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(54) Title: STABLE PHARMACEUTICAL COMPOSITION OF HISTAMINE H₂-RECEPTOR ANTAGONIST

(57) Abstract: The present disclosure relates to a stable pharmaceutical composition comprising a Histamine H₂-receptor antagonist or a pharmaceutically acceptable salt thereof and a stabilizing amount of at least one alkalizer. The composition provides effective control of the level of nitrosamine drug substance-related impurities (NDSRIs) such as NDMA in the drug product during shelf life of the product.

STABLE PHARMACEUTICAL COMPOSITION OF HISTAMINE H2-RECEPTOR ANTAGONIST

FIELD OF THE INVENTION

[0001] The present invention relates to a stable pharmaceutical composition comprising a Histamine H2-receptor antagonist or a pharmaceutically acceptable salt thereof and a stabilizing amount of at least one alkalizer. The composition shows an improved stability with controlled levels of potentially carcinogenic nitrosamine drug substance-related impurities (NDSRIs).

BACKGROUND OF THE INVENTION

[0002] Histamine H2-receptor antagonist are a class of medications that block the action of histamine at the histamine H2 receptors of the parietal cells in the stomach. This decreases the production of stomach acid. H2 antagonists can be used in the treatment of dyspepsia, peptic ulcers and gastroesophageal reflux disease. Various H2 blockers are cimetidine, ranitidine, famotidine, nizatidine, roxatidine, lafutidine.

[0003] Among H2 blockers ranitidine was found to have a much better tolerability profile (i.e. fewer adverse drug reactions), longer-lasting action, and ten times the activity of cimetidine. Ranitidine is a competitive, reversible inhibitor of the action of histamine at the histamine H2 receptors found in gastric parietal cells. This results in decreased gastric acid secretion and gastric volume, and reduced hydrogen ion concentration. It is sold under the brand name Zantac® among others, is a medication used to decrease stomach acid production. It is commonly used in treatment of peptic ulcer disease, gastroesophageal reflux disease, and Zollinger–Ellison syndrome. It can be given by mouth, injection into a muscle, or injection into a vein.

[0004] The recent unexpected finding of nitrosamine impurities, which are probable human carcinogens, in drugs such as angiotensin II receptor blockers (ARBs), H2 blockers such as ranitidine, nizatidine, and biguanides such as metformin, has made clear the need for a risk assessment strategy for potential nitrosamines in any

pharmaceutical product at risk for their presence. FDA has been investigating the presence of nitrosamine impurities in certain drug products. Since 2018, several drug products including ARBs, ranitidine, nizatidine, and metformin have been found to contain unacceptable levels of nitrosamines.

[0005] In June 2018, FDA was informed of the presence of an impurity identified as N-nitrosodimethylamine (NDMA) in the ARB valsartan. Through investigation, the Agency determined that numerous lots of valsartan and a few other ARB drug products from different manufacturers contained unacceptable levels of nitrosamines. The drug product manufacturers voluntarily recalled the affected batches of these drug products, which led to a drug shortage in some of the affected products.

[0006] In September 2019, FDA learned that some common heartburn products (ranitidine, commonly known as Zantac, and nizatidine, commonly known as Axid®) contained unacceptable levels of NDMA. FDA recommended that manufacturers voluntarily recall ranitidine and nizatidine products with NDMA levels above what the Agency considers acceptable. Recently, preliminary findings from FDA stability testing raised concerns that NDMA levels in some ranitidine products stored at room temperature can increase with time to unacceptable levels. FDA's preliminary results using accelerated stability testing demonstrated that elevated levels of NDMA were measured in all products after 2 weeks. FDA's testing suggests that NDMA levels increase with storage time. On April 1, 2020, FDA requested that all ranitidine products be withdrawn from the U.S. market.

[0007] N-Nitrosodimethylamine (NDMA) is an organic compound with the formula $(\text{CH}_3)_2\text{NNO}$ which is formed by the combination of dimethyl amine with nitrates. Whilst NDMA is a known common environmental contaminant, nitrosamine such as NDMA are known to be carcinogenic. Chronic ingestion of NDMA is postulated to cause an increase in liver and other cancers.

[0008] Ranitidine can generate NDMA, classified by the IARC as "probably carcinogenic to humans" (Class 2A carcinogen), as a decomposition product. Also, in August 2019, preliminary results in a random selection and testing by official medicinal control laboratories (OMCLs) of ranitidine API batches and finished products available in the EU showed levels of NDMA in a range that raised concerns

according to the principles of ICH-M7. All ranitidine products, including the oral liquid/syrup, was banned by USFDA.

[0009] Therefore, there is a strong need for development of formulations with controlled or minimal content of Nitrosamine Drug Substance Related Impurities (NDSRIs). Various references although have talked about methods to optimize the level of nitrosamine impurities by using approaches. However, there are limited disclosures available that are actually enabled to control the nitrosamine impurities in drug product during storage period.

[0010] The inventors in the present application have evaluated various formulation strategies to mitigate the risk associated by nitrosamine compounds in drug product, and surprisingly arrived at a stable formulation.

SUMMARY OF THE INVENTION

[0011] The present disclosure relates to a stable composition comprising Histamine H₂-receptor antagonist or a pharmaceutically acceptable salt thereof, a stabilizing amount of at least one alkalizer and one or more pharmaceutically acceptable excipient. The composition provides effective control of the level of nitrosamine drug substance-related impurities (NDSRIs) in the drug product during shelf life of the product.

[0012] In one aspect, the present invention relates to stable pharmaceutical composition of ranitidine hydrochloride comprising an alkali metal stabilizer and one or more pharmaceutically acceptable excipients.

[0013] In one aspect, the composition according to the present invention comprises of Histamine H₂-receptor antagonist with an alkali stabilizer and has controlled level of impurities including the nitrosamine drug substance-related impurities (NDSRIs). In some aspects, the nitrosamine drug substance-related impurity is *N*-nitrosodimethylamine (NDMA).

