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(54) Title: AN INTRANASAL COMPOSITION COMPRISING 5HT_{1B/1D} RECEPTOR AGONISTS

(57) Abstract: The present invention relates to an intranasal composition comprising 5HT_{1B/1D} receptor agonists for treatment of cluster headache, migraine, pain, chronic paroxysmal hemicrania and headache associated with vascular disorders, and other disorders arising from deficient serotonergic neurotransmission. More particularly, the invention relates to an intranasal composition comprising at least one efflux modulator along with other pharmaceutically acceptable excipients.



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AN INTRANASAL COMPOSITION COMPRISING 5HT_{1B/1D} RECEPTOR AGONISTS

5 FIELD OF THE INVENTION:

The present invention provides an intranasal composition comprising 5HT_{1B/1D} receptor agonists for treatment of cluster headache, migraine, pain, chronic paroxysmal hemicrania and headache associated with vascular disorders, and other disorders arising from deficient serotonergic neurotransmission. More particularly, the invention relates to an intranasal composition comprising at least one efflux modulator along with other pharmaceutically acceptable excipients.

The intranasal composition of present invention, when administered to a mammal, the necessary blood level of the drug is provided to effectively treat the migraine pain.

15 BACKGROUND OF THE INVENTION:

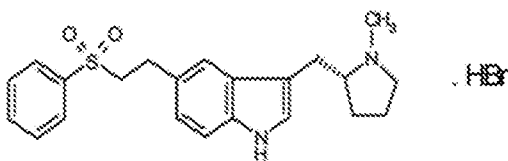
Migraine is a common neurovascular disorder characterized by attacks of severe headache and autonomic and neurological symptoms. The disease is beset by myths, including that it is mainly “a psychological response to stress”. Migraine is among the most undertreated neurological conditions. Migraine headaches occur in approximately 12% of the World’s population. Women are three times more likely to be affected by migraine headaches than men.

The two main types of migraine are migraine without aura (common migraine), occurring in 75% of migraineurs, and migraine with aura (classic migraine), occurring in one-third of patients. The traditional view—aura is caused by vasoconstriction, headache by vasodilation—is too simplistic. The current view is that the aura is caused by “cortical spreading depression” (CSD), a depolarisation wave that propagates across the brain cortex at 2–3 mm/min and is associated with transient depression of spontaneous and evoked neuronal activity.

The current therapies to treat migraine headaches include the administration of serotonin 5HT_{1B/1D} receptor agonists collectively called as triptans, which chemically are tryptamine-based drugs. Sumatriptan was the first

of these compounds to be developed, which offered improved efficacy and tolerability over ergot-derived compounds. The development of sumatriptan was quickly followed by a number of second generation triptans including zolmitriptan, naratriptan, and rizatriptan. Recent polls of migraineurs (people who suffer from
5 migraines more than twice a month) suggest that more lipophilic formulations of other triptans, given orally, are still preferred over the sumatriptan nasal spray (IMITREX®). While these alternative triptans have slightly different binding affinities for the various 5HT_{1B/1D} receptors, the single guiding factor in success with these formulations seems to be the speed of action.

10 Eletriptan (trade name Relpax, used in the form of eletriptan hydrobromide) is a second generation triptan drug intended for treatment of migraine headaches. Eletriptan is chemically designated as (R)-3-[(1-Methyl-2-pyrrolidinyl)methyl]-5-[2-(phenylsulfonyl)ethyl]-1Hindole monohydrobromide, and it has the following chemical structure:



15 Eletriptan has longer half-life of 4-6 hrs and is more lipophilic than any other triptan known (Pharmacotherapy, 2006 Jan; 26(1):115-28; Safety and efficacy of eletriptan in the treatment of acute migraine; Takiya L1, Piccininni LC, Kamath V.); hence make it more potential candidate for development of Nasal
20 Spray in Migraine Therapy. Longer half-life of eletriptan further reduces the incidence of recurrent headaches and more lipophilicity further results into more rapid onset of action through nasal route.

25 US Patent no. 6,713,461 discloses formulation of a complex of eletriptan and a sulphobutylether-beta-cyclodextrin, to prevent irritancy in the nasal mucosa and hence provide a well-tolerated, stable, aqueous, pharmaceutical formulation containing eletriptan, which is suitable for parenteral as well as intranasal administration.

US Patent no. 6,750,237 disclose intranasal formulation of Zolmitriptan wherein the formulation is buffered by a mixture of citric acid and disodium phosphate and provided effective and improved fast relief for migraine sufferers.

PCT patent publication no. WO2004093917 discloses aqueous sumatriptan formulation suitable for intranasal administration along with cyclodextrin as an absorption enhancer which improves the transmucosal $T_{\max}$ and $C_{\max}$ of sumatriptan.

US Patent no. 8,440,631 disclose intranasal composition containing 5HT_{1B/1D} agonist along with an alkylsaccharide, wherein the alkylsaccharide has an alkyl chain including between 10 to 16 carbons, and wherein the $T_{\max}$ is 20 minutes or less.

US Patent No. 5,466,699 discloses a class of chemical compounds for the treatment and prophylaxis of migraine. Also, discloses that this class of compounds may be formulated for oral, sublingual, buccal, parenteral (for example subcutaneous, intramuscular or intravenous), rectal, topical and intranasal administration and examples of such possible formulations, including an example of an intranasal formulation, are disclosed. The intranasal formulation consists of an active ingredient, methyl hydroxybenzoate (0.2%), propyl hydroxybenzoate (0.02%), citrate buffer and sufficient hydrochloric acid to take the pH to 7.

