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IMPROVED PHARMACOKINETICS OF S-ADENOSYLMETHIONINE FORMULATIONS

ABSTRACT

Compositions and methods to improve the pharmacokinetic profile of S-Adenosylmethionine (SAMe) are provided, as are methods of treating various disorders using SAMe formulations with improved pharmacokinetic profiles. More specifically, the invention is directed to methods of treating a disease or disorder in a subject and/or improving the nutritional status of a subject by administering formulations exhibiting improved pharmacokinetic profiles of exogenous SAMe. The method also includes the step of orally administering compositions of the invention to the subject once per day after overnight fast; that is prior to food intake in the morning.

Fig. 1

We claim:

1. A composition comprising a physiologically effective amount of S-adenosylmethionine (SAMe), wherein non-parenteral administration of said composition to a selected subject group produces in said selected subject group an effect comprising an average maximum SAMe blood plasma concentration (average Cmax) of at least about 100 ng/mL and an average SAMe plasma area under curve (average AUC) of at least about 450 ng·h/mL per 100 mg dosage of SAMe ion.

2. The composition of claim 1, wherein said physiologically effective amount of SAMe comprises about 800 mg to 1600 mg of SAMe ion.

3. The composition of claim 2, wherein 800 mg of SAMe ion produces an average Cmax of at least about 850 ng/mL and an average AUC of at least about 4000 ng·h/mL.

4. The composition of claim 2, wherein 1600 mg of SAMe ion produces an average Cmax of at least about 1800 ng/mL and an average AUC of at least about 7500 ng·h/mL.

5. The composition of one of claims 1 to 4, wherein the composition is in a dosage form that comprises a functional coating, wherein the functional coating constitutes (i) less than or equal to 5% of the total weight of the dosage form, or (ii) from 1 to 5% of the total weight of the unit dosage form; or wherein the composition contains less than or equal to 3.5% water.

6. The composition of one of claims 1 to 4, wherein the composition exhibits an *in vitro* dissolution profile in pH 6.0 aqueous solution such that greater than 20% and less than 90% of total SAMe in the composition is released from 30 to 90 minutes of incubation in said pH 6.0 aqueous solution.

7. The composition of one of claims 1 to 4, wherein dissolution of the dosage form in pH 6.0 aqueous solution provides about 25-80% release or about 30-70% of SAMe release after 45 to 75 minutes of being in said aqueous solution having an initial pH of about 6.

8. The composition of claim 6 or 7, wherein said *in vitro* dissolution profile is measured in a USP II dissolution apparatus at 100 rpm in said aqueous solution or wherein the composition is exposed to an acid phase for 2 hours prior to said incubation.

9. The composition of one of claims 1 to 8, wherein the composition is formulated for oral administration, and wherein the composition comprises a suitable excipient, optionally wherein:
(i) the composition comprises one of tablets, pastes, capsules, granules, caplets, lozenges, pastes, and suppositories;
(ii) the dosage is divided into one, two, three, four, five, six or more dosage units; or
(iii) the composition comprises a dietary supplement or a medical food.

10. A composition comprising a physiologically effective amount of S-adenosylmethionine (SAMe) in a compressed tablet dosage form comprising an enteric coating, wherein the composition exhibits an *in vitro* dissolution profile in pH 6.0 aqueous solution such that greater than 25% and less than 80% of total SAMe in the composition is released from 30 to 90 minutes of incubation in said pH 6.0 aqueous solution.

11. The composition of claim 10, wherein the composition exhibits an *in vitro* dissolution profile in pH 6.0 aqueous solution such that about 25-80% or about 30-70% of SAMe is released after 60 minutes of being in an aqueous solution having an initial pH of about 6.

12. The composition of claim 10 or 11, wherein said *in vitro* dissolution profile is measured in a USP II dissolution apparatus at 100 rpm in said aqueous solution or wherein the composition is exposed to an acid phase for 2 hours prior to said incubation.

