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Stable oxaliplatin formulation

Abstract

A storage stable pharmaceutical composition comprising a solution of Oxaliplatin in water and a catalytic amount of a carbohydrate. A process for forming such pharmaceutical composition comprising dissolving a known amount of Oxaliplatin in water; adding an amount of carbohydrate in the range of 0.0010% to 0.05% w/v with respect to such solution; agitating the mixture to get clear solution; filtering it through a filter membrane under aseptic conditions; and filling the solution resulting into glass vials sealed with elastomeric stoppers and aluminium flip-off seals.

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Claims

1. A storage stable pharmaceutical composition comprising a solution of Oxaliplatin in water and a catalytic amount of a carbohydrate.
2. A pharmaceutical composition according to claim 1, wherein the amount of carbohydrate ranges from 0.0010% to 0.05% w/v of the solution of Oxaliplatin in water.
3. A pharmaceutical composition according to claim 1, wherein the amount of carbohydrate ranges from 0.0010% to 0.02% w/v of the solution of Oxaliplatin in water.
4. A pharmaceutical composition according to claim 1, wherein the amount of carbohydrate ranges from 0.0010% to 0.005% w/v of the solution of Oxaliplatin in water.
5. A pharmaceutical composition according to claim 1, wherein the carbohydrate is selected from lactose, dextrose, sucrose and glucose.
6. A pharmaceutical composition according to claim 1, wherein the carbohydrate is lactose.
7. A process for preparation of pharmaceutical composition according to claim 1, which comprises the steps of: (a) dissolving a known amount of Oxaliplatin in water; (b) adding an amount of carbohydrate in the range of 0.0010% to 0.05% w/v with respect to the solution of step (a); (c) agitating the mixture of step (b) to get clear solution; (d) filtering the solution of step (c) through a filter membrane under aseptic conditions; and (e) filling the solution resulting from step (d) into glass vials sealed with elastomeric stoppers and aluminium flip-off seals.
8. A process for preparation of pharmaceutical composition according to claim 7, wherein the water used in step (a) is water-for-injection.
9. A process for preparation of pharmaceutical composition according to claim 7, wherein carbohydrate used in step (b) is selected from lactose, dextrose, sucrose and glucose.
10. A process for preparation of pharmaceutical composition according to claim 7, wherein the carbohydrate is lactose.

Description

No. 6,306,902, Anderson et al disclose a stable oxaliplatin solution formulation comprising therapeutically effective amount of oxaliplatin, an effective stabilizing amount of a buffering agent and a pharmaceutically acceptable carrier wherein the buffering agent is oxalic acid or an alkali metal salt thereof. [0014] c) In U.S. Pat. No. 6,476,068, Lauria et al disclose a stable oxaliplatin solution formulation comprising oxaliplatin, and effective stabilizing amount of lactic acid and/or a pharmaceutically acceptable salt of lactic acid and a pharmaceutically acceptable carrier. [0015] d) In WO 01/15691, Ibrahim et al disclose pharmaceutically stable solutions of at least 7-mg/ml oxaliplatin containing a sufficient amount of a solvent having at least a hydroxylated derivative selected from 1,2-propane-diol, glycerol, maltitol, saccharose and inositol. The specification states that these are the only suitable agents and the limited choice of hydroxylated derivatives to use has been done following a very large number of experiments and after consideration of several options. [0016] e) In U.S. Ser. No. 03/0,109,515, Lauria et al disclose a stable oxaliplatin solution formulation comprising oxaliplatin, and effective stabilizing amount of malonic acid and/or a pharmaceutically acceptable salt of malonic acid and a pharmaceutically acceptable carrier. [0017] f) In EP 1466599, Schridde et al disclose a infusion-concentrate containing oxaliplatin and a physiologically compatible carbohydrate as solubility enhancer.

[0018] The specification states that, with higher concentrations of carbohydrates, the formation of the degradation or the reaction products of oxaliplatin caused by the presence of hydroxide anions is drastically reduced or suppressed. Further, since these solutions containing carbohydrates are suitable for solubilising the oxaliplatin, the concentration of carbohydrates, preferably glucose, should be at least 50 mg/ml. [0019] g) In EP 1466600, Schridde et al disclose an oxaliplatin solution, which preferably in addition contain sulfuric acid, phosphoric acid, ethane sulfonic acid, or paratoluosofonic acid. [0020] h) In U.S. Ser. No. 05/0,090,544, Whittaker et al disclose a pharmaceutical liquid formulation of oxaliplatin for parenteral administration comprising oxaliplatin, water and an additive selected from the group consisting of tartaric acid, a salt of tartaric acid, a pharmaceutically acceptable derivative of tartaric acid and mixtures thereof.

[0021] From the abovementioned disclosures, it would be apparent that most, if not all the methods for stabilization of oxaliplatin solutions involve utilization of buffering agents to adjust the pH of the formulation and to maintain the formulation within a desired pH range. As mentioned above, several dicarboxylic acids such as oxalic acid, lactic acid, malonic acid, tartaric acid, several monocarboxylic acid such as sulfuric acid, phosphoric acid, ethane sulfonic acid, or para-toluenesulfonic acid and their pharmaceutically acceptable salts have been proposed as a buffering and stabilizing agent for oxaliplatin.

[0022] However, most of these auxiliary substances have several disadvantages, which limits their use in pharmaceutical products. For example utilization of oxalic acid or its salt, which because of Le Chatelier's principle reduces the formation of oxalate ion, generated by hydrolysis of oxaliplatin in aqueous solution, has notable nephrotoxicity. Further, in the intravenous therapy, higher concentrations of oxaliplatin or oxalate ion pose the risk of local and systemic side effects such as local pain, aggregation of thrombocytes, thrombosis, kidney stones etc. making, in general, the addition of oxalate ions in injection non-desirable, a plausible reason why oxalic acid or for that matter malonic acid utilized as additives in U.S. Pat. No. 6,306,902 and U.S. Ser. No. 03/0,109,515 are not approved by the USFDA for inclusion into a parenteral composition.

