ABSTRACT

INHALABLE FORMULATION FOR HEAVY METAL POISONING

The present invention provides an inhalable pharmaceutical formulation for preventing and/or treating heavy metal poisoning, said formulation comprising; a chelating agent selected from a group consisting of Ethylene diamine tetraacetic acid (EDTA) and Diethylene triamine pentaacetic acid (DTPA), or its salts, derivatives or mixtures thereof, having particle size in the range of 10 nm to 5000nm; at least one or more of an ingredient selected from 0.03-2% w/w of a surfactant on the weight of the chelating agent; and optionally one or more pharmaceutically acceptable excipients.

The pharmaceutical formulation of present invention is suitable for inhalation for used in treating, preventing, or in the management of heavy metal poisoning, including that radioactive materials, particularly those entering the body through the inhalation route. Typically, the mode of administration of pharmaceutical formulation of present invention includes either drug aerosols released through nebulization process from fluid formulations or through dry aerosols using Dry Powder Inhalation (DPI) methodology.

We claim:

1. An inhalable pharmaceutical formulation for preventing and/or treating heavy metal poisoning, said formulation comprising:

   a chelating agent selected from a group consisting of Ethylene diamine tetraacetic acid (EDTA) and Diethylene triamine pentaacetic acid (DTPA), or its salts, derivatives or mixtures thereof, having particle size in the range of 10 nm to 5000nm;

   atleast one surfactant in the range of 0.03-2% w/w on the weight of the chelating agent; and

   optionally one or more pharmaceutically acceptable excipients.

2. The formulation as claimed in claim 1, wherein the salts of the chelating agent are calcium or zinc salts.
3. The formulation as claimed in claim 1 , wherein the surfactant is selected from the group consisting of polysorbate 80, lecithin, chitosan and sodium lauryl sulfate, or mixtures thereof.
4. The formulation as claimed in claim 1, wherein the pharmaceutically acceptable excipients are selected from ethanol, isopropyl alcohol, lecithin, sodium lauryl sulfate, lactose, chitosan, polysorbate 80 (Tween 80), or combinations thereof.
5. The formulation as claimed in claim 1, wherein the formulation is in a form of a dry powder or a wet aerosol.
6. The formulation as claimed in claim 1 comprising:

   a chelating agent selected from a group consisting of Ethylene diamine tetraacetic acid (EDTA) and Diethylene triamine pentaacetic acid (DTPA), or its salts, derivatives or mixtures thereof, having particle size in the range of 10nm to 5000nm,

   0.02-1% w/w of surfactant on the weight of the chelating agent; and

   ethanol in the range of 90 to 110 times of weight of the chelating agent;

7. The formulation as claimed in claim 6, wherein the particle size is in the range of 100 nm to 400nm.
8. The formulation as claimed in claim 6, wherein the chelating agent is in the form of an aqueous or saline solution having concentration in the range of 0.1 to 15%; preferably 0.01-5%, and less than 1 mg for DPI.
9. The formulation as claimed in claim 1, comprising:

a chelating agent selected from a group consisting of Ethylene diamine tetraacetic acid (EDTA) and Diethylene triamine pentaacetic acid (DTPA), or its salts, derivatives or mixtures thereof in the range of 5 to 500 mg having particle size in the range of 10 nm to 5000nm; and

0.02-1% w/w of lecithin on the weight of the chelating agent.

10. The formulation as claimed in claim 9, wherein the particle size is in the range of 10-900 nm, preferably 60-300nm.

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To,
The Controller of Patents,
The Patent Office,
At New Delhi

FIELD OF INVENTION

The present invention relates to an inhalable pharmaceutical formulation comprising a chelating agent like EDTA or DTPA, its salt, derivative or mixtures thereof, at least one surfactant and optionally one or more pharmaceutically acceptable excipients. The formulation is in the form of Dry powder for Inhalation (DPI) or drug aerosol of micronic, submicronic or nano-particle size. These drug aerosols may be used for treating, preventing, or in the management of heavy metal poisoning, including that radioactive metals particularly those entering the body through the inhalation route.