[0014] In one aspect the stable pharmaceutical composition according to the present invention comprises a Histamine H₂-receptor antagonist, a stabilizing amount of at least one alkalizer and one or more pharmaceutically acceptable excipient, wherein the alkalizer effectively control the formation of nitrosamine drug substance-related impurities (NDSRIs) in the composition, to a level below about 11

ppm, upon storage or acid exposure. Preferably, the Histamine H₂-receptor antagonist is ranitidine hydrochloride

[0015] In one aspect, the stable pharmaceutical composition according to the present invention comprises the ratio of a Histamine H₂-receptor antagonist and an alkalizer in the composition in the range of 100:0.1 to 100:5.

[0016] In one aspect, the stable pharmaceutical composition according to the present invention the nitrosamine drug substance-related impurity is N-nitrosodimethylamine (NDMA) impurity.

[0017] In one aspect, the stable pharmaceutical composition according to the present invention the alkalizer is selected from alkali metal oxide, pH modifier, nitrite quencher. Preferably, the alkalizer is alkali metal oxide. More preferably, the alkali metal oxide is magnesium oxide

[0018] In one aspect the stable pharmaceutical composition according to the present invention the level of nitrosamine drug substance related impurities (NDSRIs) level is below about 11 ppm upon storage under controlled room temperature condition of 25°C/60% RH for at least 12 months.

[0019] In one aspect the stable pharmaceutical composition according to the present invention comprises ranitidine hydrochloride and magnesium oxide, wherein the magnesium oxide is present in the composition in an amount present in an amount ranging from about 0.1% w/w to about 10% w/w of the composition, wherein the composition is characterized by a level of N- Nitrosodimethylamine (NDMA) impurity below 11 ppm, upon storage at 25°C/60% RH for a period of at least 12 months. More preferably, the amount of magnesium oxide ranges from about 0.1% w/w to about 2% w/w of the composition.

[0020] In one aspect, the stable pharmaceutical composition according to the present invention is characterized by a level of nitrosamine drug substance related impurity below 3 ppm, upon storage at 25°C/60% RH for a period of 12 months.

[0021] In one aspect according to the present invention, the composition is a stable oral dosage form of ranitidine Hydrochloride with controlled levels of N-nitrosodimethylamine (NDMA) impurity.

[0022] In another aspect, the present invention also provides method for controlling nitrosamine drug substance-related impurities (NDSRIs) in amine containing drug products.

[0023] In yet another aspect, the present invention provides a method for preparing a stable pharmaceutical composition comprising a Histamine H₂-receptor antagonist or a pharmaceutically acceptable salt and at least one alkali metal stabilizer, wherein the alkali metal stabilizer is placed in the composition in a way to effectively control the formation of nitrosamine drug substance-related impurities (NDSRIs) in the composition.

DESCRIPTION OF THE INVENTION

[0024] As used herein, the word “a” or “plurality” before a noun represents one or more of the particular nouns.

[0025] For the terms “for example” and “such as,” and grammatical equivalences thereof, the phrase “and without limitation” is understood to follow unless explicitly stated otherwise. As used herein, the term “about” is meant to account for variations due to experimental error. All measurements reported herein are understood to be modified by the term “about,” whether or not the term is explicitly used, unless explicitly stated otherwise. The term “about” as used herein, refers to any value which lies within the range defined by a variation of up to $\pm 10\%$ of the value.

[0026] The term “coating” as used herein the description, can be used interchangeably with the term “coat” or “layer” around the core.

[0027] The term “Histamine H₂-receptor antagonist” as used herein the description, can be used interchangeably to “HR₂as” or “H₂ blockers”. The most commonly used Histamine H₂-receptor antagonist that can be used according to the present invention including but not limited to cimetidine, ranitidine, famotidine, nizatidine, roxatidine, lafutidine. Alternatively the disclosure according to present invention can also be used with other amine drugs such as sartans, antidiabetic drugs, antihistamines, and antibiotics; for e.g. the drugs include Amoxicillin, Bendroflumethiazide, Betahistine, Bisoprolol, Bromazepam, Carvedilol, Cetirizine, Desloratadine, Diclofenac, Doxylamine, Duloxetine, Enalapril, Ergometrine,

Felodipine, Flecainide, Fluoxetine, Hydrochlorothiazide (HCT), Levofloxacin, Metoprolol, Metformin, Mirabegron, Mirtazapine, Moxifloxacin, Nebivolol, Opipramol, Pergolide, Propranolol, Quetiapine, Ramipril, Roxithromycin, Sertraline, Sotalol, Sumatriptan, Sitagliptin, Valsartan, Varenicline, Metformin, ranitidine, Gliclazide, Sitagliptin, Prucalopride, Clarithromycin, Oxcarbazepine, Sunitinib, Rivaroxaban, Citalopram, Escitalopram, Tamsulosin, Diltiazem, Amlodipine or pharmaceutically acceptable salt thereof, and combination thereof.

[0028] The term “shelf life” as used herein, means the shelf life of the drug product, in its form as a product sold for use by consumers, during which period the product is suitable for use by a patient. The shelf life of the drug product can be greater than 3, 6, 12, 18, or preferably 24 months. The shelf life may be achieved when the product is stored at room temperature at about 25° C, protected from light and moisture.

[0029] The term “dosage form” or “composition” as used herein the description, can be used interchangeably with the term ‘pharmaceutical composition’ or ‘pharmaceutical formulation’ or ‘pharmaceutical preparation’ or ‘drug product’, wherein the drug product is defined as a composition of H2 blocker drug and one or more pharmaceutical excipients.

[0030] The term “alkalizer” as used in the description, represents the chemical entity responsible for increasing the pH of the composition, and comprises alkali metal stabilizers such as alkali metal oxides, alkali metal salts; pH modifiers; and Nitrite quenchers.

[0031] The present invention provides a stable pharmaceutical composition of an H2 blocker or a pharmaceutically acceptable salt thereof, and at least one alkali metal stabilizer in the composition, wherein the alkali metal stabilizer effectively controls the level of the nitrosamine drug substance-related impurities (NDSRIs) in the composition. In some aspects the nitrosamine drug substance-related impurities (NDSRIs) in the composition is *N*-nitrosodimethylamine (NDMA) impurity.