13. The composition of claim 10 or 11, wherein said physiologically effective amount of SAMe comprises about 100 to 1600 mg SAMe ion and, wherein non-parenteral administration of said composition to a selected subject group produces in said selected subject group an effect comprising an average maximum SAMe blood plasma concentration (average Cmax) of at least about 100 ng/mL and an average

SAMe plasma area under curve (average AUC) of at least about 450 ng·h/mL per 100 mg dosage of SAMe ion

14. The composition of one of claims 10 to 13, wherein the enteric coating constitutes (i) less than or equal to 5% of the total weight of the dosage form, or (ii) from 1 to 5% of the total weight of the unit dosage form; or
wherein the composition contains less than or equal to 3.5% water.

15. A composition comprising a physiologically effective amount of S-adenosylmethionine (SAMe), wherein non-parenteral administration of said composition to a selected subject group produces in said selected subject group an effect comprising at least one of:
    a. an average maximum SAMe blood plasma concentration (average C_{max}) of at least about 2000 ng/mL for a 1600 mg dosage of SAMe ion;
    b. an average SAMe plasma area under the curve (average AUC) of at least about 8000 ng·h/mL for a 1600 mg dosage of SAMe ion;
    c. an average maximum SAMe blood plasma concentration (average C_{max}) of at least about 875 ng/mL and/or an average SAMe plasma area under the curve (average AUC) of at least about 4000 ng·h/mL for a 800 mg dosage of SAMe ion;
    d. an average maximum SAMe blood plasma concentration (average Cmax) of at least about 450 ng/mL and/or an average SAMe plasma area under curve (average AUC) of at least about 1800 ng·h/mL for a 400 mg dosage of SAMe ion; or
    e. an average maximum SAMe blood plasma concentration (average Cmax) of at least about 110 ng/mL and/or an average SAMe plasma area under curve (average AUC) of at least about 500 ng·h/mL for a 100 mg dosage of SAMe ion.

16. The composition of one of claims 1 to 15, wherein the composition
    (i) when administered to a select subject group provides in said selected subject group an improved pharmacokinetic profile through: a reduced variation of T_{max} and equivalent AUC to bi-daily dosing and/or reduced side effects through once a day dosing;

(ii) when administered to a subject provides in the subject one of an average T_{max} or C_{max} with reduced variation or a reduced effective dose in comparison to a SAMe reference data set; or

(iii) when administered to a subject provides in the subject a reduced side effect profile in comparison to a SAMe reference data set.

17. The composition of one of claims 1 to 16, wherein said composition comprises physical or chemical dosage form characteristics which modulate one of said average SAMe C_{max} and said average SAMe AUC; optionally wherein said dosage form characteristics comprise one of hardness, thickness, friability, speed of disintegration, speed of dissolution, shape, size, density, coating and combinations thereof; or said dosage form characteristics are modulated by controllably manipulating during production or manufacturing of said composition one of physical mixing specifications, drying time, pressing conditions, environmental parameters and combinations thereof.

18. The composition of one of claims 1 to 17, wherein the composition comprises at least one excipient which is one of matrix materials; binders; lubricants; glidants; coatings; disintegrants, super-disintegrants; polysaccharides, oligosaccharides; polypeptides, proteins synthetic oligomers, synthetic polymers, monomeric organic molecules, hydrophobic organic molecules, hydrophilic organic molecules, amphoteric organic molecules, inorganic salts inorganic metals, and combinations thereof.

19. The composition of one of claims 1 to 18 for use in the treatment of a disease condition or disorder selected from the group consisting of a mental or psychiatric disorder, nervous system disease or disorder, neurological disease or disorder, condition associated with injury to the central nervous system, liver disease or disorder, cancer, joint disease or disorder, inflammatory disease or disorder, autoimmune disease or disorder, degenerative disease or disorder, soft-tissue disease or disorder, pain disease or disorder, genetic disorder related to hyper- or hypo-methylation, gastrointestinal disease or disorder, cardiovascular disease or disorder, and disorder induced in whole or in part by oxidative or free-radical damage.

