

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

08 August 2019 (08.08.2019)



(10) International Publication Number

WO 2019/150381 A1

(51) International Patent Classification:

A61K 31/137 (2006.01) A61K 9/08 (2006.01)

Published:

— with international search report (Art. 21(3))

(21) International Application Number:

PCT/IN2018/000028

(22) International Filing Date:

14 May 2018 (14.05.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

201841003813 01 February 2018 (01.02.2018) IN

(72) Inventor; and

(71) Applicant: **JOSHI, Mahendra R.** [IN/IN]; IDRS Labs Private Limited, #235-H, Phase-3, Bommasandra Industrial Area, Hosur Road, Bangalore 560099 (IN).

(72) Inventors: **S, Kamalanathan**; 266B, Railway Quarters, Goods Shed Road Arakkonam, Vellore District, Tamilnadu 631001 (IN). **MANDAPATI, Ravindhar Reddy**; Marlapadu (V), Vemsoor (M), Khammam (D), Telangana State (IN). **IMMANNI, Trinath Kumar**; Plot No. 806, Pragathi Nagar, Opposite JNTU, Hyderabad, Andhra Pradesh (IN). **BHOWMICK, Ananya De**; 3/69, Bibek Nagar, Santoshpur, Kolkata, West Bengal 700075 (IN).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- of inventorship (Rule 4.17(iv))

(54) Title: A STABLE PHARMACEUTICAL COMPOSITION AND PROCESS FOR PRODUCTION OF ISOPROTERENOL HYDROCHLORIDE INJECTION

(57) Abstract: In one aspect, the invention relates to a stable liquid formulation for parenteral composition comprising a therapeutically effective amount of Isoproterenol In an aqueous solution having controlled oxygen level in the head space of a container and in bulk solution.



WO 2019/150381 A1

A stable pharmaceutical composition and process for production of Isoproterenol Hydrochloride Injection

FIELD OF THE INVENTION

The present invention refers to stable pharmaceutical compositions of Isoproterenol Hydrochloride for pharmaceutical use and to a method of preparation.

BACKGROUND OF THE INVENTION

It is common knowledge that some active ingredients are having stability problems in solution. Some of these problems are due to the fact that the active ingredients easily oxidize, by reacting either with atmospheric oxygen or with dissolved oxygen in the aqueous solution, with consequent production of non-desirable degradation products.

Isoproterenol Hydrochloride is 3,4-Dihydroxy- α -[(isopropylamino)methyl] benzyl alcohol hydrochloride, a synthetic sympathomimetic amine that is structurally related to epinephrine but acts almost exclusively on beta receptors. Isoproterenol hydrochloride is a racemic compound.

Isoproterenol Hydrochloride Injection 0.2 mg/mL administered by intravenous infusion or bolus intravenous injection use in the treatment of bradycardia (slow heart rate), heart block, and rarely for asthma. Isoproterenol is a potent nonselective beta-adrenergic agonist with very low affinity for alphaadrenergic receptors. Intravenous infusion of Isoproterenol in man lowers peripheral vascular resistance, primarily in skeletal muscle but also in renal and mesenteric vascular beds.

Innovator product is available in the brand name of ISUPREL[™] (Isoproterenol Hydrochloride) sterile Injection, USP in US market.

The sterile solution is nonpyrogenic and can be administered by the intravenous, intramuscular, subcutaneous, or intracardiac routes. ISUPREL[™] is supplied in 1 mL & 5ml ampoule 0.02% sterile, non-pyrogenic aqueous solution.

Catecholamines such as Isoproterenol and epinephrine are highly subject to degradative oxidation in solutions. During Drug product development stage, it is observed that, Isoproterenol HC injection in aqueous solutions is highly unstable when packed without control on dissolved oxygen and head space oxygen in glass vials and ampoules. Due to the fact that Isoproterenol in aqueous medium is unstable in the presence of oxygen and/or light, it is difficult to obtain a pharmaceutical ready-to-use solution for intravenous perfusion.