[0032] In some embodiment according to the present invention, the pharmaceutical composition is a stable composition comprising an H2 blocker or a pharmaceutically acceptable salt thereof, with stabilizing amount of one or more alkali metal stabilizer

in an amount effective for controlling the level of nitrosamine related impurities in the drug product during shelf life of the product.

[0033] In another embodiment according to the present invention, the alkali metal stabilizer is an alkali metal oxide present in the composition in such a way that it effectively controls the level of nitrosamine drug substance-related impurities (NDSRIs) in the drug product.

[0034] In one aspect of the above embodiments, the alkali metal oxide is present in the core of the composition for effective control of the level of nitrosamine drug substance-related impurity in the drug product. In another aspect of the above embodiment, the alkali metal oxide is present in the composition within a coating for effective control of the level of nitrosamine drug substance-related impurity in the drug product.

[0035] The nitrosamine drug substance-related impurities (NDSRIs) in the composition may be formed due to nitrosating reaction between amines (primary, secondary, tertiary, or quaternary amines) of drug and/or excipients present in the drug product, and the applicant surprisingly found that the alkali metal stabilizer in claimed concentration ranges and arrangement play crucial role in controlling nitrosamine drug substance-related impurities (NDSRIs) as well as other impurities simultaneously in the composition below acceptable levels.

[0036] In some embodiment according to present invention, the composition comprises of an amine containing drug and stabilizing amount of at least one alkalizer. In one aspect according to above embodiment, the alkalizer characteristically controls or prevents formation of nitrosamine drug substance-related impurity in the drug product upon storage or acid exposure.

[0037] The term “stable” as used herein, refers to a chemical stability of the composition which means that the level of nitrosamine drug substance related impurity (NDSRIs) in the composition remains below about 11 ppm, preferably below about 10 ppm, below about 9 ppm, below about 8 ppm, below about 7 ppm, below about 6 ppm, below about 5 ppm, below about 4 ppm, below about 3 ppm, below about 2 ppm, or below about 1 ppm, upon storage under the temperature and humidity conditions of 40°C/75% RH for at least 3 months and at controlled room

temperature condition of 25°C/60% RH for at least 12 months, 18 months or 24 months.

[0038] The term “stable” as used herein, also refers to physical stability which means that the composition retain its structural integrity and does not rupture in a significant way after exposure to storage conditions which means the composition is stable when stored under the temperature and humidity conditions of 40°C./75% RH and 30°C./75% RH for at least 3 months or at controlled room temperature condition of 25°C/60% RH for at least 12 months, 18 months or 24 months

[0039] According to another embodiment, the disclosed composition comprises of an H2-blocker drug or a pharmaceutically acceptable salt thereof, with one or more alkalizer in an amount effective for controlling the level of nitrosamine drug substance-related impurities (NDSRIs) in the drug product, the drug product is coated with a suitable coating. In one aspect, the coating is a film coating. In some aspect, the coating is an aqueous film coating. In one related aspect, the coating is a non-aqueous film coating.

[0040] In some embodiment according to the present invention, the disclosed stable composition comprises amine drug or a pharmaceutically acceptable salt thereof, with one or more alkalizer in an amount effective for controlling the level of nitrosamine drug substance-related impurities (NDSRIs) in the drug product and the drug product is coated with an aqueous film coating.

[0041] In one aspect of the above embodiment, the amine drug is ranitidine or a pharmaceutical acceptable salt thereof.

[0042] In another embodiment according to the present invention, the disclosed stable composition comprises amine drug or a pharmaceutically acceptable salt thereof, with one or more alkalizer in an amount effective for controlling the level of nitrosamine drug substance-related impurities (NDSRIs) in the drug product and the drug product is coated with a non-aqueous film coating.

[0043] In one aspect of the above embodiment, the amine drug is ranitidine or a pharmaceutical acceptable salt thereof.

[0044] In another embodiment according to present invention, the disclosed stable dosage form comprises ranitidine or a pharmaceutically acceptable salt thereof with one or more alkalizer for controlling the level of nitrosamine drug substance related

impurities (NDSRIs) to a level below about 11 ppm. In one aspect the level of nitrosamine drug substance related impurity (NDSRIs) in the composition remains below about 11 ppm, preferably below about 10 ppm, below about 9 ppm, below about 8 ppm, below about 7 ppm, below about 6 ppm, below about 5 ppm, below about 4 ppm, below about 3 ppm, below about 2 ppm or below about 1 ppm upon storage under the temperature and humidity conditions of 40°C./75% RH or 30°C./75% RH for at least 3 months and at controlled room temperature condition of 25°C/60% RH for at least 12 months, 18 months or 24 months. In one aspect of the above embodiment the nitrosamine drug substance related impurities (NDSRIs) is N-Nitrosodimethylamine (NDMA).

[0045] In one aspect, the level of N- nitrosodimethylamine (NDMA) is below about 11 ppm, preferably below 5 ppm, more preferably below 3 ppm for shelf life period.

[0046] The term “N- nitrosodimethylamine (NDMA)” as used herein the specification, refers to the nitrosamine drug substance related impurities (NDSRIs) associated with ranitidine or its pharmaceutical acceptable salts. Such impurities may be present in active pharmaceutical ingredients or can be formed in the drug product up on storage.

[0047] In yet another embodiment according to present invention the disclosed stable dosage form comprises an H2 blocker drug or a pharmaceutically acceptable salt thereof and at least one alkalizer. In one aspect, the alkalizer is selected from alkali metal oxide, pH modifier, nitrite quencher. In one aspect, the alkali metal oxide is magnesium oxide. In another aspect, the alkalizer is sodium metabisulfite. In yet another aspect the pH modifier is selected from meglumine.

[0048] In one embodiment according to present invention, the disclosed stable dosage form comprises an H2 blocker drug or a pharmaceutically acceptable salt thereof and a combination of two or more alkalizer, in an amount and ratio effective for controlling the Nitrosamine drug substance related impurities (NDSRIs).

[0049] In an aspect of the above embodiment, the H2 blocker drug is ranitidine or a pharmaceutical acceptable salt thereof and the alkalizer is a combination of alkali metal oxide and pH modifier. In one aspect, the composition further comprises alkalizer as alkali metal oxide and an additional antioxidant component. In another aspect, the composition comprises alkalizer as a pH modifier and an additional

antioxidant component. In yet another aspect the alkalizer is a combination of alkali metal oxide and pH modifier, with an additional antioxidant component.

