(12) PATENT APPLICATION PUBLICATION
(19) INDIA
(22) Date of filing of Application :19/04/2021

(21) Application No.202121018095 A
(43) Publication Date : 30/07/2021

(54) Title of the invention : A FREEZE DRIED PARENTERAL COMPOSITION OF OMADACYCLINE TOSYLATE AND PROCESS FOR PREPARATION THEREOF

(51) International classification	:A61K0009190000, A61K0009000000, A61K0009200000, A61K0009480000, A61K0047400000
(31) Priority Document No	:NA
(32) Priority Date	:NA
(33) Name of priority country	:NA
(86) International Application No Filing Date	:NA :NA
(87) International Publication No	: NA
(61) Patent of Addition to Application Number Filing Date	:NA :NA
(62) Divisional to Application Number Filing Date	:NA :NA

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(57) Abstract :
Disclosed herein is a stable, freeze dried pharmaceutical composition, free of Sucrose comprising Omadacycline Tosylate along with a suitable stabilizing agent for parenteral administration. The pharmaceutical composition provides a process for stabilization of Omadacycline Tosylate thereby improving the shelf life during storage. The invention further discloses a process for preparation of said composition.

No. of Pages : 25 No. of Claims : 6

FORM 2

THE PATENTS ACT, 1970

(39 of 1970)

AND

The Patents Rules, 2003

COMPLETE SPECIFICATION

(See section 10 and rule 13)

1. TITLE OF THE INVENTION:

"A FREEZE DRIED PARENTERAL COMPOSITION OF OMADACYCLINE TOSYLATE AND PROCESS FOR PREPARATION THEREOF"

2. APPLICANT:

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(b) Nationality: Indian Company incorporated under the Companies Act, 1956

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3. PREAMBLE TO THE DESCRIPTION:

The following specification particularly describes the invention and the manner in which it is to be performed.

Technical Field of the Invention:

The present invention relates to a stable, freeze dried pharmaceutical composition of Omadacycline Tosylate along with a suitable stabilizing agent and acidifying agent for parenteral administration. The pharmaceutical composition provides process for stabilization of Omadacycline Tosylate to improve the shelf life of the freeze dried composition during storage. The invention further relates to a process for preparation of said composition.

Background of the Invention:

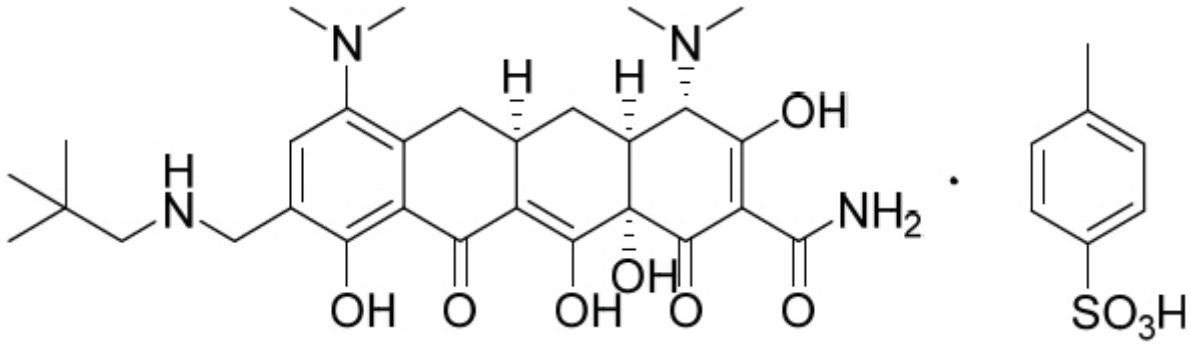
In the past 15 to 20 years the threat of bioterrorism has increased as a result of increasing political and economic unrest in many parts of the world. The Centers for Disease Control (CDC) has classified bioterrorism agents into three categories based on their potential to cause severe disease that results in high rates of mortality, and according to how readily these agents can be disseminated in the general population. Among the bioterrorism agents that pose the highest threat are Bacillus anthracis and Yersinia pestis, which are the causative pathogens for anthrax and plague, respectively. Current antibiotic treatment options against these Category A Bio threat pathogens are limited and the potential for engineered antibiotic resistance is high, thus, new therapeutic options are needed for prophylaxis and treatment of the diseases caused by these pathogens. Few new oral antibiotics are in development for the treatment of bio threat pathogens, and those older agents that have been approved are facing increasing resistance problems and could face engineered resistance.