PCT patent publication no. WO2011036521 discloses a pharmaceutical composition comprising a salt of sumatriptan or a physiologically acceptable solvate thereof, a mucosal permeation enhancer and optionally at least one pharmaceutically acceptable excipient, wherein the said composition provides $T_{\max}$ value of less than 30 minutes upon said administration.

The existing marketed formulations of 5HT_{1B/1D} receptor agonists (Imitrex®- Sumatriptan & Zomig®-Zolmitriptan) have early onset of action as compared to their oral preparation. Thereby It is highly desirable to develop a formulation where there would be an onset of action quicker than existing formulation of eletriptan or salts thereof, after dosing, so that there will be faster relief of pain in migraine and also provides longer effects to decrease the recurrence rate.

The present invention relates to high performance intranasal delivery of 5HT_{1B/1D} receptor agonists, which has a number of significant and unexpected

advantages over previously used routes of 5HT_{1B/1D} receptor agonist's administration. The advantages of this intranasal route of administration are improved safety, reduced exposure variability resulting in reduced incidence of adverse side effects, more rapid onset of action compared to subcutaneous and a non-invasive route of administration.

Hence, there is a long felt need to develop alternate 5HT_{1B/1D} receptor agonist's formulations that have an increased speed or onset of action as well as an improved permeability over the earlier 5HT_{1B/1D} receptor agonist's formulations and meeting the unmet requirements in the treatment of migraine attacks.

SUMMARY OF THE INVENTION:

In one aspect, the present invention provides an intranasal pharmaceutical composition comprising from about 1 mg to about 20 mg of at least one 5HT_{1B/1D} agonist or salts thereof and at least one pharmaceutically acceptable excipient.

In one another aspect, the present invention provides an intranasal pharmaceutical composition comprising from about 1 mg to about 20 mg of at least one 5HT_{1B/1D} agonist or salts thereof, at least one efflux modulator and at least one pharmaceutically acceptable excipient.

In one another aspect, the present invention provides an intranasal pharmaceutical composition comprising of at least one 5HT_{1B/1D} agonist or salts thereof and at least one pharmaceutically acceptable excipient, wherein the intranasal composition provides at least two times increase in bioavailability than the current recommended doses of 5HT_{1B/1D} agonist or salts thereof.

In yet another aspect, the present invention provides an intranasal pharmaceutical composition comprising from about 1 mg to about 20 mg of at least one 5HT_{1B/1D} agonist or salts thereof, at least one efflux modulator and at least one pharmaceutically acceptable excipient, wherein the pH of the composition is below 7.

In another aspect, the present invention provides an intranasal pharmaceutical composition comprising from about 1 mg to about 20 mg of eletriptan or salts thereof, at least one efflux modulator and at least one pharmaceutically acceptable excipient, wherein the pH of the composition is below 7.

In yet another aspect, the present invention provides an intranasal pharmaceutical composition comprising of eletriptan or salts thereof, at least one efflux modulator and at least one pharmaceutically acceptable excipient, wherein the intranasal composition provides bioavailability (F) values of more than 10.

5 In yet another aspect, the present invention provides an intranasal pharmaceutical composition comprising of eletriptan or salts thereof, at least one efflux modulator and at least one pharmaceutically acceptable excipient, wherein the composition retains at least 80% of the potency of eletriptan or salts thereof in the pharmaceutical composition, after storage for at least one month, or at least
10 three months, or at least six months, or at least twelve months, at room temperature.

In yet another aspect, the present invention provides an intranasal pharmaceutical composition comprising of eletriptan or salts thereof, at least one efflux modulator and at least one pharmaceutically acceptable excipient, wherein
15 the composition retains at least 99% of the transmittance after storage for at least one month, or at least three months, or at least six months, or at least twelve months, at room temperature.

In yet another aspect, the present invention provides an intranasal pharmaceutical composition comprising of eletriptan or salts thereof, at least one
20 efflux modulator and at least one pharmaceutically acceptable excipient, wherein when said composition is stored at 40°C/75% RH in closed vials one month, or three months, or six months, or twelve months, the total amount of related substances does not increase more than 1.2%.

In another aspect, the present invention provides an intranasal
25 pharmaceutical composition comprising of eletriptan or salts thereof, at least one efflux modulator and at least one pharmaceutically acceptable excipient, wherein the composition when stored at 40°C/75% RH in closed vials for one month, or three months, or six months, or twelve months, the amount of single specified impurity does not increase more than 0.5%.

30 In another aspect, the present invention provides a process of preparing an intranasal pharmaceutical composition comprising of 5HT_{1B/1D} agonist or salts thereof and at least one pharmaceutically acceptable excipient, wherein the process comprising:

1. mixing one or more pharmaceutically acceptable excipient under continuous stirring at $60\pm 5^{\circ}\text{C}$;
2. dissolving the $5\text{HT}_{1\text{B}/1\text{D}}$ agonist or salts thereof to the solution of step (1) under continuous stirring at $60\pm 5^{\circ}\text{C}$;
- 5 3. filtering and purging the solution of step (2) with nitrogen at $50\pm 5^{\circ}\text{C}$ and pack in suitable container.

