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(71) Applicant *(for all designated States except US)*: **CADILA HEALTHCARE LIMITED** [IN/IN]; Zydus Tower, Satellite Cross Road, Ahmedabad 380 015, Gujarat (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ROY, Sunilendu, Bhushan** [IN/IN]; Sarkhej-Bavla N.H. No. 8A, Moraiya, Tal. Sanand, Dist. Ahmedabad 382 210, Gujarat (IN). **KULKARNI, Sushrut, Krishnaji** [IN/IN]; Sarkhej-Bavla N.H. No. 8A, mORAIYA, Tal. Sanand, Dist. Ahmedabad 382 210, Gujarat (IN). **PANCHAL, Maulik, Kiritkumar** [IN/IN]; Sarkhej-Bavla N.H. No. 8A, mORAIYA, Tal. Sanand, Dist. Ahmedabad 382 210, Gujarat (IN). **MANDGE, Shailendra, Shubhashchandra** [IN/IN]; Sarkhej-Bavla N.H. No. 8A, mORAIYA, Tal. Sanand, Dist. Ahmedabad 382 210, Gujarat (IN).

(74) Agent: **SUBRAMANIAM, Hariharan**; Subramaniam, Nataraj & Associates, E- 556, Greater Kailash-II, New Delhi 110 048 (IN).

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(54) **Title**: STABLE PHARMACEUTICAL COMPOSITIONS OF CLOPIDOGREL FOR PARENTERAL DELIVERY

(57) **Abstract**: The present invention relates to stable pharmaceutical compositions of clopidogrel or salts thereof for parenteral administration. The invention relates to pharmaceutical compositions containing concentrate of clopidogrel or pharmaceutically acceptable salts thereof, which can be mixed with suitable aqueous vehicle for preparation of infusion solution suitable for administration to patients. Such compositions exhibit excellent stability. The invention also includes process of preparation of such compositions.

STABLE PHARMACEUTICAL COMPOSITIONS OF CLOPIDOGREL FOR PARENTERAL DELIVERY

Field of the Invention

The present invention relates to stable pharmaceutical compositions of clopidogrel or salts thereof for parenteral administration. The invention relates to pharmaceutical compositions containing concentrate of clopidogrel or pharmaceutically acceptable salts thereof, which can be mixed with suitable aqueous vehicle for preparation of infusion solution suitable for administration to patients. Such compositions exhibit excellent stability. The invention also includes process of preparation of such compositions.

Background of the Invention

Clopidogrel is a platelet aggregation inhibitor that has selective irreversible inhibition of adenosine diphosphate (ADP)-induced platelet aggregation, acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPHb/IIIa complex.; with no significant effect on thromboxane A2 or prostacyclin synthesis, or phospholipase A activity. Clopidogrel is indicated for reduction of atherothrombotic events like recent myocardial infarction, recent stroke or established peripheral arterial disease, acute coronary syndrome.

Chemically, it is (+)-(S)-methyl-2-(2-chlorophenyl)-2-(6,7-dihydrothieπo[3,2-c]pyridin-5(4H)-yl)acetate.

Clopidogrel is available as its bisulphate salt in the form of immediate release tablets equivalent to 75 and 300 mg base. It is marketed in US under the brand name Plavix® by Sanofi Aventis. Typically the oral formulation takes more than 2 hours to show its pharmacological effect. Intravenous injections are known to provide the activity immediately.

The parenteral route of administration has advantage over oral administration for immediate release, as there is no lag time corresponding to the drug reaching sufficient concentration in the systemic circulation to start surgery in cases of coronary intervention. Coronary intervention is a medical emergency, during which the rapid achievement of therapeutic drug concentrations in the blood and rapid onset of action is a priority and to achieve the same, intravenous administration is the best preferred

route. The medication is used particularly for the reduction of accidents related to atherosclerosis (myocardial infarction, stroke, arthritis, vascular death) in patients who have had a recent myocardial infarction, stroke or with recent arterial obstructions proved in the lower limbs. Hence, there is need of injection dosage form for patients who are in urgency for medication and for whom oral administration is difficult.

U. S. Patent No. 4,847,265 dislcoses clopidogrel, its salts and pharmaceutical compositions thereof

U. S. Patent No. 6,284,277 discloses freeze-dried or lyophilized compositions containing mannitol and alanine. However, at the time of reconstitution of such lyophilisate in solvent, one often encounters a problem of self-aggregation of the clopidogrel.

PCT International Publication No. WO 2008/134600 discloses compositions comprising clopidogrel and sulfoalkyl ether cyclodextrin (SAE- CD).

