid to maintain a stable concentration timely; not only produce significant postoperative analgesia demand but decline opioids significantly; and the patient can quickly enhance the effect by pressing their own administration.

CN102552126B discloses a high-security Ropivacaine hydrochloride and its preparation method. The high Ropivacaine hydrochloride injection safety formula consisting of: Ropivacaine hydrochloride 20-200g, sodium chloride 70-100g, or the amount of hydrochloric acid, sodium hydroxide, and water for injection was added to 10000ml; the formula is made into 1000 injections, and pH of the injection is 4.0-6.0. This product has good stability, high drug content, and the effect is safe and reliable.

CN102038651B discloses a mesylate Ropivacaine freeze-dried powder, the freeze-dried powder consist of Ropivacaine mesylate and PH regulator and

prepared by freeze-drying method uses: (1) sub-IQF stage: the filling good Mesylate Ropivacaine solution was maintained at 10 ~ 30min 0°C, 1 ~ 2h and then kept at -35°C ~ -45°C; (2) sublimation drying stage : the degree of vacuum 10 ~ 20Pa , temperature 2 ~ 10°C/h warmed to 0°C rear holder 1 ~ 3h; (3) Analytical drying stage: the degree of vacuum in the 0 ~ 10Pa, temperature 5 ~ 10°C/h was raised to 30°C, and maintained for 2 ~ 5h. The obtained Freez-dried powder has a high yield, good soluble complex, more stable quality and so on.

In view of the above, there is still a need to develop the hyperbaric solution for injection of Ropivacaine for making the spread of anaesthesia more predictable with greater spread in the direction of gravity and stable during its shelf life.

Therefore, it is the object of the present invention to provide a stable hyperbaric solution for Injection of Ropivacaine.

Summary of the Invention:

In accordance with the objective, the present invention provides a stable hyperbaric solution for injection of pharmaceutically acceptable salt of Ropivacaine Hydrochloride.

In a preferred aspect, the present invention provides a stable hyperbaric solution for injection comprising Ropivacaine Hydrochloride; a baricity adjuster to make solution hyperbaric, a base/acid to adjust the pH and water as a vehicle.

In another preferred aspect, the invention provides a process for preparation of said stable hyperbaric injection solution of Ropivacaine Hydrochloride.

Detailed description of the Invention:

The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated.

The main rational of the present invention is to provide more rapid onset and greater spread of anasthesia but a shorter duration of anaesthesia and analgesia. Thus this solution is primarily useful for abdominal surgery procedures of limited duration.

According to present invention Ropivacaine may be provided in hyperbaric solution for injection for spinal anaesthesia.

Hyperbaric solutions have a greater specific gravity than the cerebrospinal fluid often making the spread of anaesthesia more predictable with greater spread in the direction of gravity. Hyperbaric solutions gravitate to the thoracic kyphosis in the supine patient, therefore assuring an adequate level of spinal anesthesia, which is T-6 in the average patient.

Hyperbaric Ropivacaine solution gravitates to dependent areas and provides reliable spinal anaesthesia of shorter duration than bupivacaine. The recovery profile of Ropivacaine may be useful where prompt mobilization is required. Since Bupivacaine has long duration of sensory blockade with delayed return of motor activity and prolongs postanesthesia care unit stay after delivery.

For surgical procedure performed on patients who are not in the supine position, the baricity of the local anaesthetic solution and gravity are employed to direct the local anaesthetic towards the spinal nerves innervating the surgical site.

The present invention provides a stable hyperbaric solution for injection of Ropivacaine Hydrochloride comprising pharmaceutically acceptable salt of Ropivacaine Hydrochloride, a baricity adjuster to make solution hyperbaric, a base/acid to adjust the pH and water as a vehicle.