In another general aspect, there is provided a method of treating a disease condition wherein agonism of $5\text{HT}_{1\text{B}/1\text{D}}$ -receptors is beneficial more preferably in treating migraine or related disease conditions; wherein method comprises
10 administering an effective amount of an intranasal pharmaceutical composition comprising of eletriptan or salts thereof, at least one efflux modulator and optionally at least one pharmaceutically acceptable excipient.

In a further aspect, the invention relates to a pharmaceutical kit comprises an intranasal pharmaceutical composition comprising of eletriptan or salts thereof,
15 at least one efflux modulator and optionally at least one pharmaceutically acceptable excipient, and a nasal device for accurate delivery of said intranasal pharmaceutical composition.

Additional objects and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or
20 may be learned by practice of the invention.

DETAILED DESCRIPTION OF THE INVENTION:

Technical and scientific terms used herein have the meaning commonly understood by one of skill in the art to which the present invention pertains, unless
25 otherwise defined. Reference is made herein to various methodologies and materials known to those of skill in the art. Standard reference works setting forth the general principles of pharmacology include Goodman and Gilman's "The Pharmacological Basis of Therapeutics", 10th Ed., McGraw Hill Companies Inc., New York (2001).

30 Any suitable materials and/or methods known to those of skill can be utilized in carrying out the present invention. However, preferred materials and methods are described. Materials, reagents and the like to which reference are

made in the following description and examples are obtainable from commercial sources, unless otherwise noted.

As used in this specification, whether in a transitional phrase or in the body of the claim, the terms “comprise(s)” and “comprising” are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases “having at least” or “including at least”. When used in the context of a process, the term “comprising” means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound or composition, the term “comprising” means that the compound or composition includes at least the recited features or components, but may also include additional features or components.

As used in this specification, the singular forms “a,” “an” and “the” specifically also encompass the plural forms of the terms to which they refer, unless the content clearly dictates otherwise.

Intranasal drug delivery is considered as a lucrative route of drug delivery system. A large number of factors influenced therapeutic efficacy as well as toxicity of nasally administered drug product. A large number of factors serve as barrier for systemic bioavailability of nasal drug product: (i) Low bioavailability- Bioavailability of polar drugs is generally low, about 10% for low molecular weight drugs. (ii) Mucociliary clearance- The general fast clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechanism is another factor of importance for low membrane transport. This is especially the case when the drug is not absorbed rapidly enough across the nasal mucosa. iii) Enzymatic Degradation-Another contributing, but often less considered factor to the low bioavailability of peptides and proteins across the nasal mucosa is the possibility of an enzymatic degradation of the molecule in the lumen of the nasal cavity or during passage through the epithelial barrier. These sites both contain exopeptidases such as mono and diaminopeptidases that can cleave peptides at their N and C termini and endopeptidases, which can attack internal peptide bonds. IV) P glycoprotein efflux - Drug absorption may be hindered by efflux transporters such as P-glycoproteins (Pgps). Basically, Pgps are a group of glycosylated membrane proteins found in the epithelial cells of small intestine and

other body tissues. A large variety of hydrophilic and amphiphilic compounds are detoxified through active Pgp mediated efflux transport in nasal mucosa.

Currently, eletriptan hydrobromide is available as oral tablets in 20 mg and 40 mg strengths. In the oral drug delivery, the systemic bioavailability of a drug is often subjected to variable gastrointestinal transit time and biotransformation in the liver by "first pass metabolism". Hence, to achieve the desired therapeutic effect the dose needs to be increased which leads to undesired side effects.

Accordingly, it would be desirable to improve the bioavailability of eletriptan or salts thereof and to reduce the necessary daily dose of eletriptan or salts thereof. The most important approach to enhance the bioavailability of eletriptan or salts thereof is to formulate it as a composition, wherein drug will be delivered through nasal route and hence may reduce the dose to a significant extent in comparison to the oral dose.

Accordingly, it would be advantageous to have a composition of eletriptan or salts thereof which increases the drug's bioavailability and thus could be dosed at lower doses and provides the efficacy benefits of a higher dose. An especially useful formulation could provide rapid onset and consistent action using a lower dose and reducing drug interactions and side-effects because of more consistent delivery and improved bioavailability. For example, a formulation which is, say, 50% more bioavailable could be dosed at 10 mg and provide the same systemic exposure as currently available formulations when dosed at 20 mg.

The invention is based, in part, on the results of a comparison of the efficacy of intranasal composition of eletriptan or salts thereof with efflux modulator to the oral composition of eletriptan for the treatment of treatment of cluster headache, migraine, pain, chronic paroxysmal hemicrania and headache associated with vascular disorders, and other disorders arising from deficient serotonergic neurotransmission. The efficacy of low dose intranasal composition of eletriptan at several dose levels suggests a faster onset of action. Most notably, low dose intranasal composition of eletriptan provides single-dose efficacy at about 50%, about 25%, about 12.5% and about 5% of the current recommended doses of eletriptan.

Therefore, in an embodiment, there is provided an intranasal pharmaceutical composition comprising from about 1 mg to about 20 mg of at

least one 5HT_{1B/1D} agonist or salts thereof and optionally at least one pharmaceutically acceptable excipient.