European Patent No. EP 099802 discloses composition of clopidogrel or a pharmaceutically acceptable salt thereof for parenteral administration as an injectable solution. This type of formulation containing a salt of clopidogrel in isotonic solution in a solvent is difficult to use. Since salts of the clopidogrel are strong acids, in aqueous solution, it gives solutions presenting a pH below 2, making the resulting injection very painful and thus can hinder patient compliance.

European Patent No. EP 1105102 discloses injectable aqueous solutions containing a salt of clopidogrel, pluronic F68, a basic pH modifier and solutol HS 15. The patent application further discloses lyophilized formulations containing these ingredients and kits containing such lyophilized compositions in two parts. However, according to the instant European patent, it is necessary to achieve a lyophilisate since the salts of clopidogrel are unstable in aqueous solution and leads to deterioration of clopidogrel.

PCT International Publication No. WO 2009/133455 discloses ready-to-use aqueous injection of clopidogrel or its salts.

In freeze drying and lyophilization, the various variables which affect the stability of the formulation are mainly the pH, the quantity of salts present, the type and quantity of excipients in the formulation, the type of cryoprotective chosen, as well as the temperature, pressure and time chosen for freezing, sublimation and drying operations. Also these variables influence the physical state of the freeze-dried product

obtained, namely: vitreous amorphous, soft amorphous, crystalline or a combination of these states.

It is preferred to provide aqueous based Intravenous injection of clopidogrel so that biocompatibility is achieved. However, the aqueous solution has only a limited shelf-life at room temperature and it is also known that aqueous solution of salts of the clopidogrel gives solutions presenting a pH below 2, making the resulting injection very painful and thus can affect patient compliance to parenteral dosage. Moreover, due to the low water solubility of clopidogrel at pharmaceutically acceptable pH, hydrolysis and conversion of the salt to it's free base, it is difficult to formulate a predominantly aqueous based clopidogrel compositions with a sufficiently long shelf life. Also, there is no injection formulation available in the market for clopidogrel as of today.

Thus, there exists a continual need for stable aqueous based compositions of clopidogrel or pharmaceutically acceptable salts thereof, which are also suitable for parenteral administration, hence can prove useful in cardiac emergency situations. The compositions of the invention overcome all the encountered problems exemplified above.

Summary of the Invention

In one general aspect, there is provided a stable injectable pharmaceutical composition comprising concentrate of clopidogrel or salts thereof.

In another general aspect, there is provided a stable injectable pharmaceutical composition comprising concentrate of clopidogrel or salts thereof, wherein said concentrate further comprises of one or more of suitable aqueous solvents, surfactants optionally with a co-solvent.

In another general aspect, there is provided a stable injectable pharmaceutical composition comprising concentrate of clopidogrel or salts thereof, wherein said concentrate is adjusted to the form suitable for parenteral administration.

In another general aspect, there is provided a stable injectable pharmaceutical composition comprising concentrate of clopidogrel or salts thereof, wherein said concentrate is adjusted to the form suitable for parenteral administration by addition of suitable aqueous vehicle.

In another general aspect, there is provided a stable injectable pharmaceutical composition comprising concentrate of clopidogrel or salts thereof, wherein said concentrate is adjusted to the form suitable for administration by addition of suitable

aqueous vehicle, characterized in that the vehicle comprises one or more of buffers, surfactants and aqueous solvents.

In another general aspect, there is provided a kit for the reduction of atherothrombotic events comprising concentrate of clopidogrel or salts thereof, and a suitable aqueous vehicle.

In another general aspect, there is provided a kit for the reduction of atherothrombotic events comprising concentrate of clopidogrel or salts thereof, and a suitable diluent, wherein the concentrate and aqueous vehicle are admixed together for preparation of infusion prior to administration to patients.

In another general aspect, there is provided a process for preparation of stable Injectable pharmaceutical composition comprising concentrate of clopidogrel or salts thereof, which process comprises of mixing concentrate of clopidogrel or pharmaceutically acceptable salts thereof with suitable aqueous solvent, which is subsequently adjusted to form suitable for administration.

In one general aspect, there is provided method of reducing of atherothrombotic events like recent myocardial infarction and treating recent stroke or established peripheral arterial disease, acute coronary syndrome comprising administering to human patient in need thereof an injectable pharmaceutical composition comprising a concentrate of clopidogrel or salts thereof.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the pharmaceutical composition may further include one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may include surfactants, solvents, buffering agents, co-solvents and stabilizers.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description.

Detailed Description of the Invention

The inventors of the present invention have surprisingly found that it is possible to develop stable and aqueous based injectable compositions of clopidogrel or pharmaceutically acceptable salts thereof. The inventors have prepared clopidogrel or its salt in the form of a concentrate which can be further admixed or reconstituted with a suitable aqueous vehicle prior to administration to patient.