Accordingly, in a preferred embodiment, the instant invention provides a stable hyperbaric solution for injection of Ropivacaine Hydrochloride comprising

Ropivacaine Hydrochloride; a baricity adjuster such as Sucrose in the form of Mannitol or Dextrose; a base/acid to adjust the pH and water as a vehicle.

The Ropivacaine Hydrochloride used in hyperbaric solution is present in an amount of 5mg.

The Dextrose used in hyperbaric solution is present in an amount of 2%w/v to 25% w/v, preferably, 4%w/v to 15%w/v.

Mannitol used in hyperbaric solution is present in an amount of 5% w/v to 10% w/v.

The pH of hyperbaric solution is adjusted with base/acid such as potassium hydroxide or sodium hydroxide/Glacial acetic acid or hydrochloric acid, preferably, sodium hydroxide or Hydrochloric acid.

The pH of hyperbaric solution is maintained between 3.5 to 6.0, preferably between 4.0 to 6.0.

The present invention provides a process for preparation of a stable hyperbaric solution for injection of Ropivacaine Hydrochloride comprises, dissolving baricity adjuster in water, followed by addition of API; adjusting the pH of the solution between 4 to 6 using a base/acid and making the required volume with cool water to obtain the injection.

Accordingly, in another preferred embodiment, the present invention provides a process for preparation of a stable hyperbaric solution for injection of Ropivacaine Hydrochloride comprises;

a) Dissolving Dextrose or Mannitol in water followed by addition of Ropivacaine Hydrochloride;

b) adjusting the pH of the solution of step (a) between 4.0 to 6.0 using a sodium hydroxide or Hydrochloric acid and
c) making the required volume with cool water to obtain the injection.

In another embodiment, a hyperbaric solution of Ropivacaine Hydrochloride according to invention comprises 4%w/v to 15%w/v Dextrose to make the solution hyperbaric.

In yet another embodiment, a hyperbaric solution of Ropivacaine Hydrochloride according to the invention, wherein, the 4%w/v to 15%w/v Dextrose is dissolved in aqueous vehicle.

In another embodiment, a hyperbaric solution of Ropivacaine Hydrochloride according to invention comprises 5%w/v to 10% w/v mannitol to make the solution hyperbaric.

Several different trials were conducted & tested for stability. Some of these trials are discussed below in brief.

Examples:

The following examples, which include preferred embodiments, will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of examples and for purpose of illustrative discussion of preferred embodiments of the invention.

Example 1:

Ingredient	Quantity/mL
Ropivacaine Hydrochloride	5mg
Mannitol	5%w/v
Sodium Hydroxide/ Hydrochloric acid	q.s. to pH 4.0 to 6.0
Water For Injections	q.s. to 1ml

Procedure:

a) Dissolving Mannitol in a cool water, followed by addition of Ropivacaine Hydrochloride and adjusting pH of the solution to 4.0 to 6.0 with solution of Sodium Hydroxide or Hydrochloric acid;

b) making up the required volume with cool water for injections.

The results are discussed in **Table 1** herein below:

Table 1:

Stage	Assay %	Baricity	Chromatography Impurity
			Limit of 2,6-Dimethylaniline (Ropivacaine related compound A)
			N.M.T. 0.1%
Initial	102.65	Hyperbaric	Nil
1M/25°C	103.56	Hyperbaric	Nil
2M/25°C	103.49	Hyperbaric	Nil
3M/25°C	101.13	Hyperbaric	Nil
1M/40°C	103.93	Hyperbaric	Nil
2M/40°C	102.80	Hyperbaric	Nil
3M/40°C	101.57	Hyperbaric	Nil

Example 2:

Ingredient	Quantity/mL
Ropivacaine Hydrochloride	5mg
Mannitol	10% w/v
Sodium Hydroxide/ Hydrochloric acid	q.s. to pH 4.0 to 6.0
Water For Injections	q.s. to 1ml

Procedure:

a) Dissolving Mannitol in a cool water, followed by addition of Ropivacaine Hydrochloride and adjusting pH of the solution to 4.0 to 6.0 using solution of Sodium Hydroxide or Hydrochloric acid;

b) making up the required volume with cool water for injections.