20. The composition of claim 19, further comprising one or more active ingredient that is used for treatment or prophylaxis of a mental or psychiatric disorder, optionally wherein the mental or psychiatric disorder is depression.

21. The composition of claim 20, further comprising one or more active ingredient is selected from the group consisting of tricyclic antidepressants (TCAs), tetracyclic antidepressants, aminoketones, phenylpiperazines, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-serotonin reuptake inhibitors (NSRIs), dopamine reuptake inhibitors, norepinephrine-dopamine reuptake inhibitors, norepinephrine reuptake inhibitors, selective serotonin reuptake enhancers, noradrenergic and serotonin specific antidepressants, substance P receptor antagonists, neurokinin receptor antagonists such as saredutant, corticotrophin release factor antagonists such as mifepristone, atypical antipsychotics such as aripiparazole, or commonly used antidepressant augmenters such as lithium or triple reuptake inhibitors.

22. The composition of one of claims 19 to 21, wherein

(i) the mental or psychiatric disorder is selected from the group consisting of an anxiety disorder, schizophrenia, major depressive disorder, multi-infarct dementia, minor depression, postpartum depression, inflammatory depression, late-life depression, Parkinson's depression, HIV-associated depression, and bipolar disorder;

(ii) the inflammatory disease or disorder is selected from the group consisting of systemic lupus, inflammatory bowel disease, allergic rhinitis, contact dermatitis, asthma, autoimmune hepatitis, and pelvic inflammatory disease;

(iii) the cardiovascular disease or disorder is selected from the group consisting of hyper- or hypo-homocysteinemia, coronary heart disease, stroke, peripheral vascular disease, and atherosclerotic disease;

(iv) the depressive disorder is a comorbid depression arising in a subject who is or has been undergoing treatment for one or more diseases or disorders selected from the group consisting of cancer, Parkinson's and HIV;

(v) the nervous system disease or disorder or injury is selected from the group consisting of Parkinson's disease, Alzheimer's disease, and cognitive impairment;

(vi) the liver disease or disorder is selected from the group consisting of alcoholic liver disease, non-alcoholic fatty liver disease, viral or non-viral hepatitis, liver cancer, oxidative liver disease, drug induced liver injury, cholestasis, and cirrhosis;

(vii) the cancer is selected from the group consisting of liver cancer, colon cancer, rectal cancer, stomach cancer, esophageal cancer, and adenocarcinoma;

(viii) the joint disease or disorder is arthritis or osteoarthritis;

(ix) the soft-tissue disease or disorder is fibromyalgia;

(x) the pain disease or disorder is selected from the group consisting of fibromyalgia, and abdominal pain; or

(xi) the genetic disorder related to hyper- or hypo-methylation such as methylenetetrahydrofolate reductase deficiency.

Dated this 21st day of February 2012

NEHA CHUGH
PATENT AGENT

Applicant Name: **METHYLATION SCIENCES INTERNATIONAL SRL**

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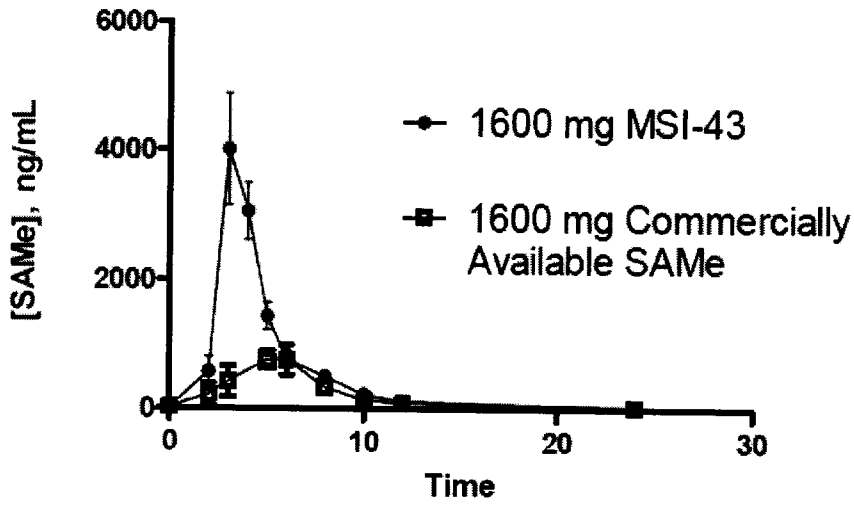

