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Method of Ameliorating Oxidative Stress and Supplementing the Diet

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(12) United States Patent

Haley et al.

(54) METHOD OF AMELIORATING OXIDATIVE STRESS AND SUPPLEMENTING THE DIET

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- (58) Field of Classification Search None See application file for complete search history.

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ABSTRACT (57)

A method of supplementing a diet and ameliorating oxidative stress in a mammal includes administering a pharmaceutically effective amount of lipid soluble, hydrophobic active compounds having a chemical structure:



wherein R¹ is an aromatic backbone and R² is a sulfur containing ligand. Through formation of disulfide linkages other moieties can be attached to R² converting the hydrophobic base into a water soluble entity, for ease of delivery, which can be reconverted back to the original compound by biochemical reduction in the blood stream.

45 Claims, No Drawings

METHOD OF AMELIORATING OXIDATIVE STRESS AND SUPPLEMENTING THE DIET

This application is a continuation-in-part (CIP) of U.S. patent application Ser. No. 12/731,415 filed on 25 Mar. 2010, ⁵ the full disclosure of which is incorporated herein by reference.

TECHNICAL FIELD

The present invention relates generally to the field of dietary supplements for mammals and, more particularly, to methods of supplementing a diet, removing heavy metals and other toxins and ameliorating oxidative stress.

BACKGROUND OF THE INVENTION

Heavy metals such as mercury, lead, cadmium and silver can bind to proteins on the proteins' incorporated cysteine residues which contain sulfhydryl or -SH groups. This 20 abnormally inhibits or activates their biological properties. Further, a heavy metal binding specific proteins can induce damage that leads to overproduction or leakage of reactive oxygen species (ROSs) from their normal locations. These ROSs, mostly produced in the mitochondria of the cells of the 25 body, then react with protein, nucleic acid (DNA, RNA) and lipid molecules in the healthy cell changing their property/ chemistry and leading to unhealthy cells that may die or at least be unable to defend themselves from other stress factors such as viral infection. In addition to heavy metals there are 30 many other chemical toxicants that can induce oxidative stress including, for example, radiation toxicity, acetominophen and dioxin. Further, it is well known that the oxidation of reduced glutathione (GSH) to oxidized glutathione (G-S-S-G) is one of the first biochemical signals for apoptotic cell 35 death (or programmed cell death). The inadvertent oxidation of GSH by toxin produced ROSs could lead to increased GSSG and cell death also. In the healthy body GSH accomplishes protection against heavy metal toxicity, organic toxins and hydroxyl free radical damage due to its chemical ability 40 to; (1) chelate heavy metals, (2) its use by the enzyme glutathione-S-transferase (GST) to produce GS-toxin complexes that are actively removed from the intracellular location into the blood and then actively removed from the blood by GStoxin receptors in the bilary transport system of the liver and 45 into the bile and feces and (3) GSH's ability to scavenge and eliminate hydroxyl free radicals.

It is well known that excess exposures to heavy metals, above the capacity of the normal cellular GSH capability to bind and remove, inhibit the enzymes involved in the synthe-50 sis of GSH and the recovery of oxidized GSH from GSSG (oxidized glutathione) leading to decreased GSH levels that are identified as oxidative stress. Also, such heavy metal excesses lead to an overproduction of free radicals by the mitochondrial and further oxidizes GSH to GSSG and 55 decreases the cells ability to remove toxins (organic and heavy metals) by the lowering of the intracellular concentration of GSH. Therefore, an ideal way to recover GSH levels would be to develop a non-toxic compound with membrane penetrating abilities, heavy metal binding properties and 60 reactive oxygen species scavenging properties that were superior to GSH.

With these properties a well designed compound with both heavy metal chelation properties and antioxidant properties could; (1) easily penetrate cell membranes and the blood 65 brain barrier, (2) bind heavy metals preventing their inhibition of enzymes needed to synthesize GSH and recover GSH

from GSSG, (3) decrease free radical formation by reversing heavy metal inhibition of the mitochondrial electron transport system, and (4) scavenge hydroxyl free radicals preventing oxidation of naturally produced GSH to GSSG. With these four properties such a compound could dramatically increase intracellular GSH and reduce free radical damage and allow the cells to recover to a normal state. In addition, the increase in intracellular GSH would allow GST to remove organic toxins built up during periods of toxicity and enhance the ability of the P-450 system to further detoxify the subject using the natural system. For example, it is well known that GSH is directly involved in binding to components of viral replication systems inhibiting viral replication. Low GSH levels are a major risk factor for several viral infections and high GSH seems involved in reversing and preventing such viral infections.

In order to medically prevent or reduce the oxidative stress problem identified as low GSH levels, heavy metals must be excreted by natural means or complexed by medically based chelator compounds that render them biologically unavailable to elicit their toxic effects. To effect this removal and tightly bind the heavy metals, the treating compound must be able to effectively remove the metal from the single sulfur residue and bind it more tightly than is capable with only one sulfur to metal bond. That is, the compound must make at least two intramolecular sulfur to metal bonds to be able to prevent subsequent reaction or exchange of the complexed metal with other biomolecules. This requires that the chelating molecule contain at least two sulfhydryls that are one extended arms that allow for extended freedom of rotation and movement of the sulfhydryls so that the most stable orientiation for binding the heavy metal can be obtained. For example, the ideal chelating compound must have degrees of freedom of rotation and movement of the sulfur bonds to be able to bind different heavy metals that have different coordination chemistries (e.g. different bond angles that confer tighter bonding). For example, Hg²⁺ and Pb²⁺ both can form two bonds with -SH groups, but the most stable binding of each metal would have different bond angles.

To be effective at treating both intracellular heavy metal toxicity and radiation toxicity as well as oxidative stress associated therewith, the treating compound has to be able to cross the cellular membrane with efficiency and, if the brain is involved, the treating compound must be able to cross the blood brain barrier. In order to be able to do this the compound has to be quite hydrophobic in nature in order to be able to pass through the lipid bilayer of the cell membrane to reach the site of heavy metal binding and intercept the ROS produced by the mitochondria before they react and damage cellular constituents. Further, the ideal treating compound must be of very low toxicity to cells and not disrupt membranes or biological pathways and it should not be involved in any natural metabolism that would destroy its physical character. In addition, the treating compound must be efficiently excreted from all tissues of the body in a non-toxic form. For example, if the treating compound binds mercury cation (Hg^{2+}) it must carry this metal ion out of the body and not distribute it to other organs such as the kidney.

The ideal treatment compound must also exhibit stability to air oxidation and breakdown so that the treating compound can be effectively stored and packaged for delivery to the patient in original, active form. The treating compound ideally must also be suited for ease of administration to a patient. Further, the treating compound must not deplete the body of essential metals such as zinc and copper. In addition, it should also have an adequately long plasma half-life such that it is possible to take eight hours rest and not have the treating compound significantly depleted from the plasma and tissues.

The present invention relates to methods of supplementing the diet of a mammal, removing heavy metals and other toxins 5 from a mammal and ameliorating undesirable oxidative stress in a mammal using a single molecule with cell membrane penetrating abilities, metal chelation and oxygen radical scavenging properties, and non-toxic character. To aid in intraveneous delivery, some hydrophobic (lipophilic) com-10pounds are made to be hydrophilic by formation of hydrophilic (water soluble) analogs via attachment by disulfide linkages that are converted after delivery by the body's reducing capability back to the hydrophobic state. Other compounds have the reverse ability in that they are delivered as 15 hydrophobic esters and converted intracellular, by well known esterases, into water soluble, hydrophilic compounds that are more excretable through the kidneys.

SUMMARY OF THE INVENTION

In accordance with the purposes of the present invention as described herein, a method of supplementing a diet of a mammal is provided. That method comprises: administering to said mammal a pharmaceutically effective amount of a ²⁵ compound having a chemical formula:

$$R^2 R^2 R^2$$





 teine, alphadihydrolipoic acid, cystamine, thiolphosphate,
 5'thioladenosine, L-homocysteine, co-enzyme A, 2-mercaptoethanol, dithiothreitol, iodoacetate, bromoacetate, fluoro-

where R¹=

acetate or chloroacetate and n=2-4. The R⁴ attachment, other than hydrogen, converts the hydrophobic base compound to a hydrophilic, water soluble compound. The R³ attachment makes the base compound susceptible to esterase conversion intracellular into a hydrophilic compound.

In accordance with yet another aspect of the present invention, a method to remove heavy metals and toxins from a mammal comprises: administering to said mammal a pharmaceutically effective amount of a compound having a 10 chemical formula:

$$R^2$$
 R^2 R^2

where R¹=





where R²=



where R³=ethyl or methyl, R⁴=hydrogen, glutathione, cysteine, alphadihydrolipoic acid, cystamine, thiolphosphate, 55 5'thioladenosine, L-homocysteine, co-enzyme A, 2-mercaptoethanol, dithiothreitol, iodoacetate, bromoacetate, fluoroacetate or chloroacetate and n=2-4. The R⁴ attachment, other than hydrogen, converts the hydrophobic base compound to a hydrophilic, water soluble compound. The R³ attachment 60 makes the base compound susceptible to esterase conversion intracellular into a hydrophilic compound.

In accordance with yet another aspect of the present invention a method is provided for relieving oxidative stress in a 65 mammal. That method comprises: administering to said mammal a pharmaceutically effective amount of a compound having a chemical formula:

R2

where R¹=







where R3=ethyl or methyl, R4=hydrogen, glutathione, cysteine, alphadihydrolipoic acid, cystamine, thiolphosphate, ⁴⁰ 5'thioladenosine, L-homocysteine, co-enzyme A, 2-mercaptoethanol, dithiothreitol, iodoacetate, bromoacetate, fluoroacetate or chloroacetate and n=2-4. The R^4 attachment, other than hydrogen, converts the hydrophobic base compound to a hydrophilic, water soluble compound. The R³ attachment 45 makes the base compound susceptible to esterase conversion intracellular into a hydrophilic compound.

In accordance with yet another aspect of the present invention, a pharmaceutical composition is provided comprising: a pharmaceutically effective amount of a compound hav-50 ing a chemical formula:



where R¹=

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and 20 where R²=



30 where R³=ethyl or methyl, R⁴=hydrogen, glutathione, cysteine, alphadihydrolipoic acid, cystamine, thiolphosphate, 5'thioladenosine, L-homocysteine, co-enzyme A, 2-mercaptoethanol, dithiothreitol, iodoacetate, bromoacetate, fluoro- $_{35}\,$ acetate or chloroacetate and n=2-4; The R⁴ attachment, other than hydrogen, converts the hydrophobic base compound to a hydrophilic, water soluble compound. The R³ attachment makes the base compound susceptible to esterase conversion intracellular into a hydrophilic compound. and 40

a pharmaceutically acceptable excipient.

In accordance with yet another aspect of the present invention, a pharmaceutical composition is provided comprising:

between about 99.5 and about 5 weight percent of a pharmaceutically effective amount of a compound having a 45 chemical formula:



where R¹=

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and where R²=



- where R3=ethyl or methyl, R4=hydrogen, glutathione, cys-25 teine, alphadihydrolipoic acid, cystamine, thiolphosphate, 5'thioladenosine, L-homocysteine, co-enzyme A, 2-mercaptoethanol, dithiothreitol, iodoacetate, bromoacetate, fluoroacetate or chloroacetate and n=2-4; The R⁴ attachment, other than hydrogen, converts the hydrophobic base compound to a ³⁰ hydrophilic, water soluble compound. The R³ attachment makes the base compound susceptible to esterase conversion intracellular into a hydrophilic compound.
- between about 0.0 and about 50 weight percent of an additional antioxidant; 35
 - between about 0.0 and about 20 weight percent of a water soluble metal chelator;
 - between about 0.0 and about 50 weight percent of glutathione;
- 40 between about 0.0 and about 50 weight percent of an additional dietary supplement that supports glutathione synthesis; and

between about 0.5 and about 50 weight percent of a phar-45 maceutically acceptable excipient.

In the following description there is shown and described several different embodiments of the invention, simply by way of illustration of some of the modes best suited to carry out the invention. As it will be realized, the invention is 50 capable of other different embodiments and its several details are capable of modification in various, obvious aspects all without departing from the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION

The present invention relates to various methods of supplementing the diet of a mammal, removing heavy metals and other toxins from a mammal and relieving or ameliorating 60 oxidative stress in a mammal. Each of the methods relies upon administering to said mammal a pharmaceutically effective amount of a compound having a chemical formula:

$$R^2 \xrightarrow{R^1} R^2$$





and

where R²=



where R³=ethyl or methyl, R⁴=hydrogen, glutathione, cysteine, alphadihydrolipoic acid, cystamine, thiolphosphate, 5'thioladenosine, L-homocysteine, co-enzyme A, 2-mercaptoethanol, dithiothreitol, iodoacetate, bromoacetate, fluoroacetate or chloroacetate and n=2-4. The R⁴ attachment, other than hydrogen, converts the hydrophobic base compound to a hydrophilic, water soluble compound. The R³ attachment makes the base compound susceptible to esterase conversion intracellular into a hydrophilic compound. The active compounds and their synthesis are described in detail in copending U.S. patent application Ser. No. 12/731,415 filed Mar. 25, 2010, the full disclosure of which is incorporated herein by reference.

The pharmaceutically effective amount of the compounds 55 in question may be administered in any appropriate manner including, but not limited to, oral administration, transdermal administration, nasal administration, intravenous administration and administration by suppository. The method of supplementing a diet of a mammal includes administering 60 between about 0.5 and about 40.0 mg of the compound per kilogram of the mammal's total body weight per day although, due to the lack of toxicity higher dose levels are acceptable. The compound may be administered in combination with another antioxidant or chelator. That antioxidant 65 may be selected from a group including but not limited to vitamin-E, vitamin-D, cysteine, cystine, glutathione, lipoic acid and combinations thereof.

In the method of removing heavy metals and other toxins from a mammal, the compound is administered in an amount between about 0.5 and about 60.0 mg per kilogram of the mammal's total body weight per day. In this method the compound may be administered with a water soluble metal 5 chelator. That water soluble metal chelator may be selected from a group consisting of glutathione (GSH), dihydrolipoic acid (DLPA), lipoic acid (LPA), N-acetylcysteine (NAC), dimercaptopropane sulfonate (DMPS), dimercaptosuccinic acid (DMSA), ethylenediaminetetraacetic acid (EDTA), and 10 mixtures thereof. It should be appreciated, however, that other water soluble metal chelators besides those listed could be utilized.