Omadacycline is a novel aminomethylcycline of the tetracycline family, designed to overcome mechanisms of resistance to the tetracycline class .The extensive preclinical and clinical development program for Omadacycline is based on its demonstrated potent activity against key pathogens for serious community-acquired infections, including methicillin-resistant Staphylococcus aureus, multidrug resistant Streptococcus pneumoniae, Gram-negative aerobes, and atypical pathogens, and its lack of cross resistance to older generation tetracyclines and

other antibiotic classes. Omadacycline is currently in clinical development for acute bacterial skin and skin structure infection (ABSSSI) and community acquired bacterial pneumonia (CABP) as oral and intravenous (IV) monotherapy. Because of its broad in vitro spectrum of activity, clinical profile, and oral bioavailability, Omadacycline could be well suited for use in the treatment or post-exposure prophylaxis of infections of concern in both the biodefense and public health settings. This study evaluated the in vitro and in vivo activity of Omadacycline against B. anthracis and Y. pestis.

As a class, tetracyclines have been used for over 60 years and have proven effective and well tolerated for the treatment of a variety of bacterial infections including those caused by many of the bacterial pathogens considered to be high priority biologic threats (Plague, Anthrax). However, reports of resistance to tetracyclines, including doxycycline, and to fluoroquinolones and beta-lactams, have appeared in the literature, and these reports highlight the need for new treatment options for these bio threat agents. In addition, recent safety concerns for the fluoroquinolones potentially limits their utility. (Antimicrobial Agents and Chemotherapy (21 February 2017) doi:10.1128/AAC.02434-16 Copyright © 2017 Steenbergen et al.). Omadacycline tosylate, an aminomethylcycline which is a semisynthetic derivative of the tetracycline class of antibacterial drugs, for intravenous or oral administration. The chemical name of Omadacycline tosylate is (4S,4aS,5aR,12aS)-4,7-bis(dimethylamino)-9-(2,2-dimethylpropylaminomethyl)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide, 4-methylbenzenesulfonate.

The molecular formula is C36H48N4O10S (monotosylate salt) and the molecular weight is 728.9 (monotosylate salt). The following represents the chemical structure of omadacycline tosylate:



Omadacycline is marketed as lyophilized product for intravenous infusion by Paratek Pharmaceuticals, Inc. Boston, MA, USA under the trade name NUZYRA®. Omadacycline is indicated for the treatment of adult patients for Complicated skin and skin structure infections, complicated intra-abdominal infections and Community-acquired bacterial pneumonia.

Currently available formulations of Omadacycline is in lyophilized vial containing Sucrose as Lyoprotectant which does not provide desirable stability due to the sensitivity of Omadacycline against environmental stress. NUZYRA for Injection needs to be stored at 20°C to 25°C (68°F to 77°F); This Product is unstable while storage at 40°C, 75% RH (Accelerated condition) considering Zone IV-B for Indian market, Impurity profile for Total impurities rise up to around 6.0% at 40°C, 75% RH after 3 months. Once the vial reconstituted and diluted for infusion, it should be used within 1 hour. Therefore, there is a need for stable pharmaceutical composition comprising of Omadacycline. Moreover, it would be desirable to provide compositions having a good stability and a long shelf life.

Further, Omadacycline Tosylate is generally unstable to heat, humidity, acid and alkali, and forms degradation product, epimer, hence, it is necessary to develop a pharmaceutical composition which stabilizes the active compound and salt thereof for parenteral administration.

In view of unstable nature of Omadacycline Tosylate and the resultant challenges in preparing the lyophilized product for parenteral administration as mentioned above, the present inventors felt a need to develop a stable Omadacycline injectable composition using a suitable stabilizing agent which lowers the degradation of the active ingredient and improves shelf life of the composition.

Indian Patent Application No: 6812/CHENP/2010 discloses a stable pharmaceutical composition of Omadacycline Tosylate in lyophilized form comprising Sucrose as Lyoprotectant and Sodium bisulfite as Anti-oxidant.

The present inventors have unexpectedly discovered that, it is possible to provide a pharmaceutical composition free of Sucrose as used in prior art compositions and yet reduce the impurities formation leading to enhanced stability of the composition.