More preferably, at least one 5HT_{1B/1D} agonist or salts thereof is present from about 4 mg to about 12.5 mg.

5 Further, the Inventors of the present invention surprisingly found that the physiological barrier of Pgp efflux system in nasal drug delivery not only affects the peripheral drug concentration, but also certainly affects the brain drug concentration of centrally acting drugs. Hence, Inventors of the present invention surprisingly found that when 5HT_{1B/1D} agonist or salts thereof was formulated
10 along with efflux modulators, the intranasal composition so formed crosses the physiological barrier of Pgp efflux system effectively and provides better brain drug concentration at short interval of time and provided effective and improved fast relief for migraine sufferers at significantly low doses..

Efflux modulators can be called as P-gp inhibitors/P-gp modulators/
15 chemosensitizers/reversal agents. P-glycoprotein (P-gp), the permeability glycoprotein or plasma glycoprotein is an active, efflux, membrane bound transport protein pump discovered in 1976 (Juliano, Ling, 1976). P-gp is extensively distributed especially in the capillary endothelial cells composing the blood-brain barrier. This efflux carrier decreases the bioavailability of
20 administered drugs by preventing their sufficient accumulation intracellularly. Ultimately, the efficacy of drugs is lowered. It also alters the pharmacokinetics and pharmacodynamics of its substrates by dictating their ADMET (absorption, distribution, metabolism, elimination and toxicity) characteristics (Lin, 2003). The optimal P-gp expression is always appreciated for its protective function. But, P-
25 gp over expression leads to MDR while its low expression leads to toxic reactions. Hence, it is envisioned that certain efflux modulators will facilitate drug accumulation in and so enhance the effectiveness of the therapy and therefore increase the bioavailability.

Therefore, in an embodiment, there is provided an intranasal
30 pharmaceutical composition comprising of at least one 5HT_{1B/1D} agonist or salts thereof, at least one efflux modulator and optionally at least one pharmaceutically acceptable excipient, wherein the intranasal composition provides at least three

times increase in bioavailability than the current recommended doses of 5HT_{1B/1D} agonist or salts thereof.

Examples of suitable efflux modulator which can be employed in the intranasal pharmaceutical composition of 5HT_{1B/1D} agonist or salts thereof may be selected from, but not limited to polysorbates, their ether ethoxylates, produced by reaction of sorbitan esters with ethylene oxide, polyoxyethylene alkyl phenol, polyoxyethylene cetyl ether, polyoxyethylene alkyl-aryl ether, polyoxyethylene monolaurate, polyoxyethylene vegetable oil, polyoxyethylene sorbitan monolaurate, polyoxyethylene esters or mixed fatty and resin acids, polyoxyethylene sorbitol lanolin derivative, polyoxyethylene tridecylether, polyoxyethylene sorbitan esters of mixed fatty and resin acids, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monooleate, polyoxyethylene monostearate, polyoxyethylene stearyl ether, polyoxyethylene oleyl ether, polyoxyethylene tridecyl ether, polyoxyethylene fatty alcohol, polyoxyethylene alkyl amine, polyoxyethylene glycol monopalmitate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene cetyl ether, polyoxyethylene oxypropylene stearate, polyoxyethylene lauryl ether, polyoxyethylene lanolin derivative, sodium oleate, quaternary ammonium derivative, potassium oleate, N-cetyl N-ethyl morpholinium ethosulfate, sodium lauryl sulfate or mixtures thereof. The amount of the efflux modulator present in the pharmaceutical composition may range from about 5% w/w to about 15% w/w relative to the total weight of the composition.

Surprisingly, Inventors of present invention have found that solutions of 5HT_{1B/1D} agonist or salts thereof having a pH of the composition is below 7 have excellent solubility properties and also composition is acceptable to the general patient population and did not cause unnecessary irritancy as pH of the composition is below 7. The nasal mucosal pH is in the range of 5.5-6.5. Moreover, eletriptan is prone to acid hydrolysis. Hence, to avoid the acid hydrolysis and to provide stable intranasal formulation of eletriptan or salts thereof the pH of the formulation is maintained below 7.

In further embodiment, there is provided an intranasal pharmaceutical composition comprising from about 1 mg to about 20 mg of at least one 5HT_{1B/1D} agonist or salts thereof, at least one efflux modulator and optionally at least one

pharmaceutically acceptable excipient, wherein the pH of the composition is below 7.

Examples of 5HT_{1B/1D} agonist includes sumatriptan, rizatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan and/or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, prodrug or mixtures thereof.

In further embodiment, there is provided an intranasal pharmaceutical composition comprising eletriptan or salts thereof, at least one efflux modulator and at least one pharmaceutically acceptable excipient, wherein the intranasal composition provides bioavailability (F) values of more than 10.

The most preferred mechanism for transport of drug through blood brain barrier is a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions.

Therefore, the preferred 5HT_{1B/1D} agonist of the present invention is eletriptan or salts thereof. It is very well known in the art that eletriptan or salts thereof is the most lipophilic triptan known till date (Safety and Efficacy of Eletriptan in the Treatment of Acute Migraine; Liza Takiya et al.; Pharmacotherapy 2006;26(1):115–128). The amount of the eletriptan or salts thereof present in the pharmaceutical composition may range from about 0.5% w/w to about 5% w/w relative to the total weight of the composition.