In the method of relieving oxidative stress in a mammal the compound may be administered orally, transdermally, 15 nasally, intravenously, injected subcutaneously, by suppository and other appropriate methods. Typically the compound is administered in an amount of between about 0.5 and about 100.0 mg of the compound per kilogram of the mammal's total body weight per day. The exceptionally low level of 20 mammalian toxicity would also allow higher doses to be used in cases of acute toxicity or high oxidative stress. Here, it should also be noted that the present method may be used to treat oxidative stress resulting from virtually any cause or source including, but not limited to, heavy metal toxicity, 25 drugs such as acetaminophen, xenobiotics, aging, infection, physical injury and disease.

These compounds are not used to directly produce intracellular glutathione and work primarily by salvaging naturally produced reduced glutathione (GSH) by the process of scav- 30 enging the intracellular ROSs preventing the oxidation to oxidized glutathione (GSSG). Also, the inhibitory binding of Hg²⁺ and Pb²⁺ and their removal from enzyme involved in the synthesis (e.g. glutatmine synthetase) and recovery of GSH (e.g. glutathione reductase) would additionally aid in the 35 recovery of GSH to optimal levels. In accordance with an additional aspect of the present invention the compound may be administered with a precursor of glutathione. That glutathione precursor may be selected from a group of precursors consisting of cysteine, N-acetylcysteine, glycine, glutamate 40 and combinations thereof. Also, removal of heavy metals from the iron-sulfur centers and other elements of the mitochondrial electron transport system would dramatically reduce the mitochondrial production of hydroxyl free radicals. It is well known that heavy metals make the mitochon- 45 dria into hydroxyl free radical producing species where one heavy metal atom can cause the production of orders of magnitude higher levels of hydroxyl free radicals.

In yet another possible embodiment the compound is administered with a dietary supplement that supports glu- 50 tathione synthesis. Such dietary supplements include, but are not limited to, whey protein, N-acetylcysteine, cysteine, glutathione, nicotine adenine dinucleotide (NAD⁺), reduced nicotine adenine dinucleotide (NADH), glycylcysteine (glycyc), glutamylcysteine (glu-cys), and combinations thereof. 55

The compounds used in the present invention provide a number of unique benefits that make them attractive for use in methods of (a) supplementing the diet, (b) removing heavy metals and other toxins and (c) ameliorating oxidative stress in mammals. Many of the compounds exhibit very low if any 60 toxicity and do not adversely affect commonly used blood/ urine tests commonly used to measure human health. This low toxicity is attributed to the fact that the aromatic rings are attached to the sulfhydryl containing chains via an amide connection that contains a carboxylate attached to the aromatic system. Any cleavage of this bond would produce an aromatic carboxylate. Benzocarboxylate (e.g. monosodium

benzoate, a food preservative) and many other benzoates, and other more complex carboxylated aromatic ring systems, are not usually toxic due to their hydrophilic nature and ease of excretion.

Advantageously the base compounds with hydrogen at R⁴, are lipid soluble and, accordingly, after entering the plasma can enter cells of all tissues, cross the blood brain barrier and enter the bone marrow. This is important because the damage caused by heavy metals and the oxidative stress produced by hydroxyl free radicals and other free radicals of the reactive oxygen species mostly occur in the intracellular space. In contrast, most dietary antioxidants are water soluble and cannot enter into cells effectively nor can they cross the blood/ brain barrier. As a further advantage, the lipid solubility of the compounds increases the time they spend in the body allowing them to be more effective at chelating heavy metals and scavenging hydroxyl free radicals. Chemical attachment of charged, natural compounds through the disulfide linkage produces water soluble analogs (for intravenous application) of the base compounds which would be rapidly reduced in the blood back to the original hydrophobic compounds and allow cell membrane permeation. Additionally, compounds containing the methylester and ethylester linkages offer the advantage of being made into charged water soluble species by enzymatic action of the natural esterases found in the mammalian body. This compound form starts out hydrophobic, can penetrate cell membranes after which it is convertible to the charged water soluble species by intracellular esterase activity, which may have advantages for excretion through the kidneys.

The compounds do not detectably disrupt any biochemical process in a mammal. They simply partition into the hydrophobic areas, bind heavy metals, react with free radicals eliminating them and are then excreted from the body primarily through the biliary transport system of the liver. The pharmaceutical compositions of the present invention are characterized by having relatively high ORAC (Oxygen-Radical-Absorbance-Capacity) scores. The ORAC score is measured by a compound or composition's ability to enter separate reactive oxygen species or free radicals and prevent them from oxidizing a water soluble fluorescent vitamin-E derivative. The pharmaceutical compositions of the present invention have the ability in the body to protect vitamin E (a fat soluble vitamin) and other fat soluble natural compounds such as lipids from damage by oxidizing free radicals since the compositions partition into the hydrophobic areas where they exist and react with free radicals more effectively thereby scavenging the hydroxyl free radicals and preventing them from doing damage. Significantly, vitamin-E has been recommended for Alzheimers diseased subjects to prevent oxidizing damage to their brain membranes or membrane lipids due to vitamin's E reactivity with hydroxyl free radicals. The pharmaceutical compositions of the present invention are more capable of reacting with these radicals than vitamin E and, accordingly, the pharmaceutical compositions should provide even better protection. Mass Spectrometry evaluations of some of the compounds after incubation with human and rat liver homogenates have shown that the major products produced were those with two and three oxygen atoms attached to the terminal sulfhydryl groups. This would convert the sulfhydryl (-SH) to higher oxidized levels such as sulfites (-SO3-) which are charged and eliminated through the kidneys.

The pharmaceutical compositions of the present invention are also characterized by an ability to increase the reduced (GSH) over oxidized (GSSG) glutathione ratio as well as to increase the total glutathione in the whole blood. Thus, more

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glutathione is available to scavenge free radicals and participate in the p-450 system to remove insoluble organic toxins from the membranes and cells. Thus, the body is better able to maintain a healthy glutathione level when the diet of the mammal is supplemented with compositions of the present ⁵ invention.

Further, the pharmaceutical compositions of the present invention are characterized by good stability when stored. They also generally exhibit a very low odor level thereby $_{10}$ making them more palatable for oral administration.

Generally, the pharmaceutical compositions of the present invention are better than glutathione delivered by IV or transdermally for increasing the intracellular level of glutathione. The rationale behind this is based on the very low level of glutathione found in the plasma versus the intercellular levels which are one thousand to ten thousand times higher. Any glutathione molecule that enters the blood by IV or transdermal delivery is immediately bound and removed by the glu-20 tathione receptors in the liver that are used to take glutathione labeled toxins and viruses out of the plasma and place them in the bile (biliary transport system). Glutathione in the blood would not remain long enough to enter cells where it could be used, plus do to its highly charged character (2 negative and 1 $_{25}$ positive charges/molecule) GSH would have to enter via specific carriers in the face of a significant concentration gradient that would prevent this. This statement is based on the fact that many water insoluble toxicants are removed from the body by first oxidizing them, attaching glutathione (by the 30 enzyme glutathione-s-transferase) to this oxidized site on the toxin, then actively transporting the glutathione labeled toxicant out of the cell and into the blood where it is actively removed by the glutathione receptors of the biliary transport system. In contrast, pharmaceutical compositions of the 35 present invention face no concentration gradients and can enter all cells and due to their hydrophobic nature, insert to some degree into the lipid membrane or other hydrophobic sites where they can scavenge hydroxyl free radicals, the 40 major chemical species that oxidize glutathione and cause its levels to drop. The pharmaceutical compositions salvage naturally produced glutathione intracellular enhancing its longevity and raising glutathione levels in-vivo without having to battle transport across a membrane against a high 45 gradient of glutathione.

Pharmaceutical compositions of the present invention may be prepared by combining a pharmaceutically effective amount of a compound having a chemical formula:















where R³=ethyl or methyl, R⁴=hydrogen, glutathione, cysteine, alphadihydrolipoic acid, cystamine, thiolphosphate, 5'thioladenosine, L-homocysteine, co-enzyme A, 2-mercaptoethanol, dithiothreitol, iodoacetate, bromoacetate, fluoroacetate or chloroacetate and n 2-4, with an excipient. Sub- 35 stantially any suitable excipient may be utilized including but not limited to albumin, almond oil, ascorbic acid, benzoic acid, calcium stearate, canola oil, calcium carboxymethylcellulose, sodium carboxymethylcellulose, castor oil, hydrogenated castor oil, microcrystalline cellulose, corn oil, cotton 40 seed oil, cyclodextrins, ethylene glycol palmitostearate, gelatin, glycerin, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, hypermellose, low-substituted hydroxypropyl cellulose, lanolin, linoleic acid, magnesium silicate, magnesium stearate, medium-chain triglyc- 45 erides, mineral oil, olive oil, peanut oil, pectin, compressible sugar, sunflower oil, hydrogenated vegetable oil, water and combinations thereof. In order to provide multiple antioxidant potential, the pharmaceutical compositions may further include other antioxidants including, but not limited to vita- 50 min-E, vitamin-D, cystine, glutathione, lipoic acid and combinations thereof. Further the pharmaceutical compositions may include a water soluble metal chelator to enhance removal of toxic metals both through the liver and kidney and with an enhanced rate. Substantially, any suitable water 55 soluble metal chelator may be utilized including but not limited to glutathione (GSH), dihydrolipoic acid (DLPA), lipoic acid (LPA), N-acetylcysteine (NAC), dimercaptopropane sulfonate (DMPS), dimercaptosuccinic acid (DMSA), ethylenediaminetetraacetic acid (EDTA), and mixtures thereof. Fur- 60 ther, in order to further enhance the levels of glutathione in the subject, the pharmaceutical compositions may include a precursor of glutathione which may be selected from a group including but not limited to cysteine, glycine, glutamate and combinations thereof. Further pharmaceutical compositions may include a dietary supplement that supports glutathione synthesis. Substantially any appropriate dietary supplement

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that supports glutathione synthesis may be utilized including but not limited to whey protein, N-acetylcystein, cysteine, glutathione, nicotine adenine dinucleotide (NAD⁺), reduced nicotine adenine dinucleotide (NADH), glycylcysteine (glycys), glutamylcysteine (glu-cyc), and combinations thereof. Pharmaceutical compositions may also include various binders, preservatives, mineral supplements, bulking agents, diluents, carriers, flavoring agents that are widely known to be used in pharmaceutical compositions. Exemplary pharma-10 ceutical compositions include between about 95.5 and about 85 weight percent active compound, between about 0.5 and about 15 weight percent excipient. The optional additional antioxidant(s) may be provided at between about 0 and about 50 weight percent. The optional additional water soluble metal chelator may be provided at between about 0 and about 20 weight percent. The optional additional precursor of glutathione may be provided at between about 0 and about 50 weight percent. Further the optionally additional dietary supplement that supports glutathione synthesis may be provided at between about 0 and about 50 weight percent. One or 20 more of any of the optional additives may be included. The optional additive replaces a like percentage of the compound in the final composition.

Preferred dosage forms for oral administration include the 25 isolated compounds in powder form. Such powders may be taken up with a scoup and spread onto food or mixed into drinks for easy consumption without bad taste. The pure compounds may be pre-mixed with certain dietary ingredients such as butter, olive oil, corn oil, albumin, whey or other foods which will help in absorption of the compounds by the mere process of dissolving them. It has been determined that it takes about two hours post ingestion for the maximum level of active ingredient to show up in the plasma of all tested animals. Further, after 24 hours post-ingestion the active ingredient levels were shown to drop between 4-12% of the peak values seen at hour 2.

Some of the commercially available solubilizers that can be used for parenteral (injectible), oral, topical or intranasal delivery in different combinations and ratios according to need include: (a) co-solvents such as polyethylene glycol 300/400, Macrogol 300/400, Lutrol E300/E400, propylene glycol, Soluphor P and NMP; (b) PEG derivatives such as Cremophor RH40, Cremophor EL/ELP and Solutol HS-15; and (c) polyoxamers such as Lutrol F68, Lutrol F127, Lutrol Micro 68 and Lutrol Micro 127.

The pure compound may be encapsulated in several weight forms (eg. 50, 100, 200, 500 mg/capsule) and taken orally. The pure compound may be mixed with excipients (eg. microcrystalline cellulose, hypermellose, magnesium stearate) to provide a mixed material that can be efficiently encapsulated by machines for mass production at a rapid rate.

The pure compound may also be made into tablet form by mixing with common agents or binders used to induce adhesive properties for tablet formation.

Any of the other hydrophobic compounds may be dissolved in simple oils and applied to the skin. The compounds dissolved in DMSO (dimethylsulfoxide) are rapidly taken up through the skin without local irritation. Also, dissolving the compounds in warm butter allows them to be applied transdermally.

The compounds may be placed in suppository capsules either in powder form or dissolved in oils or as mixed with protein based material (eg. human serum albumin, HSA) for delivery. The compounds may also be dissolved in human serum albumin for intravenous delivery. Similarly, blood could be pulled from a patient and the compounds added to that blood before being returned to the patient. This property

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is allowed as HSA is a water soluble protein with hydrophobic areas designed to carry natural hydrophobic molecules through the blood to cells where they are transferred to cell membranes.

The compositions and methods of the present invention 5 may be accomplished by various means which are illustrated in the examples below. These examples are intended to be illustrative only as numerous modifications and variations will be apparent to those skilled in the art.

EXAMPLE 1

Compounds have been produced and used by test animals and humans in pure powder form in resealable plastic bags accompanied with a pharmaceutical spoon that allows delivery of compound at 50 to 100 mg/spoonful. The pure powder can be taken directly into the oral cavity for sublingual delivery or mixed with foods and drinks. The mixing of these compounds has been done with oily foods such as butter, olive oil, peanut butter to enhance their solubilization prior to ingestion and uptake in the digestive tract.