Hence by provision of aqueous based injectable compositions of clopidogrel or salts thereof using aforesaid technique, the stability issues associated with ready to use aqueous solutions of clopidogrel can be circumvented. Moreover such formulation also provides an alternative treatment for cardiac interventions which many a time requires emergency consideration, which is not possible with oral route.

In an embodiment, the invention provides a method of stabilizing an injectable pharmaceutical composition comprising clopidogrel or salt thereof comprising admixing or reconstituting a clopidogrel concentrate and aqueous vehicle together for preparation of infusion prior to administration.

The inventors have further noticed that present invention offers many advantages over the conventional dosages form available in the market; which includes-

- solubilizing therapeutically effective amount of poorly-water soluble clopidogrel.
- homogeneous and thermodynamically stable compositions with long shelf life.
- compositions with small and narrow particle size distribution suitable for parenteral administration and rapid onset.
- compositions having a hydrophilic surfactant and organic solvent in amount such that upon dilution with intravenous infusion a clear aqueous dispersion is formed.

The term "clopidogrel" used throughout the specification refers to not only clopidogrel per se, but also its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs and pharmaceutically acceptable prodrugs thereof. It is also possible to use any salts and free base form of memantine, including polymorphs, hydrates, solvates or amorphous forms. The preferred salt of clopidogrel is besylate and bisulphate salt. Particularly preferred salt is besylate.

The term "concentrate of clopidogrel" or "clopidogrel concentrate" or "concentrate" used throughout the specification refers to a clopidogrel and pharmaceutically acceptable salt thereof per se suitable for parenteral administration, for example, sterilized clopidogrel or salts thereof and lyophilized clopidogrel or salts thereof. The term also includes solution, suspension or admixture of clopidogrel or salt

thereof in which clopidogrel is present in concentrated form in a parenterally acceptable excipient.

The term "concentrated" means a concentration of clopidogrel or salt thereof which is usually too high to enable the corresponding concentrate, solution or suspension to be used therapeutically without being diluted.

In an embodiment, the clopidogrel concentration in the concentrate ranges between 0.5% and 50% w/v, preferably the concentration ranges between 1.5% w/v and 15% w/v of the composition. The concentration range is related to % weight of free base clopidogrel relative to % volume of the composition.

The stable injectable pharmaceutical composition in accordance with the present invention comprises concentrate of clopidogrel or salt thereof.

The injectable composition in accordance with the present invention is prepared in two parts. First part comprises clopidogrel concentrate and second part comprises aqueous vehicle.

In an embodiment, the concentrate of clopidogrel is in the form of sterilized clopidogrel or salt thereof and optionally with one or more parenterally acceptable excipients.

In a further embodiment, the concentrate of clopidogrel is in the form of lyophilized mixture of clopidogrel or salt thereof per se or with one or more parenterally acceptable excipient suitable for lyophilization.

In a further embodiment, the concentrate of clopidogrel comprises one or more parenterally acceptable excipients selected from surfactants, aqueous solvents, co-solvents, diluents or mixtures thereof.

The second is an aqueous vehicle which comprises one or more of aqueous solvents and/or co-solvents.

It has been found that aqueous based diluent when prepared using mixture of surfactant and buffer in addition to aqueous solvent, it leads to improvement in the stability of solutions containing clopidogrel or salt thereof and moreover, resulting solution is also suitable for parenteral administration.

In an embodiment, the injectable pharmaceutical composition comprises a concentrate of clopidogrel diluted with aqueous vehicle comprising one or more surfactant/s, one or more buffer/s and one or more aqueous solvents and optionally one or more co-solvents.

In an embodiment, the injectable pharmaceutical composition comprises a concentrate of clopidogrel comprising polyethylene glycol hydroxyl stearate (e.g. Solutol® HS 15) diluted with aqueous vehicle comprising a copolymer of ethylene oxide and propylene oxide (e.g. Pluronic F68®), citrate buffer and one or more aqueous solvents and optionally one or more co-solvents.

In an embodiment, the injectable pharmaceutical composition comprises a concentrate of clopidogrel comprising polyethylene glycol hydroxyl stearate (e.g. Solutol® HS 15) diluted with aqueous vehicle comprising a polyoxyethylene castor oil derivative (e.g. Cremophor®), citrate buffer and one or more aqueous solvents and optionally one or more co-solvents.

In an embodiment, the injectable pharmaceutical composition comprises a concentrate of clopidogrel diluted with aqueous vehicle system comprising polyethylene glycol hydroxyl stearate (e.g. Solutol® HS 15), a polyoxyethylene castor oil derivative (e.g. Cremophor®), citrate buffer and one or more aqueous solvents and optionally one or more co-solvents.

In an embodiment, a pharmaceutical kit which present in the form of two containers (preferably, sterile), one containing a clopidogrel concentrate and the other contains aqueous vehicle comprising a surfactant, a buffer, a solvent and optionally a cosolvent.