The results are discussed in **Table 2** herein below:

Table 2:

Stage	Assay %	Baricity	Chromatography Impurity
			Limit of 2,6-Dimethylaniline (Ropivacaine related compound A)
			N.M.T. 0.1%
Initial	104.28	Hyperbaric	Nil
1M/25°C	103.71	Hyperbaric	Nil
2M/25°C	102.34	Hyperbaric	Nil
3M/25°C	105.06	Hyperbaric	Nil
1M/40°C	103.76	Hyperbaric	Nil
2M/40°C	105.21	Hyperbaric	Nil
3M/40°C	103.41	Hyperbaric	Nil

Example 3:

Ingredient	Quantity/mL
Ropivacaine Hydrochloride	5mg
Dextrose	5%w/v
Sodium Hydroxide/ Hydrochloric acid	q.s. to pH 4.0 to 6.0
Water For Injections	q.s. to 1ml

Procedure:

a) Dissolving Dextrose in a cool water, followed by addition of Ropivacaine Hydrochloride and adjusting pH of the solution to 4.0 to 6.0 using solution of Sodium Hydroxide or Hydrochloric acid;

b) making up the required volume with cool water for injections.

The results are discussed in **Table 3** herein below:

Table 3:

Stage	Assay %	Baricity	Chromatography Impurity
			Limit of 2,6-Dimethylaniline (Ropivacaine related compound A)
			N.M.T. 0.1%
Initial	102.40	Hyperbaric	Nil
1M/25°C	101.08	Hyperbaric	Nil
2M/25°C	102.19	Hyperbaric	Nil

3M/25°C	104.63	Hyperbaric	Nil
1M/40°C	104.17	Hyperbaric	Nil
2M/40°C	103.94	Hyperbaric	Nil
3M/40°C	104.50	Hyperbaric	Nil

Example 4:

Ingredient	Quantity/mL
Ropivacaine Hydrochloride	5mg
Dextrose	8%w/v
Sodium Hydroxide/ Hydrochloric acid	q.s. to pH 4.0 to 6.0
Water For Injections	q.s. to 1ml

Procedure:

a) Dissolving Dextrose in a cool water, followed by addition of Ropivacaine Hydrochloride and adjusting pH of the solution to 4.0 to 6.0 using solution of Sodium Hydroxide or Hydrochloric acid;

b) making up the required volume with cool water for injections.

The results are discussed in **Table 4** herein below:

Table 4:

Stage	Assay %	Baricity	Chromatography Impurity
			Limit of 2,6-Dimethylaniline (Ropivacaine related compound A)
			N.M.T. 0.1%
Initial		Hyperbaric	Nil
1M/25°C	103.67	Hyperbaric	Nil
2M/25°C	101.63	Hyperbaric	Nil
3M/25°C	100.35	Hyperbaric	Nil
1M/40°C	103.55	Hyperbaric	Nil
2M/40°C	100.29	Hyperbaric	Nil
3M/40°C	99.97	Hyperbaric	Nil

Example 5:

Ingredient	Quantity/mL
Ropivacaine Hydrochloride	5mg
Dextrose	10%w/v

Sodium Hydroxide/ Hydrochloric acid	q.s. to pH 4.0 to 6.0
Water For Injections	q.s. to 1ml

Procedure:

a) Dissolving Dextrose in a cool water, followed by addition of Ropivacaine Hydrochloride and adjusting pH of the solution to 4.0 to 6.0 using solution of Sodium Hydroxide or Hydrochloric acid;

b) making up the required volume with cool water for injections.