EXAMPLE 2

Compounds have been mixed with excipients magnesium stearate, microcrystalline cellulose, hypermellose and silicon dioxide to form a pharmaceutical composition administered in capsules of 50, 100 and 200 mg quantities of compound for oral ingestion by humans.

EXAMPLE 3

Compounds have been dissolved in natural oils such as olive oil, cod liver oil, corn oil, butter and taken orally by humans.

Compounds have been dissolved in natural oils such as olive oil, cod liver oil, corn oil, butter and applied to the skin with rubbing to affect a transdermal delivery of the compound into humans.

EXAMPLE 5

Compounds have been dissolved in DMSO (dimethylsulfoxide):isotonic sodium chloride (25%:75% mixtures) and injected subcutaneously into test animals with excellent ⁴⁵ results.

EXAMPLE 6

Compounds have been dissolved in Solutol HS 15 and ⁵⁰ NMP mixtures for both subcutaneous and intravenous delivery into test animals as follows:

1. Prepare 1:1 w/v of NMP and Solutol HS 15

2. Weigh out the required amount of the pharmaceutically effective compound in powder form. 55

3. Add required amount of the 1:1 mixture. (20% of final volume)

4. Vortex to make sure that the compound is in solution.

5. Slowly add the Normal saline (80% of final volume)

6. Sonicate for a few minutes to get a clear solution.

EXAMPLE 7

Pharmaceutically effective compounds of the invention have been dissolved in Cremophor and ethyl alcohol mixtures 65 for both subcutaneous and intravenous delivery into test animals as follows: 1. Prepare a 1:1 w/v of ethyl alcohol and Cremophor.

- 2. Weigh out the required amount of OSR#1 powder.
- 3. Add the required amount to the 1:1 mixture.
- 4. Vortex to make sure OSR is in solution.
- 5. Sonicate if necessary for a few minutes.
 - 6. Slowly add Normal Saline 50 to 80% of the final volume.

EXAMPLE 8

A dosing solution for intravenous administration (IV) into test animals was prepared at 1 mg/mL in a formulation consisting of 80% normal saline (NS) and 20% of a 1:1 mixture of N-methylpyrrolidone (NMP) and Solutol HS15. This was used successfully to determine the plasma half life of one of the compounds in mice.

EXAMPLE 9

Medicament and/or preparation of dosage form. To prepare a medicament and/or suitable dosage form, the pharmaceutically active compound of the invention may be admixed and/ or contacted with one or more of the excipients listed in Table 9-1.

TABLE 9-1

| Excipients | | | |
|--------------------------------------|--|--|--|
| Acacia | | | |
| Acesulfame Potassium | | | |
| Acetic Acid, Glacial | | | |
| Acetone | | | |
| Acetyltributyl Citrate | | | |
| Acetyltriethyl Citrate | | | |
| Agar | | | |
| Albumin | | | |
| Alcohol | | | |
| Alginic Acid | | | |
| Aliphatic Polyesters | | | |
| Alitame | | | |
| Almond Oil | | | |
| Alpha Tocopherol | | | |
| Aluminum Hydroxide Adjuvant | | | |
| Aluminum Oxide | | | |
| Aluminum Phosphate Adjuvant | | | |
| Aluminum Stearate | | | |
| Ammonia Solution | | | |
| Ammonium Alginate | | | |
| Ascorbic Acid | | | |
| Ascorbyl Palmitate | | | |
| Aspartame | | | |
| Attapulgite | | | |
| Bentonite | | | |
| Benzalkonium Chloride | | | |
| Benzethonium Chloride | | | |
| Benzoic Acid | | | |
| Benzyl Alcohol | | | |
| Benzyl Benzoate | | | |
| Boric Acid | | | |
| Bronopol | | | |
| Butylated Hydroxyanisole | | | |
| Butylated Hydroxytoluene | | | |
| Butylparaben | | | |
| Calcium Alginate | | | |
| Calcium Carbonate | | | |
| Calcium Phosphate, Dibasic Anhydrous | | | |
| Calcium Phosphate, Dibasic Dihydrate | | | |
| Calcium Phosphate, Tribasic | | | |
| Calcium Stearate | | | |
| Calcium Sulfate | | | |
| Canola Oil | | | |
| Carbomer | | | |
| Carbon Dioxide | | | |
| Carboxymethylcellulose Calcium | | | |
| Carboxymethylcellulose Sodium | | | |
| Carrageenan | | | |