FIGURE 1

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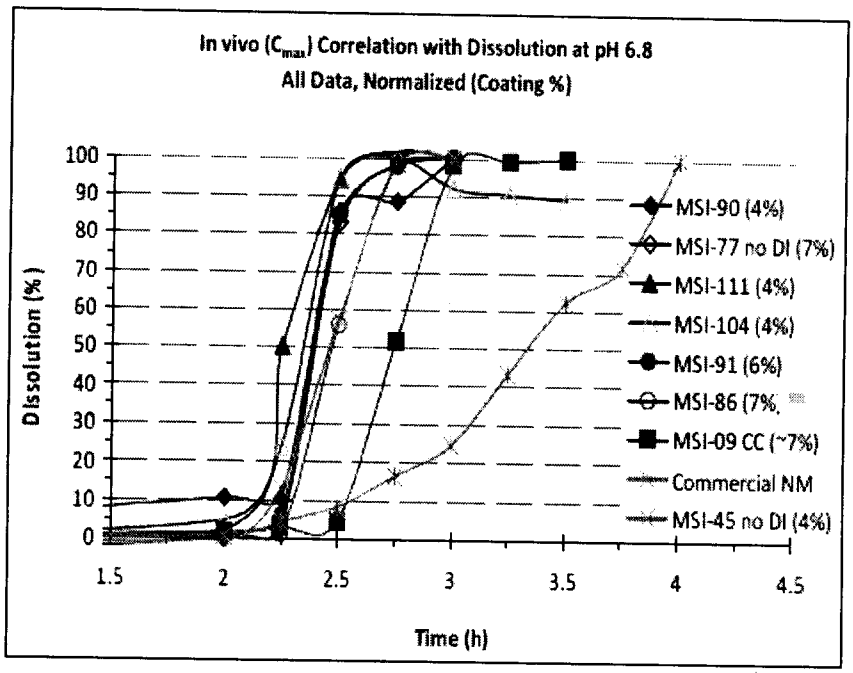

FIGURE 2A

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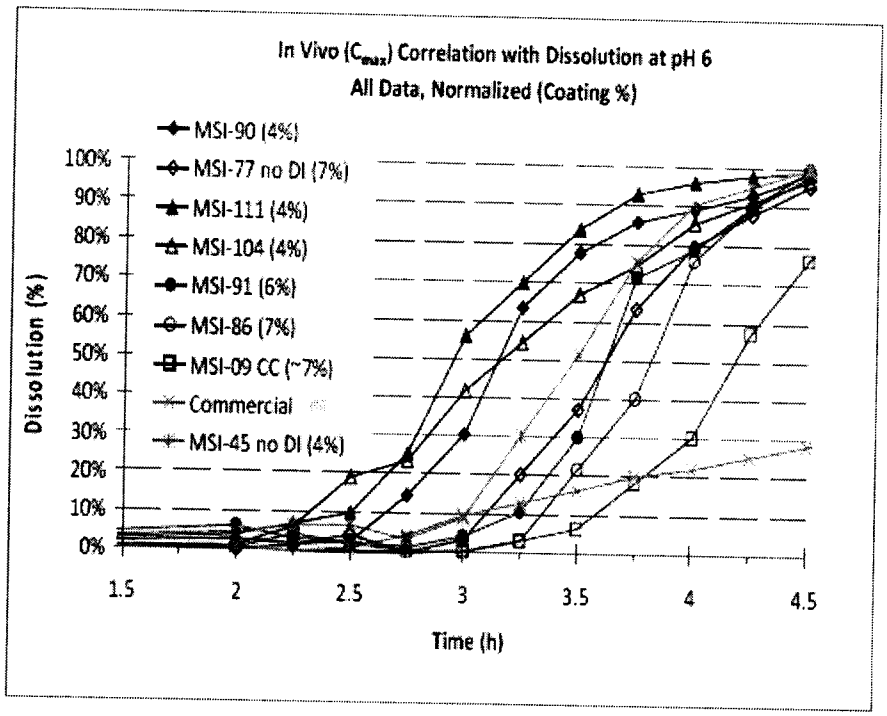