In light of the above, it is therefore the object of the present invention to provide a stable, freeze-dried pharmaceutical composition, free of sucrose, for parenteral administration comprising Omadacycline or its pharmaceutical salt as an active ingredient using a suitable stabilizing agent and acidifying agent which lowers the degradation of active and improves the shelf life of the composition by equally reducing the impurities formation.

Summary of the Invention:

In accordance with above, the present invention provides a stable, freeze dried pharmaceutical composition, free of Sucrose, comprising Omadacycline Tosylate along with a suitable stabilizing agent and acidifying agent for parenteral administration.

In the present invention, Omadacycline is stabilized by adding stabilizing agents selected from Amino acids, specially, Arginine.

In an aspect, the pharmaceutical composition of Omadacycline Tosylate and stabilizing agent is freeze dried and is provided as a drug concentrate.
In another aspect, the present invention provides a method for stabilization of Omadacycline Tosylate in an aqueous solution.

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 fully understood and appreciated.

The present invention discloses a stable, freeze-dried pharmaceutical composition, free of Sucrose, for parenteral administration comprising Omadacycline Tosylate as an active ingredient along with stabilizing agent and acidifying agent. The composition provides stabilization of Omadacycline with low degradation of the active ingredient thereby improving shelf life of the composition during storage and equally reducing the impurities formation.

Accordingly, in a preferred embodiment, the present invention provides a stable, freeze dried pharmaceutical composition, free from sucrose, for parenteral administration comprising;

i. Omadacycline Tosylate, and
ii. Stabilizing agent selected from Amino acids,
    Wherein the pH of said composition of the bulk solution is maintained within the range of 5.6 to 6.6 using acidifying agent before freeze drying.

Omadacycline Tosylate is present in the composition in an amount of 1 mg to 200 mg/vial; more preferably, 100mg/vial and 200mg/vial of Omadacycline.

Omadacycline is stabilized using a suitable stabilizing agent where Omadacycline can be maintained in a dissolved state in the aqueous solution thereby preventing

crystallization or crystalline growth of Omadacycline. The stabilizing agent is selected from the Amino acids preferably, the amino acid is Arginine.

The composition of the present invention comprises Arginine as stabilizing agent present in an amount of 100mg to 400 mg/ vial, more preferably, 100mg to 200mg/ vial.

The pH of the composition is maintained within the range of 5.6 to 6.6 using acidifying agent, such as dilute hydrochloric acid solution.
In an embodiment, the present invention discloses a stable, freeze-dried pharmaceutical composition, free of sucrose, for parenteral administration comprising;

a) Omadacycline Tosylate in an amount equivalent to 1 mg to 200 mg Omadacycline /vial
b) stabilizing agent such as Arginine in an amount of 100mg to 400mg/ vial and
c) Acidifying agent such as dilute hydrochloric acid solution for adjusting the pH of in the range of 5.6 to 6.6.

In another embodiment, the present invention discloses a stable, freeze-dried pharmaceutical composition comprising;

a) Omadacycline Tosylate in an amount equivalent to 100mg Omadacycline /vial;
b) Arginine in an amount of 100mg / vial and
c) Dilute hydrochloric acid solution for adjusting the pH in the range of 5.6 to 6.6.

In yet another embodiment, the present invention discloses a stable, freeze-dried pharmaceutical composition comprising;

a) Omadacycline Tosylate in an amount equivalent to 200mg Omadacycline/vial;

b) Arginine in an amount of 200mg/ vial and
c) Dilute hydrochloric acid solution for adjusting the pH in the range of 5.5 to 6.6.

The composition of the present invention after freeze drying is chemically and physically stable over an extended period of time and is suitable for intended pharmaceutical use after reconstitution with water for injection, 0.9% w/v sodium chloride injection or 5% w/v dextrose injection.

In another embodiment, the invention provides a process for the manufacture of a stable freeze dried pharmaceutical composition of Omadacycline Tosylate comprising the following steps:

a) Preparing an aqueous solution of arginine in water for injection;
b) Adjusting the pH of the Solution prepared in step (a) to between 7.8 to 8.0 with dilute hydrochloric acid solution and cool the solution between temperature of 2°C to 8°C and maintain the temperature throughout the manufacturing under nitrogen purging.
c) Dissolving the Omadacycline Tosylate in the Solution obtained in step (b);
d) adjusting the pH of the Solution prepared in step (c) to between 5.6 to 6.6 with Dilute Hydrochloric acid solution and make up volume to batch size with water for injection.
e) filtering the solution obtained in step (d) and fill the vials;
f) freezing the Solution filled in vials obtained in step (e) and
g) freeze drying the frozen solution filled in vials obtained in step (f).