[0050] In some embodiment according to present invention, the disclosed stable dosage form comprises a ranitidine or a pharmaceutically acceptable salt thereof and one or more alkalizer, in an amount and ratio effective for controlling the nitrosamine drug substance related impurities (NDSRIs).

[0051] In an aspect, the composition comprises ranitidine hydrochloride and magnesium oxide, wherein the magnesium oxide is present in the composition in an amount effective for controlling the nitrosamine drug substance related impurities (NDSRIs) of ranitidine.

[0052] In some aspect the nitrosamine drug substance related impurities (NDSRIs) of ranitidine is N- Nitrosodimethylamine (NDMA).

[0053] In some aspect, the alkalizer is magnesium oxide and is present in an amount ranging from about 0.1% w/w to about 10% w/w, preferably about 0.1% w/w to about 2% w/w.

[0054] Some exemplary embodiments:

[0055] In one embodiment, the present invention provides a stable pharmaceutical composition comprising of a Histamine H₂-receptor antagonist drug or a pharmaceutically acceptable salt thereof and an alkalizer, wherein the composition is characterized by a level of nitrosamine drug substance related impurity below 11 ppm, preferably below 5 ppm, more preferably below 3 ppm.

[0056] In one related aspect of the above embodiment, the alkalizer is selected from an alkali metal stabilizer such as alkali metal oxides, alkali metal salts, pH modifiers and nitrite quencher, or mixture thereof.

[0057] In another related aspect of the above embodiment, the alkalizer is an alkali metal stabilizer selected from magnesium oxide, sodium oxide and potassium oxide or mixture thereof. In one aspect, the alkali metal stabilizer is magnesium oxide.

[0058] In yet another related aspect in the pharmaceutical composition the alkalizer can be selected from sodium sulfites, sodium metabisulfite, sodium bisulfite, or combination thereof.

- [0059] In one aspect, the alkalizer can be used in combination with an antioxidant selected from ascorbic acid, tocopherol, sodium ascorbate, butylated hydroxy anisole, butylated hydroxyl toluene, and propyl gallate or mixture thereof.
- [0060] In some related aspects of the above embodiment in the pharmaceutical composition, the alkalizer is a nitrite quencher selected from ascorbic acid or salt thereof. In one aspect, the nitrite quencher is sodium ascorbate.
- [0061] In a further related aspect of the above embodiment in the pharmaceutical composition, the alkalizer is a pH modifier selected from meglumine or salt thereof.
- [0062] In some aspects of the above embodiment, the alkalizer is present in the composition in a concentration range of about 0.1% w/w to about 10% w/w of the composition, preferably about 0.1% w/w to about 5% w/w, more preferably about 0.1 to about 3% w/w of the composition. In one aspect, the alkalizer is alkali metal oxide. In one preferred aspect, the alkali metal oxide is magnesium oxide.
- [0063] In some aspects of the above embodiments, in the pharmaceutical composition the Histamine H2-receptor antagonist drug is selected from cimetidine, ranitidine, famotidine, nizatidine, roxatidine, lafutidine or a pharmaceutically acceptable salt thereof. In one aspect, the Histamine H2-receptor antagonist drug is ranitidine or a pharmaceutically acceptable salt thereof. In another aspect, the Histamine H2-receptor antagonist drug is Nizatidine or a pharmaceutically acceptable salt thereof.
- [0064] In some aspects of the above embodiment in the pharmaceutical composition, the nitrosamine drug substance related impurity is N-nitrosodimethylamine (NDMA) impurity.
- [0065] In another embodiment the present invention provides a stable pharmaceutical composition of ranitidine comprising ranitidine or a pharmaceutically acceptable salt thereof, at least one alkali metal stabilizer, and one or more pharmaceutically acceptable excipient, wherein the composition is characterized by nitrosamine drug substance-related impurities (NDSRIs) in the composition below 11 ppm, preferably below 5 ppm, more preferably below 3 ppm upon storage at 25°C./60% RH for a period of 24 months.
- [0066] In yet another embodiment the present invention provides a stable pharmaceutical composition comprising of ranitidine hydrochloride and magnesium

oxide with one or more pharmaceutically acceptable excipients, wherein the composition is characterized by nitrosamine drug substance related impurity as N-Nitrosodimethylamine (NDMA) below 11 ppm, preferably below 5 ppm, more preferably below 3 ppm upon storage at 25°C/60% RH for a period of 24 months.

[0067] In some aspects of the above embodiment, the pharmaceutical composition is further coated with a film coating. In one aspect, the film coating is an aqueous film coating. In another aspect, the film coating is a non-aqueous film coating.

[0068] In some embodiments, the pharmaceutical composition according to present invention comprises Histamine H2-receptor antagonist or a pharmaceutically acceptable salt thereof and an alkalizer, wherein a ratio of a Histamine H2-receptor antagonist drug or a pharmaceutically acceptable salt thereof and an alkalizer in the composition is 100:0.1 to 100:10, preferably 100:0.1 to 100:5. In one aspect according to the embodiment the presence of Histamine H2-receptor antagonist or a pharmaceutically acceptable salt thereof and an alkalizer in a ratio of 100:0.1 to 100:10 is effective for controlling the level of N-Nitrosodimethylamine (NDMA) impurity below 11 ppm, preferably below 5 ppm, more preferably below 3 ppm upon storage at 25°C/60% RH for a period of 24 months.

[0069] In one embodiment the present invention provides a process for preparing a stable pharmaceutical composition of Histamine H2-receptor antagonist comprising a Histamine H2-receptor antagonist or a pharmaceutically acceptable salt and at least one alkali metal stabilizer, wherein the alkali metal stabilizer is placed in the composition for effective control of the formation of nitrosamine drug substance-related impurities (NDSRIs) in the composition below 11 ppm, preferably below 5 ppm, more preferably below 3 ppm upon storage at 25°C./60% RH for a period of 24 months.