[0023] Moreover, for selection of an appropriate auxiliary substance to achieve stabilization, there is neither any general guideline nor can an inference be drawn from the teachings of the abovementioned specification. For e.g. U.S. Pat. No. 6,306,902 discloses that, except oxalic acid, utilization of other buffering agents such as acetate, citrate, phosphate, glycine or tris buffer does not stabilize the aqueous solution of oxaliplatin. U.S. Pat. No. 6,476,068 also supports and suggests that acetate and citrate

buffers are not suitable for oxaliplatin solutions. However, exactly opposite is the teaching of EP 1,466,600, which states that phosphoric, sulfuric and other acids could be utilized for preparing a stable oxaliplatin solution.

[0024] Another approach utilized in stabilizing the oxaliplatin solution is through enhancing the solubility of oxaliplatin as disclosed in WO 01/15691, by adding 1,2-propane diol, glycerin, maltitol, saccharose, or inositol or as disclosed in EP 1,466,599 by adding a physiologically compatible carbohydrate in at least 50 mg/ml concentrations.

[0025] However, all these additives have immense disadvantages when used at the specified concentrations for preparation of injectable medicinal solutions. All of these carbohydrates are most easily available sources of energy, which can lead unbalancing of metabolism, especially owing to widely spread diabetes mellitus in the therapy of oxaliplatin caused by age. Moreover, inositol and glucose are physiologically important intracellular sugars and their salts are essential components of signal transduction cascade. Inositol is also administered orally and intravenously in experimental therapy as maturing promoter in pre-mature babies. Further it also has unwanted potential of neurological side effects.

[0026] Further, it might be mentioned that other hydroxylated derivatives as disclosed in WO 01/15691 do not belong to the standard auxiliary substances with known side effects, which are used for preparing the parenteral solutions. These compounds are normally used only in pharmaceutical preparations as auxiliary substances for external or oral use and are not recommended by Health Authorities worldwide or the parenteral use.

[0027] It might be further mentioned that Health Authorities all over the world are very concerned about the level of degradation products and impurities present in a drug substance or a drug product. As a consequence, regulatory approval norms today are very stringent about the level of impurities present in a drug substance or a drug product. In view of this, it is rather intriguing how an oxaliplatin solution containing more often than not amounts of additives in such a higher percentage as suggested by the prior teachings could comply with pharmacopoeial specifications, even though such solutions may be stable.

[0028] From the foregoing, it would be apparent that there is no universal method or system for stabilization of an oxaliplatin solution, which is simple, convenient, economical and is not dependent on the vagaries of critical parameters like pH, amount and nature of additives, specially requisite mono carboxylic acid or dicarboxylic acid, or nature of hydroxylated solvents etc.

[0029] A need, therefore, exists for a pharmaceutical composition of oxaliplatin which is universal, simple, convenient, and is not dependent on the vagaries of critical parameters like pH, nature and amount of additives specially requisite monocarboxylic acid or dicarboxylic acid, nature of hydroxylated solvents etc.

[0030] The present invention is a step forward in this direction and overcomes most, if not all the limitations of the prior art methods in providing a novel and simple method for stabilization of oxaliplatin solutions.

OBJECTS OF THE INVENTION

[0031] An object of the present invention is to provide a pharmaceutical composition of oxaliplatin, which is stable on storage for pharmaceutically acceptable duration of time.

[0032] Another object of the present invention is to provide a pharmaceutical composition of oxaliplatin, which is stable and undergoes less degradation.

[0033] Yet another object of the present invention is to provide a pharmaceutical composition of oxaliplatin, which can be stabilized by use of a catalytic amount of a suitable additive.

[0034] Yet further object of the present invention is to provide a pharmaceutical composition of oxaliplatin, which can be stabilized by use of a catalytic amount of a suitable additive, which is not associated with nephrotoxicity, as well as other local systemic side effects.

[0035] Another object of the present invention is to provide a pharmaceutical composition of oxaliplatin, which can be stabilized by use of a catalytic amount of a suitable additive, which does not lead to any unbalancing of metabolism, especially diabetes mellitus.

[0036] Yet another object of the present invention is to provide a process for preparation of a stable pharmaceutical composition of oxaliplatin, which is simple, convenient and economical.

[0037] A further object of the present invention is to provide a method for treatment of a human or an animal cancerous disease, comprising administration of such stable pharmaceutical compositions of oxaliplatin, to the human or animal in need of said treatment.

SUMMARY OF THE INVENTION

[0038] Thus according to main aspect of present invention there is provided a storage stable pharmaceutical composition comprising a solution of Oxaliplatin in water and a catalytic amount of a carbohydrate.

DETAILED DESCRIPTION OF THE INVENTION

[0039] In their endeavor to find a suitable method for stabilization of a ready-to-use aqueous solution of oxaliplatin, the present inventors have found to their surprise that indeed such a solution could not only be rendered to possess a remarkably long storage life but also, exhibit a negligible drop in potency as well as significantly superior quality in terms of minimal and acceptable levels of degradation products and impurities formed during storage of the solution.

[0040] It has been found that such a ready-to-use aqueous solution of oxaliplatin possessing long storage life with a negligible drop in potency and significantly superior quality in terms of minimal and acceptable levels of degradation products and impurities formed during storage of the solution could be obtained by addition of a catalytic amount of an additive to the solution.

[0041] Further, it has been found that such a ready-to-use aqueous solution of oxaliplatin possessing long storage life with a negligible drop in potency and significantly superior quality in terms of minimal and acceptable levels of degradation products and impurities formed during storage of the solution could be obtained by addition of a catalytic amount of a carbohydrate to the solution.

[0042] The carbohydrates that could be used for stabilization of the composition are selected from those routinely utilized in pharmaceutical preparations such as glucose, lactose, dextrose, sucrose etc.