The process of freeze drying comprises the following steps:

a) freezing the solution of Omadacycline Tosylate filled in vials at a temperature below -35°C and maintaining said temperature for at least 3 hours;
b) primary drying of the frozen solution of step (a) under vacuum from 50 mtorr to 100 mtorr and at a temperature between -30 and 15°C, and maintaining said conditions for at least 50 hours; and

c) secondary drying of the primary dried frozen Solution of step (b) under vacuum from 10 mtorr to 50 mtorr and at a temperature between 15°C and 40°C, and maintaining said conditions for at least 8 hours, to achieve water content not more than 2.0%.

The freeze dried Omadacycline when reconstituted with 5 ml of suitable vehicle contains final drug concentrate of 20 mg/ml.

In another embodiment, the pharmaceutical composition of the invention described herein is freeze dried composition, which may also be prepared by dissolving Omadacycline Tosylate first in aqueous vehicle containing stabilizing agent having pH between 4.0 to 4.3 then filter the solution and fill in to 10 ml glass vial.

The freeze dried drug may be diluted with suitable diluents before administration as IV injection. The final concentration of solution may be reduced to further desired level using 5% Dextrose infusion prior to administration to a patient.

The pharmaceutical composition of the present invention is useful in the treatment of various gram-positive and gram-negative bacterial infections such as complicated skin and skin structure infections, complicated intra-abdominal infections and community-acquired bacterial pneumonia.

The pharmaceutical compositions of the present invention are administered to a patient according to a dosing regimen. It should be understood that the specific dosing regimen for any particular patient will depend on a variety of factors, including age, body weight, general health, sex, diet, time of administration, specific disease being treated, and the severity of the condition among other factors and the judgment of the treating physician.

Industrial Advantages:

1. The pharmaceutical composition comprising Omadacycline Tosylate as active with Arginine improves the stability of drug and its solution, before Lyophilisation, has a pH between 5.6 to 6.6.
2. The composition is stable for the entire period of the shelf life.

Other features and embodiments of the invention will become apparent by the following examples which are given for illustration of the invention rather than limiting its intended scope. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art.

Experimental:

Different trials were conducted using different Excipients and tested before arriving at the present composition.

Quantity/Vial in mg

Trial No	1	2	3	4	5	6	7
Omadacycline Tosylate eq.to.Omadacycline	100	100	100	100	100	100	100
Sucrose	100	100	-	-	-	-	-
Sodium Bisulfite	-	1	-	-	-	-	-
Sulfobutyl ether betacyclodextrin sodium	-	-	500	-	-	-	-
Sodium Ascorbate	-	-	-	100	-	-	-
Lactose Monohydrate	-	-	-	-	100	-	-
Maltose	-	-	-	-	-	100	-
Arginine	-	-	-	-	-	-	100

pH of bulk solution adjusted with Dilute HCL solution/Dilute NaoH solution	4.24	4.25	4.23	4.22	4.21	4.32	4.35
Assay of Lyophilized composition (Initial)	99.18	99.16	99.11	99.13	99.17	99.09	99.34
Total impurities (Initial)	0.85	0.87	0.94	0.96	0.88	1.02	0.69
Assay of Lyophilized composition (after 3 months kept at 40°C)	94.64	94.62	94.18	94.19	94.51	94.71	97.05
Total impurities (after 3 months kept at 40°C)	5.25	5.29	5.78	5.76	5.45	5.25	3.09

Based on above trial experiments, Omadacycline tosylate gives better stability with Arginine (trial 7) than innovator's compositions containing sucrose (trails 1 and 2) at pH range 4.0 to 4.5 at bulk solution stage. Therefore, further experimental trials have been conducted with Sucrose and Arginine at different bulk solution pH level (i.e. 4.0 to 4.5, 4.6 to 5.5 and 5.6 to 6.6)

The trials of Innovator formulation in comparison with present invention under different pH conditions are discussed in brief below to emphasize the inventiveness of the current invention and analysis was carried out as per Standard and approved test Procedure.