In a further embodiment, pharmaceutical kit which present in the shape of a double syringe compartment, one of the compartments contains clopidogrel concentrate and the other compartment containing aqueous vehicle comprising a surfactant, a buffer, a solvent and optionally a cosolvent.

The injectable composition of the invention is prepared in two parts. First part involves preparation of concentrate by dissolving clopidogrel or salts thereof in suitable solvent/co-solvent systems along with one or more surfactants. The concentrate may be sterilized and aseptically filled in sealed vials.

Second part involves preparation of aqueous vehicle by mixing one or more surfactants, buffers, aqueous solvents and optionally co-solvents. The diluent may be sterilized and aseptically filled in suitable device or container. Both the parts may be suitably mixed to form a infusion solution prior to administration to patients.

Suitable devices or containers which can be used to accommodate clopidogrel concentrate and aqueous vehicle in accordance of the present invention may be any

container or device suitable for parenteral formulation those are know to person skilled in the art. Examples of such devices are vials, ampoules, bottles, prefilled syringes (e.g. two compartment syringes).

In an embodiment, the process for the preparation of a stable injectable pharmaceutical composition of clopidogrel or salt thereof comprises-

(a) providing a concentrate of clopidogrel or salts thereof, optionally containing one or more parenterally acceptable excipients.

(b) providing an aqueous vehicle comprising one or more parenterally acceptable excipients.

(c) admixing or reconstituting the clopidogrel concentrate with aqueous vehicle prior to administration.

The clopidogrel concentrate and aqueous based diluent may be sterilized by methods known to person skilled in the art, such as filtration, and aseptically filled in sealed vials.

The compositions of the present invention can be administered parenterally by direct injection or with infusion.

When the stability of the clopidogrel concentrate was tested (clopidogrel concentrate was exposed to 40°C / 75% RH and 25°C / 60% RH for 2 months and 3 months period, it was observed that all the impurities were within the limits (Table 3).

Moreover on reconstituting such stable clopidogrel concentrate with aqueous based diluent, the resulting solution can provide advantages of aqueous based parenteral formulations and thus can improve patient compliance.

In an embodiment, the stable injectable pharmaceutical composition of clopidogrel or salt thereof comprising concentrate of clopidogrel or salts thereof admixed or reconstituted with an aqueous vehicle for preparation of infusion prior to administration, wherein said concentrate retains at least 80% of the potency of clopidogrel or salts thereof in the said concentrate after storage for three months at 40° C and 75% relative humidity.

Suitable "surfactants" which can be used for preparing injectable pharmaceutical composition of clopidogrel or salt thereof may include one or more of anionic, cationic, non-ionic or zwitterionic surfactants or mixtures thereof. These surfactants may comprise from about 0.01% to about 65% w/v of the composition.

In a preferred embodiment, the surfactant used in preparing injectable pharmaceutical composition of clopidogrel or salt thereof is one or more polyoxyethylene fatty alcohol ethers (Macrogol and Brij), polyoxyethylene sorbitan fatty acid esters (Polysorbates), polyoxyethylene fatty acid esters (Myrj), sorbitan esters (Span), glycerol monostearate, polyethylene glycols, polypropylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, aryl alkyl polyether alcohols, polyoxyethylene-polyoxypropylene copolymers (poloxomers), polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, and polyvinylpyrrolidone. Among polyoxyethylene fatty acid esters is included those having short alkyl chains. Preferred non-ionic surfactant is Solutol®. HS 15, polyethylene-660-hydroxystearate and the like.

In an embodiment, surfactant suitable for employing in the injectable pharmaceutical composition possesses HLB (hydrophilic-lipophilic Balance) value ranging from 6 to 20.

Suitable "aqueous solvents and co-solvents" may include one or more of water and its various grades suitable for parenteral administration such as water for injection, bacteriostatic water for injection, sterile, aqueous solutions of electrolytes and/or dextrose; alcohols such as ethanol, isopropanol; polyols such as propylene glycol, polyethylene glycol, glycerol; dimethyl sulfoxide (DMSO); dimethyl acetamide (DMAC); 3-dimethyl-2-imidazolidinone (DMI) and N-Methyl-2-Pyrrolidone (M-PYROL). The amount of aqueous solvent and co-solvent may range from about 0.01% w/v to about 95% w/v of the composition.

Suitable "buffers" may include one or more of borate buffers, tartarate buffers, lactate buffers, citrate buffers, phosphate buffers, citric acid/phosphate buffers, carbonate/carbonic acid buffers, succinate/succinic acid buffers, and tris(hydroxymethyl)aminomethane /hydrochloric acid buffers and the like. The amount of aqueous solvent and co-solvent may range from about 0.01% w/v to about 15% w/v of the composition.