FIGURE 2B

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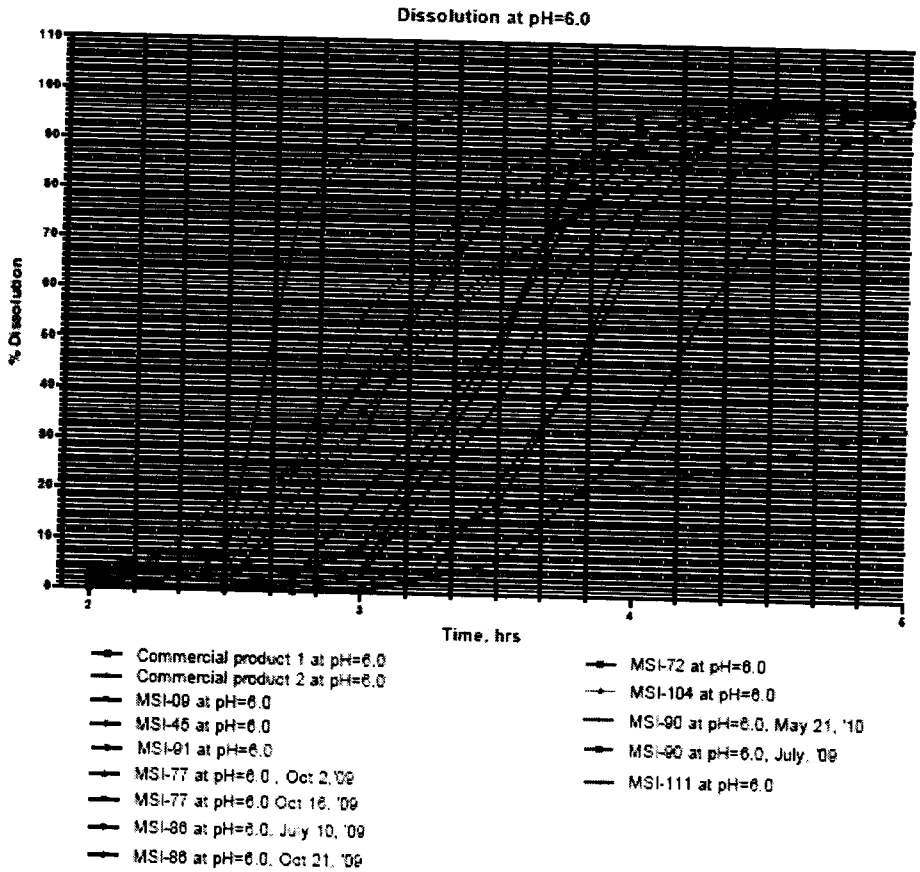