Various attempts were undertaken to develop a stable Isoproterenol solutions. One of the attempt was by Nayak et al., (1986) investigated the effect of various additives on the stability of Isoproterenol Hydrochloride solutions (Nayak et al., Drug Development and Industrial Pharmacy, Volume 12, 1986, Pages 589-601). They found that Ascorbic acid and sodium bisulfite appear to be the most efficient antioxidants in the system. Further they concluded the effectiveness of Sequestering agents such as EDTA and citric acid in reducing degradation rate of Isoproterenol. They observed that the reaction appears to be an oxidation of the catechol ring system of Isoproterenol similar to that observed with epinephrine.

Smith et al (1984) investigated the effects of ascorbic acid and disodium edetate on the stability of isoprenaline hydrochloride injection (Smith et al., J ClinHosp Pharm. 1984 Sep; 9(3):209-15). Experimentation results further concluded that Disodium edetate (0.01%), either alone or in combination with ascorbic acid (0.1%) was an effective stabilizer for isoprenaline injection B.P., but adjustment to pH 2.8 was necessary. The bubbling of nitrogen through the solution in the ampoule before sealing did not prevent degradation in unprotected solutions. Solutions sterilized by filtration or by autoclaving for 30 min at 116 degrees C were stable for at least 1 year at 5 degrees C or 25 degrees C.

US patent 3039928 also address the problem of stability of Isoproterenol and solutions by adding ascorbic acid effectively prevents breakdown and deterioration of isoproterenol in aqueous compositions. The inherent properties of ascorbic acid are unique because many other

antioxidants fail to display the beneficial properties of stabilizing Isoproterenol. Among other antioxidants which have been found undesirable are butylatedhydroxy anisole, propyl gallate, nor-dihydroguarectic acid, sodium metabisulfite, ethyl hydrocatfeate, di-tertbutyl-paracresol and others.

The present inventors have carried out various researches in order to develop a Isoproterenol pharmaceutical formulation in the form of a solution for injection, having an improved stability.

The present inventors surprisingly found that, when headspace oxygen in the vials & ampoules filled with solution for injection was substantially removed (i.e., approximately less than 2%) by e.g., bubbling of nitrogen gas into the solution & purging nitrogen gas over head space of vials/ ampoules after solution filling, a stable liquid formulation containing Isoproterenol or its salt is obtained.

Therefore, the present invention provides a method for preparing a pharmaceutical formulation in the form of a stable solution for injection containing Isoproterenol or its salt as an active ingredient.

The present invention overcomes the limitations of Isoproterenol solutions by stabilizing solutions of Isoproterenol by controlling the level of dissolved oxygen content and head space oxygen in the container.

BRIEF SUMMARY OF THE INVENTION

Two factors affecting the stability of pharmaceutical composition of Isoproterenol solution such as exposure to oxygen in the unfilled area of a container carrying the drug solution (headspace) as well as the absorption of gaseous oxygen (dissolved oxygen) into the drug solution.

Methods for controlling the oxygen content of the headspace are insufficient for reliably controlling the levels of oxygen necessary to obtain a stable liquid formulation of Isoproterenol having desirable potency and stability over the shelf life of the composition.

Stringent control of the oxygen levels in the headspace and the dissolved oxygen that is absorbed into the drug solution provide beneficial effects for decreasing the total impurities of the drug product. Purging a sufficient amount of nitrogen over headspace of the composite solution affords an overall more stable formulation of Isoproterenol.

We have determined that to provide a stable composition of Isoproterenol formulation, the composition should have less than or equal to 5.0ppm oxygen in bulk solution, and less than or equal to 2% head space oxygen content in the unit dose container.

Therefore, one object of the present invention relates to providing a composition of Isoproterenol having low oxygen levels of less than or equal to 5.0 ppm oxygen in bulk solution.