Oxidation is one of the main routes of degradation of eletriptan or salts thereof in solutions. Surprisingly, the inventors of the present invention found that when low dose of eletriptan or salts thereof was formulated with at least one efflux modulator further enhances the stability of eletriptan or salts thereof in solutions.

In further embodiment, there is provided an intranasal pharmaceutical composition comprising of eletriptan or salts thereof, at least one efflux modulator and at least one pharmaceutically acceptable excipient, wherein the composition retains at least 80% of the potency of eletriptan or salts thereof in the pharmaceutical composition, after storage for at least one month, or at least three months, or at least six months, or at least twelve months, at room temperature.

Transmittance is the ratio of the light energy falling on the solution to that transmitted through it. So, if all the light passes through a solution without any

absorption, then absorbance is zero, and percent transmittance is 100%. If all the light is absorbed, then percent transmittance is zero, and absorption is infinite.

Thus, transmittance is a tool to determine a solution's concentration based on the level of light absorbed. Hence, solution must be clear, meaning there should not be any precipitate in the liquid for 100% transmittance. The inventors of present invention surprisingly found that if an intranasal pharmaceutical composition comprising eletriptan or salts thereof is prepared with at least one efflux modulator and the pH of the composition is below 7, there would not be any precipitation and the solution so formed would be stable and retains atleast 99% of the transmittance after storage for at least one month at room temperature

Therefore, in yet another embodiment, there is provided an intranasal pharmaceutical composition comprising of eletriptan or salts thereof, at least one efflux modulator and optionally at least one pharmaceutically acceptable excipient, wherein the composition retains at least 99% of the transmittance after storage for at least one month, or at least three months, or at least six months, or at least twelve months, at room temperature.

In yet another embodiment, there is provided a process of preparing an intranasal pharmaceutical composition comprising of at least one 5HT_{1B/1D} agonist or salts thereof and optionally at least one pharmaceutically acceptable excipient, the process comprising:

1. mixing one or more pharmaceutically acceptable excipient under continuous stirring at 60±5°C;
2. dissolving the low dose of 5HT_{1B/1D} agonist or salts thereof to the solution of step (1) under continuous stirring at 60±5°C;
3. filtering and purging the solution of step (2) with nitrogen at 50±5°C and pack in suitable container.

In yet another embodiment, there is provided a process of preparing an intranasal pharmaceutical composition comprising of eletriptan or salts thereof, at least one efflux modulator and optionally at least one pharmaceutically acceptable excipient, the process comprising:

1. mixing one or more pharmaceutically acceptable excipient under continuous stirring at 60±5°C;

2. dissolving the low dose of eletriptan or salts thereof to the solution of step (1) under continuous stirring at $60\pm 5^{\circ}\text{C}$;
3. filtering and purging the solution of step (2) with nitrogen at $50\pm 5^{\circ}\text{C}$ and pack in suitable container.

5 In another embodiment, the intranasal pharmaceutical composition comprising of at least one $5\text{HT}_{1\text{B}/1\text{D}}$ agonist or salts thereof further comprises one or more pharmaceutically acceptable excipients selected from cosolvents, isotonicity agents, chelating agents, preservative, pH adjusting agents, absorption promoters, viscosifiers, sweetener/taste masking agents.

10 Eletriptan or salts thereof are poorly water soluble i.e. $\approx 3 \text{ mg/mL}$ which is a major concern in development of formulation for intranasal administration. There are several established methods to improve the solubility of hydrophobic drug in aqueous vehicles. Co-solvency, the addition of water miscible solvents to an aqueous system, is one of most important, convenient and easy method of these.

15 Co-solvent solubilization is important in nasal dosage forms where it is recommended to incorporate the required dose as a true solution in 100-200 μL volume of liquid.

Suitable cosolvents for the composition according to the invention include aqueous based vehicles suitable for intranasal administration. In addition to

20 aqueous (purified water), oil or gel vehicles, other vehicles which may be used in the compositions according to the invention comprise solvent systems containing ethyl alcohol, isopropyl alcohol, glycerin, propylene glycol, polyethylene glycol, mixtures thereof or mixtures of one or more of the foregoing with water.

Examples of the suitable preservatives for the composition according to the

25 invention may be selected from, but not limited to benzyl alcohol, quaternary ammonium halides, phenylcarbinol, thimerosal, disodium edetate and phenyl ethyl alcohol. The amount of the preservative present in the pharmaceutical composition may range from about 0.005 to about 1% w/w relative to the total weight of the composition.

30 Eletriptan or salts thereof are stable when subjected to light, heat, and base hydrolysis however, they are very unstable towards oxidation and acid hydrolysis. In order to stabilize the intranasal composition of Eletriptan or salts thereof, antioxidants and/or chelating agent are added.

Examples of suitable antioxidants for the composition according to the invention may be selected from, but not limited to ascorbic acid, alpha-tocopherol (vitamin-E), butylated hydroxyanisole, butylated hydroxytoluene, glutathione and the like. The amount of the antioxidant present in the pharmaceutical composition may ranges from about 0.0002 to about 0.5% w/w relative to the total weight of the composition.