BACKGROUND OF INVENTION

Heavy metals are chemical elements that have a specific gravity (a measure of density) at least five times that of water. The heavy metals most often implicated in human poisoning are lead, mercury, arsenic, thallium and cadmium. Some heavy metals, such as zinc, copper, chromium, iron, and manganese, are required by the body in small amounts, but these same elements can be toxic in larger quantities. Radioactive heavy metals of importance include uranium, plutonium, strontium, americium, polonium, cobalt etc.

Most heavy metals form complexes upon inhalation or absorption through the gastrointestinal tract. These complexes then bind to essential amino acids, precipitate proteins, inhibit enzymes, or enter cell directly, often causing cell deterioration and death. Many effects of heavy metal poisoning are reversible, particularly if treatment is begun at an early stage.

The treatment for most heavy metal poisoning is chelation therapy. A chelating agent specific to the metal involved is given either orally, intramuscularly, or intravenously. The three most common chelating agents are calcium disodium edentate, dimercaprol (BAL), and penicillamine. The Chelating agent encircles and binds to the metal in the body's tissues, forming a complex; that complex is then released from the tissue to travel in the bloodstream. The complex is filtered out of the blood by the kidneys and excreted in the urine. This process may be lengthy and painful, and typically requires hospitalization. Chelation therapy is effective in treating lead, mercury, and arsenic poisoning, but is not useful in treating cadmium poisoning. Thallium poisoning is treated with a combination of Prussian blue (potassium ferric hexacyanoferrate) and a diuretic,

because about 35% of it is excreted in the urine; however, if treatment is not started within 72 hours of ingesting the poisoning, damage to the patient's as shock, anemia, and kidney failure.

Chelation therapy is administering ethylenediamine tetraacetic acid (EDTA), a man-made amino acid, into the veins. EDTA has often been used in cases of heavy metal poisoning (lead or mercury) because it can bind these metals creating a compound that can be excreted in the urine. Besides binding heavy metals, EDTA also chelates calcium. This has lead to the speculation that EDTA could remove calcium deposits from buildup or calcific lesions in the arteries. At present, chelation therapy is normally administered intravenously to a patient who must remain relatively immobile. It is believed that oral ingestion of EDTA is impractical because stomach acids destroy its effectiveness. A single intravenous chelation treatment usually lasts about four hours and is generally administered three times a week for about three months. Patients often are advised to continue preventative treatment once or twice a month, over a two-year period. Such frequent immobilization inconveniences the patient, and requires considerably large and dedicated floor space at the administration facility. DTPA works the same way.

Current antidotes/treatments for heavy metal poisoning are generally limited to acute poisoning. Generally, the patient is given emesis-inducing compounds, such as syrup of ipecac, to induce vomiting in an attempt to rid the body of the substance. However, in the case of chronic poisoning, or when a substantial amount of the poison has already been absorbed into the bloodstream, such methods are ineffective. The present form of treatment essentially scavenges the metals ions from the blood but once the metals get entrapped in their target tissue, mostly, bone liver and muscles; it is not a particularly effective.

Inhalation route is the most common route for environmental poisoning. By using the same route for drug delivery, it can be ensured that the metals are chelated and thus are not available for the absorption in the body. The chelate metals harmlessly pass through the feces after transport into the throat through the muco-ciliary pathway. This route is a promising alternative due to the fact that the prevention of toxic metal at the entry level represents the best and most effective form of treatment. No such treatment modality however exists presently. Presently, there are no EDTA/DTPA based inhalation

formulations in the prior art. This is a new concept and new formulations, and new route of drug delivery of EDTA/DTPA or their congener molecules.

Summary of the invention

The present invention relates to therapeutic compositions and methods for the administration of calcium EDTA, DTPA and/or their salts like Zn, Ca etc by inhalation route and more particularly in micronic, submicronic or nano-particule either separately or in concert. The compositions can be wet drug aerosols formed by nebulization or such process, or dry powder formulations for treating heavy metal poisoning or radio-metal poisoning particularly that occurs through the inhalation route.