Another object of the invention relates to preparing a unit dose system in a sealed vessel comprising an aqueous solution of a therapeutic amount of Isoproterenol having oxygen levels less than or equal to 2.0% in the headspace.

In one aspect, the invention relates to a composition comprising a therapeutically effective amount of Isoproterenol in an aqueous solution having less than or equal to 2.0% oxygen in the headspace of a container when determined immediately after container sealing, said solution consisting essentially of a complexing agent and buffers. The compositions provide a stable low oxygen formulation having less than or equal to 5 ppm of oxygen.

Yet another aspect of the invention relates to a process for preparing a low oxygen composition of aqueous Isoproterenol, comprising the steps of:

Step-1: Add and dissolve batch quantity of complexing agent in 80% of water for injection at 60-65°C.

Step-2: To the step-1 solution add buffers and stabilizing agents at room temperature.

Step-3: Nitrogen purge the bulk solution continuously to get dissolved oxygen below 5ppm.

Step-4: Add and dissolve drug substance to step-3 solution and adjust the pH of bulk solution to 3.5- 4.5 either by use of hydrochloric acid or sodium hydroxide.

Step-5: Make up the volume to 100% V/V with use of water for injection.

Step-6: Continuously nitrogen purge the bulk solutions to maintain dissolved oxygen below 5ppm.

Step-7: Filter the bulk solution using 0.2 micron PVDF sterile filter membrane.

Step-8: Fill the filtered solution in to 5 mL clear glass vial (USP type I glass) stoppered with coated rubber stopper and flip off seal. And ensure that the head space was blanketed with nitrogen gas.

The composition can be prepared in a vial according to steps (1) through (8) as described above. Appropriate means of closure was placed into the opening of the filled container in a manner which does not allow the exchange of gas from an interior side of the container to an exterior side of the container. The container headspace was treated with vacuum and purging the container headspace with an inert gas (nitrogen); and repeating the vacuum treating and purging step to control oxygen content in the container headspace before suitably sealing the container.

DETAILED DESCRIPTION OF THE INVENTION

Drug stability means the ability of the pharmaceutical dosage form to maintain the physical, chemical, therapeutic and microbial properties during the time of storage and usage by the patient. It is measured by the rate of changes that take place in the pharmaceutical dosage forms.

Stability is defined by the criteria set by ICH Q1A for injections.

The invention relates to the use of a stable Pharmaceutical composition of Isoproterenol.

It also relates to said composition characterized in that it is as a liquid stable Isoproterenol formulation.

Preferably the solution is an aqueous solution. The formulations as developed by the Inventors of the present Application are suitable for parenteral administration. Such stable liquid formulation of Isoproterenol can be developed with the use of tonicity agent, chelating agents and buffers and by controlling the oxygen content of drug solution and vial/ampoule headspace with the use of an inert gas viz nitrogen. These formulations are presented as a single unit dose (vial/ ampoule) presentation having Isoproterenol concentrations 0.2 mg/ml. These pharmaceutical compositions are then administered usually via intravenous infusion or bolus intravenous injection. In dire emergencies, the drug may be administered by intracardiac injection. If time is not of the utmost importance, initial therapy by intramuscular or subcutaneous injection is preferred.

The stable ready-to-use pharmaceutical composition of Isoproterenol is usually solvated in an aqueous solvent comprising water for injection. In one embodiment of the present invention, the ready-to-use pharmaceutical composition of Isoproterenol has a pH between about 2.5 and about 4.5, preferably between about 3.5 and about 4.5 and more preferably in the range of about 3.5 and about 4.0.

The pH of such ready-to-use pharmaceutical compositions of Isoproterenol may be achieved by use of suitable buffers and adjusted with a pharmacologically acceptable pH adjusting agent such as an acid & base. In an embodiment of the present invention, the pH adjusting agents are citrate buffers, acid and bases or their combination thereof. The hydrochloric acid or sodium hydroxide may be in any suitable form, such as a 0.01N to 1N solution.