Examples of suitable chelating agents for the composition according to the invention may be selected from, but not limited to edetate disodium (EDTA); edetate trisodium; edetate tetrasodium; and diethyleneamine pentaacetate, preferably EDTA. The amount of the chelating agent present in the pharmaceutical composition may range from about 0.0001 to 1% w/w relative to the total weight of the composition.

Examples of viscosifiers for the composition according to the invention may be selected from, but not limited to water insoluble polymers, cellulosic polymers, acrylic polymers, polyoxyethylene-polyoxypropylene block copolymers, xanthan gum, tragacanth gum, alginates and agar-agar. The composition of the invention is often a solution, but with increased viscosity. The viscosity of the composition is preferably greater than that of water and less than 50cps.

Examples of suitable pH adjusting agents for the composition according to the invention may be selected from, but not limited to sodium hydroxide, hydrochloric acid, citric acid, acetic acid, fumaric acid, hydrochloric acid, malic acid, nitric acid, phosphoric acid, propionic acid, sulfuric acid, tartaric acid, or combinations thereof. The composition of the present invention comprises an amount of a pH adjusting agent sufficient to adjust the pH below 7.

Examples of suitable buffers may include one or more of borate buffers, tartarate buffers, lactate buffers, citrate buffers, phosphate buffers (e.g. potassium phosphate monobasic), 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 0.005% w/w to about 1% w/w of the composition.

Examples of suitable sweetener/taste masking agents may be selected from, but not limited to sucralose, thaumatin (e.g., Talin®) sucrose, saccharin (including the salt forms: sodium, calcium, etc.), fructose, glucose, dextrose, corn

syrup, aspartame, acesulfame-K, xylitol, sorbitol, erythritol, ammonium glycyrrhizinate, thaumatin, neotame, mannitol, eucalyptus oil, camphor, and natural or artificial flavors or flavoring agents (for example menthol, mints, vanilla, orange, etc.), or combinations of two or more of such agents.

5 In yet another embodiment, there is provided a method of treating a disease condition wherein agonism of 5HT_{1B/1D} receptors is beneficial more preferably in treating migraine or related disease conditions; wherein method comprises administering an effective amount of an intranasal pharmaceutical composition comprising from about 1 mg to about 20 mg of eletriptan or salts
10 thereof, at least one efflux modulator and optionally at least one pharmaceutically acceptable excipient.

In yet another embodiment, there is provided a pharmaceutical kit comprises an intranasal pharmaceutical composition comprising from about 1 mg to about 20 mg of eletriptan or salts thereof, at least one efflux modulator and
15 optionally at least one pharmaceutically acceptable excipient, and a nasal device for accurate delivery of said intranasal pharmaceutical composition.

The intranasal compositions of this invention are most effective when proper product delivery design is utilized. The preferred product design includes a composition of the invention contained within a delivery system, such as a bottle
20 and a pump, for nasal delivery of the formulation in a mist of spray droplets to coat the mucosa of the nasal cavity upon administration. Preferred pumps for use in such products of the invention are metered multi-dose pumps; however, single unit-dose containers are also acceptable to deliver the therapeutic dose of eletriptan or salts thereof to the nasal cavity. The selection of the pump is based
25 on the desired dose/spray volume and spray pattern appropriate for local delivery to the nasal mucosa. In certain such embodiments of the invention, the compositions can be effectively contained in a package comprising a high density polyethylene bottle fitted with a screw cap, and are delivered by a metered-dose spray pump designed for intranasal application in volumes of 0.01 to 1.0 ml.
30 Suitable compositions of the present invention include about 0.5% w/w to about 5% w/w of eletriptan or salts thereof relative to the total weight of the composition.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

5 **Example 1**

Sr No	Ingredient	%w/w
1	Eletriptan Hydrobromide (Beta Form)	2.500
2	Polyethylene Glycol 400	20.000
3	Propylene Glycol	20.000
4	Polysorbate 80	10.000
5	Butylated Hydroxyanisole	0.010
6	Butylated Hydroxytoluene	0.010
7	Disodium Edetate Dihydrate	0.050
8	Benzyl Alcohol	0.500
9	Purified Water	QS to 100

Process:

1. Polyethylene glycol 400, propylene Glycol and polysorbate 80 were mixed
10 under continuous stirring,
2. solution of the step 1 was heated at $60\pm 5^{\circ}\text{C}$ and butylated hydroxyanisole and butylated hydroxytoluene were dissolved in it under continuous stirring,
3. benzyl alcohol was mixed in step 2 under continuous stirring at $60\pm 5^{\circ}\text{C}$,
4. eletriptan hydrobromide was dissolved in the solution of step 3 under
15 continuous stirring at $60\pm 5^{\circ}\text{C}$,
5. disodium edetate dihydrate was dissolved in 25 g of purified water,
6. solution of Step 5 was mixed with solution of step 4 under continuous stirring at $60\pm 5^{\circ}\text{C}$ and final weight was made up with purified water
7. the solution of step 6 was filtered through PES filter and the nitrogen was
20 purged in it at $50\pm 5^{\circ}\text{C}$ for 3 hrs.