[0070] In some aspect according to above embodiment the process comprises of:

- a) blending Histamine H2-receptor antagonist and alkali metal stabilizer and sifting with one or more pharmaceutically acceptable excipient to form the core blend;
- b) lubricating the core blended, followed by compressing into tablets;
- c) coating the tablet and packing.

- [0071] In one related aspect of the above embodiment in the process of preparation of said composition, the Histamine H₂-receptor antagonist and alkali metal stabilizer are mixed prior to co-sifting with other excipients.
- [0072] In one related aspect of the above embodiment, the process according to present invention is carried out under sodium light with low relative humidity condition.
- [0073] In some embodiments, the present invention provides a method for controlling N-nitrosodimethylamine in a pharmaceutical composition of an amine drug, wherein the method comprises mixing an amine drug with an alkali metal oxide during preparation of the pharmaceutical composition followed by sifting the mixture with pharmaceutical acceptable excipient. In one related aspect of the embodiment the method characteristically controls the level of the N-Nitrosodimethylamine below 11 ppm, preferably below 5 ppm, more preferably below 3 ppm upon storage at 25°C/60% RH for a period of 24 months.
- [0074] In some embodiment according to the present invention, the stable dosage form comprising ranitidine or a pharmaceutically acceptable salt thereof with at least one or more alkalizer, wherein alkalizer is selected from magnesium oxide, meglumine, aluminum oxide, ammonium hydroxide, magaldrate, an alkali metal salt or alkaline earth metal salt, such as sodium bicarbonate, calcium carbonate or sodium citrate, an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide, or an alkaline earth metal hydroxide such as calcium hydroxide or magnesium hydroxide. In some aspects of the embodiment, the preferred alkalizer according to the present invention is magnesium oxide. In some aspect of the above embodiment the dosage form is characterized by controlled level of the N-Nitrosodimethylamine below 11 ppm, preferably below 5, more preferably below 3 ppm upon storage at 25°C/60% RH for a period of 24 months.
- [0075] The dosage form according to present invention may be present in the form of solid oral dosage form such as tablet, pellet, granule, capsules.
- [0076] The dosage form according to present invention comprises one or more pharmaceutically acceptable excipients selected from one or more of fillers, disintegrants, lubricants, glidants, anti-adherents, coating agents, and mixtures thereof.

- [0077] Suitable diluents are selected from the group consisting of lactose, microcrystalline cellulose, starch, pregelatinized starch, calcium sulphate, calcium carbonate, powdered cellulose, mannitol, sorbitol, xylitol, lactitol, magnesium carbonate, dicalcium phosphate, tricalcium phosphate, calcium sulphate, and mixtures thereof.
- [0078] Suitable binders are selected from the group consisting of cellulose derivatives (for example methylcellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose (HPMC / Hypromellose), ethylcellulose, hydroxyl ethyl cellulose, L-hydroxy propyl cellulose); polyvinylpyrrolidone (for example povidone, copovidone); starch (for example corn starch, pre-gelatinized starch and hydroxypropyl starch), polymethacrylates (for example Eudragit RS, RL), and mixtures thereof.
- [0079] Suitable disintegrants are selected from the group consisting of low substituted hydroxypropyl cellulose, crospovidone, croscarmellose sodium, starch derivatives, and mixtures thereof.
- [0080] Suitable lubricants are selected from the group consisting of magnesium stearate, calcium stearate, zinc stearate; stearic acid, hydrogenated vegetable oil, hydrogenated castor oil, glyceryl palmitostearate, glyceryl behenate, polyethylene glycols, corn starch, sodium stearyl fumarate, sodium benzoate, mineral oil, talc, and mixtures thereof.
- [0081] Suitable glidants or antiadherents are selected from the group consisting of talc, colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, tribasic calcium phosphate, and mixtures thereof.
- [0082] Non-limiting examples of suitable coating gents selected from the group comprising of aqueous and non-aqueous coating agents selected from Hypromellose, polyvinyl acetate, cellulose acetate, ethyl cellulose or combination thereof.
- [0083] Additional excipients present in the coating include one or more of film forming polymers, plasticizers, anti-adherents, opacifiers, colorants, pigments, antifoaming agents, and polishing agents.
- [0084] Suitable film-forming polymers are selected from the group consisting of hydroxypropylmethyl cellulose, ethyl cellulose, methyl cellulose, hydroxyethyl

cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, cellulose acetate, hydroxypropyl methyl cellulose phthalate, cellulose acetate trimellitate, and methacrylic acid copolymers, e.g., Eudragit®, polyvinylpyrrolidone, polyvinylalcohol, polyethylene glycol, and mixtures thereof. Other suitable film-forming polymers which are known in the art may also be used. Many suitable film coating products which are commercially available, e.g., Opadry®, Colorezy and Opaglos® may be used.

[0085] Suitable plasticizers are selected from the group consisting of propylene glycol, triethyl citrate, tributyl citrate, dibutyl sebacate, acetyl tributyl citrate, glyceryl monostearate, triacetin, polyethylene glycol, diethyl phthalate, acetylated monoglycerides, diacetylated monoglycerides, cetyl alcohol, and mixtures thereof.

[0086] Suitable opacifiers are selected from the group consisting of titanium dioxide, manganese dioxide, iron oxide, silicon dioxide, and mixtures thereof.

[0087] Suitable coloring agents are selected from FDA approved colorants such as iron oxide, lake of tartrazine, allura red, titanium dioxide, and mixtures thereof.

[0088] Suitable polishing agents are selected from the group consisting of polyethylene glycols of various molecular weights or mixtures thereof, talc, surfactants (glycerol monostearate and poloxamers), fatty alcohols (stearyl alcohol, cetyl alcohol, lauryl alcohol and myristyl alcohol), waxes (carnauba wax, candelilla wax and white wax), and mixtures thereof.

[0089] Various solvents that may be employed during the preparation of the dosage form of the present invention are selected from the group consisting of water, methyl alcohol, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, acetone, acetonitrile, chloroform, methylene chloride, water, and mixtures thereof.

[0090] The coating may be carried out by using any conventional coating techniques known in the art, such as spray coating in a conventional coating pan or fluidized bed processor, or dip coating.