FIGURE 3

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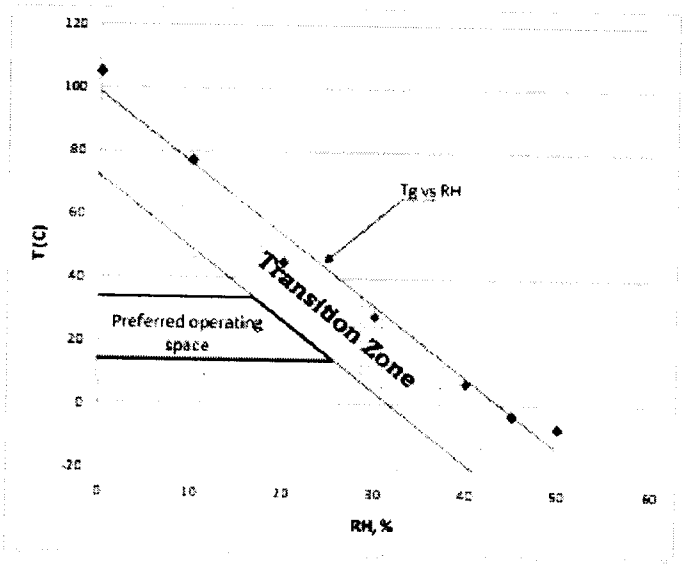

FIGURE 4

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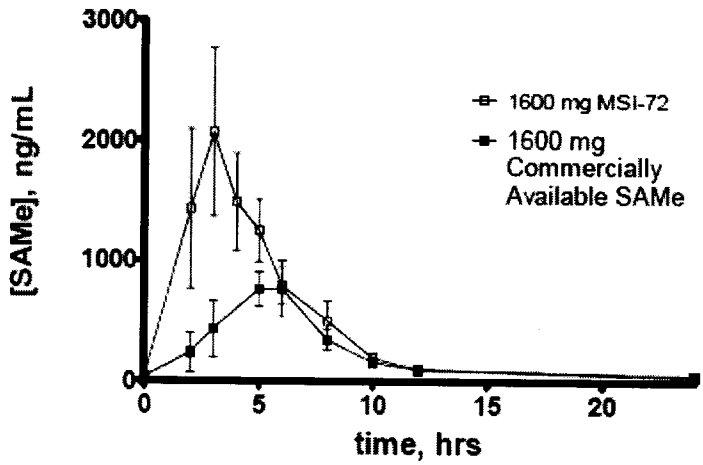

FIGURE 5A

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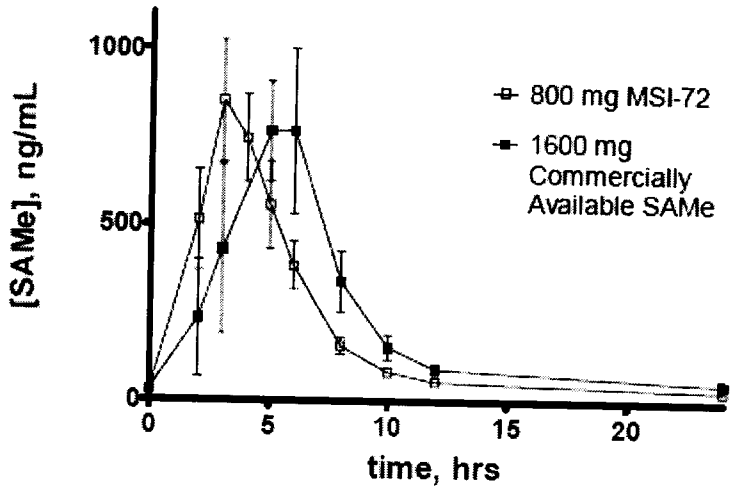