In addition, the composition can contain one or more chelating agents whose presence will further improve the stability of the Isoproterenol present therein. Chelating agents which may be mentioned in particular are ethylenediamine tetraacetic acid, diethylenetriaminepentaacetic acid, 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid, trans-1,2-cyclohexylenediamine-N,N,N',N'-tetraacetic acid, N⁶-carboxymethyl-N³,N⁹-2,3-dihydroxy-N-methylpropylcarbamoylmethyl-3,6,9-triazaundecanedioic acid, N⁶-carboxymethyl-N³,N⁹-bis (methylcarbamoylmethyl)-3,6,9-triazaundecanedioic acid, N³,N⁶-bis (carboxymethyl) -N⁹-3-oxapentamethylene-carbamoylmethyl-3,6,9-triazaundecanedioic acid or N³,N⁶-bis (carboxymethyl)-N⁹-3,3-bis (dihydroxyphosphoryl)-3-hydroxypropyl-carbamoylmethyl-3,6,9-triazaundecanedioic acid. The chelating agents can be present in a quantity 0.02% by weight, relative to the total weight of the composition.

According to the invention the compositions are obtained by a deoxygenation process and inerting. Deoxygenation and inerting is carried out by use of inert gas and preferably dense as nitrogen is circulated and / or sparging facilities and other tubing and solutions in order to eliminate most of any trace of oxygen and residual volumes in solution.

According to the invention the pharmaceutical composition is characterized by its oxygen content which is less than 5ppm in bulk solution and less than 5% in head space. In other embodiments and depending on the intended stability times, the oxygen content may be less than 5ppm in bulk solution and less than 2% in head space.

The gas used for purging the sealable container may be any appropriate inert gas known to those in the art, the most commonly used gases being argon, helium or nitrogen, or mixtures thereof. However the most preferred inert gas is nitrogen.

In another embodiment of the present invention, so as to minimize oxidation of the sensitive material it is also desirable to remove headspace oxygen from the sealable vessel as quickly as possible. This may be aided by, for example, purging the sealable container with a gas which is substantially oxygen-free, or substantially oxygen and moisture free before, during or after step, or any combination thereof. Purging can be expected to reduce the oxygen level in the sealable container to a level of from about 0% to about 5% typically about 2% or lower, depending on the efficiency of flushing and how quickly the container is sealed after flushing.

The invention is further illustrated by way of the following example, which in no way should be construed as limiting the scope of the invention. The following examples further illustrate the invention and is not to be construed as limiting of the specification and claims in any way. Below are the experiment details performed to demonstrate the product instability when packed without head space nitrogen purging in 5mL glass vials.

Table #1: Formula composition for evaluation of product stability in glass vials

S. No.	Batch No.	IDRSFD010-FD/042-015
	Ingredients	Mg/mL
1.	Isoproterenol Hydrochloride, USP	0.20
2.	Edetate Disodium	0.20
3.	Sodium chloride USP	7.00
4.	Trisodium citrate, Dihydrate	2.07
5.	Citric acid anhydrous	2.50
6.	Hydrochloric acid/NaOH	pH adjusted to 3.5 to 4.5
7.	Water for injection	Q.S. to 1.0 mL
Process variables		
1.	Bulk solution Nitrogen purging	Yes (Dissolved oxygen <5ppm)
2.	Head space N ₂ purging	Yes
3.	Filtration (with N ₂ gas)	Yes
4.	Packing material	5 ml clear glass (USP type 1) vial stoppered with coated rubber stopper

Manufacturing Procedure:

Step-1: Add and dissolve batch quantity of edetate disodium in 80% of water for injection at 60-65°C.

Step-2: To the step-1 solution add sodium chloride, trisodium citrate and citric acid at room temperature.

Step-3: Nitrogen purge the bulk solution continuously to get dissolved oxygen below 5ppm.

Step-4: Add and dissolve drug substance to step-3 solution and adjust the pH of bulk solution to 3.5 - 4.5 either by use of dilute Hydrochloric acid or sodium hydroxide solution.