[0091] The present invention is illustrated below by reference to the following examples. However, one skilled in the art will appreciate that the specific methods and results discussed are merely illustrative of the invention, and not to be construed as limiting the invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

[0092] **EXAMPLES**

[0093] Examples 1 and 2:

Category	Ex-1 (%w/w) (Non – Aq. Coating)	Ex-2 (%w/w) (Aq. Coating)
Core Tablet		
H2 Blocker / Amine Drug	35 – 75 %	
Diluent	20 – 90 %	
Alkalizer	0.1 – 10 %	
Glidant	0.1 – 1 %	
Disintegrant	0.5 – 5 %	
Lubricant	0.1 – 5 %	
Film Coating		
Non-Aqueous Coating material	2.5 – 8.0 %	-
Aqueous Coating material	-	2.5 – 8.0 %
Purified water	-	q. s.
Solvent	q. s.	-

[0094] Manufacturing Process:

- Raw material including excipient and active pharmaceutical ingredient were weighed and dispensed for manufacturing the tablet;
- Sifting drug, diluent, disintegrant, alkalizer, glidant, through suitable sieve;
- Blending the sifted material followed by adding lubricant and lubricating to formed blend;
- Compression of the lubricated blend, followed by coating the compressed tablet as per coating requirement.
- During manufacturing relative humidity was kept below about 40% under sodium light.

[0095] Example 3: Formulation with aqueous and non-aqueous coating using different alkalizer:

Ingredients (mg/tablet)	Ay	B	C	D	E	F	G	H	I
Ranitidine Hydrochloride*	341.8	341.8	341.8	341.8	341.8	341.8	341.8	170.9	170.9
Microcrystalline Cellulose	222.5	222.5	222.5	222.5	226.0	219.9	164	113.0	111.2
Sodium Metabisulphite	3.5	-	-	-	-	6.2	62	-	-
Meglumine	-	3.5	-	-	-	-	-	-	-
Sodium Ascorbate	-	-	-	3.5	-	-	-	-	-

Magnesium Oxide	-	-	3.5	-	-	-	-	-	1.7
Colloidal Anhydrous silica	2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0
Croscarmellose Sodium	11.8	11.8	11.8	11.8	11.8	11.8	11.8	5.9	5.9
Talc	4.7	4.7	4.7	4.7	4.7	4.7	4.7	2.3	2.3
Magnesium Stearate	3.6	3.6	3.6	3.6	3.6	3.6	3.6	1.8	1.8
Core Tablet weight	590.0	590.0	590.0	590.0	590.0	590.0	590.0	295.0	295.0
Film Coating									
Opadry white	26.5	26.5	26.5	26.5	-	26.5	26.5	-	13.2
Colorezy white	-	-	-	-	26.5	-	-	13.2	-
Purified water	-	-	-	-	q. s.	-	-	q. s.	-
Isopropyl alcohol	q. s.	q. s.	q. s.	q. s.	-	q. s.	q. s.	-	q. s.
Dichloromethane	q. s.	q. s.	q. s.	q. s.	-	q. s.	q. s.	-	q. s.
Coated Tablet weight	616.5	616.5	616.5	616.5	616.5	616.5	616.5	308.2	308.2

* Ranitidine Hydrochloride is taken in a weight equivalent to 300 mg of ranitidine base for example A to G and 150 mg of ranitidine base for example H and I respectively.

[0096] Manufacturing process:

1. All the ingredients were weighed.
2. LOD of Microcrystalline Cellulose was checked; (if LOD is not complying to a limit of NMT 3.0 % w/w then dry the Microcrystalline Cellulose in Tray Dryer or Fluidized bed dryer, to get the desired LOD)
3. Ranitidine Hydrochloride, Microcrystalline Cellulose (RQ 102S) (Dried from step-2), respective alkalizer, Colloidal anhydrous silica and Croscarmellose sodium through were sifted through suitable sieve.
4. The step-3 ingredients were blended in blender for 30 minutes at suitable speed.
5. Magnesium Stearate and Talc were sifted through suitable sieve.
6. Step-4 material were lubricated with the material of step-5 in a blender for suitable time at suitable speed.
7. The lubricated blend was unloaded in double polyethylene lined HDPE container.
8. Then the lubricated blend was compressed using approved tooling for both the strengths.
9. Then the core tablets were stored in double polyethylene lined HDPE container.

10. A 6% w/w dispersion of Opadry white OY-S-58910 prepared in a mixture of Isopropyl Alcohol and Methylene Chloride (60:40) under stirring to form uniform dispersion. (For aqueous coating separate material were used)
11. Then the core tablets of step 10 were coated with dispersion of step 10 respectively to achieve a target weight buildup of $4.5 \pm 0.5\%$ w/w.
12. Followed by packing in suitable packaging.

[0097] **Example 4:** Stability data of Sample F & G with different percentage of Sodium metabisulfite

Sample Name		F (1% SMBS)			G (10% SMBS)	
Stage		Initial	2M ACC	3M ACC	Initial	2M ACC
Pack		Alu strip	Alu strip	Alu strip	Alu strip	Alu strip
Impurity*	Limits	BLQ	0.845	-	0.02	1.328
NDMA	11.2 PPM	BLQ	0.845	-	0.02	1.328
Any one impurity	NMT 0.5	< 0.5% w/w	-	ND	< 0.5% w/w	> 0.5% w/w (1.544)
3 other impurities	NMT 0.3	< 0.3% w/w	-	2 (0.126)	< 0.3% w/w	> 0.3% w/w
All other impurity	NMT 0.1	< 0.1% w/w	-	Below 0.1 % w/w	< 0.1% w/w	> 0.1% w/w (1.544)

* All impurity profile specification is in line with Indian Pharmacopoeia drug product monograph, except for NDMA.

[0098] **Observation:**

- NDMA results was found to be controlled in both the concentration of SMBS i.e. 1% and 10%.
- Significant increase in related substance (impurity) was observed in 10%SMBS as compared to 1%SMBS.