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TABLE 9-1-continued

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TABLE 9-1-continued

| Cater Off, Hydrogened Calibles, Marcrosystaline Calibles, Marcrosystaline Calibles, Powiered Calibles, Powiered Calibles, Powiered Calibles, Silicate Access Structured Hydrogenetics Calibles, Silicate Access Structure Calibles, Silicate Access Structure, S | Excipients | | Excipients |
|--|--|-----|---|
| Cate Coll, Hydrosynepsite StarthChildsee, PowlardExpendices Controls SuccinateChildsee, Norecory salineExpendices ControlsChildseeIExpendices Controls </td <td>Castor Oil</td> <td></td> <td>Hydroxypropyl Cellulose, Low-substituted</td> | Castor Oil | | Hydroxypropyl Cellulose, Low-substituted |
| Cellukes, Money fundional interpretation interpreta | Castor Oil, Hydrogenated | 5 | Hydroxypropyl Starch |
| Chlusice, PortugingHyporenelses, Subief MercoynthineHyporenelses PutatakeCultures, Shafed MercoynthineHumbraCultures, Shafed MercoynthineHumbraCultures, Shafed MercoynthineHumbraCultures, ActivationHumbraCultures, ActivationHumbra <td>Cellulose, Microcrystalline</td> <td></td> <td>Hypromellose</td> | Cellulose, Microcrystalline | | Hypromellose |
| Celluses Aberlander Aberlander Services Aberlander Frahalander Services Aberlander Frahalander Services Aberlander Frahalander Services Aberlander | Cellulose, Powdered | | Hypromellose Acetate Succinate |
| Chlukes ActaleInitianesChlukes Actale PhiladeInCensoia10Censoia10CensoiaIncomposition CharacterizationCentrolina10CentrolinaIncomposition CharacterizationCentrolina15CentrolinaIncomposition CharacterizationCentrolina15CatoriaIncomposition CharacterizationChroniaIncomposition CharacterizationChroniaIncomposition CharacterizationChroniaIncomposition CharacterizationChroniaIncomposition CharacterizationChroniaIncomposition CharacterizationChronic Characterization CharacterizationIncomposition CharacterizationChronic Characterization CharacterizationIncomposition CharacterizationChronic Characterization CharacterizationIncomposition CharacterizationChronic CharacterizationIncomposition CharacterizationChronic CharacterizationIncomposition CharacterizationChronic CharacterizationIncomposition CharacterizationCon Chroic CharacterizationIncomposition CharacterizationCon Chronic Characterizatio | Cellulose, Silicified Microcrystalline | | Hypromellose Phthalate |
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| Centenia and a second s | Cellulose Acetate Phthalate | | Inulin |
| Ceiostary/Akobal Ceinink Ceini | Ceratonia | 10 | Iron Oxides |
| Certrinics | Cetostearyl Alcohol | | Isomalt |
| Cety Akobal Cety Kabbal Cety Synthesis Cety Synthes | Cetrimide | | Isopropyl Alcohol |
| Cetypynelame ChenneIsopony ParlameteChenore15LactiolChicrobataol15LactiolChicrobataolLactiolLactiolChicrobataolLactiolLactiolChicrobataolLactiolLactiolChicrobataolLactiolLactiolChicrobataolLactiolLactiolChicrobataolLactiolLactiolChicrobataolLactiolLactiolChicrobataolLactiolLactiolChicrobataolLactiolLactiolColoidal Silicon DioxideLactiolLactiolColoidal Silicon DioxideLactiolLactiolColoidal Silicon DioxideLactiolMagnesianColoidal Silicon DioxideMagnesianMagnesianConsol25MagnesianCorsolMagnesianStateleCrosolMagnesianStateleCrosolMagnesianStateleCrosolMattolMattoleDibury PhalataeMattoleMattoleDibury PhalataeMattoleMattoleD | Cetyl Alcohol | | Isopropyl Myristate |
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| Delationin behaviore Devirates District Products District Prod | Cyclomethicone | | Magnesium Stearate |
| Dextrain j0 Mail Acta Dextrom Malticol Distry | Denatonium Benzoate | | Magnesium Trisilicate |
| Destrinse Destrinse Distry Phthalate Dibty Phthalate Dictbanolamine Dictb | Dextrates | 30 | Malic Acia |
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| Dimethyl EtherMethylcelluloseDimethyl SulfoxideMethylcelluloseDimethyl SulfoxideMineral OilDimethyl SulfoxideMineral OilDimethyl SulfoxideMineral OilDimethyl SulfoxideMineral OilDimethyl SulfoxideMineral OilDisodium EdetateMineral OilDecusate SodiumMineral OilErythorbic AcidMonesodium GlutamateErythorbic AcidMonesodium GlutamateErythorbic AcidMonesodium GlutamateErythorbic AcidMonesodium GlutamateErythorbic AcidMonesodium GlutamateErythorbic AcidMonesodium GlutamateEthyl AcetateMonesodium GlutamateEthyl OkateNitrous OxideEthyl OleateOctyldodecanolEthyl OleateOleic AcidEthyl One OreitParaffinFuructoseParaffinFuructoseParaffinGlucose, LiquidPetrolatum and Lanolin AlcoholsGlyceryl BehenateStoreGlyceryl MonostearatePhenyl MonostearateGlyceryl PalmitostearatePhenyl MonostearateGlyceryl PalmitostearatePhenyl MonostearateGlyceryl PalmitostearatePhenyl MonostearateGlyceryl PalmitostearatePhenyl MonostearateGlyceryl PalmitostearatePhenyl M | Dimethicone | | Meglumine |
| Dimethyl Phthalate Dimethyl Shifoxide Dimethyl Shifoxide Dimethyl Acetamide Dimethyl Acetamide Disodium Edetate Docusate Softium Edetic Acid Edetic Acid Etythorbic Acid Etythorbic Acid Erythritol Etythorbic Acid Erythritol Etythate Erythritol Ethyl Acetate Ethyl Acetate Ethyl Nattel Ethyl Nattel Ethyl Nattel Ethyl Vanillin Ethyl Vanil | Dimethyl Ether | | Menthol |
| Dimethyl SulfoxideMethylparabenDimethyl sulfoxide40Mineral OilDisodium Edetate40Mineral Oil and Lanolin AlcoholsDocusate SodiumMonosodium GlutamateMonosodium GlutamateErythorbic AcidMonosodium GlutamateMonosodium GlutamateErythorbic AcidMonosodium GlutamateMonosodium GlutamateErythorbic AcidMyristic AcidMineral Oil AlcoholsEthyl Acetate45NicrogenEthyl NatlolNitrous OxideEthyl OleateOctyldodecanolEthyl NatlolOctyldodecanolEthyl NatlolOlei CacidEthyl OleateOlei CacidEthyl NatlolOlei CacidEthyl RectateOlei CacidEthyl RectatePalamitic AcidFunaric AcidPeanut OilGlucose, LiquidPetrolatum and Lanolin AlcoholsGlyceryl BehenatePhenolGlyceryl MonostearatePhenolymercuric RectateGlyceryl MonostearatePhenylmercuric AcetateGlyceryl MonostearatePhenylmercuric RectateGlyceryl MonostearatePhenylmercuric RectateGlyceryl MonostearatePhenylmercuric RectateGlyceryl MonostearatePhenylmercuric RectateGlyceryl MonostearatePhenylmercuric Rectat | Dimethyl Phthalate | | Methylcellulose |
| Dimethylacetamide Mineral Oil Mineral Oil Disodum Edetate Mineral Oil Light Mineral Oil Light Constate Sodium Mineral Oil Light Mineral Oil Alcohols Edetic Acid Monoethanolamine Monoethanol Monoethanolamine Monoethanolamine Monoethanolamine Monoethanolamine Monoethanolamine Monoethanolamine Monoethanol Monoethanolamine Monoethanol | Dimethyl Sulfoxide | | Methylparaben |
| bisodium Edetate de de montante de la contra de la mineral Oil and Lanolin Alcohols Bietric Acid Mineral Oil and Lanolin Alcohols Monoethanolamine Monoethanolamine Erythritol Monoethanolamine Monoethanolamine Erythritol Monostenante Monoethanolamine Erythritol Monostenante Monostinglycerol Ethyl Acetate Myristic Acid Myristic Acid Ethyl Acetate 45 Nohesperidin Dihydrochalcone Ethyl Oleate Nitrougen Ethyl Oleate Oleyl Alcohol Ethyl Oleate Oleyl Alcohol Ethylene Giycol Palmitostearate Oleyl Alcohol Ethylene Giycol Palmitostearate S0 Olice Acid Ethylene Giycol Palmitostearate S0 Olice Oli Ethylene Giycol Palmitostearate S0 Olice Oli Ethylene Giycol Palmitostearate S0 Olice Acid Ethylene Giycoryl Behenate S5 Petrolatum Glucose, Liquid Glycerri Behenate S5 Petrolatum Glycerryl Behenate S6 Petrolatum Glycerryl Behenate Minerate S6 Phenol Glycerryl Behenate S5 Phenol Glycerryl Behenate Menyleneuric Acetate Phenyleneuric Acetate Glycerryl Behenate Minerate Phenyleneuric Acetate Glycerryl Behenate Menyleneuric Acetate Glycerryl Monosleate Phenyleneuric Acetate Glycerryl Monostearate Phenyleneuric Acetate Glycerryl Monostearate Phenyleneuric Acetate Glycerryl Monostearate Phenyleneuric Acetate Glycerryl Monostearate Phenyleneuric Acetate Hevetidine Polycarhophil Hydroxythyl Cellulose Polycearbophil Hydroxythyl Cellulose Polycearbophil Hydroxythyl Cellulose Polycearbophile Hydroxythyl Cellulose Polycearbophile Hydroxythyl Cellulose Polycearbore Hydroxythyl Ce | Dimethylacetamide | 40 | Mineral Oil |
| Decusate SodiumMineral Oil and Lanolin AlcoholsEdetic AcidMonosthanolamineErythorbic AcidMonosthanolamineErythorbic AcidMonosthanolamineErythorbic AcidMonosthanolamineErythorbic AcidMonosthanolamineErythorbic AcidMyristic AcidEthyl Acetate45Ethyl AcetateNitrous OxideEthyl MaltolOtryldodecanolEthyl VanillinOtryldodecanolEthyl VanillinOtryldodecanolEthyl vanilloseOlice AcidEthyl vanilloseOlice AcidEthyl VanillinPalmitostearateEthyl vanilloseOlive OilEthyl vanilloseOlive OilEthyl vanilloseParaffinFructoseParaffinFunaric AcidPetrolatum and Lanolin AlcoholsGlyceryl BehenatePhenolGlyceryl BehenatePhenolGlyceryl BehenatePhenolGlyceryl PalmitostearatePhenolGlyceryl PalmitostearatePhenolGlyceryl PalmitostearatePhenolGlyceryl PalmitostearatePhenolGlyceryl PalmitostearatePhenolGlyceryl PalmitostearatePhenolGlyceryl PalmitostearatePhenylmercuric AcetateGlyceryl PalmitostearatePhenylmercuric BorateGlyceryl PalmitostearatePhosphoric AcidHetoritePoloxamerHydroxehoric AcidPoloxamerHydroxehoric AcidPoloxamerHydroxehoric AcidPolycathophiliHydroxehoric Acid <td>Disodium Edetate</td> <td>40</td> <td>Mineral Oil, Light</td> | Disodium Edetate | 40 | Mineral Oil, Light |
| Extle Acid Monosciume Glutamate Erythorbic Acid Monosocium Glutamate Erythorbic Acid Monosocium Glutamate Erythytic Acetate 45 Ethyl Acetate Virogen Ethyl Maltol Nitrous Oxide Ethyl Vanillin Oetyldodecanol Ethyl Vanillin Oetyldodecanol Ethyleeliulose Oleic Acid Ethyleeliulose Oleic Acid Ethylene Vinyl Acetate 50 Ethylparaben Palmitic Acid Fructose Paraffin Functose Pectin Glucose, Liquid Petrolatum Glyceryl Behenate 55 Glyceryl Behenate Phenol Glyceryl Behenate Phenol Glyceryl Behenate Phenyl Mercuric Acetate Glyceryl Behenate Phenyl Mercuric Borate Glyceryl Palmitostearate Phenyl Mercuric Borate Phenylmercuric Ace | Docusate Sodium | | Mineral Oil and Lanolin Alcohols |
| Erythriol Monesodum Gutanate Erythriol Monesticajycerol Ethyl Acetate Myristic Acid Ethyl Lactate 45 Neohesperidin Dihydrochalcone Ethyl Oleate Nitrogen Ethyl Oleate Nitrogen Ethyl Oleate Oleic Acid Ethyl catate Oleic Acid Ethyl catate Oleic Acid Ethyleulose Oleic Acid Ethylene Vinyl Acetate 50 Ethylene Vinyl Acetate 50 Fructose Paraffin Fructose Paraffin Glyceryl Behenate Petrolatum and Lanolin Alcohols Glyceryl Monooleate Phenol Glyceryl Nonooleate Phenylentyl Alcohol Glycoryl Palmitostearate Phenylentyl Alcohol Glyceryl Palmitostearate Phenylentyl Alcohol Hydrochoric Acid Po | Edetic Acid | | Monoethanolamine |
| ErynntolMonomogiycerolEthyl Acetate45Noohesperidin DihydrochalconeEthyl Lactate45Neohesperidin DihydrochalconeEthyl MaltolNitrous OxideEthyl MaltolNitrous OxideEthyl IoeateOleic AcidEthyl IoeateOley AlcoholEthylene Vinyl AcetateOley AlcoholEthylene Vinyl Acetate50Ethylene Vinyl Acetate9FructoseParaffinFructoseParaffinGleatinPetrilatum and Lanolin AlcoholsGlyceryl MonoleatePhenolGlyceryl MonoleatePhenolGlyceryl MonostearatePhenolGlyceryl MonostearatePhenolGlyceryl MonostearatePhenolGlyceryl MonostearatePhenolGlyceryl MonostearatePhenolGlyceryl MonostearatePhenolGlyceryl MonostearatePhenolGlyceryl MonostearatePhenolGlyceryl MonostearatePhenylmercuric NitrateGlyceryl MonostearatePhenolGlyceryl MonostearatePhenolGlyceryl MonostearatePhenylmercuric NitrateGlyceryl MonostearatePhenylmercuric NitrateHectoritePolacrilin PotasiumHectoritePolocarcin PotasiumHydrocarbons (HC)PolycartophilHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydroxythylnethyl CellulosePolychylene GiycelHydroxythylnethyl CellulosePolychylene RovideHydroxythylnethyl Cellulose | Erythorbic Acid | | Monosodium Glutamate |
| Duty ActatateMyrkut ActaEthyl Lactate45Neohesperidin DihydrochalconeEthyl MaltolNitrogenEthyl OleateNitrous OxideEthyl OleateOctyl dodecanolEthyl VanillinOctyl dodecanolEthyl celluloseOleic AcidEthylene Giycol PalmitostearateOleyl AlcoholEthylene Giycol PalmitostearateOley AlcoholEthylene Vinyl Acetate50Ethylene Vinyl AcetateS0Ethylene Vinyl AcetatePalmitic AcidFructoseParaffinFructosePerunt OilGlucose, LiquidPetrolatum and Lanolin AlcoholsGlyceryl BehenatePetrolatumGlyceryl MonostearatePhenoyGlyceryl MonostearatePhenoylethyl AlcoholGlyceryl MonostearatePhenylmercuric AcidGlyceryl MonostearatePhenylmercuric NitrateGlyceryl MonostearatePhenylmercuric NitrateGlyceryl MonostearatePhenylmercuric NitrateGlyceryl MonostearatePhenylmercuric NitrateGlyceryl MonostearatePhenylmercuric NitrateGlucorinPhenylmercuric NitrateHeetchinePolycathophilHydrochons (HC)PolycathophilHydrochonic AcidPolycathophilHydrochoric AcidPolycathophilHydrochoric AcidPolycathophilHydroxytehylnethyl CelluloseFolycethylene OxideHydroxytehylnethyl CellulosePolycethylene GiycolHydroxytehylnethyl CellulosePolycethylene CoxideHydroxytehylnethyl Cellulo | Erythritol Ethel A setete | | Monothiogiycerol |
| LinkHorkNotrogenEthyl MaltolNitrous OxideEthyl OleateNitrous OxideEthyl VanillinOctyldodecanolEthylene Glycol PalmitostearateOleic A cidEthylene Glycol PalmitostearateOleic A cidEthylene Singl Acetate50Olive OilEthylene Singl Acetate50Olive OilEthylene Singl Acetate9almitic AcidPalmitic AcidFructoseParaffinPetrolatum and Lanolin AlcoholsGelatinPetrolatum and Lanolin AlcoholsPetrolatumGlycerin55PetrolatumGlyceryl MonooleatePhenolGlyceryl MonooleatePhenolGlyceryl MonooleatePhenylmercuric AcetateGlyceryl MonooleatePhenylmercuric NitrateGuar Gum60Phenylmercuric NitrateHeetorite60Phosphoric AcidHeetorite60Phosphoric AcidHeetoritePolycarbophilHydroxyethyl CelluloseFolycarbophilHydroxyethyl CelluloseFolycarbophilHydroxyethyl CelluloseFolycethylene GlycolHydroxyethyl CellulosePolyethylene Glycol | Ethyl Lactate | 45 | Mynsuc Aciu Neoharneridin Dihydrochalcone |
| Ethyl National Stream S | Ethyl Maltol | -15 | Neonesperium Dinyurochaicone |
| Ethyl Vanillin Octyl dodecanol Ethyl Vanillin Octyl dodecanol Ethylene Silve Palmitostearate Oleic Acid Ethylene Vinyl Acetate 50 Olive Oil Ethylparaben Palmitic Acid Palmitic Acid Fructose Paraffin Pertolatum and Lanolin Alcohols Glucose, Liquid Petrolatum and Lanolin Alcohols Petrolatum Glyceryl Behenate S5 Phenol Glyceryl Monosleate Phenol Phenol Glyceryl Monosleate Phenylethyl Alcohol Phenol Glyceryl Monosleate Phenylmercuric Nitrate Phenylmercuric Nitrate Glyceryl Nonostearate Phenylmercuric Nitrate Phenylmercuric Nitrate Glyceryl Nonostearate Phenylmercuric Nitrate Phenylmercuric Nitrate Glyceryl Varonostearate Phenylmercuric Nitrate Phenylmercuric Nitrate Hetaffuoropropane (HFC) Polacrilin Potassium Poloxamer Hydrocarbons (HC) Polycarbophil Polycarbophil Hydrochoric Acid Polycarbophil Polycetrose Hydroxyethyl Cellulose Polyethylene Giycol Polyethylene Giycol Hydroxyethyl Cellulose | Ethyl Oleste | | Nitrous Oxide |
| EthyleelluloseOleic AcidEthyleelluloseOleic AcidEthylene Glycol PalmitostearateOley AlcoholEthylene Vinyl Acetate50EthylparabenPalmitic AcidFructoseParaffinFurnaric AcidPectinGelatinPectinGlyceryl MonosleatePhenolGlyceryl MonosleatePhenolGlyceryl PalmitostearatePhenolGlyceryl PalmitostearatePhenolGlyceryl PalmitostearatePhenolGlyceryl PalmitostearatePhenolGlyceryl PalmitostearatePhenolGlyceryl PalmitostearatePhenylmercuric AcetateGlyceryl PalmitostearatePhenylmercuric NitrateGlyceryl PalmitostearatePhenylmercuric NitrateGlyceryl PalmitostearatePhenylmercuric NitrateHectorite60Plosphoric AcidHeytorateonson (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydroxyethyl Cellulose65Polyethylene GiycolHydroxyethyl Cellulose65Polyethylene GiycolHydroxyethyl Cellulose65Polyethylene Giycol | Ethyl Vanillin | | Octyldodecanol |
| Ethylene Glycol PalmitostearateOleyl AlcoholEthylene Vinyl Acetate50Olive OilEthylparabenPalmitic AcidFructoseParaffinFunaric AcidPeanut OilGelatinPectinGlucose, LiquidPetrolatum and Lanolin AlcoholsGlyceryl Behenate55Glyceryl BehenatePhenolGlyceryl MonooleatePhenolGlyceryl PalmitostearatePhenolGlyceryl PalmitostearatePhenylerturi AcetateGlyceryl PalmitostearatePhenylmercuric AcetateGlyceryl PalmitostearatePhenylmercuric NitrateGuar Gum60Phosphoric AcidHectorite60Phosphoric AcidHeptafluoropropane (HFC)PoloxamerHexetidinePoloxamerHydroxyethyl Cellulose65Polyethylene GlycolHydroxyethyl Cellulose65Polyethylene OxideHydroxyethyl CellulosePolyethylene Oxide | Ethylcellulose | | Oleic Acid |
| Ethylene Vinyl Acetate50Olive OilEthylparabenPalmitic AcidFructoseParaffinFumaric AcidPeanut OilGelatinPectinGlucose, LiquidPetrolatum and Lanolin AlcoholsGlyceryl BehenateS5Glyceryl BehenatePhenolGlyceryl MonooleatePhenolyetholdGlyceryl MonostearatePhenolyetholdGlycofrolPhenylinercuric AcetateGlycofrolPhenylinercuric NitrateGuar Gum60HectoritePhosphoric AcidHesteidinePoloxamerHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydroxyethyl Cellulose65Polycethylene (SteuePolycethylene (SteueHydroxyethyl CellulosePolycethylene (SteueHydroxyethyl CellulosePolycethylene (SteueHydroxyethyl CellulosePolycethylene (SteueHydroxyethylenethyl CellulosePolycethylene (SteueHydroxyethylenethyl CellulosePolycethoreHydroxyethylenethyl CellulosePolycethoreHydroxyethylenethyl CellulosePolycethylene (SteueHydroxyethylenethyl CellulosePolycetholdHydroxyethylenethyl CellulosePolycetholdHydroxyethylenethyl CellulosePolycetholdHydroxyethylenethyl CellulosePolycethacrylates | Ethylene Glycol Palmitostearate | | Oleyl Alcohol |
| EthylparabenPalmitic AcidFructoseParaffinFumaric AcidPeanut OilGelatinPetrolatum and Lanolin AlcoholsGlycose, LiquidPetrolatum and Lanolin AlcoholsGlycerin55Glyceryl MonooleatePhenolGlyceryl MonooleatePhenolGlyceryl PalmitostearatePhenylmercuric AcetateGlycofurolPhenylmercuric NitrateGuar Gum60Heptafluoropropane (HFC)PolozmerHeydrocarbons (HC)PolozmerHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolydextroseHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolydextroseHydrocarbons (HC)PolydextroseHydrocarbons (HC)PolydextroseHydrocarbons (HC)PolydextroseHydrocarbons (HC)PolydextroseHydrocarbons (HC)PolydextroseHydrocarbons (HC) | Ethylene Vinyl Acetate | 50 | Olive Oil |
| FructoseParaffinFumaric AcidPeanut OilGucose, LiquidPetrolatum and Lanolin AlcoholsGlycerinPetrolatum and Lanolin AlcoholsGlyceryl Behenate55Glyceryl BehenatePhenolGlyceryl MonostearatePhenolGlyceryl NonostearatePhenolynetrucic AcetateGlyceryl PalmitostearatePhenylethyl AlcoholGlyceryl PalmitostearatePhenylmercuric BorateGlycofurolPhenylmercuric BorateGuar GumPhenylmercuric NitrateHeetorite60HeetoritePoloxamerHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydroxyethyl Cellulose65Hydroxyethyl CellulosePolycethylene GiycolHydroxyethyl CellulosePolycethylene CycleHydroxyethyl CellulosePolycethylene CycleHydroxyethyl CellulosePolycethylene Giycol | Ethylparaben | | Palmitic Acid |
| Funaric AcidPeanut OilGelatinPetrinGlucose, LiquidPetrolatum and Lanolin AlcoholsGlycerin55Glyceryl BehenatePhenolGlyceryl MonooleatePhenolGlyceryl MonostearatePhenolGlyceryl PalmitostearatePhenylethyl AlcoholGlyceryl PalmitostearatePhenylmercuric AcetateGlycofurolPhenylmercuric BorateGuar GumPhenylmercuric NitrateHectorite60HetofinePolacrilin PotassiumHexetidinePolocrilin PotassiumHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydrocarbons (HC)PolycarbophilHydroxyethyl Cellulose65Hydroxyethyl CellulosePolycarbophilHydroxyethyl CellulosePolycethylene OxideHydroxyethyl CellulosePolycethylene OxideHydroxyethyl CellulosePolycethylene OxideHydroxyethyl CellulosePolycethylene CycleHydroxyethyl CellulosePolycethylene Cycle <td>Fructose</td> <td></td> <td>Paraffin</td> | Fructose | | Paraffin |
| Gelatin Pectin Glucose, Liquid Petrolatum and Lanolin Alcohols Glycerin 55 Glyceryl Behenate Phenol Glyceryl Monooleate Phenol Glyceryl Monostearate Phenol Glyceryl Palmitostearate Phenylethyl Alcohol Glyceryl Palmitostearate Phenylethyl Alcohol Glyceryl Palmitostearate Phenylethyl Alcohol Glyceryl Palmitostearate Phenylmercuric Borate Guar Gum Phenylmercuric Nitrate Hectorite 60 Phosphoric Acid Heptafluoropropane (HFC) Poloxamer Hydrocarbons (HC) Polycarbophil Hydrocarbons (HC) Polycarbophil Hydrocysethyl Cellulose 65 Hydroxyntmyl Cellulose 65 Hydroxyntmyl Cellulose Polythylene Giycol | Fumaric Acid | | Peanut Oil |
| Glucose, Liquid Petrolatum and Lanolin Alcohols Glycerin 55 Petrolatum Glyceryl Behenate Phenol Glyceryl Monooleate Phenoylethanol Glyceryl Monostearate Phenylethyl Alcohol Glycoryl Palmitostearate Phenylmercuric Acetate Glycoryl Palmitostearate Phenylmercuric Nitrate Guar Gum Phenylmercuric Nitrate Hectorite 60 Hestelfiluoropropane (HFC) Polacrilin Potassium Hexetidine Poloxamer Hydrocarbons (HC) Polycarbophil Hydrocarbons (HC) Polycarbophil Hydroxyethyl Cellulose 65 Polyethylene Glycol Hydroxyethyl Cellulose Polyethylene Store Hydroxyethyl Cellulose Polyethylene Store | Gelatin | | Pectin |
| Glycerin 55 Petrolatum Glyceryl Behante Phenol Glyceryl Monooleate Phenol Glyceryl Monostearate Phenolylethyl Alcohol Glyceryl Palmitostearate Phenylmercuric Acetate Glyceryl Palmitostearate Phenylmercuric Nitrate Glyceryl Palmitostearate Phenylmercuric Nitrate Guar Gum Phenylmercuric Nitrate Hectorite 60 Heptafluoropropane (HFC) Poloxamer Hexetidine Poloxamer Hydrocarbons (HC) Polycarbophil Hydrochloric Acid Polycarbophil Hydroxythyl Cellulose 65 Hydroxythyl Cellulose 65 Polyethylene Glycol | Glucose, Liquid | | Petrolatum and Lanolin Alcohols |
| Giyceryl Behenate Phenol Giyceryl Monooleate Phenoxyethanol Giyceryl Monostearate Phenylethyl Alcohol Glyceryl Palmitostearate Phenylmercuric Acetate Glycoryl Palmitostearate Phenylmercuric Borate Guar Gum Phenylmercuric Nitrate Hectorite 60 Phosphoric Acid Heptafhuoropropane (HFC) Polacrilin Potassium Hextidine Poloxamer Hydrocarbons (HC) Polycarbophil Hydrochloric Acid Polydextrose Hydroxyethyl Cellulose 65 Hydroxyethyl Cellulose Polyethylene Giycol | Glycerin | 55 | Petrolatum |
| Giyceryl Monooleate Phenoxyethanol Giyceryl Monooleate Phenoxyethanol Giyceryl Palmitostearate Phenylmercuric Acetate Glycofurol Phenylmercuric Borate Guar Gum Phenylmercuric Nitrate Hectorite 60 Heptafluoropropane (HFC) Poloxinin Potassium Hextidine Poloxamer Hydrocarbons (HC) Polycarbophil Hydrochloric Acid Polydextrose Hydroxyethyl Cellulose 65 Hydroxymproyl Cellulose Polyethylene Giycol | Glyceryl Behenate | | Phenol |
| Giyceryl Monostearate Phenylenyl Alcohol Giyceryl Palmitostearate Phenylmercuric Acetate Glycofurol Phenylmercuric Borate Guar Gum Phenylmercuric Nitrate Hectorite 60 Heptafluoropropane (HFC) Polacrilin Potassium Hexetidine Polycarbophil Hydrocarbons (HC) Polycarbophil Hydrocarbons (HC) Polycarbophil Hydroxyethyl Cellulose 65 Hydroxyronzyl Cellulose Polyethylene Giycol | Glyceryl Monooleate | | Phenoxyethanol |
| Giycefyr Fainfiostearate Phenylmercuric Acetate Giycofurol Phenylmercuric Borate Guar Gum Phenylmercuric Nitrate Hectorite 60 Heptafluoropropane (HFC) Polacrilin Potassium Hexetidine Poloxamer Hydrocarbons (HC) Polycarbophil Hydrocarbons (HC) Polycarbophil Hydroxyethyl Cellulose Polydextrose Hydroxyethyl Cellulose 65 Hydroxyropnyl Cellulose Polymethecrylates | Giverni Balmitesteerete | | Phenylethyl Alcohol Bhanylmanaynia Apatata |
| Guar Gun Phenylmercuric Nitrate Guar Gun 60 Hectorite 60 Heptafluoropropane (HFC) Polacrilin Potassium Hexetidine Poloxamer Hydrocarbons (HC) Polycarbophil Hydrochloric Acid Polycarbophil Hydroxyethyl Cellulose Polyethylene Glycol Hydroxyethyl Cellulose 65 Polymethacrvlates | Glycofurol | | Phenylmercuric Acetate |
| Hectorite 60 Phosphoric Acid Heptafluoropropane (HFC) Polacrilin Potassium Hexetidine Poloxamer Hydrocarbons (HC) Polycarbophil Hydrochloric Acid Polycarbophil Hydrochloric Acid Polycarbophil Hydroxyethyl Cellulose Polyethylene Glycol Hydroxyropayl Cellulose 65 Polymethacrvlates | Guar Gum | | Phenylmercuric Nitrate |
| Heptafluoropropane (HFC) Polacrilin Potasium Hexetidine Poloxamer Hydrocarbons (HC) Polycarbophil Hydrochloric Acid Polydextrose Hydroxyethyl Cellulose 65 Hydroxyropnyl Cellulose Polymethacrivitates | Hectorite | 60 | Phosphoric Acid |
| Hexetidine Poloxamer Hydrocarbons (HC) Polycarbophil Hydrochloric Acid Polydextrose Hydroxyethyl Cellulose 65 Hydroxyronpyl Cellulose 65 Polymethacrylates | Heptafluoropropane (HFC) | | Polacrilin Potassium |
| Hydrocarbons (HC) Polycarbophil Hydrochloric Acid Polydextrose Hydroxyethyl Cellulose Polyethylene Glycol Hydroxyronyl Cellulose 65 Hydroxyronyl Cellulose Polymethacrulates | Hexetidine | | Poloxamer |
| Hydrochloric Acid Polydextrose Hydroxyethyl Cellulose Polydextrose Hydroxyethyl Cellulose 65 Hydroxypropyl Cellulose Polymethacrulates | Hydrocarbons (HC) | | Polycarbophil |
| Hydroxyethyl Cellulose Polyethylene Głycol Hydroxyethylmethyl Cellulose 65 Polyethylene Oxide Hydroxypropyl Cellulose Polymethacrylates | Hydrochloric Acid | | Polydextrose |
| Hydroxyethylmethyl Cellulose 65 Polyethylene Oxide Hydroxypropyl Cellulose Polymethacrylates | Hydroxyethyl Cellulose | | Polyethylene Glycol |
| Hydroxypropyl Cellulose Polymethacrylates | Hydroxyethylmethyl Cellulose | 65 | Polyethylene Oxide |
| i orymotiation i orymotiation | Hydroxypropyl Cellulose | | Polymethacrylates |