[0043] It has been found that the carbohydrates when utilized in an amount ranging from 0.0010% to 0.05% w/v of the solution of oxaliplatin are found to impart the desired storage stability to the solution. However, optimum stability with negligible drop in potency and significantly superior quality in terms

of minimal and acceptable levels of degradation products and impurities formed during storage is found to be achieved when the carbohydrates are utilized in an amount ranging from 0.0010% to 0.02% w/v of the solution of oxaliplatin, more preferably in an amount ranging from 0.0010% to 0.005% w/v of the solution of oxaliplatin.

[0044] Further, utilization of the abovementioned concentration of the carbohydrate in the composition has been found to not only conserve the original/initial potency or assay of the drug substance i.e. Oxaliplatin during thermal storage but also found to lead to minimal formation of related substances or degradation products as well as other impurities, which moreover, comply with pharmacopoeial requirements.

[0045] In particular, an aqueous ready-to-use solution of oxaliplatin containing a catalytic amount of any one of the aforementioned carbohydrates in a concentration of 0.0010% to 0.02% w/v is found to be superior to those solutions wherein a "non-catalytic amount" of same carbohydrates have been employed, especially in a concentration of >0.05%, and in particular, in a concentration of 5% to 50% as taught by Schridde et al in EP 1466599. Further, it has been found that an aqueous ready-to-use solution of oxaliplatin containing catalytic amount of a carbohydrate exhibits a pharmaceutically acceptable shelf-life at a temperature up to 40.degree. C. for 3 months at 75% RH, wherein, a minimal or no loss in potency/assay compared to the solution wherein higher quantities of same carbohydrates have been employed, as taught by Schridde et al in EP 1466599.

[0046] It might be mentioned that a solution of Oxaliplatin in water on storage invariably results in formation of certain degradation products as well as impurities, both known, characterized and reported in the Pharmacopoeial Forums as well as those, which have not been characterized or are unknown.

[0047] The known degradation products/impurities of oxaliplatin referred to in European pharmacopoeial monograph are the following:

1) Oxalic acid referred to as Impurity `A`

2) (SP-4-2)-diaqua[(1R,2R)-cyclohexane-1,2diamine-.kappa.N,.kappa.N']platinum(diaquo diamino cyclohexane platinum) referred to as Impurity `B`

3) (OC-6-33)-[(1R,2R)-cyclohexane-1,2 diamine-.kappa.N,.kappa.N'] [ethanediota(2-)-.kappa.O.sup.1, -.kappa.O.sup.2] dihydroxyplatinum referred to as Impurity `C`

4) (SP-4-2)-diaqua[(1S,2S)-cyclohexane-1,2diamine-.kappa.N,.kappa.N'] [ethanediota(2-)-.kappa.O.sup.1, -.kappa.O.sup.2] platinum (S,S-enantiomer of oxaliplatin) referred to as Impurity `D`

[0048] 5) SP-4-2)-di-.mu.-oxobis [(1R, 2R)-cyclohexane-1,2diamine-.kappa.N,.kappa.N'] diplatinum (diaquodiaminocyclohexane platinum dimer) referred to as Impurity `E`; whose chemical structures are given below:

[0049] It has been found that when a catalytic amount of a carbohydrate is employed, the level of total impurities decreases as compared to when a higher concentration of 5% to 50% of a carbohydrate is used.

[0050] Also, the formulation remains stable over a long period of time at a temperature up to 40.degree. C. for 3 months at 75% RH as compared to the teachings of the prior art, EP 1466599, which advocates a cold storage at 2-8.degree. C. for long term stability of oxaliplatin solution concentrates. (Please refer Table 6 of EP 1466599).

[0051] In addition, EP 1466599 teaches that reducing the pH of the solution by adding acids or buffers further stabilizes the solution. However, the addition of acid along with the higher amount of glucose does not significantly reduce the decomposition of the active substance in the Oxaliplatin solution concentrate. (Please refer Table 7 of EP 1466599).

[0052] Lastly, but not the least an aqueous ready-to-use solution of oxaliplatin containing catalytic amount of carbohydrate of the present invention is found to exhibit negligible loss in potency as compared to such aqueous solutions wherein no additive is added as taught in U.S. Pat. No. 5,716,988.

[0053] The advantages and superiority of the ready-to-use aqueous solution formulation containing a catalytic amount of a carbohydrate as per the present invention over ready-to-use aqueous solution of Oxaliplatin containing no carbohydrate or no acid or large amounts of carbohydrates could be best understood from a comparison given in Table I. TABLE-US-00001 TABLE I Stability Studies of an Aqueous Ready-to-Use Solution of Oxaliplatin Containing Catalytic amount of a Carbohydrate as per the Present Invention in Comparison to those Containing No Carbohydrate or Higher Concentration of a Carbohydrate and/or an Acid Storage Condition at 75% Additive RH of Impurities (% w/w) Nature of Concentration oxaliplatin Assay Highest Total Total Sr. No. Additive (%) solutions (%) A B C