Trial: 8 (Formulation prepared as per Indian patent Application No 6812/CHENP/2010)

Dissolved 2.0 gm of Sucrose in 56 ml Water for injection and added 4.25 ml of 1M hydrochloric acid solution and 20 mg of sodium bisulfite. 2.620 gm of Omadacycline Tosylate equivalent to 2.0 gm Omadacycline free base was then added. After the Active was added, the pH was adjusted to 4.0 to 4.5 using 0.1 M sodium hydroxide solution or 0.1 M hydrochloric acid solution, as appropriate. The volume of the resulting solution was adjusted to 70 ml with additional water for injection. The mixture was then filtered through a sterile 0.22 pm filter. Type 1 glass vials were then filled with 3.5 ml of the solution per vial. The solution in each vial was lyophilized using freeze dryer according to conventional method, thereby obtaining the lyophilized compositions each comprising 100 mg of Omadacycline. The resulting lyophilized preparation was stored at different storage temperatures at different time intervals and the residue of Omadacycline was tested.

Period		Assay (%)	pH	Total impurities (%)	Storage temp.	Colour
Initial	Bulk solution	99.23	4.23	0.74	2-8° C	Clear light orange colour solution
	Lyophilized	99.04	-	0.88	25° C	Orange colour lyophilized cake
After 3 months		94.65	-	5.33	40°C	Dark Orange colour lyophilized cake

Trial: 9 (Formulation prepared as per US RLD)

Dissolved 2.0 gm of Sucrose in 56 ml Water for injection and added 4.25 ml of 1M hydrochloric acid solution. 2.620 gm of Omadacycline Tosylate equivalent to 2.0 gm Omadacycline free base was then added. After the Active was added, the pH was adjusted to 4.0 to 4.5 using 0.1 M sodium hydroxide solution or 0.1 M hydrochloric acid solution, as appropriate. The volume of the resulting solution was

adjusted to 70 ml with additional water for injection. The mixture was then filtered through a sterile 0.22 pm filter. Type 1 glass vials were then filled with 3.5 ml of the solution per vial. The solution in each vial was lyophilized using freeze dryer according to conventional method, thereby obtaining the lyophilized compositions each comprising 100 mg of Omadacycline. The resulting lyophilized preparation was stored at different storage temperatures at different time intervals and the residue of Omadacycline was tested.

Period		Assay (%)	pH	Total impurities (%)	Storage temp.	Colour
Initial	Bulk solution	99.27	4.19	0.71	2-8° C	Clear light orange colour solution
	Lyophilized	99.09	-	0.91	25° C	Orange colour lyophilized cake
After 3 months		94.85	-	5.12	40°C	Dark Orange colour lyophilized cake

Trial: 10

Dissolved 2.0 gm of Sucrose in 56 ml Water for injection and added 4.25 ml of 1M hydrochloric acid solution. 2.620 gm of Omadacycline Tosylate equivalent to 2.0 gm Omadacycline free base was then added. After the Active was added, the pH was adjusted to 4.6 to 5.5 using 0.1 M sodium hydroxide solution or 0.1 M hydrochloric acid solution, as appropriate. The volume of the resulting solution was

adjusted to 70 ml with additional water for injection. The mixture was then filtered through a sterile 0.22 pm filter. Type 1 glass vials were then filled with 3.5 ml of the solution per vial. The solution in each vial was lyophilized using freeze dryer according to conventional method, thereby obtaining the lyophilized compositions each comprising 100 mg of Omadacycline. The resulting lyophilized preparation was stored at different storage temperatures at different time intervals and the residue of Omadacycline was tested.

Period		Assay (%)	pH	Total impurities (%)	Storage temp.	Colour
Initial	Bulk solution	99.17	5.32	0.81	2-8° C	Clear light orange colour solution
	Lyophilized	99.02	-	0.95	25° C	Orange colour lyophilized cake
After 3 months		93.85	-	6.12	40°C	Dark Orange colour lyophilized cake

Trial: 11

Dissolved 2.0 gm of Sucrose in 56 ml Water for injection and added 4.25 ml of 1M hydrochloric acid solution. 2.620 gm of Omadacycline Tosylate equivalent to 2.0 gm Omadacycline free base was then added. After the Active was added, the pH was adjusted to 5.6 to 6.6 using 0.1 M sodium hydroxide solution or 0.1 M hydrochloric acid solution, as appropriate. The volume of the resulting solution was

adjusted to 70 ml with additional water for injection. The mixture was then filtered through a sterile 0.22 pm filter. Type 1 glass vials were then filled with 3.5 ml of the solution per vial. The solution in each vial was lyophilized using freeze dryer according to conventional method, thereby obtaining the lyophilized compositions each comprising 100 mg of Omadacycline. The resulting lyophilized preparation was stored at different storage temperatures at different time intervals and the residue of Omadacycline was tested.