[0099] **Example 5:** Stability data of Sample A-D and H-H[#] with different percentage of Alkalizer:

Stage	Pack.	NDMA (µg/g)					
		H	H [#]	A	B	D	C
Initial		0.329	0.14	BLQ	ND	ND	ND
1M	HDPE+ 1g 2 in 1	-	0.28	0.307	0.101	0.112	0.106

ACC			(Alu strip)				
2M ACC	Alu strip	-	3.123 (2.5 M)	0.845	0.504	0.295	0.239
	HDPE+ 1g 2 in 1	-	-	0.404	0.155	0.155	0.145
3M ACC	Alu strip	-	-	68.7	55.515	0.488	0.367
	HDPE+ 1g 2 in 1	-	-	0.650	0.253	0.236	0.232
2M LT	Alu strip	8.127 (6 M)	0.404 (5 M)	0.119	0.060	0.102	0.058
	HDPE+ 1g 2 in 1	-	-	0.131	0.057	0.060	0.054
3M LT	Alu strip	-	-	0.196	0.105	0.092	0.074
	HDPE+ 1g 2 in 1	-	-	0.145	0.064	0.061	0.059
9M LT	Alu strip	-	-	-	-	-	0.451
2M CRT	Alu strip	1.009 (6 M)	-	0.085	0.038	0.052	0.038
	HDPE+ 1g 2 in 1		-	0.078	0.039	0.035	0.037
3M CRT	Alu strip	-	-	0.107	0.038	0.052	0.043
	HDPE+ 1g 2 in 1		-	0.098	0.041	0.044	0.041
9M CRT	Alu strip	-	-	-	-	-	0.463

- Sample H#: Controlled batch with modified API 150 mg, composition same as batch H

[00100] Observation:

- Bottle pack is comparatively better than strip pack to control NDMA using at least one alkalizer as shown in above table.
- Alu strip samples are having higher percentage of impurities in samples A and B, however the impurity levels were significant controlled in case of sample C & D under accelerate stability condition i.e. 40°C/75%RH conditions, which depicts that magnesium oxide and sodium ascorbate provides a comparatively better NDMA control in case of HDPE over Alu strip packings.
- NDMA data for alkali oxide batch at 9M_LT & CRT was also found to be controlled.

[00101] Example 6: Formulation approaches with different coating and API strategy:

Batch Code	Strength	Coating Composition	NDMA (µg/g)				
			Initial	60°C 14 days		40°C/75% RH 1M	
				Alu Strip	PVC / PVD C	Alu Strip	PVC / PVDC
J	150 mg	Non-aqueous Coating - (60:40) (IPA:DCM) in Opadry white OY-S-58910	0.02	#	30.82	7.05	Brown spots formed on Tablet surface *

K	300 mg	Non-aqueous Coating - 60:40 (IPA: DCM) Opadry white OY-S- 58910	0.03	13.24	#	1.37	Tablet broken and Yellow coloration *
L	300 mg		0.02	ND	#	0.028	Tablet broken and slightly yellow coloration *
M	150 mg		0.15	#	3.10	7.54	7.54
N	150 mg	Hydro Alcoholic Coating IPA: Water (70:30)	0.02	56.53	#	0.37	Tablet broken and yellow coloration *
O	150 mg	Non Aqueous Coating - 60:40 (IPA:DCM) Opadry white OY-S- 58910	0.01	53.02	#	2.955	Tablet broken and yellow coloration *
P	150 mg	Hydro Alcoholic Coating IPA:Water (75:25)	0.05	#	#	6.581	Tablet broken and yellow coloration *

Sample not charged; * Samples not analysed due to failed description

[00102] Batch Description with coating composition and process as provided in above table:

Batch J: Prepared with modified milled API using similar process as in example 3, with a granulation step including Isopropyl alcohol granulation without alkalizer.

Batch K: Prepared with modified coarse API using similar process as in example 3, with 10% ascorbic acid.

Batch L: Prepared with modified coarse API using similar process as in example 3, with alkalizer as 10% sodium metabisulphite.

Batch M: Prepared with modified coarse API using similar process as in example 3, with alkalizer as 5% Sodium Carbonate.

Batch N: Prepared with modified coarse API using similar process as in example 3, without alkalizer.

Batch O: Prepared with modified milled API using similar process as in example 3, with 1.2% Vitamin E.

Batch P: Prepared with modified milled API using similar process as in example 3, with 1.2% Vitamin E.

[00103] Observation:

- Samples of Batch J to P with different type of API viz., coarse / milled API, different coating composition and alkalizer or stabilizers strategy were evaluated and found to be unstable.
- The sample tablets were brown or yellow colored and were found with cracks, hence found to be undesirable and failing.
- Based on experiments it can be considered that PVC/PVDC is not an appropriate pack as tablets failing in description as compared to Alu Strip pack.
- Also, the samples which were loaded for stability were unstable and have higher NDMA levels within 1M at 40°C/75%RH and 14 days at 60°C.

[00104] Example 7: Stability data of composition of Example 3C with aqueous coating and non-aqueous coating stored in 25x30's Strips

1. With Non-aqueous film coating - at ACC for 6 months and 30°C/75%RH for 12 months

Batch Number	A'										B'										C'									
Test Name	Acceptance criteria (months)	40°C/75%RH			30°C/75%RH					40°C/75%RH			30°C/75%RH					40°C/75%RH			30°C/75%RH									
		0	3	6	0	3	6	9	12	0	3	6	0	3	6	9	12	0	3	6	0	3	6	9	12					
NDMA (µg/g) (By HPLC)	NMT 11.2 PPM	ND	ND	ND	ND	ND	ND	0.2	0.9	ND	ND	ND	ND	ND	ND	1.1	1.1	ND	ND	ND	ND	ND	ND	1.0	1.2					

2. With aqueous film coating - at ACC for 6 months and 30°C/75%RH for 12 months

Batch No.	A''								B''								C''							
Test Name	Acceptance criteria (months)	40°C/75%RH			30°C/75%RH				40°C/75%RH			30°C/75%RH				40°C/75%RH			30°C/75%RH					
		0	3	6	0	3	6	12	0	1	6	0	3	6	12	0	3	6	0	3	6	12		
NDMA (µg/g) (By HPLC)	NMT 11.2 PPM	ND	1.131	1.696	ND	ND	0.322	1.194	ND	BLQ	3.835	ND	BLQ	BLQ	1.529	ND	BLQ	5.12	ND	BLQ	BLQ	1.944		

ND: Not detected

BLQ: Below limit of quantification

[00105] Based on the data it was observed that the composition are stable with an NDMA amount of less than 11ppm when stored for 12 months at 30°C/75%RH and at 40°C/75%RH for 6 months.