Unknown	Unknown	Impurities	1	None	--	Initial	102.1	0.280	0.300	0.004	0.174	0.176	0.760													
(As taught in 1M/40.degree. C. 100.9 0.447 0.054 0.009 0.041 0.056 0.566 U.S. Pat. No. 5,716,988)																										
2M/40.degree. C.	99.2	0.220	0.015	ND	0.101	0.133	0.368	3M/40.degree. C.	99.3	0.350	0.240	0.005	0.161	0.174	0.769											
2 Carbohydrate	5	Initial	105.3	0.175	0.032	0.362	0.059	0.247	0.815	Lactose	1M/40.degree. C.	101.3	0.190	0.030	0.833	0.261	0.607	1.660								
(As taught in 2M/40.degree. C. 101.8 0.198 0.024 1.023 0.514 0.934 2.179 EP 1,466,599)																										
3M/40.degree. C.	100.8	0.215	0.031	1.111	0.792	1.326	2.682	3 Carbohydrate	5 + 1	Initial	96.9	0.393	0.023	0.258	0.099	0.494	1.168									
(Lactose) + Acid 1M/40.degree. C. 96.6 0.389 0.029 0.311 0.127 0.703 1.432 (Tartaric acid) 2M/40.degree. C. 96.9 0.403 0.032 0.325 0.186 0.734 1.494 (As taught in 3M/40.degree. C. 92.2 0.419 0.024 0.329 0.255 0.891 1.663 EP 1,466,599)																										
4 Carbohydrate-	0.0010	Initial	97.6	0.200	0.250	0.019	0.159	0.250	0.719	(Lactose)	1M/40.degree. C.	95.9	0.233	0.240	0.006	0.126	0.245	0.731								
In Catalytic 2M/40.degree. C. 97.2 0.310 0.270 0.003 0.142 0.236 0.819 Amount 3M/40.degree. C. 98.6 0.290 0.220 0.003 0.019 0.055 0.568 (As per the 0.0020 Initial 97.7 0.168 0.250 0.005 0.151 0.267 0.712 present 1M/40.degree. C. 96.6 0.234 0.210 0.006 0.139 0.243 0.709 invention) 2M/40.degree. C. 97.9 0.260 0.260 0.004 0.133 0.224 0.748 3M/40.degree. C. 98.6 0.340 0.310 0.002 0.028 0.051 0.703 0.0025 Initial 99.6 0.164 0.260 0.005 0.104 0.192 0.657 1M/40.degree. C. 98.5 0.226 0.220 0.004 0.125 0.212 0.666 2M/40.degree. C. 99.5 0.250 0.270 0.003 0.140 0.254 0.777 3M/40.degree. C. 100.5 0.270 0.230 0.003 0.123 0.129 0.632 0.0050 Initial 97.3 0.165 0.280 0.013 0.137 0.235 0.738 1M/40.degree. C. 96.8 0.244 0.210 0.004 0.135 0.218 0.692 2M/40.degree. C. 98.2 0.260 0.270 0.004 0.126 0.230 0.764 3M/40.degree. C. 99.4 0.320 0.230 0.005 0.134 0.149 0.704 0.010 Initial 99.9 0.184 0.290 0.016 0.125 0.220 0.756 1M/40.degree. C. 98.0 0.245 0.230 0.004 0.134 0.183 0.637 2M/40.degree. C. 99.6 0.250 0.290 0.004 0.143 0.259 0.803 3M/40.degree. C. 100.6 0.310 0.180 0.006 0.149 0.170 0.666 0.020 Initial 98.8 0.160 0.250 0.013 0.118 0.210 0.633 1M/40.degree. C. 98.6 0.220 0.240 0.006 0.099 0.194 0.600 2M/40.degree. C. 99.8 0.230 0.280 0.006 0.122 0.229 0.745 3M/40.degree. C. 100.8 0.300 0.210 0.008 0.166 0.181 0.699 0.03 Initial 108.1 0.16 0.29 ND 0.01 0.02 0.52 1M/40.degree. C. 109.4 0.22 0.19 ND 0.02 0.05 0.56 2M/40.degree. C. 106.7 0.26 0.21 0.01 0.05 0.08 0.68 3M/40.degree. C. 107.9 0.25 0.18 0.01 0.07 0.12 0.67 0.05 Initial 107.1 0.14 0.29 ND 0.01 0.03 0.48 1M/40.degree. C. 106.7 0.18 0.21 0.04 0.09 0.14 0.62 2M/40.degree. C. 105.4 0.20 0.21 0.01 0.05 0.07 0.56 3M/40.degree. C. 105.8 0.20 0.17 0.01 0.06 0.11 0.56 5 Carbohydrate-																										
0.0010	Initial	100.2	0.250	0.320	0.002	0.097	0.098	0.670	(Dextrose)	1M/40.degree. C.	99.7	0.260	0.003	0.003	ND	ND	ND	In Catalytic	2M/40.degree. C.	100.4	0.320	0.00	0.00	ND	ND	0.520
Amount	3M/40.degree. C.	98.6	0.200	ND	ND	0.020	0.050	(As per the 0.0020 Initial 101.2 0.180 0.310 0.001 0.120 0.121 0.612 present 1M/40.degree. C. 101.1 0.270 0.220 0.002 ND ND 0.492 Invention) 2M/40.degree. C. 101.7 0.31 0.230 0.00 ND ND ND 3M/40.degree. C. 101.8 0.200 0.190 ND 0.020																		