The present particularly relates to an inhalable pharmaceutical formulation for preventing and/or treating heavy metal poisoning, said formulation comprising a chelating agent selected from a group consisting of Ethylene diamine tetraacetic acid (EDTA) and Diethylene triamine pentaacetic acid (DTPA), or its salts, derivatives or mixtures thereof, having particle size in the range of 10 nm to 5000nm; atleast one surfactant in the range of 0.03-2% w/w on the weight of the chelating agent; and optionally one or more pharmaceutically acceptable excipients.

These and other features, aspects, and advantages of the present subject matter will become better understood with reference to the following description and appended claims. This Summary is provided to introduce a selection of concepts in a simplified form. It is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used to limit the scope of the claimed subject matter.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to an inhalable pharmaceutical formulation for preventing and/or treating heavy metal poisoning, said formulation comprising; a chelating agent selected from a group consisting of Ethylene diamine tetraacetic acid (EDTA) and Diethylene triamine pentaacetic acid (DTPA), or its salts, derivatives or mixtures thereof, having particle size in the range of 10 nm to 5000nm; atleast one surfactant in the range of 0.03-2% w/w on the weight of the chelating agent; and optionally one or more pharmaceutically acceptable excipients.

An embodiment of the present invention is an inhalable pharmaceutical formulation, wherein the salts of the chelating agent are calcium or zinc salts.

Yet another embodiment of the present invention is an inhalable pharmaceutical formulation, wherein the surfactant is selected from the group consisting of polysorbate 80, lecithin, chitosan and sodium lauryl sulfate, or mixtures thereof.

Yet another embodiment of the present disclosure is an inhalable pharmaceutical formulation, wherein the pharmaceutically acceptable excipients are selected from ethanol, isopropyl alcohol, lecithin, sodium lauryl sulfate, lactose, chitosan, polysorbate 80 (Tween 80), or combinations thereof.

Still another embodiment of the present disclosure is an inhalable formulation, wherein the formulation is in a form of a dry powder or a wet aerosol.

An embodiment of the present disclosure is an inhalable pharmaceutical formulation comprising a chelating agent selected from a group consisting of Ethylene diamine tetraacetic acid (EDTA) and Diethylene triamine pentaacetic acid (DTPA), or its salts, derivatives or mixtures thereof, having particle size in the range of 10nm to 5000nm; 0.02-1% w/w of surfactant on the weight of the chelating agent; and ethanol in the range of 90 to 110 times of weight of the chelating agent.

Further an embodiment of the present invention is an inhalable pharmaceutical formulation, wherein the particle size is in the range of 1000 nm to 5000nm.

Yet another embodiment of the present invention is an inhalable pharmaceutical formulation, wherein the particle size is preferably in the range of 100 nm to 400nm.

Still another embodiment of the present disclosure is an inhalable pharmaceutical formulation, wherein the chelating agent is in the form of an aqueous or saline solution having concentration in the range of 0.1 to 15%.

Another embodiment of the present disclosure is an inhalable pharmaceutical formulation, wherein the chelating agent is in the form of an aqueous or saline solution having concentration preferably in the range of 0.01-5%, and less than 1 mg for DPI.

An embodiment of the present invention is an inhalable pharmaceutical formulation comprising; a chelating agent selected from a group consisting of Ethylene diamine tetraacetic acid (EDTA) and Diethylene triamine pentaacetic acid (DTPA), or its salts,

derivatives or mixtures thereof in the range of 5 to 500 mg having particle size in the range of 10 nm to 5000nm; and 0.02-1% w/w of lecithin on the weight of the chelating agent.

Still another embodiment of the present invention is an inhalable pharmaceutical formulation, wherein the particle size is in the range of 10-900 nm.

Yet another embodiment of the present invention is an inhalable pharmaceutical formulation, wherein the particle size is in the range of preferably 60-300nm.

