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(54) **Title**: STABLE PHARMACEUTICAL COMPOSITION OF SODIUM OXYBATE

(57) **Abstract**: The present invention refers to a stable pharmaceutical composition of Sodium oxybate or free base thereof. The invention relates to pharmaceutical composition of sodium oxybate comprising sodium oxybate and one or more preservative(s) and optionally other pharmaceutically acceptable excipients. Such compositions control the level of sodium oxybate impurities along with other impurities formed due to sodium oxybate over the storage period. The invention also includes process of preparing such composition.

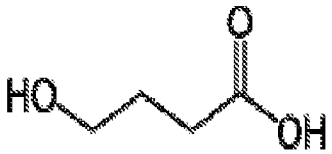
STABLE PHARMACEUTICAL COMPOSITION OF SODIUM OXYBATE

Field Of The Invention

The present invention relates to a stable oral pharmaceutical composition of sodium oxybate or free base thereof. In particular, present invention relates to a pharmaceutical composition of sodium oxybate comprising one or more preservatives and optionally with other pharmaceutically acceptable excipients. The invention also includes process of preparing such composition.

Background Of The Invention

Sodium oxybate, also known as sodium salt of gamma-hydroxybutyrate (GHB), is a central nervous system depressant. Chemically, sodium oxybate is sodium 4-hydroxybutyrate, with the following structure:



Sodium oxybate is approved in United States under the proprietary name Xyrem® as oral solution and marketed by Jazz Pharms. Sodium oxybate is a white to off-white, crystalline powder that is very soluble in aqueous solutions. Xyrem® oral solution contains 500 mg of sodium oxybate per milliliter of USP purified water, neutralized to pH 7.5 with malic acid.

The Xyrem® oral solution is prescribed for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.

GHB is the pharmacologically active metabolite of both gamma-butyrolactone (GBL) and 1, 4-butanediol (1, 4-BD), both of which have been abused recreationally." It is also known that GHB and GBL are interconverted in aqueous solution via hydrolysis and intramolecular esterification reactions.

U.S. Patent No. 6,780,889 discloses a pharmaceutical composition comprising an aqueous solution of 500 mg/ml sodium gamma-hydroxybutyrate, and malic acid as a pH adjusting agent. The composition has a pH of about 7.5, chemically stable, resistant to microbial growth and the composition is free of preservatives.

U.S. Patent No. 6, 472,431 discloses a method of preparing an aqueous medium resistant to microbial growth comprising adding the gamma-hydroxybutyrate salt to the aqueous medium, adjusting the concentration of the gamma-hydroxybutyrate salt in the aqueous medium to a final concentration of at least about 250 mg/ml and the pH of the medium to of about 6 to about 10.

The Patent No. 6,780,889 discloses that use of preservative in sodium oxybate composition may adversely affect the pH of the composition and thus gamma-hydroxybutyrate's stability.

Thus, the prior arts disclosure suggests that use of preservative sodium oxybate formulations may adversely affect the pH of the composition and thus, may result ultimately in unstable formulations of gamma-hydroxybutyrate.

Thus, there still exists an enduring need to develop an improved, stable pharmaceutical composition of sodium oxybate which will provides an alternative to existing formulation of sodium oxybate.

Summary Of The Invention

In one aspect, the present invention provides a stable oral pharmaceutical composition comprising sodium oxybate and one or more preservatives and optionally with one or more pharmaceutically acceptable excipients, wherein the amount of preservative in the composition ranges from about 0.006% to about 0.2% w/v.

In another aspect, the present invention provides a stable oral pharmaceutical composition comprising sodium oxybate, butylparaben, and optionally one or more

pharmaceutically acceptable excipients, wherein the amount of butylparaben in the composition range from about 0.006 % to 0.05 % w/v.

In another aspect, the present invention provides a stable oral pharmaceutical composition comprising sodium oxybate, one or more preservative and optionally other pharmaceutically acceptable excipients, wherein the amount of preservatives comprising butylparaben in the composition range from about 0.006 % to 0.05 % by weight/volume (w/v), characterized in that the level of total impurity in the said composition is not more than 1.5%

In another aspect, the present invention provides a stable oral pharmaceutical composition comprising sodium oxybate and butylparaben, wherein the amount of butylparaben in the composition ranges from about 0.006 % to 0.05 % by w/v and characterized in that the level of individual impurity in the said composition is not more than 0.1%.