0.040 0.510 0.0025 Initial 100.0 0.210 0.310 0.002 0.099 0.114 0.636 1M/40.degree. C. 99.1 0.260
0.210 0.003 0.022 0.029 0.502 2M/40.degree. C. 99.8 0.300 0.200 0.000 ND ND ND 3M/40.degree. C.
98.9 0.210 0.180 ND 0.090 0.090 0.560 0.0050 Initial 101.4 0.150 0.330 0.002 0.079 0.080 0.562
1M/40.degree. C. 101.1 0.270 0.220 0.003 0.012 0.019 0.512 2M/40.degree. C. 101.2 0.28 0.21 0.000
ND ND ND 3M/40.degree. C. 102.2 0.200 0.220 ND 0.020 0.050 0.530 0.010 Initial 101.4 0.170 0.300
0.003 0.074 0.075 0.548 1M/40.degree. C. 100.9 0.270 0.220 0.002 0.005 0.005 0.497 2M/40.degree. C.
101.5 0.290 0.210 0.010 ND ND ND 3M/40.degree. C. 101.7 0.200 0.170 ND 0.030 0.080 0.520 0.020
Initial 100.9 0.170 0.310 0.003 0.090 0.091 0.574 1M/40.degree. C. 100.5 0.340 0.220 0.004 0.013
0.019 0.583 2M/40.degree. C. 100.6 0.280 0.230 0.010 ND ND ND 3M/40.degree. C. 101.0 0.200 0.190
0.010 0.030 0.100 0.570 6 Carbohydrate- 0.0010 Initial 99.8 0.190 0.330 0.002 0.067 0.067 0.589
(Sucrose) 1M/40.degree. C. 99.2 0.260 0.230 0.002 0.017 0.017 0.509 In Catalytic 2M/40.degree. C.
100.1 0.280 0.250 0.000 ND ND ND Amount 3M/40.degree. C. 99.2 0.200 0.210 ND 0.020 0.030 0.520
(As per the 0.0020 Initial 101.3 0.150 0.330 0.002 0.061 0.061 0.543 present 1M/40.degree. C. 100.8
0.50 0.220 0.002 0.016 0.029 0.501 Invention) 2M/40.degree. C. 101.8 0.260 0.250 0.000 ND ND ND
3M/40.degree. C. 101.8 0.180 0.210 ND 0.020 0.040 0.510 0.0025 Initial 100.8 0.210 0.310 0.002 0.099
0.114 0.636 1M/40.degree. C. 99.1 0.260 0.210 0.003 0.022 0.029 0.502 2M/40.degree. C. 99.8 0.300
0.200 0.000 ND ND ND 3M/40.degree. C. 98.9 0.210 0.180 ND 0.030 0.090 0.560 0.0050 Initial 99.0
0.150 0.340 0.002 0.060 0.060 0.552 1M/40.degree. C. 99.2 0.280 0.240 0.001 0.008 0.008 0.529
2M/40.degree. C. 99.5 0.270 0.260 0.000 ND ND ND 3M/40.degree. C. 99.8 0.210 0.200 ND 0.020
0.030 0.530 0.010 Initial 100.5 0.210 0.330 0.002 0.055 0.055 0.597 1M/40.degree. C. 99.7 0.280 0.260
0.002 0.011 0.011 0.533 2M/40.degree. C. 100.8 0.250 0.270 0.000 ND ND ND 3M/40.degree. C. 100.3
0.190 0.170 ND 0.020 0.030 0.470 0.020 Initial 102.0 0.200 0.350 0.002 0.065 0.065 0.617
1M/40.degree. C. 100.5 0.260 0.240 0.002 0.009 0.009 0.511 2M/40.degree. C. 101.7 0.270 0.280 0.000
ND ND ND 3M/40.degree. C. 100.7 0.190 0.190 ND 0.020 0.040 0.500 *ND: Not Determined

[0054] Further, the effect in assay and level of impurities on utilizing a carbohydrate at a concentration higher than 0.02 w/v solution of oxaliplatin was also studied which indicates that when the carbohydrate, especially lactose is employed in a concentration ranging from 0.05%-5% w/v of the solution is found to result in gradual drop in assay as well as gradual increase in level of degradation products. These are summarized in Table II. TABLE-US-00002 TABLE II Comparison of Stability of an Aqueous Ready-to-Use Oxaliplatin Solutions containing various amounts of Carbohydrate ("Catalytic Amount" as per the present invention vis-a-vis "Non-catalytic Amount" as per the Prior Art) Storage Condition at 75% Selected Carbohydrate RH of Impurities (% w/w) Auxiliary Concentration oxaliplatin Assay Highest Total Total Additives (%) solutions (%) A B C Unknown Unknown Impurities Lactose 0.0010 Initial 97.6 0.200 0.250 0.019 0.159 0.250 0.719 1M/40.degree. C. 95.9 0.233 0.240 0.006 0.126 0.245 0.731 2M/40.degree. C. 97.2 0.310 0.270 0.003 0.142 0.236 0.819 3M/40.degree. C. 98.6 0.290 0.220 0.003 0.019 0.055 0.568 Lactose 0.0020 Initial 97.7 0.168 0.250 0.005 0.151 0.267 0.712 1M/40.degree. C. 96.6 0.234 0.210 0.006 0.139 0.243 0.709 2M/40.degree. C. 97.9 0.260 0.260 0.004 0.133 0.224 0.748 3M/40.degree. C. 98.6 0.340 0.310 0.002 0.028 0.051 0.703 Lactose 0.0025 Initial 99.6 0.164 0.260 0.005 0.104 0.192 0.657 1M/40.degree. C. 98.5 0.226 0.220 0.004 0.125 0.212 0.666 2M/40.degree. C. 99.5 0.250 0.270 0.003 0.140 0.254 0.777 3M/40.degree. C. 100.5 0.270 0.230 0.003 0.123 0.129 0.632 Lactose 0.0050 Initial 97.3 0.165 0.280 0.013 0.137 0.235 0.738 1M/40.degree. C. 96.8 0.244 0.210 0.004 0.135 0.218 0.692 2M/40.degree. C. 98.2 0.260 0.270 0.004 0.126 0.230 0.764 3M/40.degree. C. 99.4 0.320 0.230 0.005 0.134 0.149 0.704 Lactose 0.010 Initial 99.9 0.184 0.290 0.016 0.125 0.220 0.756 1M/40.degree. C. 98.0 0.245 0.230 0.004 0.134 0.183 0.637 2M/40.degree. C. 99.6 0.250 0.290 0.004 0.143 0.259 0.803 3M/40.degree. C. 100.6 0.310 0.180 0.006 0.149 0.170 0.666 Lactose 0.020 Initial 98.8 0.160 0.250 0.013 0.118 0.210 0.633 1M/40.degree. C. 98.6 0.220 0.240 0.006 0.099 0.194 0.600 2M/40.degree. C. 99.8 0.230 0.280 0.006 0.122 0.229 0.745 3M/40.degree. C. 100.8 0.300 0.210 0.008 0.166 0.181 0.699 Lactose 0.03 Initial 108.1 0.16 0.29 ND 0.01 0.02 0.52 1M/40.degree. C. 109.4 0.22 0.19 ND 0.02 0.05 0.56 2M/40.degree. C. 106.7 0.26 0.21 0.01 0.05 0.08 0.68 3M/40.degree. C. 107.9 0.25 0.18 0.01 0.07 0.12 0.67 Lactose 0.045 Initial