Period		Assay (%)	pH	Total impurities (%)	Storage temp.	Colour
Initial	Bulk solution	99.14	5.92	0.79	2-8° C	Clear light orange colour solution
	Lyophilized	99.03	-	0.94	25° C	Orange colour lyophilized cake
After 3 months		93.35	-	6.55	40°C	Dark Orange colour lyophilized cake

Trial: 12

Dissolved 2.0 gm of Arginine in 42 ml Water for injection and added 3.5 ml of 3M hydrochloric acid solution were also added to adjust pH to 7.8 to 8.0 and cooled the solution between temperature of 2°C to 8°C and maintained the temperature throughout the manufacturing under nitrogen purging, 2.620 gm of Omadacycline Tosylate equivalent to 2.0 gm Omadacycline free base was then added. After the

Active was added, the pH was adjusted to 4.0 to 4.5 using 0.1 M hydrochloric acid solution, as appropriate. The volume of the resulting solution was adjusted to 60 ml with additional water for injection. The mixture was then filtered through a sterile 0.22 pm filter. Type 1 glass vials were then filled with 3.0 ml of the solution per vial. The solution in each vial was lyophilized using freeze dryer as per following method,

The process of freeze drying comprises the following steps:

a) freezing the solution at a temperature below -35°C and maintaining said temperature for at least 3 hour;
b) primary drying the frozen solution of step (a) under vacuum from 50 mtorr to 100 mtorr and at a temperature between -30 and 15°C, and maintaining said conditions for at least 50 hours; and
c) secondary drying the primary dried frozen Solution of step (b) under vacuum from 10 mtorr to 50 mtorr and at a temperature between 15°C and 40°C, and maintaining said conditions for at least 8 hours, thereby obtaining the lyophilized compositions each comprising 100 mg of Omadacycline.

The resulting lyophilized preparation was stored at different storage temperatures at different time intervals and the residue of Omadacycline was tested.

Period		Assay (%)	pH	Total impurities (%)	Storage temp.	Colour
Initial	Bulk solution	99.28	4.19	0.68	2-8° C	Clear light orange colour solution
	Lyophilized	99.21	*4.09	0.72	25° C	Orange colour

						lyophilized cake
After 3 months		96.75	*4.12	3.15	40°C	Dark Orange colour lyophilized cake

*for determination of pH - one lyophilized vial reconstituted with 5 ml water for Injection.

As is evident from the above trial 12, when the pH of the bulk solution is adjusted between 4.0 to 4.5; the composition was unstable and exhibits more impurities after the 3months.

Trial: 13

Dissolved 2.0 gm of Arginine in 42 ml Water for injection and added 3.5 ml of 3M hydrochloric acid solution were also added to adjust pH to 7.8 to 8.0 and cool the solution between temperature of 2°C to 8°C and maintained the temperature throughout the manufacturing under nitrogen purging, 2.620 gm of Omadacycline Tosylate equivalent to 2.0 gm Omadacycline free base was then added. After the Active was added, the pH was adjusted to 4.6 to 5.5 using 0.1 M hydrochloric acid solution, as appropriate. The volume of the resulting solution was adjusted to 60 ml with additional water for injection. The mixture was then filtered through a sterile 0.22 pm filter. Type 1 glass vials were then filled with 3.0 ml of the solution per vial. The solution in each vial was lyophilized using freeze dryer as per following method,

The process of freeze drying comprises the following steps:

a) Freezing the solution at a temperature below -35°C and maintaining said temperature for at least 3 hour;

b) primary drying the frozen solution of step (a) under vacuum from 50 mtorr to 100 mtorr and at a temperature between -30 and 15°C, and maintaining said conditions for at least 50 hours; and

c) secondary drying the primary dried frozen Solution of step (b) under vacuum from 10 mtorr to 50 mtorr and at a temperature between 15°C and 40°C, and maintaining said conditions for at least 8 hours, thereby obtaining the lyophilized compositions each comprising 100 mg of Omadacycline.