The results are discussed in **Table 5** herein below:

Table 5:

Stage	**Assay %**	**Baricity**	**Chromatography Impurity**
			Limit of 2,6-Dimethylaniline (Ropivacaine related compound A)
			N.M.T. 0.1%
Initial	105.13	Hyperbaric	Nil
1M/25°C	104.34	Hyperbaric	Nil
2M/25°C	103.63	Hyperbaric	Nil
3M/25°C	104.92	Hyperbaric	Nil
1M/40°C	104.64	Hyperbaric	Nil
2M/40°C	103.57	Hyperbaric	Nil
3M/40°C	102.83	Hyperbaric	Nil

We Claim,

1. A stable hyperbaric injection solution of Ropivacaine Hydrochloride comprising;
    a) pharmaceutically acceptable salt of Ropivacaine Hydrochloride;
    b) a baricity adjuster to make solution hyperbaric;
    c) a base/acid to adjust the pH and
    d) water as a vehicle.

2. The stable hyperbaric injection solution of Ropivacaine Hydrochloride as claimed in claim 1; wherein the baricity adjuster is selected from Mannitol or Dextrose.

3. The stable hyperbaric injection solution of Ropivacaine Hydrochloride as claimed in claim 2; wherein the baricity adjuster is preferably a Dextrose.

4. The stable hyperbaric injection solution of Ropivacaine Hydrochloride as claimed in claim 2 and 3; wherein the Dextrose is present in an amount of 2%w/v to 25%w/v, preferably, 4%w/v to 15%w/v.

5. The stable hyperbaric injection solution of Ropivacaine Hydrochloride as claimed in claim 2; wherein the Mannitol is present in an amount of 5% w/v to 10% w/v.

6. The stable hyperbaric injection solution of Ropivacaine Hydrochloride as claimed in claim 1; wherein a base/acid is selected from potassium hydroxide or sodium hydroxide/Glacial acetic acid or hydrochloric acid.

7. The stable hyperbaric injection solution of Ropivacaine Hydrochloride as claimed in claim 6; wherein a base/acid is preferably sodium hydroxide/hydrochloric acid.

8. The stable hyperbaric injection solution of Ropivacaine Hydrochloride as claimed in claim 1; wherein pH of the solution adjusted between 3.5 to 6.0, preferably 4.0 to 6.0.

9. A process for preparation of stable hyperbaric injection solution of Ropivacaine Hydrochloride comprises,
    a) Dissolving Dextrose or Mannitol in water followed by addition of Ropivacaine Hydrochloride;
    b) adjusting the pH of the solution of step (a) using between 4.0 to 6.0 using a sodium hydroxide or Hydrochloric acid and
    c) making the required volume with cool water to obtain the injection.

10. The process as claimed in claim 9; wherein the Dextrose is present in an amount of 2%w/v to 25%w/v, preferably, 4%w/v to 15%w/v.

11. The process as claimed in claim 9; wherein the Mannitol is present in an amount of 5% w/v to 10% w/v.

12. A stable hyperbaric injection solution of Ropivacaine Hydrochloride as claimed in any of the preceding claims comprises 2%w/v to 25%w/v Dextrose to make the injection solution hyperbaric.

13. A stable hyperbaric injection solution of Ropivacaine Hydrochloride as claimed in claim 12, wherein 2%w/v to 25%w/v Dextrose is dissolved in aqueous vehicle.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2016/050100

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/167,C07D211/60 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, C07D

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)

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Feroz Ahmad Dar, Neelofar Jan, American Journal of Advanced Drug Delivery, Evaluation of Hyperbaric Spinal Ropivacaine in Lower Limb and Hip Surgery: A Comparison with Hyperbaric Bupivacaine, Vol 1, No 5 (2013). whole document	1-8
A	whole document	9-13
Y	CN102552126 A, QINGYUAN JIABO PHARMACEUTICAL CO LTD, 11/JULY/2012. abstract and claim 1	1-8
A	abstract and claim 1	9-13

☐ 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
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"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
07-09-2016	07-09-2016
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Md Atiqullah Telephone No. +91-1125300200