Step-5: Make up the volume to 100% V/V with use of water for injection.

Step-6: Continuously nitrogen purge the bulk solutions to maintain dissolved oxygen below 5ppm.

Step-7: Filter the bulk solution using 0.2 micron PVDF sterile filter membrane.

Step-8: Fill the filtered solution in to 5 mL clear glass vial (USP type I glass) stoppered with coated rubber stopper and flip off seal. And ensure that the head space was blanketed with nitrogen gas.

Table#2: Results of with and without head space nitrogen blanketing samples-015-vial batch

Batch no.:		IDRFD010-FD/042-015		
Parameter		Batch with <5 ppm DO Level packed in 5 ml vial		
S. No.	Condition	RT	60°C	60°C
No.	Stage	Initial	2week	2week
	Head space N2 purging	With Nitrogen	Without Nitrogen	With Nitrogen
1.	Description	Colorless Solution	Slight Brown Color solution	Colorless Solution
2.	Assay	106.7	79.0	107.0
3.	pH	3.68	3.696	3.695
4.	Color	0.0001	0.1722	0.0058
5.	Clarity	99.45	93.85	99.53
6.	EDTA	106.0	NP	NP
7.	Related substances % w/w @RRT			
0.81	ND	0.22	ND	
0.93	0.03	0.95	0.10	
1.07	ND	1.16	ND	
1.18	ND	0.23	0.03	
IMP-A_1.21	0.01	0.01	0.01	
2.08	ND	0.22	ND	
2.95	ND	0.44	ND	
3.06	ND	0.55	ND	
3.12	ND	0.37	ND	
3.31	ND	0.30	ND	
3.35	ND	0.56	ND	
3.36	ND	0.42	ND	
3.45	ND	0.65	ND	
3.51	ND	0.25	ND	
3.70	ND	0.71	ND	
4.05	ND	0.68	ND	
Total Imps		0.09	10.49	0.24

Remarks: <0.2% impurities are not reported in table as the no. of impurities are more, but included in total impurity. ND-Not detected. NP-Not performed

Inference: From the above study (with and without head space nitrogen purging) without nitrogen head space samples packed in 5mL vials has 10.49% total impurities, indicating that head space oxygen & nitrogen plays major role in product stability, thus complete head space blanketing with nitrogen gas should be done to avoid degradation and to maintain product stability throughout shelf life.

Below are the experiment details performed to demonstrate the product stability when packed with purging head space nitrogen at different times i.e. without nitrogen purging, 2sec, 4 sec & 6 sec (pre and post purging time) nitrogen purging on head space for 5mL ampoules.

Table #3: Formula composition and parameters for different head space nitrogen purging trials

S. No.	Fill volume	5.3 ml (1mg/5 ml)
No.	Ingredients	Mg/mL
1.	Isoproterenol Hydrochloride, USP	0.20
2.	Edetate Disodium	0.20
3.	Sodium chloride USP	7.00
4.	Trisodium citrate, Dihydrate	2.07
5.	Citric acid anhydrous	2.50
6.	Hydrochloric acid/NaOH	pH adjusted to 3.5 to 4.5
7.	Water for injection	Q.S. to 1.0 mL

Process variables

Batch No:	IDRFD010-	FD/042-026	FD/042-027	FD/042-028	FD/042-029
8.	Head space (pre and post N ₂ flushing) purging time	Without head space N ₂ Purge	2 sec	4sec	6 sec
9.	Filtration (N ₂ gas)	✓	✓	✓	✓
10.	Packing material	5 ml fiolax clear scoring ampoule with blue band			

Note: Dissolved oxygen level less than 2 ppm and head space of ampoules were purged with nitrogen gas (preandpost N₂ purging) as per the respective plan.