The buffer system is useful over the desired dose range of the composition to provide ease of manufacture of the composition, to maintain pH stability during and after manufacture including terminal sterilization by filtration and thus to render the composition compatible with a range of infusion fluids.

The pH of the injectable pharmaceutical composition of clopidogrel or salts thereof in accordance with the present invention ranges from about 3.5 to about 7.5, preferably from about 4.0 to about 6.5.

The control of pH of the injectable composition is essential to maintain the aqueous solubility of the clopidogrel salts to a sufficient extent that the therapeutically desirable dose strengths can be manufactured and are physically stable, i.e. do not give evidence of precipitation. Maintenance of the necessary pH range can be controlled by the use of a suitable buffer system.

The pharmaceutically acceptable buffer may be selected from any of the buffers that are effective to maintain the pH in the range of about 3.0-7.0. More preferably, the buffer may be selected from citrate, acetate, phosphate and lactate buffers. Most preferably, the buffer is a citrate or acetate buffer, for example, citric acid plus sodium citrate in appropriate proportions which will maintain the pH at about 3.5-7.0.

Referring to the citrate buffer (citrate buffer system) by way of example, i.e. the buffer is essentially a mixture of a sodium citrate prepared by the neutralization of citric acid by sodium hydroxide plus residual citric acid. The ratio of citric acid to sodium citrate determines the pH of the buffer. Such a buffer system is well known to those skilled in the art and is described in neary all standard textbooks e.g., Physical Pharmacy by A. N. Martin, J. Swarbrick and A. Cammarata, Lee and Fabiger, 2nd edition, page 237 onwards.

Suitable "stabilizers" may include one or more of EDTA (ethylene diamine tetraacetic acid), para-hydroxybenzoic acid ester derivatives, alcohol, benzalkonium chloride, phenol derivatives, thiomersal, acetic anhydride, ascorbic acid, sorbic acid, boric acid, adipic acid, sodium carboxylate, lauryl sulfate, retinol, tocopherol or sodium ascorbate, sulfite compounds, amino acid such as L-cysteine, thiodipropionic acid, thiolactic acid, and monothioglycerol, sulfurous acid, sulfite, ascorbate, L-cysteine, and tocopherol. N-acetyl amino acid, tocopherol, sodium formaldehyde, or tertiary-butyl hydroquinone, sodium sulfite, sodium phosphate and the like.

Other parenterally acceptable pharmaceutical excipients that can also be used in the injectable pharmaceutical composition in accordance with the present invention include tonicity modifier, diluents, antioxidants, preservatives and the like.

Suitable "diluents" may include, but not limited to mannitol, glycine, lactose, sucrose, trehalose, dextran, hydroxyethyl starch, ficoll or gelatin and the like. The

amount of diluents may range from about 0.01% w/v to about 90% w/v of the composition.

Suitable "preservatives" may include, but not limited to benzyl alcohol, EDTA, combinations thereof, and any other similar preservative known to those of skill in the art.

Suitable "tonicity modifier" may include one or more physiologically tolerated salt, such as, for example, sodium chloride or potassium chloride, or a physiologically tolerated polyol, such as, for example, a sugar alcohol, in particular sorbitol or glycerol, in the concentration necessary for rendering physiologically acceptable isotonicity.

Further the present invention provides a method of reducing of atherothrombotic events like recent myocardial infarction and treating recent stroke or established peripheral arterial disease, acute coronary syndrome comprising administering to human patient in need thereof a stable injectable pharmaceutical composition comprising a concentrate of clopidogrel or pharmaceutically acceptable salts thereof.

The invention is further illustrated by the following examples which are provided to be exemplary of the invention and do not limit the scope of the invention. While the present invention has been described in terms of its specific embodiments, 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

a) Drug concentrate

Table 1

Sr. No.	Ingredients	% w/v
1	Clopidogrel or its salt (Clopidogrel besylate)	1.5 – 15.0
2	Ethanol	1.5 - 80.0
3	Polyethylene glycol hydroxyl stearate	1.5 – 30.0
4	Propylene Glycol	1.5 – 60.0

Procedure: Clopidogrel or its salt (Clopidogrel besylate) and Polyethylene glycol hydroxyl stearate were dissolved in ethanol and propylene glycol was added. The

solution was sterilized by aseptic filtration and aseptically filled using Nitrogen flushing.

b) Diluent

Table 2

Sr. No.	Ingredients	% w/v
1	Cremophor	1.0 – 65.0
2	Citric Acid	1.5 – 5.0
3	Tri Sodium Citrate	2.0 – 10.0
4	Water For Injection	QS

Procedure: Cremophor was mixed with small quantity of Water for Injection. Citric Acid and Tri Sodium Citrate were mixed with small quantity of Water for Injection. Both solutions were mixed and the volume is adjusted with remaining quantity of Water for Injection. The solution was sterilized by aseptic filtration and aseptically filled.