FIGURE 5B

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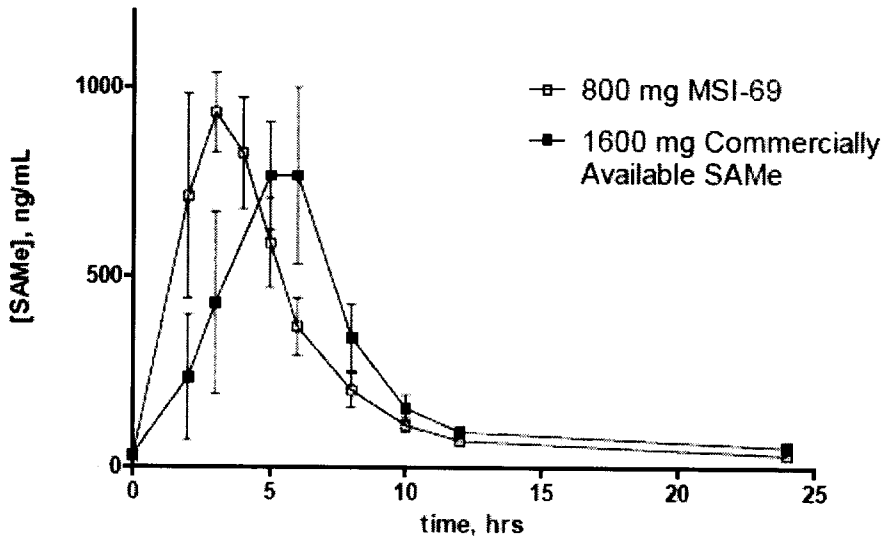

FIGURE 5C

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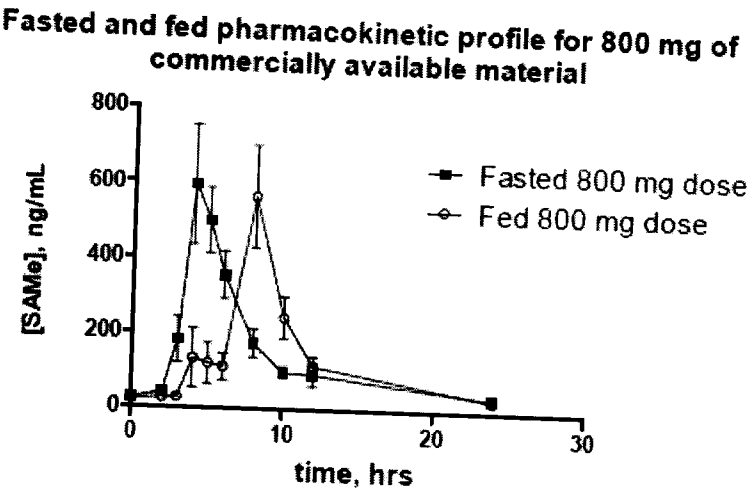

FIGURE 6

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Simulated pharmacokinetic curve for BID dosing

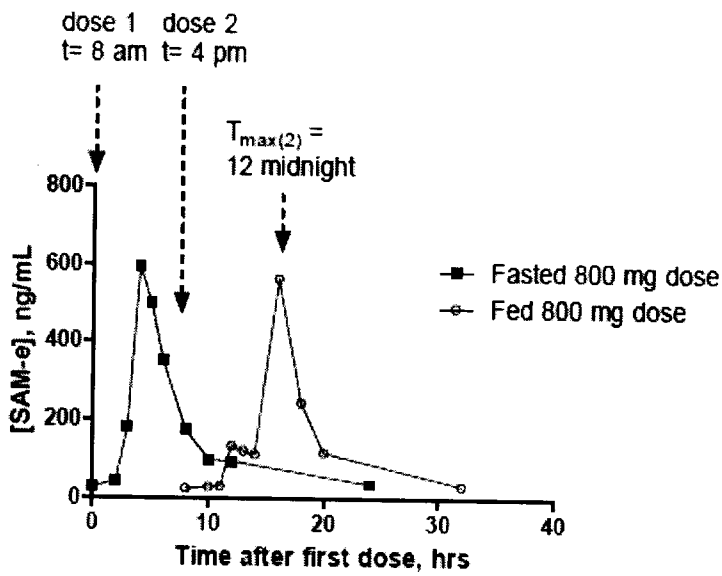

FIGURE 7

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IMPROVED PHARMACOKINETICS OF S-ADENOSYLMETHIONINE FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS AND CLAIM TO PRIORTY