The method of this invention involves the administration of an effective amount, also referred to as an antidotal amount of various formulations describable as different embodiments of the present invention to a patient suffering from heavy metal poisoning. Administration is by inhalation route only. The method is effective against heavy metal poisonings which include lead, arsenic, mercury, copper, bismuth, platinum, palladium, barium, selenium, and other metals, mostly in their ionic form. One or more pharmaceutically acceptable excipients may also be added to provide for making elegant and more effective formulations. The description given below pertains to unit doses, which can be repeated again as per the clinical situation.

An embodiment of the present invention is a formulation wherein the drug molecules may be converted into colloidal particles in the range of submicron sized particles (300-1000 nanometers) or in the micron size range, preferably 1-5 micron size.

The dry preferably stabilized drug particles are packed in the capsules (as Dry Powder for Inhalation) either alone or after through mixing with inhalable commercial lactose or any other suitable vehicle. The capsules are broken down and contents inhaled with deep inspirational breath using standard DPI inhalation devices.

Yet another embodiment of the present invention is a formulation wherein the EDTA or its salts are substituted partially or fully by DTPA or its salts like Ca- DTPA, Zn-DTPA.

In an embodiment of the present invention the dose unit of the DPI formulations is designed to deliver 10 to 50 mg of the drug into the lungs per actuation. Thus the dose filled in the capsules range from 10 mg to 50 mg with or without other excipients.

In yet another embodiment of the present invention, wet aerosols of the drug is produced using various means which produce the drug aerosols less than 5 microns, preferably less than 1 micron, and particularly less than 500 nanometers. These wet drug

aerosols are then inhaled in deep inspiration oas common to all inhaled formulations for asthma, COPD and other respirable fluids.

One of the embodiments of the present invention is wet aerosols produced by EDTA or DTPA solution (or its salts such as calcium or Zn) consists of 0.1-15% water or saline drug solution preferably containing 2-50% of ethanol, particularly in the range of 20-30%. At the time of use, 1-3 ml of the solution of the formulation is poured into standard nebulization chamber and medical air compressors available commercially for producing wet aerosols. The drug aerosols thus produced are inhaled for appropriate time intervals directly or through specially designed spacers. The drug aerosols thus produced has particles less than 5 micron, more particularly less than 1 micron and still more particularly, less than 500 nanometers.

In an embodiment of the present invention, the EDTA or its salts are substituted partially or fully by DTPA or its salts like Ca-DTPA, Zn-DTPA.

The dose of wet aerosolized drug to reach lung is expected to be in the range of 10-60 mg. To reach this effective dosage range, 2-15 min inhalation is usually sufficient.

The present description describes in general the manufacture and working of the inhalable compositions of EDTA / DTPA and their salts and derivatives but without implying any limitation thereof.

Preparation of Dry Powder for Inhalation (DPI)

a) WET MICRONIZATION BY BALL MILLING AND HIGH PRESSURE HOMOGENIZATION

Particles are composed of a predominantly crystalline drug, with surfactants or stabilizing agents such as phosphatidyl cholines, PVA or pluronics. The surfactants were required to prevent crystal growth during size reduction (dependant upon time interval of milling or precipitation and to stabilize the suspension against aggregation by forming a thin coating on the crystal surfaces. Typically, 1-50% and more particularly 20-30% of the surfactant were required to stabilize the nanosuspension with mean sizes between 120 and 300 nm. For larger size particles, lesser or even nil surfactants maybe be used and less milling or precipitation time is needed. This amount is directly proportional to the specific surface area or inversely proportional to the surface-volume mean particle diameter. The potential

problems were the difficulty to decrease the size below certain limits for very ductile materials, potential contaminations with grinding media and/or adverse effects of the high shear and temperature on the chemical stability. These problems can be minimized/overcome by utilizing innovations while formulating nano-or microparticles, including direct controlled precipitation, with stabilizer, supercritical fluid extraction of emulsions and some other emulsion based particle formation processes.

b) CONTROLLED PRECIPITATION

Antisolvent precipitation of drug solution in a water miscible organic solvent was carried out followed by addition of a bridging solvent, which was immiscible or partially miscible with water using growth retarding stabilizing additives (poly vinyl alcohol, polysorbates, alginates, cellulose derivatives etc). Precipitation can also be achieved by quenching hot organic solution or aqueous organic solution of drug with cold organic solution or aqueous organic solution of drug. The challenge of particle size control in all techniques is that most molecules tend to form relatively large crystals. This is due to the competition between the nucleation and growth mechanisms, which normally yields particle within the 10-100 μm size range, or more by adjusting the various variables involved.