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TABLE 9-1-continued

| Excipients |
|--|
| Poly(methyl vinyl ether/maleic anhydride) |
| Polyoxyethylene Alkyl Ethers |
| Polyoxyethylene Castor Oil Derivatives |
| Polyoxyethylene Stearates |
| Polyvinyl Acetate Phthalate |
| Polyvinyl Alcohol |
| Potassium Alginate |
| Potassium Bicarbonate |
| Potassium Chloride |
| Potassium Citrate |
| Potassium Metabisulfite |
| Potassium Sorbate |
| Povidone |
| Propionic Acid Propyl Galleta |
| Propylene Carbonate |
| Propylene Glycol |
| Propylene Glycol Alginate |
| Propyiparaben 2-Pyrralidone |
| Raffinose |
| Saccharin |
| Saccharin Sodium |
| Saponite Sesame Oil |
| Shellac |
| Simethicone |
| Sodium Acetate |
| Sodium Ascorbate |
| Sodium Benzoate |
| Sodium Bicarbonate |
| Sodium Chloride |
| Sodium Citrate Dihydrate |
| Sodium Cyclamate |
| Sodium Hyaluronate |
| Sodium Lactate |
| Sodium Lauryl Sulfate |
| Sodium Metabisulfite |
| Sodium Phosphate, Dibasic |
| Sodium Propionate |
| Sodium Starch Glycolate |
| Sodium Stearyl Fumarate |
| Sodium Sulfite |
| Sorbitan Esters (Sorbitan Fatty Acid Esters) |
| Sorbitol |
| Soybean Oil |
| Starch Starch Pregelatinized |
| Starch, Sterilizable Maize |
| Stearic Acid |
| Stearyl Alcohol |
| Sucrose |
| Sugar, Compressible |
| Sugar, Confectioner's |
| Sugar Spheres |
| Sulfuric Acid |
| Sunflower Oil |
| Suppository Bases, Hard Fat |
| Talc Testerio Apid |
| Tetrafluoroethane (HFC) |
| Thaumatin |
| Thymol |
| Titanium Dioxide Traggenth |
| Trehalose |
| Triacetin |
| Tributyl Citrate |

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TABLE 9-1-continued

| | Excipients |
|----|-------------------------------------|
| 5 | Triethanolamine Triethyl Citrate |
| | Vanillin |
| | Vegetable Oil, Hydrogenated |
| | Water |
| | Wax, Anionic Emulsifying |
| 10 | Wax, Carnauba |
| | Wax, Cetyl Esters |
| | Wax, Microcrystalline |
| | Wax, Nonionic Emulsifying |
| | Wax, White |
| 15 | Wax, Yellow |
| 15 | Xanthan Gum |
| | Xylitol |
| | Zein |
| | Zinc Acetate |
| | Zinc Stearate |
| 20 | |

EXAMPLE 10

Dosage form. A suitable dosage form for administration of the pharmaceutically active compound of the present invention may be chosen from among the dosage forms listed in Table 10-1.

TABLE 10-1

| | | Dosage forms | | | | | |
|----|--|--|--|--|--|--|--|
| | NAME | DEFINITION | | | | | |
| 35 | AEROSOL | A product that is packaged under pressure and contains therapeutically active ingredients that are released upon activation of an appropriate valve system; it is intended for topical application to the skin as well as local application into the nose (nasal gensols) muth (lingual gensols) or lungs | | | | | |
| 40 | AEROSOL, POWDER | (inhalation aerosols). A product that is packaged under pressure and contains therapeutically active ingredients, in the form of a powder, that are released upon activation of an appropriate valve system. | | | | | |
| 45 | BAR, CHEWABLE | A solid dosage form usually in the form of a rectangle that is meant to be chewed. | | | | | |
| | CAPSULE | A solid oral dosage form consisting of a shell and a filling. The shell is composed of a single sealed enclosure, or two halves that fit together and which are sometimes sealed with a band. Capsule shells may be made from gelatin, starch, or | | | | | |
| 50 | | cellulose, or other suitable materials, may be soft or hard, and are filled with solid or liquid ingredients that can be poured or squeezed. | | | | | |
| | CAPSULE, COATED | A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; | | | | | |
| 55 | | additionally, the capsule is covered in a designated coating. | | | | | |
| | CAPSULE, COATED PELLETS | A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; the drug itself is in the form of granules to which | | | | | |
| 60 | CAPSULE, COATED, EXTENDED RELEASE | varying amounts of coating have been applied. A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; additionally, the capsule is covered in a designated coating, and which releases a drug (or drugs) in who a memory to all us at least reduction in | | | | | |
| 65 | | dosing frequency as compared to that drug (or drugs) presented as a conventional dosage form. | | | | | |