Example 2

The accelerated stability studies conducted at 40 °C /75 % RH and 50 °C /80 % RH of the formulation prepared in accordance with example 1a is given in Table 3.

Table 3

Related Substance (API Limit)	2 Months			3 Months		
	40°C / 75%RH	25°C / 60%RH	2° - 8°C	40°C / 75%RH	25°C / 60%RH	2° - 8°C
Impurity A	0.13	0.04	-	0.20	0.07	0.03
Unknown @ RRT 0.16	0.30	0.18	0.13	0.30	0.20	0.14
Total Impurity (Excluding Impurity C)	0.52	0.22	0.17	0.88	0.27	0.17
Impurity C	0.43	0.18	-	0.90	0.18	0.14

Example 3

a) Drug concentrate (Sterile API)

Table 4

Sr. No.	Ingredients	% w/v
1	Clopidogrel or its salt (Clopidogrel besylate)	1.5 – 15.0

Procedure: Sterile Clopidogrel or its salt (Clopidogrel besylate) was filled aseptically in a suitable vial.

b) Diluent

Table 5

Sr. No.	Ingredients	% w/v
1	Polyethylene glycol hydroxyl stearate	1.5 – 30.0
2	Ethanol	1.5 - 80.0
3	Propylene Glycol	1.5 – 60.0
4	Cremophore	1.0 – 65.0
5	Citric Acid	1.5 – 5.0
6	Tri sodium citrate	2.0 – 10.0
7	Water For Injection	Q. S.

Procedure: Polyethylene glycol hydroxyl stearate was dissolved in ethanol and propylene glycol. Cremophor was mixed with small quantity of Water for Injection. Citric Acid and Tri Sodium Citrate were mixed with small quantity of Water for Injection. These solutions were mixed and the volume is adjusted with remaining quantity of Water for Injection. The solution was sterilized by aseptic filtration and aseptically filled.

Example 4

a) Drug concentrate (Dry powder)

Table 6

Sr. No.	Ingredients	Quantity (mg)
1	Clopidogrel or its salt (Clopidogrel besylate)	1.5 – 15.0
2	Mannitol (Injectable	1.0 – 90.0

	grade)/lactose monohydrate	
3	Ethanol	Q. S.
4	Water	Q. S.

Procedure: Clopidogrel or its salt (Clopidogrel besylate) was dissolved in ethanol. Mannitol / Lactose monohydrate was dissolved in water. These solutions were mixed under stirring, filtered and spray dried under aseptic condition. The resulting power was filled into a suitable vial.

b) Diluent

Table 7

Sr. No.	Ingredients	Quantity (mg)
1	Polyethylene glycol hydroxyl stearate	1.5 – 30.0
2	Ethanol	1.5 - 80.0
3	Propylene Glycol	1.5 – 60.0
4	Cremophore	1.0 – 65.0
5	Citric Acid	1.5 – 5.0
6	Tri sodium citrate dihydrate	2.0 – 10.0
7	Water For Injection	Q. S.

Procedure: Polyethylene glycol hydroxyl stearate was dissolved in ethanol and propylene glycol. Cremophor was mixed with small quantity of Water for Injection. Citric Acid and Tri Sodium Citrate were mixed with small quantity of Water for Injection. These solutions were mixed and the volume is adjusted with remaining quantity of Water for Injection. The solution was sterilized by aseptic filtration and aseptically filled.

Example 5

a) Drug concentrate (Lyophilized)

Table 8

Sr. No.	Ingredients	Quantity (mg)
1	Clopidogrel or its salt (Clopidogrel besylate)	1.5 – 15.0
2	Mannitol/Lactose Monhydrate	1.0 – 90.0

3	Solubilizer	1.5 – 30.0
4	Ethanol	Q. S.
5	Water	Q. S.

Procedure: Clopidogrel or its salt (Clopidogrel besylate) was dissolved in ethanol in presence of solubilizer. Mannitol / Lactose monohydrate was dissolved in water. These solutions were mixed under stirring, filtered and lyophilized as per suitable temperature and cycle.

b) Diluent

Table 9

Sr. No.	Ingredients	% w/v
1	Polyethylene glycol hydroxyl stearate	1.5 – 30.0
2	Ethanol	1.5 - 80.0
3	Propylene Glycol	1.5 – 60.0
4	Cremophore	1.0 – 65.0
5	Citric Acid monohydrate	1.5 – 5.0
6	Tri sodium citrate dihydrate	2.0 – 10.0
7	Water For Injection	Q. S.