In another aspect, the present invention provides a stable oral pharmaceutical composition comprising sodium oxybate and one or more preservative(s), wherein the ratio of the amount of sodium oxybate or free base thereof to preservative(s) in the composition ranges from about 1:0.0006 to about 1: 0.000075 by weight.

In another general aspect, the composition contains sodium oxybate or free base thereof having purity equal to or greater than 90%.

In another aspect, the present invention provides a stable oral pharmaceutical composition comprising sodium oxybate and one or more preservative(s), wherein the amount of preservative(s) in the composition ranges from about 0.006% to about 0.2% w/v, and characterized in that said composition contains retains at least 90% w/w of total potency of sodium oxybate or its free base when stored for real time study condition at 25°C and 40% relative humidity or for accelerated study condition at 40^0C and 25% relative humidity.

In another aspect, the present invention provides a stable oral pharmaceutical composition comprising sodium oxybate and one or more preservative(s), one or more pH adjusting agents, aqueous vehicle, sweetening agent, flavoring agent and optionally one or more other pharmaceutically acceptable excipients, wherein the amount of preservatives in the composition ranges from about 0.006% to about 0.2% by weight/volume (w/v).

In another aspect, the present invention provides a process for preparation of stable oral pharmaceutical composition comprising sodium oxybate, which process comprises of mixing sodium oxybate solution and one or more preservatives and optionally with one or more pharmaceutically acceptable excipients, wherein the amount of preservative(s) in the composition ranges from about 0.006% to about 0.2% w/v.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the pharmaceutically acceptable excipients may include solubilizers, anti-oxidants, buffering agents, pH adjusting agents, co-solvents, chelating agents, stabilizers, preservatives, lubricants, tonicity adjusting agents, cryoprotectants and the like known to the art used either alone or in combination thereof.

Detailed Description Of The Invention

The inventors of the present invention have surprisingly found that by using one or more preservatives in sodium oxybate compositions, level of impurities can be controlled significantly. Thus the present invention provides a stable pharmaceutical composition of sodium oxybate comprising one or more preservative(s) in legitimate amount and optionally other pharmaceutically acceptable excipients, which exhibits excellent storage stability.

The inventors of the present invention further empirically found that using low amount of preservative has a direct effect on the formulation stability. In particular, the inventors have found that judicial amount of the preservative, particularly paraben can effectively curb the degradation of sodium oxybate and eventually control generation of gamma-

butyrolactone (GBL) with a wide range of several other gamma-hydroxybutyrate (GHB) impurities. As a result, inventors of the present invention have found a novel way of preparing the pharmaceutical composition of sodium oxybate which can exhibit excellent storage stability.

The compositions of the present invention are stable compositions of gamma-hydroxybutyrate that improve shelf-life, and provide a titratable formulation of gamma-hydroxybutyrate for easy dose measurement.

The term "Sodium oxybate" used throughout the specification refers to not only sodium oxybate per se, but also its free base, other pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs and pharmaceutically acceptable prodrugs thereof.

The term "stable composition" or “stabilized composition” used throughout the specification refers to composition resistant to degradation of GHB into its known or unknown decomposition elements.

The term "preservative" used throughout the specification refers to substances that inhibit chemical change or microbial inhibition. Such preservatives may include, but are not limited to, parabens, xylitol, sodium benzoate, propyl gallate, sorbic acid, chlorobutanol, dihydroacetic acid, monothioglycerol, potassium benzoate, benzoic acid, benzalkonium chloride, alcohol, benzoic acid, benzalkonium chloride, benzethonium chloride, benzyl alcohol, butylparaben, cetylpyridinium chloride, ethylenediamine, ethyl vanillin, glycerin, hypophophorus acid, phenol, phenylethyl alcohol, phenymercuric nitrate, sassafras oil, sodium benzoate, sodium propionate, thimerosal and potassium sorbate. Preferred preservatives may be selected from the group comprising parabens but not limited to, methylparaben, ethylpareben propylparaben and butylparaben.

The stabilized oral pharmaceutical composition of the present invention may be characterized by sodium oxybate having purity equal to or greater than 90% by weight.