99.36 0.15 0.34 ND 0.08 0.12 0.63 1M/40.degree. C. 96.7 0.23 0.14 0.01 0.13 0.20 0.60 2M/40.degree. C. 98.94 0.24 0.13 0.01 0.12 0.20 0.60 3M/40.degree. C. ND ND ND ND ND ND ND Lactose 0.05 Initial 107.1 0.14 0.29 ND 0.01 0.03 0.48 1M/40.degree. C. 106.7 0.18 0.21 0.04 0.09 0.14 0.62 2M/40.degree. C. 105.4 0.20 0.21 0.01 0.05 0.07 0.56 3M/40.degree. C. 105.8 0.20 0.17 0.01 0.06 0.11 0.56 Lactose 0.2 Initial 107.2 0.15 0.31 ND 0.01 0.02 0.52 1M/40.degree. C. 106.2 0.18 0.18 0.01 0.03 0.06 0.49 2M/40.degree. C. 106.1 0.20 0.18 0.03 0.12 0.15 0.61 3M/40.degree. C. 106.1 0.22 0.16 0.04 0.17 0.24 0.70 Lactose 0.3 Initial 108.3 0.140 0.300 ND 0.010 0.020 0.490 1M/40.degree. C. 108.8 0.200 0.230 0.020 0.050 0.090 0.610 2M/40.degree. C. 107.5 0.190 0.170 0.040 0.140 0.170 0.610 3M/40.degree. C. 107.4 0.23 0.15 0.50 0.27 0.35 0.82 Lactose 0.5 Initial 107.2 0.140 0.290 ND 0.010 0.030 0.480 1M/40.degree. C. 106.7 0.180 0.210 0.040 0.090 0.140 0.620 2M/40.degree. C. 104.1 0.210 0.170 0.080 0.230 0.270 0.760 3M/40.degree. C. 105.4 0.23 0.13 0.080 0.42 0.52 0.98 Lactose 2.0 Initial 104.6 0.140 0.280 0.010 0.030 0.070 0.510 1M/40.degree. C. 104.2 0.180 0.170 0.120 0.130 0.200 0.680 2M/40.degree. C. 102.8 0.200 0.150 0.220 0.450 0.550 1.120 3M/40.degree. C. 103.1 0.22 0.11 0.24 0.66 0.81 1.38 Lactose 3.0 Initial 108.4 0.140 0.260 0.010 0.030 0.080 0.500 1M/40.degree. C. 108.4 0.020 0.210 0.160 0.050 0.090 0.730 2M/40.degree. C. 107.5 0.210 0.150 0.280 0.480 0.560 1.200 3M/40.degree. C. 107 0.23 0.15 0.29 0.75 0.93 1.60 Lactose 4.5 Initial 100.7 0.14 0.22 0.01 0.09 0.13 0.50 1M/40.degree. C. 99.38 0.24 0.14 0.15 0.09 0.28 0.81 2M/40.degree. C. 99.22 0.21 0.15 0.22 0.29 0.54 1.12 3M/40.degree. C. ND ND ND ND ND ND ND Lactose 5 Initial 105.1 0.175 0.032 0.362 0.059 0.247 0.815 1M/40.degree. C. 101.2 0.190 0.030 0.833 0.261 0.607 1.660 2M/40.degree. C. 101.8 0.198 0.024 1.023 0.514 0.934 2.179 3M/40.degree. C. 100.8 0.215 0.031 1.111 0.792 1.326 2.682 *ND: Not Determined

[0055] The present invention is detailed hereinbelow.

[0056] As mentioned hereinbefore, the present invention is directed to a storage stable ready-to-use aqueous solution of Oxaliplatin wherein the stabilization is achieved through an addition of catalytic amount of an additive, in particular a catalytic amount of a carbohydrate and a method for preparation of such stable aqueous ready-to-use solutions. Again as discussed hereinbefore, minimization of degradation products as well as enhanced stability could be achieved through utilization of a catalytic amount of a carbohydrate.

[0057] Suitable carbohydrates that can be employed are those that are not only routinely used in the preparation of pharmaceutical compositions but are also accepted by regulatory and health authorities.

[0058] Suitable carbohydrates include lactose, glucose, sucrose, and dextrose etc., of which lactose is the most preferred carbohydrate.

[0059] Typically the carbohydrate can be employed in a concentration ranging from 0.0010% to 0.020% w/v solution of oxaliplatin, preferably 0.0025% w/v solution of oxaliplatin. Such a pharmaceutical composition, since being meant for IV Infusion is typically a sterile solution contained in a suitable vial, which needless to mention is prepared under aseptic conditions.

[0060] Typical glass vials that can be utilized to contain the stable ready-to-use aqueous solution formulation of Oxaliplatin are normal glass vials, which are not pretreated/special grade/types of glass, even though, such glass vials could also be used to contain the pharmaceutical composition of oxaliplatin.

[0061] Vials made of USP Type I glass, commonly known as "normal hydrolytic class-I glass" or borosilicate glass are corning.RTM. Pyrex.RTM. 7740 and Wheaton 180, 200, and 400. Again, typically the glass vials can be sealed with both normal as well as special stoppers, the former being adequate.

[0062] In a specific embodiment, a stable composition would contain 5-mg/ml solution of Oxaliplatin in water and a catalytic amount of carbohydrate in glass vials typically sealed with elastomeric stoppers and aluminium flip-off seals.

[0063] A typical method for preparation of ready-to-use aqueous solution formulation of Oxaliplatin comprises dissolving known amount of oxaliplatin in water to which weighed quantity of carbohydrate is added. The amount of carbohydrate added is in the range of 0.0010% to 0.05% w/v with respect to the solution. The resultant solution is filtered through suitable grade filter membrane under aseptic conditions, filled into vials and stoppered and sealed with aluminium flip-off seals.