The resulting lyophilized preparation was stored at different storage temperatures at different time intervals and the residue of Omadacycline was tested.

Period		Assay (%)	pH	Total impurities (%)	Storage temp.	Colour
Initial	Bulk solution	99.24	5.09	0.69	2-8° C	Clear light orange colour solution
	Lyophilized	99.19	*4.88	0.74	25° C	Orange colour lyophilized cake
After 3 months		97.95	*4.83	1.95	40°C	Orange colour lyophilized cake

*for determination of pH - one lyophilized vial reconstituted with 5 ml water for Injection.

As is evident from the above trial 13, when the pH of the bulk solution is adjusted between 4.6 to 5.5; the composition was also unstable and exhibits more impurities after the 3months.

Trial: 14

Dissolved 2.0 gm of Arginine in 42 ml Water for injection and added 3.5 ml of 3M hydrochloric acid solution were also added to adjust pH to 7.8 to 8.0 and cool the solution between temperature of 2°C to 8°C and maintained the temperature throughout the manufacturing under nitrogen purging, 2.620 gm of Omadacycline Tosylate equivalent to 2.0 gm Omadacycline free base was then added. After the Active was added, the pH was adjusted to 5.6 to 6.6 using 0.1 M hydrochloric acid solution, as appropriate. The volume of the resulting solution was adjusted to 60 ml with additional water for injection. The mixture was then filtered through a sterile 0.22 pm filter. Type 1 glass vials were then filled with 3.0 ml of the solution per vial. The solution in each vial was lyophilized using freeze dryer as per following method,

The process of freeze drying comprises the following steps:

a) Freezing the solution at a temperature below -35°C and maintaining said temperature for at least 3 hour;
b) primary drying the frozen solution of step (a) under vacuum from 50 mtorr to 100 mtorr and at a temperature between -30 and 15°C, and maintaining said conditions for at least 50 hours; and
c) secondary drying the primary dried frozen Solution of step (b) under vacuum from 10 mtorr to 50 mtorr and at a temperature between 15°C and 40°C, and maintaining said conditions for at least 8 hours, thereby obtaining the lyophilized compositions each comprising 100 mg of Omadacycline.

The resulting lyophilized preparation was stored at different storage temperatures at different time intervals and the residue of Omadacycline was tested.

Period		Assay (%)	pH	Total impurities (%)	Storage temp.	Colour
Initial	Bulk solution	99.34	6.30	0.62	2-8° C	Clear light orange colour solution
	Lyophilized	99.29	*5.91	0.68	25° C	Orange colour lyophilized cake
After 3 months		98.51	*5.85	1.45	40°C	Orange colour lyophilized cake

*for determination of pH - one lyophilized vial reconstituted with 5 ml water for Injection.

Trial: 15

Dissolved 4.0 gm of Arginine in 38 ml Water for injection and added 3.8 ml of 3M hydrochloric acid solution were also added to adjust pH to 7.8 to 8.0 and cool the solution between temperature of 2°C to 8°C and maintained the temperature throughout the manufacturing under nitrogen purging, 2.620 gm of Omadacycline Tosylate equivalent to 2.0 gm Omadacycline free base was then added. After the Active was added, the pH was adjusted to 5.6 to 6.6 using 0.1 M hydrochloric acid solution, as appropriate. The volume of the resulting solution was adjusted to 60 ml with additional water for injection. The mixture was then filtered through a sterile 0.22 pm filter. Type 1 glass vials were then filled with 3.0 ml of the solution per

vial. The solution in each vial was lyophilized using freeze dryer as per following method,

The process of freeze drying comprises the following steps:

a) Freezing the solution at a temperature below -35°C and maintaining said temperature for at least 3 hour;
b) primary drying the frozen solution of step (a) under vacuum from 50 mtorr to 100 mtorr and at a temperature between -30 and 15°C, and maintaining said conditions for at least 50 hours; and
c) secondary drying the primary dried frozen Solution of step (b) under vacuum from 10 mtorr to 50 mtorr and at a temperature between 15°C and 40°C, and maintaining said conditions for at least 8 hours, thereby obtaining the lyophilized compositions each comprising 100 mg of Omadacycline.

The resulting lyophilized preparation was stored at different storage temperatures at different time intervals and the residue of Omadacycline was tested.