Procedure: Polyethylene glycol hydroxyl stearate was dissolved in ethanol and propylene glycol. Cremophor was mixed with small quantity of Water for Injection. Citric Acid and Tri Sodium Citrate were mixed with small quantity of Water for Injection. These solutions were mixed and the volume is adjusted with remaining quantity of Water for Injection. The solution was sterilized by aseptic filtration and aseptically filled.

We claim:

1. A stable injectable pharmaceutical composition of clopidogrel or salt thereof comprising concentrate of clopidogrel admixed or reconstituted with an aqueous vehicle for preparation of infusion prior to administration.

2. The stable injectable pharmaceutical composition of claim 1, wherein the clopidogrel concentrate comprises sterilized or lyophilized clopidogrel or salts thereof, optionally with one or more parenterally acceptable excipients.

3. The stable injectable pharmaceutical composition of claim 1, wherein the aqueous vehicle comprises one or more parenterally acceptable excipients.

4. The stable injectable pharmaceutical composition of claim 2 or 3, wherein the parenterally acceptable excipient comprises one or more surfactant, buffer, diluent, stabilizer, solubilizer, aqueous solvent and co-solvent.

5. The stable injectable pharmaceutical composition of claim 4, wherein the surfactant comprises one or more of anionic, cationic, non-ionic or zwitterionic surfactant.

6. The stable injectable pharmaceutical composition of claim 5, wherein the non-ionic surfactant is selected from one or more of polyoxyethylene fatty alcohol ethers, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, polypropylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, aryl alkyl polyether alcohols, polyoxyethylene-polyoxypropylene copolymers, polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, and polyvinylpyrrolidone.

7. The stable injectable pharmaceutical composition of claim 6, wherein the non-ionic surfactant is selected from polyethylene glycol hydroxyl stearate, polyoxyethylene castor oil derivative or mixture thereof.

8. The stable injectable pharmaceutical composition of claim 4, wherein the amount of surfactant ranges from about 1.5% w/v to about 30.0 % w/v of the composition.

9. The stable injectable pharmaceutical composition of claim 4, wherein the buffer is selected from one or more of borate buffers, tartarate buffers, lactate buffers, citrate buffers, phosphate buffers, citric acid/phosphate buffers, carbonate/carbonic acid buffers, succinate/succinic acid buffers, and tris(hydroxymethyl)aminomethane /hydrochloric acid buffers.

10. The stable injectable pharmaceutical composition of claim 4 or 9, wherein the buffer is citrate buffer.

11. The stable injectable pharmaceutical composition of claim 10, wherein the citrate buffer comprises citric acid and tri sodium citrate.

12. The stable injectable pharmaceutical composition of claim 4, wherein the amount of buffer ranges from about 1.5% w/v to about 15.0% w/v of the composition.

13. The stable injectable pharmaceutical composition of claim 4, wherein the diluent is selected from one or more of mannitol, glycine, lactose, sucrose, trehalose, dextran, hydroxyethyl starch, ficoll and gelatin.

14. The stable injectable pharmaceutical composition of claim 4 or 13, wherein the diluent is selected from lactose, mannitol or mixture thereof.

15. The stable injectable pharmaceutical composition of claim 4, wherein the amount of diluent ranges from about 1.0% w/v to about 90.0 % w/v of the composition.

16. The stable injectable pharmaceutical composition of claim 4, wherein the stabilizers is selected from one or more of EDTA (ethylene diamine tetraacetic acid), para-hydroxybenzoic acid ester derivatives, alcohol, benzalkonium chloride, phenol derivatives, thiomersal, acetic anhydride, ascorbic acid, sorbic acid, boric acid, adipic acid, sodium carboxylate, lauryl sulfate, retinol, tocopherol or sodium ascorbate, sulfite

compounds, amino acid such as L-cysteine, thiodipropionic acid, thiolactic acid, and monothioglycerol, sulfurous acid, sulfite, ascorbate, L-cysteine, and tocopherol. N-acetyl amino acid, tocopherol, sodium formaldehyde, or tertiary-butyl hydroquinone, sodium sulfite, sodium phosphate.

17. The stable injectable pharmaceutical composition of claim 4, wherein the aqueous solvent is selected from one or more of water for injection, bacteriostatic water for injection, sterile, aqueous solutions of electrolytes and/or dextrose; alcohols such as ethanol, isopropanol; polyols such as propylene glycol, polyethylene glycol, glycerol; dimethyl sulfoxide, dimethyl acetamide; 3-dimethyl-2-imidazolidinone; N-Methyl-2-Pyrrolidone.

18. The stable injectable pharmaceutical composition of claim 4, wherein the co-solvent is selected from one or more of alcohols such as ethanol, isopropanol; polyols such as propylene glycol, polyethylene glycol, glycerol.

19. The stable injectable pharmaceutical composition of claim 18, wherein the co-solvent is selected from ethanol, propylene glycol or mixture thereof.