[0064] The following examples describe the invention in more detail concerning the injectable preparation according to the invention, its manufacture and comparison of its stability.

[0065] These are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

Experimental

1) Preparation of Aqueous Solution of Oxaliplatin:

[0066] To double distilled water taken in a glass container, an amount of Oxaliplatin necessary for obtaining a concentration of 5 mg/ml is added and stirred at 30-35.degree. C. (maintained using suitable temperature control device) until the entire drug is dissolved.

[0067] Separately stock solutions of concentrations of the respective carbohydrates viz., lactose, Dextrose and Sucrose were prepared in double distilled water in volumetric flasks. Sufficient quantities of these stock solutions were added to the Oxaliplatin solutions, so that a final concentration of the respective carbohydrate in the solution is 0.001%, 0.002%, 0.0025%, 0.005%, 0.01% and 0.02% w/v solution of Oxaliplatin. Further, double distilled water is added to bring the solutions to their final volume. The resultant solutions were filtered through suitable grade filter membrane.

2) Packaging

[0068] Volumes of 10 ml of the solution were distributed into Type I colorless glass vials. The vials were immediately stoppered with rubber stoppers and sealed with aluminium flip-off overseal.

3) Stability Test

[0069] The solution in the vials stored in inverted configuration were subjected to accelerated conditions of 40.degree. C./75% relative humidity for up to 3 months. The stability data, obtained using high performance liquid chromatography (HPLC) is used to determine potency and impurity profile. Furthermore, the carbohydrate content of the respective carbohydrates in these solutions were determined using ion chromatography "Dionex" at initial time point and after 3 months duration at accelerated conditions. The appearance of the formulations was assessed at the initial, 1-month, 2 months and 3 months time point. For the sake of convenience, Table I is summarized again in the following examples (1, 2 and 3) hereinbelow.

[0070] These corroborates with the findings of the present invention that as the concentration of carbohydrate is increased, the level of impurities increases. At higher concentrations of carbohydrate, the level of impurities attained within one-month duration equals or exceeds the level obtained with the catalytic amount of carbohydrate of the present invention even after three months.

EXAMPLE-1

Comparative Data of Oxaliplatin Solution Containing Various Concentration of Lactose

[0071] An aqueous solution of Oxaliplatin of 5 mg/ml was prepared using double distilled water contained in a glass container and added the required quantity of lactose followed by stirring at 30-35.degree. C. until the complete dissolution of drug occurs. The stock solution of carbohydrates viz., lactose was added in the above solution to get final concentrations. The results of stability of such solutions are summarized in Table-III. TABLE-US-00003 TABLE III Stability Data of an Aqueous Ready-to-Use Oxaliplatin Solutions containing Catalytic Amounts of Lactose Selected Carbohydrate Impurities (% w/w) Auxiliary Concentration Assay Highest Total Total Additives (%) Condition (%) A B C Unknown Unknown Impurities Lactose 0.0010 Initial 97.6 0.200 0.250 0.019 0.159 0.250 0.719 1M/40.degree. C. 95.9 0.233 0.240 0.006 0.126 0.245 0.731 2M/40.degree. C. 97.2 0.310 0.270 0.003 0.142 0.236 0.819 3M/40.degree. C. 98.6 0.290 0.220 0.003 0.019 0.055 0.568 Lactose 0.0020 Initial 97.7 0.168 0.250 0.005 0.151 0.267 0.712 1M/40.degree. C. 96.6 0.234 0.210 0.006 0.139 0.243 0.709 2M/40.degree. C. 97.9 0.260 0.260 0.004 0.133 0.224 0.748 3M/40.degree. C. 98.6 0.340 0.310 0.002 0.028 0.051 0.703 Lactose 0.0025 Initial 99.6 0.164 0.260 0.005 0.104 0.192 0.657 1M/40.degree. C. 98.5 0.226 0.220 0.004 0.125 0.212 0.666 2M/40.degree. C. 99.5 0.250 0.270 0.003 0.140 0.254 0.777 3M/40.degree. C. 100.5 0.270 0.230 0.003 0.123 0.129 0.632 Lactose 0.0050 Initial 97.3 0.165 0.280 0.013 0.137 0.235 0.738 1M/40.degree. C. 96.8 0.244 0.210 0.004 0.135 0.218 0.692 2M/40.degree. C. 98.2 0.260 0.270 0.004 0.126 0.230 0.764 3M/40.degree. C. 99.4 0.320 0.230 0.005 0.134 0.149 0.704 Lactose 0.010 Initial 99.9 0.184 0.290 0.016 0.125 0.220 0.756 1M/40.degree. C. 98.0 0.245 0.230 0.004 0.134 0.183 0.637 2M/40.degree. C. 99.6 0.250 0.290 0.004 0.143 0.259 0.803 3M/40.degree. C. 100.6 0.310 0.180 0.006 0.149 0.170 0.666 Lactose 0.020 Initial 98.8 0.160 0.250 0.013 0.118 0.210 0.633 1M/40.degree. C. 98.6 0.220 0.240 0.006 0.099 0.194 0.600 2M/40.degree. C. 99.8 0.230 0.280 0.006 0.122 0.229 0.745 3M/40.degree. C. 100.8 0.300 0.210 0.008 0.166 0.181 0.699

EXAMPLE-2

Comparative Data of Oxaliplatin Solution Containing Various Concentration of Dextrose

[0072] An aqueous solution of Oxaliplatin of 5 mg/ml was prepared using double distilled water contained in a glass container and added the required quantity of dextrose followed by stirring at 30-35.degree. C. until the complete dissolution of drug occurs. The stock solution of carbohydrates viz., dextrose was added in the above solution to get final concentrations.