The stabilized oral pharmaceutical composition of the present invention is further characterized by containing total impurity of not more than 1.5% and any individual impurity of not more than 0.1%.

In an embodiment, the pharmaceutical composition of the present invention retains at 90% w/w of total potency of sodium oxybate or its free base when stored for real time study condition at 25°C and 40% relative humidity or for accelerated study condition at 40^0C and 25% relative humidity for at least 3 months.

In a further embodiment, the composition comprises total impurity of about 1.5% or less when stored at 25°C and 40% relative humidity or at 40^0C and 25% relative humidity for 3 months.

Various methods of analyzing (characterization and quantification) the impurities are well established in the art. Various spectroscopic techniques, such as NMR, MS, IR etc. and chromatographic techniques, such as HPLC, HPLC-TLC, HPLC-CE and hyphenated methods, such as LC-MS-MS, HPLC-DAD-MS, HPLC-NMR, GC-MS & LC-MS can be used for analyzing impurities.

The pharmaceutical composition of the present invention may be developed in the form of a dosage form suitable of oral administration.

Suitable dosage form includes, but not limited to a solution, suspension, dry powder for solution or suspension or syrup.

The pharmaceutical composition of the present invention may also be developed in the form of a dosage form suitable of parenteral administration. The parenteral route of administration of the compositions comprises subcutaneous, intramuscular, intravenous, transdermal, intradermal, intranasal, intraarterial and intraperitoneal injection or infusion.

The pharmaceutical composition of the present invention further comprises various pharmaceutically acceptable excipients suitable for oral administration. Such excipient includes, but not limited to pH adjusting agents or buffers, co-solvents, chelating agents/sequestering agents, sweetening agents, flavoring agents, antioxidant and aqueous vehicle.

Examples of suitable pH adjusting agents includes, but not limited to hydrochloric acid, citric acid, ascorbic acid, acetic acid, tartaric acid, phosphoric acid, metaphosphoric acid, polymetaphosphoric acid, carbonic acid, sodium hydroxide, potassium hydroxide, sodium citrate, potassium citrate, sodium bicarbonate, potassium bicarbonate, ammonium carbonate, sodium hydrogen phosphate, potassium hydrogen phosphate, ethanolamine, diethanolamine, triethanolamine, hexane-1,2-diamine, sodium carbonate, sodium potassium tartrate, potassium metaphosphate, potassium polymetaphosphate, and sodium metaphosphate. The pH of the pharmaceutical composition preferably ranges from about 6 to about 10.

Examples of suitable buffers includes, but not limited to pharmaceutically acceptable salts and acids of acetate, glutamate, citrate, tartrate, benzoate, lactate, histidine or other amino acids, gluconate, phosphate, malate, succinate, formate, propionate, and carbonate.

Examples of suitable co-solvents includes, but not limited to ethanol, glycerol, propylene glycol, polyethylene glycol, and different oils.

Examples of suitable chelating agents/ sequestering agents includes, but not limited to ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), hydroxyethylenediaminetriacetic acid (HEDTA), ethylene glycol-bis-(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), nitrilotriacetic acid (NTA), citrate and alkaline salt derivatives thereof.

Examples of suitable antioxidants include, but are not limited to, asocrbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, potassium metabisulfite, sodium metabisulfite, anoxomer and maleic acid.

The present invention further provides a process of manufacturing sodium oxybate compositions. The present process involves mixing sodium oxybate solution and one or more preservatives and optionally pharmaceutically acceptable excipients, wherein the amount of preservatives in the composition ranges from about 0.006% to about 0.2% w/v.

The process also involves preparing sodium oxybate in liquid or solid form, mixed/dissolved with one or more preservatives and optionally other pharmaceutically acceptable excipients with said sodium oxybate.

The present invention further refers to the use of the above defined composition for the preparation of medicaments useful for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.

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

Example 1: Preparation of Sodium oxybate (liquid form)

Table 1

Sr. No.	Ingredients	Quantity in mg/ mL	% Weight/ volume (w/v)
1	Gamabutyrolactone	340.62	34.062
2	Sodium Hydroxide	158.26	15.826
3	Purified water	401.12	40.112
4	Subtotal	900.00	90%

Process: The specified amount of water was transferred in jacketed tank. To this Sodium Hydroxide was added slowly to dissolve and form clear solution. The solution was mixed for specified time. This step involved exothermic reaction and temperature of

the bulk solution raised to 90ºC-95ºC. The obtained solution was cooled to 20ºC-25ºC. To this Gama-butyrolactone was added slowly and mixed with well. Temperature of bulk solution was maintained and mixed the contents for specified time. The obtained bulk solution was cooled and checked for the pH and visual clarity of solution.