Stability studies data:

Batch No. 25-F007								
Storage Condition	% Assay	%Related Substances				pH	% Transmittance	Description
		Ele 4	Ele Ethyl	Single Max Imp	Total Imp			
Initial	102.5	0.14	0.02	0.03	0.19	5.62	100.0	Light Yellow coloured clear liquid
2-8°C (1M)	99.4	ND	0.02	0.02	0.05	5.68	100.1	
RT (1M)	100.10	ND	0.02	0.02	0.05	5.58	99.52	
40°C/75% RH (1M)	99.80	ND	0.02	0.06	0.12	5.43	99.85	
50°C /80% RH (1M)	103.20	ND	0.02	0.08	0.18	5.16	99.89	

Batch No.	25-F012						
Storage Period	Initial	3 Months			6 Months		
Storage condition		2-8	25/60	40/75	2-8	25/60	40/75
Description	Light Yellow Coloured Clear Solution						
Assay (%)	98.3	100.4	99.9	99.5	99.2	98.9	99.2
% Transmittance	99.8	100	99.9	100	100	100	100
RS (%)							
Ele 4	ND	ND	ND	ND	ND	ND	ND
Ele Ethyl	0.02	0.07	0.11	0.16	0.02	0.02	0.02
Any other Individual Unspecified Impurity	0.05	0.02	0.02	0.02	0.004	0.02	0.03
Total Imp	0.09	0.11	0.14	0.21	0.02	0.07	0.18

Preclinical Studies:

Objective: To investigate the pharmacokinetic of eletriptan following single intranasal administration in SD rats.

Method: Male SD rat (n=5) received eletriptan via intranasal administration under non-fasted conditions at about 10 µL/animal. The eletriptan formulation (Batch No.: 25-F012) was prepared in pharmaceutically acceptable excipients at 25 mg/g strengths. The dose of about 1 mg/kg was achieved following an administration of dose volume of 10 µL in the animals via nasal route.

A jugular cannulated rat was used for this study. Jugular cannulation in rat was performed under xylazine-ketamine anesthesia. Animals were provided a recovery period of 24 hrs. prior to the dose administration. A serial blood sampling (approx. 0.2 mL per time point, sodium-heparin as anticoagulant) was performed from each animal via jugular vein post dose. The blood samples were collected at 0.00 (pre-dose) and 0.050, 0.083, 0.167, 0.5, 1, 2, 4, 6, and 8 hrs. The samples were centrifuged at 4000 rpm for 15 minutes to obtain plasma and stored below -70° C until further analysis. The samples were analyzed for eletriptan using a sensitive and specific fit-for-purpose liquid chromatographic tandem mass spectrometry (LC-MS/MS) method with lower limit of quantitation of 0.5 ng/mL. Pharmacokinetic parameters were calculated using the non-compartmental analysis (NCA) module of Phoenix-WinNonlin® software version 6.4.

Results:

Batch No. 25-F012		
Formulation	Intranasal Administration	Oral Administration
Dose (mg/kg)	1	4.2
T _{max} (h)	0.17 (0.08-0.5)	0.166
C _{max} (ng/mL)	53.9 ± 36.7	48.3 ± 23.6
AUC _{last} (ng*h/mL)	59.8 ± 42.9	36.8 ± 10.8
AUC _{inf} (ng*h/mL)	61.9 ± 42.5	40.4 ± 12.0
T _{1/2} (h)	1.5 ± 0.6	1.7 ± 0.8
MRT _{last} (h)	1.7 ± 0.9	1.2 ± 0.3
%F	43	6

Observations: The plasma concentration and exposure estimated after blood sampling from the jugular vein is about 5 times higher than intra-gastric route. The IN %F was 43% which is more than 3 times of the oral administration.

5

Example 2:

Sr No	Ingredient	%w/w
1	Eletriptan Hydrobromide (Beta Form)	2.500
2	Polyethylene Glycol 400	20.000
3	Propylene Glycol	20.000
4	Polysorbate 80	10.000
5	Butylated Hydroxyanisole	0.010
6	Butylated Hydroxytoluene	0.010
7	Disodium Edetate Dihydrate	0.050
8	Phenyl Ethyl Alcohol	0.500
9	Benzalkonium Chloride 50% Solution	0.05
10	Purified Water	QS to 100

Process:

1. Polyethylene glycol 400, propylene glycol and polysorbate 80 were mixed under continuous stirring,
2. the solution of step 1 at was heated $60\pm 5^{\circ}\text{C}$ and butylated hydroxyanisole and butylated hydroxytoluene were dissolved in it under continuous stirring,
3. phenyl ethyl alcohol and benzalkonium chloride 50% solution were mixed in the solution step 2 under continuous stirring at $60\pm 5^{\circ}\text{C}$,
4. eletriptan hydrobromide was dissolved in the solution of step 3 under continuous stirring at $60\pm 5^{\circ}\text{C}$,
5. disodium edetate dihydrate was dissolved in 25 g of purified water,
6. solution of step 5 was mixed with the solution of step 4 under continuous stirring at $60\pm 5^{\circ}\text{C}$ and the final weight was made up with purified water,

7. the solution of step 6 was filtered through PES filter and the nitrogen was purged in it at $50\pm 5^{\circ}\text{C}$ for 3 hrs.