[0073] The results of stability of such solutions are summarized in Table-IV. TABLE-US-00004 TABLE IV Stability Data of an Aqueous Ready-to-Use Oxaliplatin Solutions containing Catalytic Amounts of Dextrose Selected Carbohydrate Impurities (% w/w) Auxiliary Concentration Assay Highest Total Total Additives (%) Condition (%) A B C Unknown Unknown Impurities Dextrose 0.0010 Initial 100.2 0.250 0.320 0.002 0.097 0.098 0.670 1M/40.degree. C. 99.7 0.260 0.003 0.003 ND ND 0.473 2M/40.degree. C. 100.4 0.320 0.00 0.00 NA NA NA 3M/40.degree. C. 98.6 0.200 ND ND 0.020 0.050 0.520 Dextrose 0.0020 Initial 101.2 0.180 0.310 0.001 0.120 0.121 0.612 1M/40.degree. C. 101.1 0.270 0.220 0.002 ND ND 0.492 2M/40.degree. C. 101.7 0.31 0.230 0.00 NA NA NA 3M/40.degree. C. 101.8 0.200 0.190 ND 0.020 0.040 0.510 Dextrose 0.0025 Initial 100.0 0.210 0.310 0.002 0.099 0.114 0.636 1M/40.degree. C. 99.1 0.260 0.210 0.003 0.022 0.029 0.502 2M/40.degree. C. 99.8 0.300 0.200 0.000 NA NA NA 3M/40.degree. C. 98.9 0.210 0.180 ND 0.090 0.090 0.560 Dextrose 0.0050 Initial 101.4 0.150 0.330 0.002 0.079 0.080 0.562 1M/40.degree. C. 101.1 0.270 0.220 0.003 0.012 0.019 0.512 2M/40.degree. C. 101.2 0.28 0.21 0.000 NA NA NA 3M/40.degree. C. 102.2 0.200 0.220 ND 0.020 0.050 0.530 Dextrose 0.010 Initial 101.4 0.170 0.300 0.003 0.074 0.075 0.548

1M/40.degree. C. 100.9 0.270 0.220 0.002 0.005 0.005 0.497 2M/40.degree. C. 101.5 0.290 0.210 0.010
 NA NA NA 3M/40.degree. C. 101.7 0.200 0.170 ND 0.030 0.080 0.520 Dextrose 0.020 Initial 100.9
 0.170 0.310 0.003 0.090 0.091 0.574 1M/40.degree. C. 100.5 0.340 0.220 0.004 0.013 0.019 0.583
 2M/40.degree. C. 100.6 0.280 0.230 0.010 NA NA NA 3M/40.degree. C. 101.0 0.200 0.190 0.010 0.030
 0.100 0.570

EXAMPLE-3

Comparative Data of Oxaliplatin Solution Containing Various Concentration of Sucrose

[0074] An aqueous solution of Oxaliplatin of 5 mg/ml was prepared using double distilled water contained in a glass container and added the required quantity of sucrose followed by stirring at 30-35.degree. C. until the complete dissolution of drug occurs. The stock solution of carbohydrates viz., sucrose was added in the above solution to get final concentrations. The results of stability of such solutions are summarized in Table-V. TABLE-US-00005 TABLE V Stability Data of an Aqueous Ready-to-Use Oxaliplatin Solutions containing Catalytic Amounts of Sucrose Selected Carbohydrate Impurities (% w/w) Auxiliary Concentration Assay Highest Total Total Additives (%) Condition (%) A B C Unknown Unknown Impurities Sucrose 0.0010 Initial 99.8 0.190 0.330 0.002 0.067 0.067 0.589
 1M/40.degree. C. 99.2 0.260 0.230 0.002 0.017 0.017 0.509 2M/40.degree. C. 100.1 0.280 0.250 0.000
 NA NA NA 3M/40.degree. C. 99.2 0.200 0.210 ND 0.020 0.030 0.520 Sucrose 0.0020 Initial 101.3
 0.150 0.330 0.002 0.061 0.061 0.543 1M/40.degree. C. 100.8 0.50 0.220 0.002 0.016 0.029 0.501
 2M/40.degree. C. 101.8 0.260 0.250 0.000 NA NA NA 3M/40.degree. C. 101.8 0.180 0.210 ND 0.020
 0.040 0.510 Sucrose 0.0025 Initial 100.8 0.210 0.310 0.002 0.099 0.114 0.636 1M/40.degree. C. 99.1
 0.260 0.210 0.003 0.022 0.029 0.502 2M/40.degree. C. 99.8 0.300 0.200 0.000 NA NA NA
 3M/40.degree. C. 98.9 0.210 0.180 ND 0.030 0.090 0.560 Sucrose 0.0050 Initial 99.0 0.150 0.340 0.002
 0.060 0.060 0.552 1M/40.degree. C. 99.2 0.280 0.240 0.001 0.008 0.008 0.529 2M/40.degree. C. 99.5
 0.270 0.260 0.000 NA NA NA 3M/40.degree. C. 99.8 0.210 0.200 ND 0.020 0.030 0.530 Sucrose 0.010
 Initial 100.5 0.210 0.330 0.002 0.055 0.055 0.597 1M/40.degree. C. 99.7 0.280 0.260 0.002 0.011 0.011
 0.533 2M/40.degree. C. 100.8 0.250 0.270 0.000 NA NA NA 3M/40.degree. C. 100.3 0.190 0.170 ND
 0.020 0.030 0.470 Sucrose 0.020 Initial 102.0 0.200 0.350 0.002 0.065 0.065 0.617 1M/40.degree. C.
 100.5 0.260 0.240 0.002 0.009 0.009 0.511 2M/40.degree. C. 101.7 0.270 0.280 0.000 NA NA NA
 3M/40.degree. C. 100.7 0.190 0.190 ND 0.020 0.040 0.500

[0075] Clear solutions, thus obtained, can be made for human or animal consumption by conventional methods, for the treatment of a human or an animal cancerous disease, by administration of such stable pharmaceutical compositions of oxaliplatin.

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