Example 2: Sodium oxybate oral solution 500.0 mg/mL

Table 2

Sr. No.	Ingredients	Quantity in (mg)	% Weight/ volume (w/v)
1	Sodium oxybate [liquid form]	900.00	90.00
2	Butylparaben Sodium	0.075	0.0075
3	Malic acid (In the form of 10 % aqueous Solution)	q.s to adjust pH-7.5	q.s to adjust pH-7.5
4	Purified water q.s.to	1.000 mL	100.00 %

Example 3: Sodium oxybate oral solution 500.0 mg/mL

Table 3

Sr. No.	Ingredients	Quantity in (mg)	% Weight/ volume (w/v)
1	Sodium oxybate [liquid form]	900.00	90.00
2	Butylparaben Sodium	0.113	0.00375
3	Malic acid (In the form of 10 % aqueous Solution)	q.s to adjust pH-7.5	q.s to adjust pH-7.5
4	Purified water q.s.to	1.000 mL	100.00 %

Example 4: Sodium oxybate oral solution 500.0 mg/mL

Table 4

Sr. No.	Ingredients	Quantity in (mg)	% Weight/ volume (w/v)
1	Sodium oxybate [liquid form]	900.00	90.00
2	Propylparaben Sodium	0.225	0.0225
3	Malic acid	q.s to adjust pH-7.5	q.s to adjust pH-7.5
4	Purified water q.s.to	1.000 mL	100.00 %

Example 5: Sodium oxybate oral solution 500.0 mg/mL

Table 5

Sr. No.	Ingredients	Quantity in (mg)	% Weight/ volume (w/v)
1	Sodium oxybate [liquid form]	900.00	90.00
2	Propylparaben Sodium	0.112	0.0112
3	Malic acid	q.s to adjust pH-7.5	q.s to adjust pH-7.5
4	Purified water q.s.to	1.000 mL	100.00 %

Example 6: Sodium oxybate oral solution 500.0 mg/mL

Table 6

Sr. No.	Ingredients	Quantity in (mg)	% weight/ volume (w/v)
1	Sodium oxybate [liquid form]	900.00	50.000
2	Propylparaben Sodium	0.225	0.0225
3	Butylparaben Sodium	0.0025	0.0075
4	Malic acid	q.s to adjust pH-7.5	q.s to adjust pH-7.5
5	Purified water	1.000mL	Qs to 100.0 %

Process: The weighed amount of preservative(s) was dissolved in water to form clear solution. To this measured amount of bulk solution obtained in Example 1 was added and mixed for specified time. The pH adjusted using acid solution. Make up volume and mixed further for time. The obtained solution filtered, checked for the yield and finally packed.

Example 7: Stability Study

(I) Stability data of sodium oxybate composition containing preservative

Table 7

Tests	Initial	Storage condition: 40±2℃ & NMT 25% Relative Humidity			Storage condition: 25±2℃ & 40±2% Relative Humidity	
		1 Month	3 Months	3 Month	3 Months	3 Month
		Inverted	Upright	Inverted	Upright	Inverted
Description	Clear colorless Solution	Clear colorless Solution	Clear colorless Solution	Clear colorless Solution	Clear colorless Solution	Clear colorless Solution
Assay of Sodium oxybate	100.1	98.9	104.0	104.0	100.1	99.8
pH	7.827	8.192	7.97	7.95	8.11	8.07
Weight per ml	1.19	1.19	1.192	1.192	100.1	1.19
Degradation products						
GBL	0.254	0.216	0.225	0.231	0.223	0.223
RRT 4.2/4.37	0	0.112	0.124	0.108	0.106	0.104
Highest unknown	0	0.04	0.103	0.103	0.098	0.096
Total related substances	0.034	0.209	0.422	0.388	0.355	0.327