Table#4: Head space oxygen content measured by FMS- Oxygen Head space analyzer from Lighthouse

Batch No.	Batch Details	Head space oxygen content (%)
IDRFD010-FD/042-026	Without head space	20.042
IDRFD010-FD/042-027	2 sec head space	0.957
IDRFD010-FD/042-028	4 sec head space	0.335
IDRFD010-FD/042-029	6 sec head space	0.655

Table #5: Results of different head space nitrogen purging batches								
Batch No.	IDRFD010-FD/042-026	IDRFD010-FD/042-027		IDRFD010-FD/042-028		IDRFD010-FD/042-029		
Head space Nitrogen purging time	Without head space N ₂ purge	2 Sec. N ₂ purging		4 Sec. N ₂ purging		6 Sec. N ₂ purging		
Head space oxygen content	20.04%	0.96%		0.34%				
Strength		1mg / 5 ml (Fill volume-Not less than 5.3mL)						
S. No.	Condition	60°C	RT	60°C	RT	60°C	RT	60°C/
	Stage	2 week	Initial	2 week	Initial	2 week	Initial	2 week
1	Description	Light pink	Clear	Clear	Clear	Clear	Clear	Clear
2	Assay	93.4	100.6	101	101.4	101.6	101.1	100.6
3	pH	3.99	3.68	3.73	3.69	3.81	3.68	3.79
4	Color	NP	0.01	NP	0.011	NP	0.011	NP
5	Clarity	NP	98.46	NP	97.8	NP	97.92	NP
6	Dissolved Oxygenppm	NP	2.37	NP	3.95	NP	2.53	NP
7	EDTA	99.8	101.8	101	100.3	102.5	100.3	101
8	Related substances @ RRT (%w/w)							
	0.93	0.72	0.04	0.14	0.04	0.15	0.04	0.16
	1.07	0.28	ND	ND	ND	ND	ND	ND
	1.18	0.11	ND	ND	ND	ND	ND	ND
	IMP-A 1.21	0.03	0.04	0.04	0.04	0.04	0.04	0.04
	1.48	0.11	ND	ND	ND	ND	ND	ND
	2.98	0.12	ND	0.04	ND	0.04	ND	0.04
	3.14	0.19	ND	ND	ND	ND	ND	ND
	3.34	0.17	ND	ND	ND	ND	ND	ND
	3.66	0.25	ND	ND	ND	ND	ND	ND
	3.74	0.46	ND	ND	ND	ND	ND	ND
	3.76	0.29	ND	ND	ND	ND	ND	ND
	3.84	0.36	ND	0.05	ND	0.03	ND	0.02
	4.16	0.57	ND	ND	ND	ND	ND	0.06
	4.52	0.17	ND	ND	ND	ND	ND	ND
	4.6	0.32	ND	ND	ND	ND	ND	ND
	5.17	0.12	ND	ND	ND	ND	ND	ND
	Total imp.	5.01	0.11	0.32	0.08	0.31	0.11	0.34
Remarks: Impurity <0.1 % not reported, but included as total impurity; ND-Not detected. NP-Not performed								

Inference: From above stress condition (60°C) stability results, without head space nitrogen purged batch (head space oxygen content (20.042%) has more impurity formation compared to all other batches, Head space oxygen content is significantly affecting product stability. Hence final drug product should have low head space oxygen content (<2%) to maintain drug product stability throughout shelf life

Experiments performed to demonstrate the product instability when packed without head space nitrogen purging in 5mL glass vials. Experiments showed that without nitrogen head space samples packed in 5mL vials had higher total impurities, indicating that head space oxygen plays major role in product stability, thus complete head space blanketing with nitrogen gas should be done to avoid degradation and to maintain product stability throughout shelf life.

The foregoing specification, including the specific embodiments and example, is proposed to be illustrative of the present invention and is not to be taken as limiting. Numerous other variations and modifications can be effected without departing from the true spirit and scope of the present invention.