Period		Assay (%)	pH	Total impurities (%)	Storage temp.	Colour
Initial	Bulk solution	99.33	6.34	0.61	2-8° C	Clear light orange colour solution
	Lyophilized	99.26	*5.92	0.70	25° C	Orange colour lyophilized cake
After 3 months		98.44	*5.84	1.48	40°C	Orange colour lyophilized cake

*for determination of pH - one lyophilized vial reconstituted with 5 ml water for Injection.

It is observed from the above examples that, the composition comprising Omadacycline Tosylate equivalent to Omadacycline 100 mg and Arginine 100 mg within pH range of 5.6 to 6.6 at bulk solution stage exhibits good stability with less impurities and even after 3 months at 40°C in lyophilized form as shown in **Trial** 14.

Similarly, it is also observed that the composition comprising Omadacycline Tosylate equivalent to Omadacycline 100 mg and Arginine 200 mg within pH range of 5.6 to 6.6 at bulk solution stage exhibits good stability with less impurities and even after 3 months at 40°C in lyophilized form as shown in **Trial** 15.

As is evident from the trials 14 and 15, the composition comprising Omadacycline Tosylate equivalent to Omadacycline and Arginine in 1: 1 to 1: 2 ratio within pH range of 5.6 to 6.6 at bulk solution stage exhibits good stability with less impurities and even after 3 months storage at 40°C in lyophilized form.

We Claim,

1. A stable freeze-dried pharmaceutical composition for parenteral administration comprising,
   a) Omadacycline Tosylate in an amount equivalent to 50 mg to 200mg Omadacycline/vial; and
   b) Arginine as a stabilizing agent in an amount of 50 mg to 400 mg/ vial; and
   c) dilute hydrochloric acid for adjusting the pH of bulk composition between 5.6-6.6.

2. The stable freeze-dried pharmaceutical composition as claimed in claim 1, wherein the composition comprises Omadacycline Tosylate equivalent to Omadacycline and Arginine present in a ratio of 1: 1 to 1: 2.
3. The stable freeze-dried pharmaceutical composition as claimed in claim 1, wherein the composition comprises Omadacycline Tosylate equivalent to Omadacycline and
   Arginine present in a ratio of 1:1.

4. A process for the manufacture of a stable freeze dried pharmaceutical composition as defined in claim 1, wherein, the process comprising the following steps:
   a) Preparing an aqueous solution of arginine in water for injection;
   b) adjusting the pH of the solution prepared in step (a) to between 7.8 to 8.0 with Dilute Hydrochloric acid solution followed by cooling the solution between temperature range of 2°C to 8°C and maintaining the temperature throughout the manufacturing under nitrogen purging;
   c) Dissolving the active agent Omadacycline tosylate in the Solution obtained in step (b);

d) adjusting the pH of the solution of step(c) with dilute Hydrochloric acid solution prepared between 5.6 to 6.6 and made up volume to batch size with water for injection;

e) filtering the solution obtained in step (d) followed by filling into the vials;

f) freezing the solution filled in vials obtained in step (e) and

g) freeze drying the frozen solution filled in vials obtained in step (f).

5. The process according to claim 4, wherein the freeze drying process comprises the following steps:

a) freezing Omadacycline tosylate solution at a temperature below -35°C and maintaining said temperature for at least 3 hours;

b) primary drying of the frozen solution of step (a) under vacuum from 50 mtorr to 100 mtorr and at a temperature between -30 and 15°C., and maintaining the said conditions for at least 50 hours; and

c) secondary drying of the primary dried frozen solution of step (b) under vacuum from 10 mtorr to 50 mtorr and at a temperature between 15°C and 40°C., and maintaining said conditions for at least 8 hours, to achieve water content not more than 2.0%.

6. A process for increasing the stability of freeze-dried pharmaceutical composition of Omadacycline according to any one of the preceding claims, in an aqueous solution comprising a step of combining Omadacycline Tosylate with Arginine in aqueous medium and maintaining the bulk solution within pH range of 5.6 to 6.6.

Dated this 19th day of April, 2021

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“A Freeze Dried Parenteral Composition of Omadacycline Tosylate and Process for Preparation Thereof”

Abstract:

Disclosed herein is a stable, freeze dried pharmaceutical composition, free of Sucrose comprising Omadacycline Tosylate along with a suitable stabilizing agent for parenteral administration. The pharmaceutical composition provides a process for stabilization of Omadacycline Tosylate thereby improving the shelf life during storage. The invention further discloses a process for preparation of said composition.