Claims

1. A stable pharmaceutical composition comprising, a Histamine H2-receptor antagonist, a stabilizing amount of at least one alkalizer and one or more pharmaceutically acceptable excipient, wherein the alkalizer effectively control the formation of nitrosamine drug substance-related impurities (NDSRIs) in the composition, to a level below about 11 ppm, upon storage or acid exposure.
2. A stable pharmaceutical composition of claim 3, wherein the Histamine H2-receptor antagonist is ranitidine hydrochloride
3. A stable pharmaceutical composition of claim 3, wherein the ratio of a Histamine H2-receptor antagonist and an alkalizer in the composition is in the range of 100:0.1 to 100:5.
4. A stable pharmaceutical composition of claim 3, wherein the nitrosamine drug substance-related impurity is N-nitrosodimethylamine (NDMA) impurity.
5. A stable pharmaceutical composition of claim 3, wherein the alkalizer is selected from alkali metal oxide, pH modifier, nitrite quencher.
6. A stable pharmaceutical composition of claim 7, wherein the alkalizer is alkali metal oxide.
7. A stable pharmaceutical composition of claim 8, wherein the alkali metal oxide is magnesium oxide
8. A stable pharmaceutical composition of claim 7, wherein the alkali metal oxide is present in the core of the composition.
9. A stable pharmaceutical composition of claim 7, wherein the alkali metal oxide is present in the composition within a coating.
10. A stable pharmaceutical composition of claim 11, wherein the coating is an aqueous film coating.
11. A stable pharmaceutical composition of claim 11, the coating is a non-aqueous film coating.
12. A stable pharmaceutical composition of any of the preceding claims, wherein the level of nitrosamine drug substance related impurities (NDSRIs) level is below about 11 ppm upon storage under controlled room temperature condition of 25°C/60% RH for at least 12 months.

13. A stable pharmaceutical composition comprising ranitidine hydrochloride and magnesium oxide, wherein the magnesium oxide is present in the composition in an amount present in an amount ranging from about 0.1% w/w to about 10% w/w of the composition, wherein the composition is characterized by a level of N-Nitrosodimethylamine (NDMA) impurity below 11 ppm, upon storage at 25°C/60% RH for a period of at least 12 months.
14. A stable pharmaceutical composition of claim 17, wherein the amount of magnesium oxide ranges from about 0.1% w/w to about 2% w/w of the composition.
15. A stable pharmaceutical composition of claim 17, wherein the composition is characterized by a level of nitrosamine drug substance related impurity below 3 ppm, upon storage at 25°C./60% RH for a period of 12 months.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2024/051717

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/20 A61K9/28 A61K31/00 ADD.				
According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	US 2009/099154 A1 (JAIN RAJESH [IN] ET AL) 16 April 2009 (2009-04-16) examples 8, 17 -----	1-8, 12, 13, 15		
X	KR 101 567 937 B1 (KLPNG C & PHARM CO LTD [KR]) 10 November 2015 (2015-11-10) Embodiment 1; paragraphs [0001], [0011], [0048], [0025], [0097], [0103] - [0107] -----	1-15		
A	WO 2022/079287 A1 (ZENTIVA KS [CZ]) 21 April 2022 (2022-04-21) Field of Invention, Detailed description of the Invention; examples 16-20 ----- -/-	1-15		
<table><tr><td>☒ Further documents are listed in the continuation of Box C.</td><td>☒ See patent family annex.</td></tr></table>			☒ Further documents are listed in the continuation of Box C.	☒ See patent family annex.
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<table><tr><td>* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed</td><td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family</td></tr></table>			* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
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Date of the actual completion of the international search 6 May 2024		Date of mailing of the international search report 22/05/2024		
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Schwald, Claudia		

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2024/051717

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NANDA KAUSIK K. ET AL: "Inhibition of N-Nitrosamine Formation in Drug Products: A Model Study", JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 110, no. 12, 14 August 2021 (2021-08-14), pages 3773-3775, XP093146433, US ISSN: 0022-3549, DOI: 10.1016/j.xphs.2021.08.010 [retrieved on 2024-05-03] the whole document -----	1-15
A	FDA: "Updates on possible mitigation strategies to reduce the risk of nitrosamine drug substance-related impurities in drug products FDA", / 18 November 2021 (2021-11-18), pages 1-4, XP093157924, FDA Government Website Retrieved from the Internet: URL:https://www.fda.gov/drugs/drug-safety-and-availability/updates-possible-mitigation-strategies-reduce-risk-nitrosamine-drug-substance-related-impurities?utm_medium=email&utm_source=govdelivery [retrieved on 2024-05-03] the whole document -----	1-15
A	Zachary Brennen: "FDA seeks withdrawal of eartbur drugs due to new carcinogen concerns", / 1 April 2020 (2020-04-01), XP093158498, Retrieved from the Internet: URL:https://www.raps.org/News-and-Articles/News-Articles/2020/4/FDA-Seeks-Withdrawal-of-Heartburn-Drugs-Due-to-New [retrieved on 2024-05-03] the whole document -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2024/051717

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2009099154 A1	16-04-2009	AR 055070 A1 AU 2006263338 A1 BR PI0613070 A2 CA 2613407 A1 CN 101212957 A CR 9705 A EA 200800162 A1 EP 1912628 A2 JP 2009500318 A RS 20070512 A TN SN07490 A1 US 2009099154 A1 WO 2007000779 A2	01-08-2007 04-01-2007 21-12-2010 04-01-2007 02-07-2008 30-10-2008 30-06-2008 23-04-2008 08-01-2009 22-01-2009 17-03-2009 16-04-2009 04-01-2007
KR 101567937 B1	10-11-2015	NONE	
WO 2022079287 A1	21-04-2022	EP 4228607 A1 GB 2599950 A US 2023390221 A1 WO 2022079287 A1	23-08-2023 20-04-2022 07-12-2023 21-04-2022