I/WE claim

1. A stable Pharmaceutical composition of Isoproterenol having head space oxygen content less than or equal to 5.0% and dissolved oxygen in solution is less than or equal to 5ppm.
2. A stable Pharmaceutical composition of Isoproterenol according to Claim 1 having head space oxygen content less than or equal to 2.0% and dissolved oxygen in solution is less than or equal to 5ppm.
3. A stable Pharmaceutical composition of Isoproterenol according to Claim 1 is liquid composition.
4. A stable Pharmaceutical composition of Isoproterenol according to Claim 1 wherein liquid composition is in an aqueous solvent.
5. A stable Pharmaceutical composition of Isoproterenol according to Claim 1 wherein the Isoproterenol formulation in said solvent is deoxygenated by flushing an inert gas into the bulk solution during manufacturing and purging inert gas into the headspace of the final container.
6. A stable Isoproterenol aqueous formulation comprising excipients selected from stabilizer, complexing agent, buffering agent, tonicity agent, a base and an acid.
7. A stable Isoproterenol aqueous formulation according to claim 6 wherein the stabilizer is chelating agent and antioxidant.
8. A stable Isoproterenol aqueous formulation according to claim 6 wherein the chelating agent is selected from the group consisting of ethylenediaminetetraacetic acid, diethylenetriaminepentaacetic acid, 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid, trans-1,2-cyclohexylenediamine-N,N,N',N'-tetraacetic acid, N6 -carboxymethyl-N3,N9 - 2,3-dihydroxy-N-methylpropylcarbamoylmethyl-3,6,9-triazaundecanedioic acid, N6 -carboxymethyl-N3,N9 -bis (methylcarbamoylmethyl)-3,6,9-triazaundecanedioic acid, N3,N6 -bis

(carboxymethyl)-N9 -3-oxapentamethylene-carbamoylmethyl-3,6,9-triazaundecanedioic acid or N3,N6 -bis (carboxymethyl)-N9 - 3,3-bis (dihydroxyphosphoryl)-3-hydroxypropyl-carbamoylmethyl-3,6,9-triazaundecanedioic acid.

9. A liquid stable Isoproterenol aqueous formulation according to claim 7 wherein the chelating agent is ethylenediamine tetraacetic acid (disodium edetate)

10. A liquid stable Isoproterenol aqueous formulation according to any one of the claims 1 to 9 wherein the buffering agent is selected from the group consisting of phosphates and/or citrates.

11. A liquid stable Isoproterenol aqueous formulation according to claim 10 wherein the buffering agent is citrate buffer, i.e. Trisodium citrate Dihydrate, Citric acid anhydrous.

12. A liquid stable Isoproterenol aqueous formulation according to any one of the claims 1 to 12 wherein the concentration of Isoproterenol is 15 mg/ml.

13. A liquid stable Isoproterenol aqueous formulation according to any one of the claims 1 to 11 wherein the concentration of Isoproterenol is 0.2mg/ml.

14. A process for producing a liquid stable Isoproterenol aqueous formulation, wherein the formulation in said solvent is deoxygenated by flushing an inert gas into the headspace of a tank and into the headspace of the final container and wherein said formulation comprises at least one of the following excipients: Edetate Disodium, Sodium chloride USP, Trisodium citrate, Dihydrate, Citric acid anhydrous, Hydrochloric acid/NaOH.

15. A process for producing a liquid stable Isoproterenol aqueous formulation according to claim 14 wherein the inert gas is argon, nitrogen, helium or neon.

16. A process for producing a liquid stable Isoproterenol aqueous formulation according to claims 14 wherein the inert gas is nitrogen.