(II) Stability data of sodium oxybate composition free of preservative

Table 8

Tests	Initial	Storage condition: 40±2°C & NMT 25% Relative Humidity	
		1 Month	3 Months
		Inverted	Inverted
Description	Clear colorless Solution	Clear colorless Solution	Clear colorless Solution
Assay of Sodium oxybate	101.6	100.3	98.0
pH	8.06	7.93	7.87
Weight per ml	1.19	1.19	1.191
Degradation products			
GBL	0.241	0.225	0.296
RRT 4.2	0.126	0.122	0.122
Highest unknown	0.039	0.033	0.077
Total related substances	0.473	0.453	0.56

Result of the stability study conducted on the composition in accordance with the present invention indicates that sodium oxybate composition containing preservative exhibits excellent storage stability over the storage period relative to sodium oxybate composition without preservative.

Claims:

1. A stable pharmaceutical composition of sodium oxybate or free base thereof comprising one or more preservatives and optionally one or more pharmaceutically acceptable excipients.

2. The stable pharmaceutical composition of claim 1, wherein the preservative comprises one or more of parabens, xylitol, sodium benzoate, propyl gallate, sorbic acid, chlorobutanol, dihydroacetic acid, monothioglycerol, potassium benzoate, benzoic acid, benzalkonium chloride, alcohol, benzoic acid, benzalkonium chloride, benzethonium chloride, benzyl alcohol, butylparaben, cetylpyridinium chloride, ethylenediamine, ethyl vanillin, glycerin, hypophophorus acid, phenol, phenylethyl alcohol, phenymercuric nitrate, sassafras oil, sodium benzoate, sodium propionate, thimerosal and potassium sorbate.

3. The stable pharmaceutical composition of claim 1, wherein the paraben preservative comprises methylparaben, ethylpareben, propylparaben, butylparaben, or mixture thereof.

4. The stable pharmaceutical composition of claim 1, wherein the amount of preservative in the composition ranges from about 0.006% to about 0.2% w/v.

5. The stable pharmaceutical composition of claim 1, wherein the level of total impurities in the said composition is less than 1.5%.

6. The stable pharmaceutical composition of claim 1, wherein the level of individual impurities in the said composition is less than 0.1%.

7. The stable pharmaceutical composition of claim 1, wherein the ratio of the amount of sodium oxybate or free base thereof to preservatives in the composition ranges from about 1:0.0006 to about 1: 0.000075 by weight.

8. The stable pharmaceutical composition of claim 1, wherein the composition retains at least 90% w/w of the total potency of sodium oxybate or its free base when stored at 25°C and 40% relative humidity or at 40^0C and 25% relative humidity for 3 months.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/053530

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K31/19
ADD.

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)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/077334 A1 (COOK HARRY N [US] ET AL COOK HARRY [US] ET AL) 20 June 2002 (2002-06-20) table 6	1-8
X	US 2008/293698 A1 (JOHNSON JOSEPH [US]) 27 November 2008 (2008-11-27) example 1	1-8

☐ 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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"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
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Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002077334 A1	20-06-2002	AT 238783 T	15-05-2003
		AU 779354 B2	20-01-2005
		AU 2059000 A	31-07-2000
		CA 2355293 A1	06-07-2000
		DE 69907508 D1	05-06-2003
		DE 69907508 T2	20-11-2003
		DK 1140061 T3	25-08-2003
		EP 1140061 A2	10-10-2001
		ES 2193777 T3	01-11-2003
		IL 143733 A	31-10-2006
		JP 4374441 B2	02-12-2009
		JP 5204685 B2	05-06-2013
		JP 2002533388 A	08-10-2002
		JP 2009167189 A	30-07-2009
		US 2002077334 A1	20-06-2002
		US 2003125385 A1	03-07-2003
		US 2004209955 A1	21-10-2004
		US 2007270491 A1	22-11-2007
		US 2011039929 A1	17-02-2011
		US 2012020833 A1	26-01-2012
		US 2012202879 A1	09-08-2012
		US 2012202880 A1	09-08-2012
		US 2013143965 A1	06-06-2013
		WO 0038672 A2	06-07-2000
US 2008293698 A1	27-11-2008	DE 112006001234 T5	10-04-2008
		US 2008293698 A1	27-11-2008
		WO 2006124609 A2	23-11-2006