TABLE 10-1-continued

TABLE 10-1-continued

| | | - | | |
|---|---|-----------|--------------------------------|--|
| | Dosage forms | _ | | Dosage forms |
| NAME | DEFINITION | - 5 | NAME | DEFINITION |
| CAPSULE, DELAYED RELEASE | A solid dosage form in which the drug is enclosed within either a hard or soft soluble container made from a suitable form of gelatin, and which releases a drug (or drugs) at a time other than promptly after administration. Enteric-coated articles are | _ , | EXTRACT | A concentrated preparation of vegetable or animal drugs obtained by removal of the active constituents of the respective drugs with a suitable menstrua, evaporation of all or nearly all of the solvent, and adjustment of the residual masses or |
| | delayed release dosage forms. | 10 | FIDED | powders to the prescribed standards. |
| CAPSULE, DEL AVED | A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or | | FIBER, | A stender and elongated solid thread-like |
| RELEASE PELLETS | "shell" made from a suitable form of gelatin; the drug itself is in the form of granules to which enteric coating has been applied, thus delaying release of the drug until its passage into the | 15 | RELEASE | allow a reduction in dosing frequency as compared to that drug (or drugs) presented as a conventional dosage form. A thin layer or coating which is susceptible to |
| CAPSULE, | intestines. A solid dosage form in which the drug is enclosed | | FOR SOLUTION | being dissolved when in contact with a liquid. A product, usually a solid, intended for solution |
| EXTENDED RELEASE | within either a hard or soft soluble container made from a suitable form of gelatin, and which releases a drug (or drugs) in such a manner to allow a | | FOR SUSPENSION | prior to administration. A product, usually a solid, intended for suspension prior to administration. |
| | reduction in dosing frequency as compared to that drug (or drugs) presented as a conventional dosage form. | 20 | FOR SUSPENSION, EXTENDED | A product, usually a solid, intended for suspension prior to administration; once the suspension is administered, the drug will be released at a |
| CAPSULE, FILM COATED, EXTENDED RELEASE | A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; additionally, the capsule is covered in a designated | | RELEASE GEL | constant rate over a specified period. A semisolid ³ dosage form that contains a gelling agent to provide stiffness to a solution or a colloidal dispersion. ⁴ A gel may contain |
| | film coating, and which releases a drug (or drugs) in such a manner to allow at least a reduction in dosing frequency as compared to that drug (or drugs) presented as a conventional dosage form. | 25 | GLOBULE | suspended particles. Also called pellets or pilules, are made of pure sucrose, lactose, or other polysaccharides. They are formed into small globular masses of various |
| CAPSULE, | A solid dosage form in which the drug is enclosed | | | sizes, and are medicated by placing them in a vial |
| GELATIN | within either a hard or soft soluble container made | 20 | | and adding the liquid drug attenuation in the properties not loss than one percent $(y(y))$. After |
| COALED | process, the capsule is coated with additional | 30 | | shaking, the medicated globules are dried at |
| CADSULE | layers of gelatin so as to form a complete seal. | | CD AND D E | A small particle or grain |
| LIQUID | within a soluble gelatin shell which is plasticized | | GRANULE | A small medicinal particle or grain to which an |
| FILLED | by the addition of a polyol, such as sorbitol or | | DELAYED | enteric or other coating has been applied, thus |
| | glycerin, and is therefore of a somewhat thicker | 35 | RELEASE | delaying release of the drug until its passage into |
| | consistency than that of a hard shell capsule; | 55 | | the intestines. |
| | typically, the active ingredients are dissolved or | | GRANULE, | A small particle or grain containing a medicinal |
| CONCENTRATE | suspended in a liquid vehicle. A liquid preparation of increased strength and | | EFFERVESCENT | agent in a dry mixture usually composed of sodium bicarbonate, citric acid, and tartaric acid |
| | reduced volume which is usually diluted prior to administration. | 40 | | which, when in contact with water, has the capability to release gas, resulting in |
| CORE, | An ocular system placed in the eye from which the | 40 | | effervescence. |
| EXTENDED | drug diffuses through a membrane at a constant | | GRANULE, FOR | A small medicinal particle or grain made available |
| CREAM | rate over a specined period. An emulsion, semisolid ³ dosage form, usually containing >20% water and volatiles5 and/or <50% hydrocarbons, waxes, or polyols as the | | SOLUTION | in its more stable ary form, to be reconstituted with solvent just before dispensing; the granules are so prepared to contain not only the medicinal agent, but the colorants, flavorants, and any other |
| | vehicle. This dosage form is generally for | 45 | | desired pharmaceutic ingredient. |
| | external application to the skin or mucous membranes. | | GRANULE, FOR SUSPENSION | A small medicinal particle or grain made available in its more stable dry form, to be reconstituted |
| CREAM, | A cream dosage form that enhances drug delivery. | | | with solvent just before dispensing to form a |
| AUGMENTED | Augmentation does not refer to the strength of the drug in the dosage form. NOTE: CDER has | | | suspension; the granules are so prepared to contain not only the medicinal agent, but the colorants, |
| | decided to refrain from expanding the use of this dosage form due to difficulties in setting specific | 50 | | flavorants, and any other desired pharmaceutic ingredient. |
| | criteria that must be met to be considered | | GRANULE, FOR | A small medicinal particle or grain made available |
| | "augmented". | | SUSPENSION, | in its more stable dry form, to be reconstituted |
| DRUG DELIVERY | Modern technology, distributed with or as a part | | RELEASE | suspension: the extended release system achieves |
| SYSTEM | of a drug product that allows for the uniform | | KELLER KOL | slow release of the drug over an extended period |
| EI IVID | A clear placently flavored sweetened | 22 | | of time and maintains constant drug levels in the |
| ELIAIR | hydroalcoholic liquid containing dissolved | | | blood or target tissue. |
| | medicinal agents: it is intended for oral use | | INJECTABLE, | An injection, which either consists of or forms |
| EMULSION | A dosage form consisting of a two-phase system | | LIPOSOMAL | liposomes (a lipid bilayer vesicle usually |
| | comprised of at least two immiscible liquids ¹ , one | | | composed of phospholipids which is used to |
| | of which is dispersed as droplets (internal or | 60 | INIECTION | A sterile preparation intended for parenteral use: |
| | dispersed phase) within the other liquid (external | | 1.32011011 | five distinct classes of injections exist as defined |
| | or continuous phase), generally stabilized with one | | | by the USP. |
| | or more emulsifying agents. (Note: Emulsion is | | INJECTION, | An emulsion consisting of a sterile, pyrogen-free |
| | used as a dosage form term unless a more specific | | EMULSION | preparation intended to be administered |
| | term is applicable, e.g. cream, lotion, ointment.) | <i>~~</i> | | parenterally. |
| ENEMA | A rectal preparation for therapeutic, diagnostic, or nutritive purposes. | 65 | INJECTION, LIPID COMPLEX | [definition pending] |
| | | | | |

TABLE 10-1-continued

TABLE 10-1-continued

| | | - | | |
|--|--|-----|--|---|
| | Dosage forms | - | | Dosage forms |
| NAME | DEFINITION | 5 | NAME | DEFINITION |
| INJECTION, POWDER, FOR SOLUTION INJECTION, POWDER, | A sterile preparation intended for reconstitution to form a solution for parenteral use. A sterile preparation intended for reconstitution to form a suspension for parenteral use. | • > | OINTMENT, AUGMENTED | An ointment dosage form that enhances drug delivery. Augmentation does not refer to the strength of the drug in the dosage form. NOTE: CDER has decided to refrain from expanding the use of this dosage form due to difficulties in |
| FOR SUSPENSION | A dried preparation intended for reconstitution to | 10 | | setting specific criteria that must be met to be considered "augmented" |
| POWDER, FOR SUSPENSION, EXTENDED | form a suspension for parenteral use which has been formulated in a manner to allow at least a reduction in doging frequency as compared to that | | PASTE | A semisolid ³ dosage form, containing a large proportion (20-50%) of solids finely dispersed in a fatty vehicle. This dosage form is generally for external application to the skin or mucous |
| RELEASE | drug presented as a conventional dosage form | 15 | | membranes. |
| INJECTION, | (e.g., as a solution). A sterile freeze dried preparation intended for | 15 | PASTILLE | An aromatic preparation, often with a pleasing flavor, usually intended to dissolve in the mouth. |
| LYOPHILIZED, FOR LIPOSOMAL | formulated in a manner that would allow liposomes (a lipid bilayer vesicle usually composed of phospholipids which is used to | 20 | TAICH | adhesive backing that is usually applied to an external site on the body. Its ingredients either passively diffuse from, or are actively transported |
| SUSPENSION INJECTION, | encapsulate an active drug substance, either within a lipid bilayer or in an aqueous space) to be formed upon reconstitution. A liquid preparation, suitable for injection, which | 20 | | from, some portion of the patch. Depending upon the patch, the ingredients are either delivered to the outer surface of the body or into the body. A patch is sometimes synonymous with the terms |
| SUSPENSION, LIPOSOMAL | consists of an oil phase dispersed throughout an aqueous phase in such a manner that liposomes (a lipid bilayer vesicle usually composed of phospholipids which is used to encapsulate an | 25 | PATCH, EXTENDED RELEASE | 'extended release film' and 'system'. A drug delivery system in the form of a patch that releases the drug in such a manner that a reduction in dosing frequency compared to that drug |
| INJECTION, SUSPENSION, | active drug substance, either within a lipid bilayer or in an aqueous space) are formed. A liquid preparation, suitable for injection, which consists of solid particles dispersed throughout a | | DUTOU | presented as a conventional dosage form (e.g., a solution or a prompt drug-releasing, conventional solid dosage form). |
| SONICATED | liquid phase in which the particles are not soluble. In addition, the product is sonicated while a gas is bubbled through the suspension, and this results in the formation of microspheres by the solid particles. | 30 | EXTENDED RELEASE, ELECTRICALLY CONTROLLED | which is controlled by an electric current that releases the drug in such a manner that a reduction in dosing frequency compared to that drug presented as a conventional dosage form (e.g., a |
| JELLY | A class of gels, which are semisolid systems that consist of suspensions made up of either small inorganic particles or large organic molecules interpenetrated by a liquid—in which the structural coherent matrix contains a high portion of liquid, usually water. | 35 | PELLET | solution or a prompt drug-releasing, conventional solid dosage form). A small sterile solid mass consisting of a highly purified drug (with or without excipients) made by the formation of granules, or by compression and molding |
| KIT LINIMENT | A packaged collection of related material. A solution or mixture of various substances in oil, alcoholic solutions of soap, or emulsions intended for external application. | 40 | PELLETS, COATED, EXTENDED RELEASE | A solid dosage form in which the drug itself is in the form of granules to which varying amounts of coating have been applied, and which releases a drug (or drugs) in such a manner to allow a |
| EXTENDED RELEASE | A liquid that derivers a drug in such a manner to allow a reduction in dosing frequency as compared to that drug (or drugs) presented as a conventional dosage form. | | | reduction in dosing frequency as compared to that drug (or drugs) presented as a conventional dosage form. |
| LOTION | An emulsion, liquid ¹ dosage form. This dosage form is generally for external application to the skin. ² | 45 | PILL PLASTER | A small, round solid dosage form containing a medicinal agent intended for oral administration. Substance intended for external application made |
| LOTION, AUGMENTED | A lotion dosage form that enhances drug delivery. Augmentation does not refer to the strength of the drug in the dosage form. NOTE: CDER has decided to refrain from expanding the use of this dosage form due to difficulties in setting specific criteria that must be met to be considered | 50 | | of such materials and of such consistency as to adhere to the skin and attach to a dressing; plasters are intended to afford protection and support and/or to furnish an occlusion and macerating action and to bring medication into close contact with the skin. |
| LOZENGE | "augmented". A solid preparation containing one or more medicaments, usually in a flavored, sweetened base which is intended to dissolve or disintegrate | 55 | POULTICE | A soft, moist mass of meal, herbs, seed, etc., usually applied hot in cloth that consists of gruel- like consistency. An intimate mixture of dry, finely divided drugs |
| | slowly in the mouth. A lollipop is a lozenge on a stick. | | | and/or chemicals that may be intended for internal |
| MOUTHWASH | An aqueous solution which is most often used for its deodorant, refreshing, or antiseptic effect. | | POWDER, FOR SOLUTION | or external use. An intimate mixture of dry, finely divided drugs and/or chemicals, which, upon the addition of |
| OIL | An unctuous, combustible substance which is liquid, or easily liquefiable, on warming, and is soluble in ether but insoluble in water. Such substances, depending on their origin, are classified as animal, mineral, or vegetable oils. | 60 | POWDER, FOR SUSPENSION | An intimate mixture of dry, finely divided drugs and/or chemicals, which, upon the addition of suitable vehicles, yields a suspension (a liquid preparation containing the addition of |
| OINTMENT | A semisolid" dosage form, usually containing <20% water and volatiles ⁵ and >50% hydrocarbons, waxes, or polyols as the vehicle. This dosage form is generally for external application to the skin or mucous membranes. | 65 | SALVE | in the liquid vehicle). A thick ointment or cerate (a fat or wax based preparation with a consistency between an ointment and a plaster). |