20. The stable injectable pharmaceutical composition of claim 4, wherein the amount of co-solvent ranges from about 1.5% w/v to about 60.0% w/v of the composition.

21. The stable injectable pharmaceutical composition of claim 1, wherein the amount of clopidogrel or salt thereof in the clopidogrel concentrate ranges from 0.5% to 50% w/v, preferably from 1.5% w/v to 15% w/v of the composition.

22. The stable injectable pharmaceutical composition of claim 1, wherein the composition exhibits pH in the range of 3.5 to 7.0.

23. A process for the preparation of a stable injectable pharmaceutical composition of clopidogrel or salt thereof

(a) providing a concentrate of clopidogrel or salts thereof, optionally containing one or more parenterally acceptable excipients.

(b) providing an aqueous vehicle comprising one or more parenterally acceptable excipients.

(c) admixing or reconstituting the clopidogrel concentrate with aqueous vehicle prior to administration.

24. The process of claim 23, wherein the concentrate of clopidogrel is prepared by sterilizing or lyophilizing clopidogrel or salt thereof optionally with one or more parenterally acceptable excipients.

25. The process of claim 23, wherein the aqueous vehicle is prepared by mixing one or more aqueous solvent with surfactant, buffer, and optionally co-solvent.

26. The stable injectable pharmaceutical composition of claim 1, wherein concentrate of clopidogrel retains at least 80% of the potency of clopidogrel or salts thereof in the said pharmaceutical composition after storage for three months at 40° C and 75% relative humidity.

27. The stable injectable pharmaceutical composition of claim 1, wherein-

(a) a concentrate of clopidogrel comprising sterilized clopidogrel or salt thereof in amount ranging from about 1.5% w/v to about 15.0% w/v of the composition, and optionally comprising one or more parenterally acceptable excipient comprising one or more surfactants, aqueous solvents and co-solvents.

(b) an aqueous vehicle comprising one or more parenterally acceptable excipient selected from one or more of surfactant, buffer, aqueous solvent and co-solvent.

wherein said clopidogrel concentrate and aqueous vehicle are admixed or reconstituted together for preparation of infusion prior to administration.

28. The stable injectable pharmaceutical composition of claim 27, wherein-

(a) the concentrate of clopidogrel comprises-

(i) polyethylene glycol hydroxyl stearate in amount ranging from about 1.5% w/v to about 30.0 % w/v,

(ii) propylene glycol in amount ranging from amount ranging from

about 1.5% w/v to about 60.0% w/v; and

(b) the aqueous vehicle comprises-

(i) polyoxyethylene castor oil derivative ranging from about 1.0% w/v to about 65.0% w/v,

(ii) citric acid in amount ranging from about 1.5% w/v to about 5.0% w/v,

(iii) tri sodium citrate in amount ranging from about 2.0% w/v to about 10.0% w/v, and

(iv) water in quantity sufficient to make volume.

29. The stable injectable pharmaceutical composition of claim 27, wherein the aqueous vehicle comprises-

(i) polyoxyethylene glycol hydroxyl stearate in amount ranging from about 1.5% w/v to about 30.0% w/v,

(ii) Propylene glycol in amount ranging from about 1.5% w/v to about 60.0% w/v,

(iii) polyoxyethylene castor oil derivative ranging from about 1.0% w/v to about 65.0% w/v,

(iv) citric acid in amount ranging from about 1.5% w/v to about 5.0% w/v,

(v) tri sodium citrate in amount ranging from about 2.0% w/v to about 10.0% w/v, and

(vi) water in quantity sufficient to make final volume.

30. The stable injectable pharmaceutical composition of claim 27, wherein-

(a) the concentrate of clopidogrel comprises-

(i) mannitol in amount ranging from about 1.0% w/v to about 90.0 % w/v,

(ii) ethanol and water in amount sufficient to make volume,

(iii) optionally, a surfactant in amount ranging from about 1.5% w/v to about 30.0 % w/v of the composition.

31. A kit comprising a clopidogrel concentrate and aqueous vehicle wherein said clopidogrel concentrate and aqueous vehicle are admixed or reconstituted together for preparation of infusion prior to administration.

32. A kit presented in form of a double compartment syringe, one compartment comprising a clopidogrel concentrate and another comprising aqueous vehicle, wherein the syringe allows the content of both the compartments to admix or reconstitute together for preparation of infusion prior to administration.

33. A method of reducing atherothrombotic events like recent myocardial infarction and treating recent stroke or established peripheral arterial disease, acute coronary syndrome comprising administering to human patient a stable injectable pharmaceutical composition of clopidogrel or salt thereof comprising concentrate of clopidogrel and an aqueous vehicle, wherein said clopidogrel concentrate and aqueous vehicle are admixed or reconstituted together for preparation of infusion prior to administration to patient.