Stability studies data:

Batch No. 25-F008								
Storage Condition	% Assay	%Related Substances				pH	% T	Description
		Ele 4	Ele Ethyl	Single Max Imp	Total Imp			
Initial	101.6	0.13	0.02	0.03	0.18	5.53	100	Light Yellow coloured clear liquid
2-8°C (1M)	100.90	ND	0.02	0.01	0.03	5.66	100.1	
RT (1M)	98.20	ND	0.02	0.02	0.04	5.51	98.91	
40°C/75% RH (1M)	98.20	ND	0.02	0.05	0.10	5.51	100.2	
50°C /80% RH (1M)	100.80	ND	0.02	0.07	0.19	5.22	99.49	

Batch No	25-F013						
Storage Period	Initial	3 Months			6 Months		
Storage condition		2-8	25/60	40/75	2-8	25/60	40/75
Description	Yellow Coloured Clear Solution						
Assay (%)	98.8	100	100.6	98.8	99.3	98.4	98.2
% Transmittance	99.9	100	100	99.9	99.9	99.9	99.6
RS (%)							
Ele 4	ND	ND	ND	ND	ND	ND	ND
Ele Ethyl	0.02	0.14	0.15	0.26	0.02	0.02	0.02
Any other Individual Unspecified Impurity	0.07	0.02	0.02	0.02	0.02	0.03	0.08
Total Imp	0.13	0.19	0.19	0.32	0.06	0.14	0.39

We claim:

1. An intranasal pharmaceutical composition comprising from about 1 mg to about 20 mg of at least one 5HT_{1B/1D} agonist or salts thereof, and at least one pharmaceutically acceptable excipient.
2. The intranasal pharmaceutical composition as claimed in claim 1, wherein at least one 5HT_{1B/1D} agonist or salts thereof is present from about 4 mg to about 12.5 mg.
3. The intranasal pharmaceutical composition as claimed in claim 1, wherein pH of the composition is below 7.
4. The intranasal pharmaceutical composition as claimed in claim 1, wherein 5HT_{1B/1D} agonist or salts thereof is selected from a group consisting of sumatriptan, rizatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, prodrug or mixtures thereof.
5. The intranasal pharmaceutical composition as claimed in claim 1, wherein the one or more pharmaceutically acceptable excipient comprises efflux modulator, one or more of cosolvents, isotonicity agents, chelating agents, preservative, pH adjusting agents, absorption promoters, viscosifiers, sweetener/taste masking agents, or mixtures thereof.
6. The intranasal pharmaceutical composition as claimed in claim 4, wherein the composition retains at least 80% of the potency of eletriptan or salts thereof in the pharmaceutical composition after storage for six months at room temperature.
7. The intranasal pharmaceutical composition as claimed in claim 4, wherein the composition retains at least 99% of the transmittance after storage for six months at room temperature.

8. The intranasal pharmaceutical composition as claimed in claim 4, wherein the composition when stored at 40°C/75% RH in closed vials for six months, the total amount of related substances does not increase more than 1.2%.
- 5
9. The intranasal pharmaceutical composition as claimed in claim 4, wherein the composition when stored at 40°C/75% RH in closed vials for six months, the amount of single specified impurity does not increase more than 0.5%.
- 10
10. An intranasal pharmaceutical composition comprising at least one 5HT_{1B/1D} agonist or salts thereof and at least one pharmaceutically acceptable excipient, wherein the intranasal composition provides at least two times increase in bioavailability than the current recommended doses of 5HT_{1B/1D} agonist or salts thereof.
- 15
11. The intranasal pharmaceutical composition as claimed in claim 10, wherein 5HT_{1B/1D} agonist or salts thereof is selected from a group consisting of sumatriptan, rizatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, prodrug or mixtures thereof.
- 20
12. The intranasal pharmaceutical composition as claimed in claim 10, wherein the one or more pharmaceutically acceptable excipient comprises efflux modulator, one or more of cosolvents, isotonicity agents, chelating agents, preservative, pH adjusting agents, absorption promoters, viscosifiers, sweetener/taste masking agents, or mixtures thereof.
- 25
13. An intranasal pharmaceutical composition comprising eletriptan or salts thereof, at least one efflux modulator and at least one pharmaceutically acceptable excipient, wherein the intranasal composition provides bioavailability (F) values of more than 10.
- 30

14. The intranasal pharmaceutical composition as claimed in claim 13, wherein the one or more pharmaceutically acceptable excipient comprises one or more of cosolvents, isotonicity agents, chelating agents, preservative, pH adjusting agents, absorption promoters, viscosifiers, sweetener/taste masking agents, or mixtures thereof.
15. A process of preparing an intranasal pharmaceutical composition as claimed in claim 1, the process comprising:
1. mixing one or more pharmaceutically acceptable excipients under continuous stirring at $60 \pm 5^\circ \text{C}$;
 2. dissolving the $5\text{HT}_{1\text{B}/1\text{D}}$ agonist or salts thereof to the solution of step (1) under continuous stirring at $60 \pm 5^\circ \text{C}$; and
 3. filtering and purging the solution of step (2) with nitrogen at $50 \pm 5^\circ \text{C}$ and pack in a suitable container.
16. A method of treating migraine or related disease conditions, wherein the method comprises administering an effective amount of an intranasal pharmaceutical composition as claimed in claim 1.
17. A pharmaceutical kit comprising an intranasal pharmaceutical composition as claimed in claim 1 and a nasal device for accurate delivery of the intranasal pharmaceutical composition.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/050177

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/00 A61K47/10 A61K31/404 A61K31/4045 A61K31/4196
A61K31/422 A61K31/454

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.



See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"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

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

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