TABLE 10-1-continued

TABLE 10-1-continued

| | | - | | Denses farm- |
|---------------------------------------|---|----------|---|---|
| | Dosage Iomis | _ | | Dosage Iorms |
| NAME | DEFINITION | 5 | NAME | DEFINITION |
| SOLUTION | A clear, homogeneous liquid ¹ dosage form that contains one or more chemical substances dissolved in a solvent or mixture of mutually miscible solvents. | | TABLET, EFFERVESCENT | A solid dosage form containing mixtures of acids (e.g., citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water; it is intended to be dissolved or |
| SOLUTION, CONCENTRATE | A liquid preparation (i.e., a substance that flows readily in its natural state) that contains a drug dissolved in a suitable solvent or mixture of | 10 | TABLET, EXTENDED | dispersed in water before administration. A solid dosage form containing a drug which allows at least a reduction in dosing frequency as |
| COLUTION FOR | mutually miscible solvents; the drug has been strengthened by the evaporation of its nonactive parts. | | RELEASE TABLET, FILM | compared to that drug presented in conventional dosage form. A solid dosage form that contains medicinal |
| SOLUTION, FOR SLUSH | A solution for the preparation of an iced saline slush, which is administered by irrigation and used to induce regional hypothemia (in conditions such as certain open heart and kidney surgical | 15 | COALED | substances with or without suitable dilutents and is coated with a thin layer of a water-insoluble or water-soluble polymer. |
| SOLUTION, GEL FORMING/DROPS | A solution, which after usually being administered in a drop-wise fashion, forms a gel. | | COATED, EXTENDED RELEASE | substances with or without suitable diluents and is coated with a thin layer of a water-insoluble or water-soluble polymer; the tablet is formulated in |
| SOLUTION, GEL FORMING, EXTENDED | A solution that forms a gel when it comes in contact with ocular fluid, and which allows at least a reduction in dosing frequency. | 20 | | such manner as to make the contained medicament available over an extended period of time following ingestion. |
| RELEASE SOLUTION/ DROPS | A solution which is usually administered in a drop-wise fashion. | | TABLET, FOR SOLUTION TABLET, FOR | A tablet that forms a solution when placed in a liquid. A tablet that forms a suspension when placed in a |
| SUPPOSITORY | A solid body of various weights and shapes, adapted for introduction into the rectal orifice of the human body; they usually melt, soften, or | 25 | SUSPENSION TABLET, | liquid (formerly referred to as a 'dispersible tablet'). A solid dosage form containing medicinal |
| SUPPOSITORY, EXTENDED | A drug delivery system in the form of a suppository that allows for a reduction in dosing | | MULTILAYEK | substances that have been compressed to form a multiple-layered tablet or a tablet-within-a-tablet, the inner tablet being the core and the outer portion being the shell |
| SUSPENSION | A liquid dosage form that contains solid particles dispersed in a liquid vehicle. A liquid preparation consisting of solid particles | 30 | TABLET, MULTILAYER, EXTENDED | A solid dosage form containing medicinal substances that have been compressed to form a multiple-layered tablet or a tablet-within-a-tablet |
| EXTENDED RELEASE | dispersed throughout a liquid phase in which the particles are not soluble; the suspension has been formulated in a manner to allow at least a reduction in dosing frequency as compared to that | | RELEASE | the inner tablet being the core and the outer portion being the shell, which, additionally, is covered in a designated coating; the tablet is formulated in such manner as to allow at least a |
| | drug presented as a conventional dosage form (e.g., as a solution or a prompt drug-releasing, conventional solid dosage form). | 35 | TABLET. | reduction in dosing frequency as compared to that drug presented as a conventional dosage form. A solid dosage form containing medicinal |
| SUSPENSION/ DROPS SYRUP | A suspension which is usually administered in a dropwise fashion. An oral solution containing high concentrations of | | ORALLÝ DISINTEGRATING | substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue. |
| | sucrose or other sugars; the term has also been used to include any other liquid dosage form prepared in a sweet and viscid vehicle, including | 40 | TABLET, ORALLY DIS- | A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the |
| TABLET | oral suspensions. A solid dosage form containing medicinal substances with or without suitable diluents. | 15 | INTEGRATING, DELAYED RELEASE | tongue, but which releases a drug (or drugs) at a time other than promptly after administration. |
| TABLET, CHEWABLE | A solid dosage form containing medicinal substances with or without suitable diluents that is intended to be chewed, producing a pleasant to the substance of the sub-substance of the sub- | 45 | TABLET, SOLUBLE | A solid dosage form that contains medicinal substances with or without suitable diluents and possesses the ability to dissolve in fluids. |
| TADIET | swallowed and does not leave a bitter or unpleasant after-taste. | 50 | COATED | A solid dosage form that contains medicinal substances with or without suitable diluents and is coated with a colored or an uncolored water- |
| COATED | substances with or without suitable diluents and is covered with a designated coating. A solid dosage form containing a conglomerate of | 30 | Footnotes: ¹ A liquid is pourable; it f | lows and conforms to its container at room temperature. It displays |
| COATED PARTICLES TABLET, | medicinal particles that have each been covered with a coating. A solid dosage form which releases a drug (or | 55 | Newtonian or pseudopla ² Previously the definition topical suspensions, solic current definition of a lot | stic flow behavior. a of a lotion was "The term lotion has been used to categorize many utions, and emulsions intended for application to the skin." The tion is restricted to an emulsion. |
| DELAYED RELEASE TABLET, | drugs) at a time other than promptly after administration. Enteric-coated articles are delayed release dosage forms. A solid dosage form containing a conglomerate of | 55 | ³ A semisolid is not poura It does not flow at low sh ⁴ A colloidal dispersion is between 1 nm and 1 µm) ⁵ Percent water and volat | ble; it does not flow or conform to its container at room temperature. near stress and generally exhibits plastic flow behavior. s a system in which particles of colloidal dimension (i.e., typically are distributed uniformly throughout a liquid. iles are measured by a loss on drying test in which the sample is |
| DELAYED RELEASE PARTICLES | medicinal particles that have been covered with a coating which releases a drug (or drugs) at a time other than promptly after administration. Enteric- | 60 | neated at 105° C. until co | onstant weight is achieved. |
| TABLET, DISPERSIBLE | coarea articles are delayed release dosage forms. A tablet that, prior to administration, is intended to be placed in liquid, where its contents will be distributed eventy throughout the liquid. Note: | | | EXAMPLE 11 |
| | The term 'tablet, dispersible' is no longer used for approved drug products, and it has been replaced by the term 'tablet, for suspension'. | 65 | Route of admi for a dosage form pound of the pre those listed in Ta | nistration. A suitable route of administration n containing a pharmaceutically active com- esent invention may be chosen from among able 11-1. |

TABLE 11-1

34

TABLE 11-1-continued

| Rou | ites of administration | - | R | outes of administration |
|--------------------------------|--|-----|--|--|
| NAME | DEFINITION | - 5 | NAME | DEFINITION |
| BUCCAL | Administration directed toward the cheek, | •) | INTRAVITREAL | Administration wit |
| CONJUNCTIVAL | generally from within the mouth. Administration to the conjunctiva, the delicate membrane that lines the evelids | | NASAL | the eye. Administration to the by way of the nose |
| | and covers the exposed surface of the | 10 | OPHTHALMIC OP AL | Administration to a |
| CUTANEOUS ENDOSINUSIAL | Administration to the skin. Administration within the nasal sinuses of | 10 | OROPHARYNGEAL | Administration dir Administration dir pharynx. |
| ENTERAL | the head. Administration directly into the intestines. | | OTHER | Administration is on this list. |
| EPIDURAL | Administration upon or over the dura mater. | 15 | PARENTERAL | Administration by implantation. |
| EXTRACORPOREAL HEMODIALYSIS | Administration outside of the body. Administration through hemodialysate | 15 | PERCUTANEOUS PERIARTICULAR | Administration thr Administration arc |
| INFILTRATION | fluid. Administration that results in substances | | PERIDURAL | Administration to mater of the spinal |
| INTERSTITIAL | Administration to or in the interstices of a | 20 | PERINEURAL | Administration sur nerves. |
| INTRA-ABDOMINAL | Administration within the abdomen. | | RECTAL | Administration to |
| INTRA-ARTERIAL | Administration within an artery or arteries. | | RESPIRATORY | Administration with |
| INTRA-ARTICULAR | Administration within a joint. | | (INHALATION) | by inhaling orally |
| INTRACARTILAGINOUS | Administration within a cartilage; | | SOFT TISSUE | Administration int |
| INTRACAUDAL | Administration within the cauda equina. | 25 | SUBCONJUNCTIVAL | Administration be |
| INTRACORONARY | Administration within the coronary | | SUBCUTANEOUS | Administration bei |
| | arteries. | | | hypodermic. Syno: |
| INTRADERMAL | Administration within the dermis. | | CUDI INCUAT | SUBDERMAL. |
| INTRADUCIAL INTRADUODENAI | Administration within the duct of a gland. | | SUBLINGUAL | Administration bei |
| INTRADURAL | Administration within or beneath the dura. | 30 | SODMOCOS/IL | membrane. |
| INTRAEPIDERMAL | Administration within the epidermis. | 20 | TOPICAL | Administration to |
| INTRAESOPHAGEAL | Administration within the esophagus. | | | outer surface of the |
| INTRAGASTRIC | Administration within the stomach. | | | TRANSMAMMA |
| IN I KAGINGIVAL | Administration within the lymph | | TPANGDEDMAI | Administration thr |
| INTRAMEDULLARY | Administration within the marrow cavity | | TRANSDERMAL | of the skin to the s |
| | of a bone. | 35 | | diffusion. |
| INTRAMENINGEAL | Administration within the meninges (the three membranes that envelope the brain and spinal cord). | | TRANSMUCOSAL | Administration act |
| INTRAMUSCULAR | Administration within a muscle. | | The foregoing desc | ription of the prefe |
| INTRAOCULAR | Administration within the eye. | 40 | the present invention | have been preser |
| INTRAOVARIAN | Administration within the overy. | -0 | illustration and descri | ntion. It is not inter |
| INTRAPERICARDIAL | Administration within the peritoneal cavity. | | or to limit the inventio | on to the precise for |
| INTRAPLEURAL | Administration within the pleura. | | ous mounications or | variations are pos |
| INTRAPULMONARY | Administration within the lungs or its bronchi. | 45 | described to provide 1 | he best illustration |
| INTRASINAL | Administration within the nasal or periorbital sinuses | | the invention and its | practical application |
| INTRASPINAL | Administration within the vertebral column | | one of ordinary skill various embodiments | in the art to util and with various |
| INTRASYNOVIAL | Administration within the synovial cavity of a joint. | 50 | suited to the particula | r use contemplated |
| INTRATENDINOUS | Administration within a tendon. | 50 | tions and variations a | re within the scop |
| INTRATHECAL | Administration within the cerebrospinal | | determined by the a | ppended claims |
| | fluid at any level of the cerebrospinal axis, including injection into the cerebral ventricles. | | accordance with the b and equitably entitled | readth to which th . The drawings an |
| INTRATHORACIC | Administration within the thorax (internal to the ribs); synonymous with the term andathoragia | 55 | ments do not and are r ing of the claims in the | eir fair and broad |
| INTRATUMOR | Administration within a tumor. | | | |
| INTRAUTERINE | Administration within the uterus. | | What is alaimade | |
| INTRAVASCULAR | Administration within a vessel or vessels. | | 1 A method of an | nlomonting a dist |
| INTRAVENOUS | Administration within or into a vein or | 60 | 1. A method of sup | prementing a diet |
| INTR AVENOUS DOLUS | veins. Administration within or into a win or | | administering to er | id mammal a n ha |
| INTRAVENOUS BOLUS | Administration within or into a vein or veins all at once | | tive amount of a | compound having |
| INTRAVENOUS DRIP | Administration within or into a vein or | | | |
| INTRAVENTRICI II AR | Administration within a ventricle | 65 | | $R^2 \sim R^2$ |
| INTRAVENTRICOLAR | Administration within the bladder. | 55 | | к К- |

| AME | DEFINITION |
|----------------|---|
| TRAVITREAL | Administration within the vitreous body of |
| ASAL | Administration to the nose; administered |
| PHTHALMIC | Administration to the external eye. |
| RAL | Administration to or by way of the mouth. |
| ROPHARYNGEAL | Administration directly to the mouth and pharynx. |
| THER | Administration is different from others on |
| | this list. |
| ARENTERAL | Administration by injection, infusion, or |
| | implantation. |
| ERCUTANEOUS | Administration through the skin. |
| ERIARTICULAR | Administration around a joint. |
| ERIDURAL | Administration to the outside of the dura |
| | mater of the spinal cord |
| ERINEURAL | Administration surrounding a nerve or |
| | nerves. |
| ERIODONTAL | Administration around a tooth. |
| ECTAL | Administration to the rectum. |
| ESPIRATORY | Administration within the respiratory tract |
| NHALATION) | by inhaling orally or nasally for local or systemic effect. |
| OFT TISSUE | Administration into any soft tissue |
| IBCONIUNCTIVAL | Administration beneath the conjunctiva |
| IBCUTANEOUS | Administration beneath the skin: |
| obee mineded | hypodermic. Synonymous with the term |
| | SUBDERMAL. |
| JBLINGUAL | Administration beneath the tongue. |
| JBMUCOSAL | Administration beneath the mucous |
| | membrane. |
| OPICAL | Administration to a particular spot on the |
| | outer surface of the body. The E2B term |
| | TRANSMAMMARY is a subset of the |
| | term TOPICAL. |
| RANSDERMAL | Administration through the dermal layer |
| | of the skin to the systemic circulation by |
| | diffusion. |
| RANSMUCOSAL | Administration across the mucosa. |
| | |

preferred embodiments of presented for purposes of t intended to be exhaustive cise form disclosed. Obvire possible in light of the nents were chosen and tration of the principles of blication to thereby enable to utilize the invention in rious modifications as are plated. All such modificascope of the invention as aims when interpreted in nich they are fairly, legally ngs and preferred embodito limit the ordinary meanbroad interpretation in any

a diet of a mammal, com-

a pharmaceutically effecaving a chemical formula:

$$R^2 \sim R^1 \sim R^2$$



$$\underbrace{\overset{O}{\underset{C}{\overset{}}}}_{C} \underbrace{\overset{O}{\underset{C}{\overset{}}}}_{NH} \underbrace{(CH_2)_n}_{SR^4} \text{ or } \underbrace{\overset{O}{\underset{C}{\overset{}}}}_{C} \underbrace{NH}_{C} \underbrace{CH_2}_{SR^4} \underbrace{SR^4}_{\underset{C}{\overset{}}}_{\underset{R^3}{\overset{}}}$$

where R³=ethyl or methyl, R⁴=hydrogen, glutathione, cysteine, alphadihydrolipoic acid, cystamine, thiolphosphate, 5'thioladenosine, L-homocysteine, co-enzyme A, 2-mercaptoethanol, dithiothreitol, iodoacetate, bro- ₂₅ moacetate, fluoroacetate or chloroacetate and n=2-4.

2. The method of claim 1, including using oral administration.

3. The method of claim **1**, including administering between about 0.5 and about 40 milligrams of said compound per kilogram of said mammal's total body weight per day.

4. The method of claim 1, including using transdermal administration.

5. The method of claim **1**, including using nasal adminis- ³⁵ tration.

6. The method of claim 1, including using administration by suppository.

7. The method of claim 1, including using intravenous $_{40}$ administration.

8. The method of claim **1**, including administering said compound with another antioxidant.

9. The method of claim **1**. including selecting said antioxidant from a list of antioxidants consisting of vitamin-E, vitamin-D, cysteine, glutathione, lipoic acid and combinations thereof.

10. A method to remove heavy metals and toxins from a mammal, comprising:

administering to said mammal a pharmaceutically effective amount of a compound having a chemical formula:

$$R^2 \sim R^1 R^2$$



where R²=



36



15

20



where R³=ethyl or methyl, R⁴=hydrogen, glutathione, cysteine, alphadihydrolipoic acid, cystamine, thiolphosphate, 5'thioladenosine, L-homocysteine, co-enzyme A, 2-mercaptoethanol, dithiothreitol, iodoacetate, bromoacetate, fluoroacetate or chloroacetate and n=2-4.