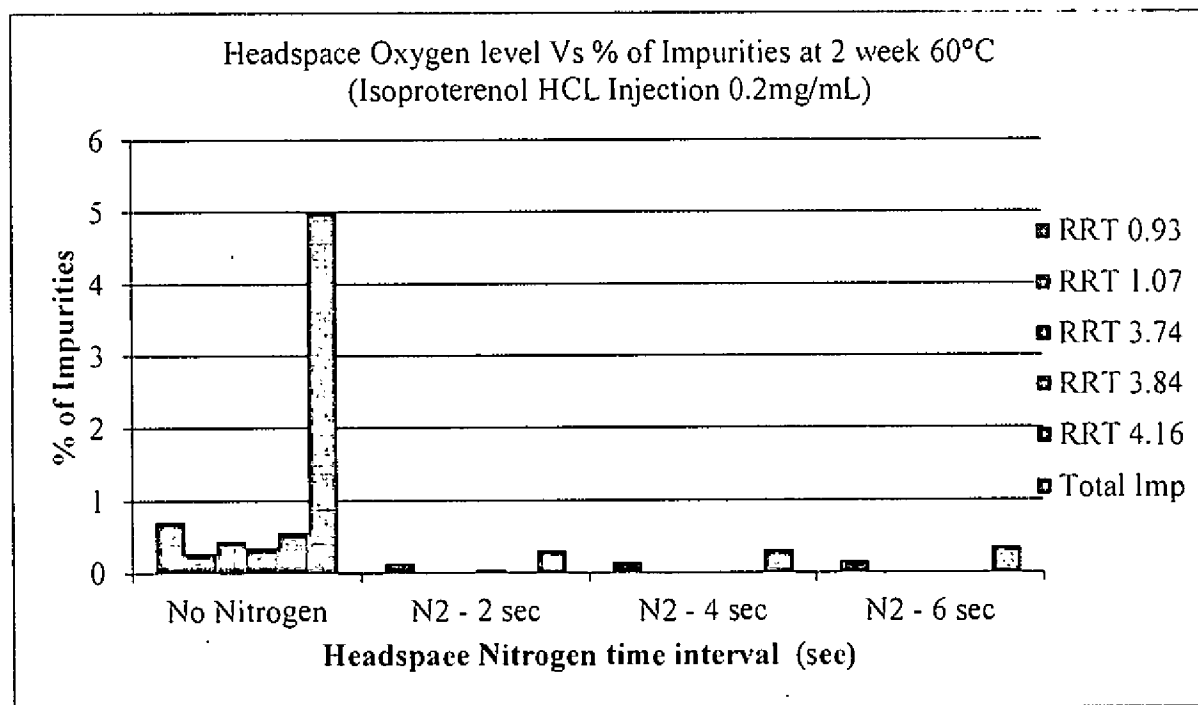


Figure 1: Graphical representation of % impurity level Vs head space nitrogen time interval

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2018/000028

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/137, A61K9/08 Version=2018.01

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)

TotalPatent One, 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.
X	US 7199269 B2 (BERNARD DINNEQUIN) 03 APRIL 2007 (03.04.2007) *col.2, lines 43-45; example 3; col.3, lines 48-54; col.4, lines 31-32; col.3, lines 55-56; col.4, lines 35-40*	1-5, 14-16
Y	*col.3, lines 47-48* -----	6-13
X	US 2004/0054012 A1 (PHARMATOP SCR) 18 MARCH 2004 (18.03.2004) *paras [0011], [0002], [0035], [0039], [0071]; claim 1*	14-16
Y	*paras [0044], [0046]* -----	1-13
Y	CN 102525894 A (SHANGHAI HEFENG PHARMACEUTICAL CO., LTD.) 04 JULY 2012 (04.04.2012) *claim 1; example 1* [FAMILY:NONE]	1-13



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

"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

24-08-2018

Date of mailing of the international search report

24-08-2018

Name and mailing address of the ISA/

Indian Patent Office
Plot No.32, Sector 14, Dwarka, New Delhi-110075
Facsimile No.

Authorized officer

Vishakha Gupta

Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2018/000028

Citation	Pub.Date	Family	Pub.Date
US 7199269 B2	03-04-2007	EP 1443902 A2	11-08-2004
		WO 2003041687 A2	22-05-2003
US 2004/0054012 A1	18-03-2004	WO 2001093830 A1	13-12-2001