c) SPRAY FREEZE-DRYING TECHNIQUE

Atomization of an aqueous drug solution via a two fluid or an ultrasonic nozzle into a spray chamber filled with cryogenic liquid (liquid nitrogen) or halocarbon refrigerant such as chlorofluorocarbon or fluorocarbon. Modification of spray freeze drying process is instead of spraying the drug solution into the cryogenic medium, the drug solution is atomized and frozen simultaneously by mixing with liquefied gas or supercritical fluid such as CO_2.

d) PARTICLE FORMATION FROM LIQUID DISPERSED SYSTEMS

Emulsion based methods

The technique involve the preparation of double or triple emulsions with subsequent removal of the oil phase (a volatile organic solvent) through evaporation, non-solvent (antisolvent) extraction, or solvent dilution. Poly(I-Lactic acid) (PLA), poly(glycolic acid) and poly(lactide co glycolide)acid (PLGA) are the various biodegradable materials that have been investigated as a carrier to encapsulate drug molecule. The drawback is the manufacturing complexity of the process which has to be carefully monitored and controlled. Another problem is the difficulty to completely remove all residual organic solvents from the polymer matrix.

Emulsion polymerization method

This method includes emulsification of monomer in the non-solvent phase with surfactant molecules that lead to the formation of monomer-swollen micelles and stabilized monomer droplets. The polymerization reaction takes place in presence of initiator (physical/chemical) the function of which is to provide energy, which creates free reactive monomers in continuous phase which then collide with unreacted monomers that initiates polymerization reaction.

Coacervation process

It is the phenomenon of phase separation in oil between two liquid phases (differing only in composition of solute species eg. Polymer rich and solvent rich) induced by change in temperature, solution composition or pH. It typically follows by hardening of the dispersed phase to yield solid particles. The advantage of the process is the utilization of an aqueous system for the production of relatively uniform protein spheres in the respirable size range.

Multiple emulsion technique and evaporation

These techniques were widely employed for the encapsulation of high molecular weight molecules such as peptides or proteins inside polyester nanoparticles. The preformed polymer is dissolved in a volatile organic solvent (e.g. chloroform, me3thylene chloride), and the organic solution is dispersed in an aqueous phase in presence of surfactants (poloxamer, polysorbate, sodium dodecyl surfate) or a stabilizer such as PVA.

Evaporation of solvent is achieved by continuous emulsification under magnetic stirring result in precipitation of polymer and finally formation of nanospheres.

Supercritical fluid technologies

Supercritical fluids which are defined as compressed gases or liquids above their critical pressure and temperatures, involve rapid precipitation when a drug solution brought in contact with supercritical CO_2. This process is able to control the physical form of drug powders. Another technique involves particle formation using supercritical fluid extraction of emulsions in which extraction of organic phase in oil-in-water or multiple emulsion were carried out using SC-CO_2. This process combines the flexibility of particle engineering using different emulsion systems with the efficiency large scale, continuous extraction with SC-CO_2.

Quality control

Nano-particles /submicron particles prepared from the above methods are stable and they are characterized by SEM, TEM, particle size analyzer and impactor. Their stability is also checked using the same equipment periodically. The product stability should preferably be more than 6 months, and more preferably more than 18 months. Invitro and invivo scintigraphy may be performed for better and more detailed characterizations of the product. For DPI compositions, it is effective to radiolabel the particulate drug (nano, submicronic or micron-sized, as the case may be) without changing the size and then nothing the radioactivity distribution invivo to confirm the lung retention fraction. This helps to fix the initial prescribable dose.

The novel compositions can be given independently or combined with other provisional or regular treatments in known or suspected cases of heavy metal poisoning.