11. The method of claim 10, including using oral administration.

12. The method of claim **10**, including administering between about 0.5 and about 40 milligrams of said compound per kilogram of said mammal's total body weight per day.

13. The method of claim 10, including using transdermal administration.

14. The method of claim 10, including using nasal administration.

15. The method of claim **10**, including using administration by suppository.

16. The method of claim 10, including using intravenous administration.

17. The method of claim 10, including administering said compound with a water soluble metal chelator.

18. The method of claim 17, including selecting said water soluble metal chelator from a group consisting of glutathione (GSH), dihydrolipoic acid (DLPA), lipoic acid (LPA), N-acetylcysteine (NAC), dimercaptopropane sultanate (DMPS), dimercaptosuccinic acid (DMSA), ethylenediaminetetraacetie acid (EDTA) and mixtures thereof.

19. A method of relieving oxidative stress in a mammal, comprising:

administering to said mammal a pharmaceutically effective amount of a compound having a chemical formula:

$$R^2 \sim R^1 R^2$$

where R¹=



65

60

55



55

60



37

and

where R3=ethyl or methyl, R4=hydrogen, glutathione, cysteine, alphadihydrolipoic acid, cystamine, thiolphosphate, 5'thioladenosine, L-homocysteine, co-enzyme A, 2-mercaptoethanol, dithiothreitol, iodoacetate, bro- 15 moacetate, fluoroacetate or chloroacetate and n=2-4.

20. The method of claim 19, including using oral administration.

21. The method of claim 19, including administering between about 0.5 and about 100 milligrams of said com- 20 pound per kilogram of said mammal's total body weight per day

22. The method of claim 19, including using transdermal administration.

23. The method of claim 19, including using nasal admin- 25 istration.

24. The method of claim 19, including using administration by suppository.

25. The method of claim 19, including using intravenous administration.

26. The method of claim 19, including administering said compound with a precursor of glutathione,

27. The method of claim 26, including selecting said precursor of glutathione from a group consisting of cysteinc, N-acetylcysteine, glycine, glutamate and combinations 35 thereof.

28. The method of claim 19, including administering said compound with a dietary supplement that supports glutathione synthesis.

29. The method of claim **28**, including selecting said 40dietary supplement from a group consisting of whey protein, N-acetylcysteine, cysteine, glutathione, nicotine adenine dinucleotide (NAD⁺), reduced nicotine adenine dinucleotide (NADH), glycylcysteine (gly-cys), glutamylcysteine (glucys), and combinations thereof.

30. A pharmaceutical composition, comprising:

a pharmaceutically effective amount of a compound having a chemical formula:

$$R^2$$
 R^2 R^2



38

where R³=ethyl or methyl, R⁴ hydrogen, glutathione, cysteine, alphadihydrolipoie acid, cystamine, thiolphosphate, 5'thioladenosine, L-homocysteine, co-enzyme A, 2-mercaptoethanol, dithiothreitol, iodoacetate, bromoacetate, fluoroacetate or chloroacetate and n=2-4; and

a pharmaceutically acceptable excipient.

31. The composition of claim 30, wherein said excipient is selected from a group of materials consisting of Acacia, Acesulfame Potassium, Acetic Acid, Acetone, Acetyltributyl Citrate, Acetyltriethyl Citrate, Agar, Albumin, Alcohol, Alginic Acid, Aliphatic Polyesters, Alitame, Almond Oil, Alpha Tocopherol, Aluminum Hydroxide Adjuvant, Aluminum Oxide, Aluminum Phosphate Adjuvant, Aluminum Stearate, Ammonia Solution, Ammonium Alginate, Ascorbic Acid, Ascorbyl Palmitate, Aspartame, Attapulgite, Bentonite, Benzalkonium Chloride, Benzethonium Chloride, Benzoic Acid, Benzyl Alcohol, Benzyl Benzoate, Boric Acid, Bronopol, Butylated Hydroxyanisole, Butylated Hydroxytoluene, Butylparaben, Calcium Alginate, Calcium Carbonate, Calcium Phosphate, Dibasic Anhydrous, Calcium Phosphate, Dibasic Dihydrate, Calcium Phosphate, Tribasic, Calcium Stearate, Calcium Sulfate, Canola Oil, Carbomer, Carbon Dioxide, Carboxymethylcellulose Calcium, Carboxymethylcellulose Sodium, Carrageenan, Castor Oil, Hydrogenated Castor Oil, Cellulose, Microcrystalline, Cellulose, Powdered, Cellulose, Silicified Microcrystalline, Cellulose Acetate, Cellulose Acetate Phthalate, Ceratonia, Cetostearyl Alcohol, Cetrimide, Cetyl Alcohol, Cetylpyridinium Chloride, Chitosan, Chlorhexidine, Chlorobutanol, Chlorocresol, Chlorodifluoroethane (HCFC), Chlorofluorocarbons (CFC), Chloroxylenol, Cholesterol, Citric Acid Monohydrate, Colloidal, Silicon Dioxide, Coloring Agents, Copovidone, Corn Oil, Cottonseed Oil, Cresol, Croscarmellose Sodium, Crospovidone, Cyclodextrins, Cyclomethicone, Denatonium Benzoate, Dextrates, Dextrin, Dextrose, Dibutyl Phthalate, Dibutyl Sebacate, Diethanolamine, Diethyl Phthalate, Difluoroethane (HFC), Dimethicone, Dimethyl Ether, Dimethyl Phthalate, Dimethyl Sulfoxide, Dimethylacetamide, Disodium Edetate, Docusate Sodium, Edetic Acid, Erythorbic Acid, Erythritol, Ethyl Acetate, Ethyl Lactate, Ethyl Maltol, Ethyl Oleate, Ethyl Vanillin, Ethylcellulose, Ethylene Glycol 50 Palmitostearate, Ethylene Vinyl Acetate, Ethylparaben, Fructose, Fumaric Acid, Gelatin, Glucose, Glycerin, Glyceryl Behenate, Glyceryl Monooleate, Glyceryl Monostearate, Glyceryl Palmitostearate, Glycofurol, Guar Gum, Hectorite, Heptafluoropropane (HFC), Hexetidine, Hydrocarbons (HC), Hydrochloric Acid, Hydroxyethyl Cellulose, Hydroxyethylmethyl Cellulose, Hydroxypropyl Cellulose, Hydroxypropyl Cellulose, Low-substituted, Hydroxypropyl Starch, Hypromellose, Hypromellose Acetate Succinate, Hypromellose Phthalate, Imidurea, Inulin, Iron Oxides, Isopropyl Alcohol, Isopropyl Myristate, Isopropyl Palmitate, Kaolin, Lactic Acid, Lactitol, Lactose Anhydrous, Lactose Monohydrate, Lactose Spray-Dried, Lanolin, Lanolin Hydrous, Lanolin Alcohols, Lauric Acid, Lecithin, Leucine, Linoleic Acid, Macrogol 15 Hydroxystearate, Magnesium Aluminum Silicate, Magnesium Carbonate, Magnesium Oxide, Magnesium 65 Silicate, Magnesium Stearate, Magnesium Trisilicate, Malic Acid, Maltitol, Maltitol Solution, Maltodextrin, Maltol, Maltose, Mannitol, Mediumchain Triglycerides, Meglumine,

where R¹=

Menthol, Methylcellulose, Methylparaben, Mineral Oil, Mineral Oil, Light, Mineral Oil and Lanolin Alcohols, Monoethanolamine, Monosodium Glutamate, Monothioglycerol, Myristic Acid, Neohesperidin Dihydrochalcone, Nitrogen, Nitrous Oxide, Octyldodecanol, Oleic Acid, Oleyl Alcohol, 5 Olive Oil, Palmitic Acid, Paraffin, Peanut Oil, Pectin, Petrolatum and Lanolin Alcohols, Petrolatum, Phenol, Phenoxyethanol, Phenylethyl Alcohol, Phenylmercuric Acetate, Phenylmercuric Borate, Phenylmercuric Nitrate, Phosphoric Acid, Polacrilin Potassium, Poloxamer, Polycarbophil, Poly-10 dextrose, Polyethylene Glycol, Polyethylene Oxide, Polymethacrylates, Poly(methyl vinyl ether/maleic anhydride), Polyoxyethylene Alkyl Ethers, Polyoxyethylene Castor Oil Derivatives, Polyoxyethylene Sorbitan Fatty Acid Esters, Polyoxyethylene Stearates, Polyvinyl Acetate, Phthalate, 15 Polyvinyl Alcohol, Potassium Alginate, Potassium Benzoate, Potassium Bicarbonate, Potassium Chloride, Potassium Citrate, Potassium Hydroxide, Potassium Metabisulfite, Potassium Sorbate, Povidone, Propionic Acid, Propyl Gallate, Propylene Carbonate, Propylene Glycol, Propylene Glycol 20 Alginate, Propylparaben, 2-Pyrrolidone, Raffinose, Saccharin, Saccharin Sodium, Saponite, Sesame Oil, Simethicone, Sodium Acetate, Sodium Alginate, Sodium Ascorbate, Sodium Benzoate, Sodium Bicarbonate, Sodium Borate, Sodium Chloride, Sodium Citrate Dihydrate, Sodium Cyclamate, Sodium Hyaluronate, Sodium Hydroxide, Sodium Lac- 25 tate, Sodium Lauryl Sulfate, Sodium Metabisulfite, Sodium Phosphate, Dibasic, Sodium Phosphate, Monobasic, Sodium Propionate, Sodium Starch Glycolate, Sodium Stearyl Fumarate, Sodium Sulfite, Sorbic Acid, Sorbitan Fatty Acid Esters, Sorbitol, Soybean Oil, Starch, Starch, Pregelatinized, Starch, 30 Sterilizable Maize, Stearic Acid, Stearyl Alcohol, Sucralose, Sucrose, Sugar, Compressible Sugar, Confectioner's Sugar, Sulfobutylether β-Cyclodextrin, Sulfuric Acid, Sunflower Oil, Suppository Bases, Hard Fat, Talc, Tartaric Acid, Tetrafluoroethane (HFC), Thaumatin, Thymol, Titanium Diox- 35 ide, Tragacanth, Trehalose, Triacetin, Tributyl Citrate, Triethanolamine, Triethyl Citrate, Vanillin, Hydrogenated Vegetable Oil, Water, Wax, Anionic Emulsifying, Wax, Carnauba, Wax, Cetyl Esters, Microcrystalline Wax, Nonionic Emulsifying Wax, White Wax, Yellow Wax, Xanthan Gum, 40 Xylitol, Zein, Zinc Acetate, Zinc Stearate and combinations thereof.

32. The composition of claim **30**, wherein said excipient is selected from a group of materials consisting of albumin, almond oil, ascorbic acid, benzoic acid, calcium stearate, canola oil, calcium carboxymethylcellulose, sodium car-⁴⁵ boxymethylellulose, castor oil, hydrogenated castor oil, microcrystalline cellulose, corn oil, cotton seed oil, cyclodex-trins, ethylene glycol palmitostearate, gelatin, glycerin, hydroxyethyl cellulose, low-substituted hydroxypropyl cellulose, lanolin, linoleic acid, magnesium silicate, magnesium stearate, medium-chain triglycerides, mineral oil, olive oil, peanut oil, pectin, compressible sugar, sunflower oil, hydro-genate vegetable oil, water and combinations thereof.

33. The composition of claim **30**, further including an ₅₅ additional antioxidant.

34. The composition of claim **33**, wherein said additional antioxidant is selected from a group consisting of vitamin-E, vitamin-D, cystine, glutathione, lipoic acid and combinations thereof.

35. The composition of claim **30**, further including a water 60 soluble metal chelator.

36. The composition of claim **35**, wherein said water soluble metal chelator is selected from a group consisting of glutathione (GSH), dihydrolipoic acid (DLPA), lipoic acid (LPA), N-acetylcysteine (NAC), dimercaptopropane sul- ⁶⁵ fonate (DMPS), dimercaptosuccinic acid (DMSA), ethylene-diaminetetraacetic acid (EDTA), and mixtures thereof.

37. The composition of claim **30**, further including a precursor of glutathione.

38. The composition of claim **37**, wherein said precursor of glutathione is selected from a group of materials consisting of cysteine, N-acetylcystein, glycine, glutamate and combinations thereof.

39. The composition of claim **30**, further including an additional dietary supplement that supports glutathione synthesis.

40. The composition of claim **39**, wherein said additional dietary supplement is selected from a group of materials consisting of whey protein, N-acetylcysteine, cysteine, glutathione, nicotine adenine dinucleotide (NAD⁺), reduced nicotine adenine dinucleotide (NADH), glycylcysteine (glycys), glutamylcysteine (glucyc), and combinations thereof.

41. The composition of claim **30**, further including a material selected from a group consisting of a binder, a preservative, a mineral supplement, a bulking agent, a flavoring agent and combinations thereof.

42. The composition of claim **30**, including between about 99.5 and about 85 weight percent active compound and between about 0.5 and about 15 weight percent excipient.

43. A pharmaceutical composition, comprising: between about 99.5 and about 5 weight percent of a pharmaceutically effective amount of a compound having a

$$\mathbf{x}^{\mathbf{R}^{1}}_{\mathbf{R}^{2}}$$
 \mathbf{x}^{2}

where $R^{1}=$

chemical formula:



and where R²=



- where R³=ethyl or methyl, R⁴=hydrogen, glutathione, cysteine, alphadihydrolipoic acid, cystamine, thiolphosphate, 5'thioladenosine, L-homocysteine, co-enzyme A, 2-mercaptoethanol, dithiothreitol, iodoacetate, bromoacetate, fluoroacetate or chloroacetate and n=2-4;
- between about 0.0 and about 50 weight percent of an additional antioxidant;
- between about 0.0 and about 20 weight percent of a water soluble metal chelator;
- between about 0.0 and about 50 weight percent of glutathione;
- between about 0.0 and about 50 weight percent of an additional dietary supplement that supports glutathione synthesis; and

between about 0.5 and about 50 weight percent of a pharmaceutically acceptable excipient.44. The composition of claim 43 wherein said compound

has a chemical formula