Administration of the formulation(s) should be made as soon as possible following diagnosis /therapeutic and industrial heavy metal poisoning. Preferred initial dose is

between 10-60 mg for nanoparticles, and about 2-5 times more for the larger particulate drugs, to be exactly estimated by scintigraphy experiments. The dose needs to be repeated at intervals and for periods determined medically. Careful observation and blood analysis is performed regularly after diagnosis as per accepted medical procedures for treating heavy metal poisoning.

Although the subject matter has been described in considerable detail with reference to certain preferred embodiments thereof, other embodiments are possible. As such, the spirit and scope of the appended claims should not be limited to the description of the preferred embodiment contained therein.

Examples

The disclosure will now be illustrated with working examples, which is intended to illustrate the working of disclosure and not intended to take restrictively to imply any limitations on the scope of the present disclosure.

Example-1

50 grams of disodium DTPA was mixed with 10 mg of lecithin, dried out and milled to 500 nanometer sized granules, divided into aliquots of 50 mg each and packed into appropriate DPI capsules.

Particle size analyzer was used every week on the sample capsules from the same batch as part of quality control.

Example-2

50 grams of disodium DTPA was mixed with 10 mg of polysorbate 80, dried out and milled to 500 nanometer sized granules, divided into aliquots of 50 mg each and packed into appropriate DPI capsules.

Particle size analyzer was used every week on the sample capsules from the same batch as part of quality control.

Example-3

50 grams of disodium DTPA was mixed with 10 mg of lecithin and 5000 grams of ethanol was mixed with double distilled water to give 2% drug solution (2grams per 100 ml). 2 ml of the solution was nebulized using standard nebulization equipment and a large spacer for reducing drug wastage, into which the patient inspired and expired again for a few minutes. The procedure continues for several minutes, till the solution dries up.

As a quality control measure and to estimate the amount of drug internalized, and to find the duration of effect of the drug, a tracer quantity of Tc-99m DTPA was mixed with one of the aliquots and inhaled as discussed above.

The internalized drug was calculated in real time by taking the radioactivity in the nebulization chamber as 100% and the activity in the lungs and body as the internalized fraction in terms of milligrams as well as percentage. Serial images were taken and the diminishing curve of radioactive label fouy in the lungs extrapolated to estimate the bioavailability of the drug in the lungs, and consequently the duration of action of the drug per nebulization.

Advantage of this invention:

The previously described versions of the subject matter and its equivalent thereof have many advantages, including those which are described below:

1. It involves trapping of the toxic metals ions at the entry level in the lungs which is the most common portal of entry in many clinical situations. Once inhaled, the chelating agent tends to remain in the lung area for a long time, 4-10 hours in the optimum concentration, so that only a few inhalation procedures can offer 24-hr protection. Inhaled EDTA, DTPA or their salts enter the blood and have systemic action over and above the main function of local trapping in the lung area.
2. Radio labeling of DTPA can be carried out to use the product for scintigraphy study for ventilation scan. The characterization of efficiency of inhalation can be done and inter/intra batch variation checked by radio labeling with ^{99m}Tc.
3. EDTA, DTPA and/or their salts do not get absorbed from GIT and pass through it; hence there is no possibility of accumulation in side the body. Lungs act as a sustained-

released system for the GIT so more effective than oral dosage formulation. Any metal ion in the GIT will therefore get chelated in addition to the main action in the lung parenchyma.

4. The efficiency of chelation will be higher in the lung region in comparison to blood, extracellular fluid or even GIT due to the confined nature of the ligand as well as the antidote.
5. Inhaled antidotes can be given both as a preventive and therapeutic measure, and are useful for the rescue teams as well as the victims.
6. The formulations are absolutely safe and the drug molecules are used in much smaller quantities as are usually given systematically.
7. The DPI of the present invention gets deposited in the lung parenchyma in a higher concentration and therefore is more effective as compared to normal DPIs which deposit only 5-10% drug in the lung spaces. The new formulations deposit 40% - 80% drug in the lung parenchyma. Reversible action is observed as it passes through lungs then trachea followed by stomach as half life of stomach emptying with its peristalsis.