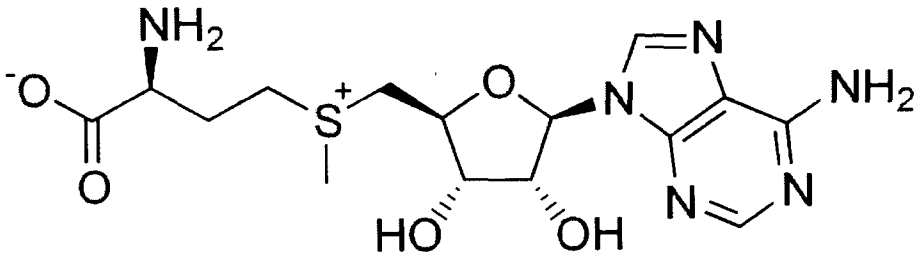
[0001] This application claims priority to United States Provisional patent application serial number 61/229,186, filed July 28, 2009, which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] The invention relates to compositions and methods for improving the pharmacokinetic profile of S-adenosyl-L-methionine ("SAM-e" or "SAMe"). More particularly, the invention concerns formulations that lead to SAMe plasma concentrations and AUC values that are increased in comparison to similar or higher doses of conventional SAMe formulations. The invention is directed to methods of treating a disease or disorder in a subject and/or improving the nutritional status of a subject by administering formulations exhibiting improved pharmacokinetic profiles of exogenous SAMe. The method also includes orally administering compositions of the invention to the subject once per day after overnight fast, that is prior to food intake in the morning, which may alleviate some of the side effects (*e.g.* insomnia and gastrointestinal) associated with conventional twice-daily (or more) dosing regimens. Compositions of the invention may also provide a faster rate of onset of exogenous SAMe in comparison to conventional oral dosage forms potentially leading to improvements in efficacy.

BACKGROUND OF THE INVENTION

[0003] S-adenosyl-L-methionine ("SAMe") is a naturally occurring compound that is present in tissues throughout the body. At the molecular level, SAMe is involved in various metabolic pathways, including transmethylation, transsulfuration and aminopropylation.



S-adenosyl-L-methionine (SAM-e)

[0004] In the body, SAMe is synthesized from an amino acid, methionine, and a triphosphate nucleotide, ATP. SAMe has been tested in numerous clinical trials for the treatment of various ailments, including arthritis, liver disease and depression.

[0005] SAMe supplementation was initially considered impractical, due to the instability of the SAMe ion during manufacturing, shipping and storage. Eventually stable salts of SAMe were developed (such as SAMe tosylate disulfate, the butanedisulfonate salt of SAMe, the di-para-toluene sulfonate disulfate of SAMe, the tri-para-toluene sulfonic acid salt of SAMe and the like). These salts can be formulated using standard, known technologies used for non-parenteral administration including but not limited to tablets, capsules and pellets. Formulations such as these may also comprise a coating which can serve multiple purposes such as reducing stomach irritation, improving taste and ease of swallowing, as well as stabilizing the encapsulated SAMe from elements such as moisture. Stable salts of SAMe are described in, for example, United States Patent Numbers 3,954,726 and 4,057,686, both of which are incorporated herein by reference in their entirety. Conventional SAMe API is supplied as a molecular entity comprising an ion along with several counter-ions. For example, SAMe ion plus a tosylate and 2 sulfonic acid counter-ions make up commercially available adenosylmethionine disulfate-*p*-toluenesulfonate (also referred to as SAMe tosylate disulfate). When referring to SAMe dosing, it is currently accepted in the art that the numerical dose (usually in milligrams) refers to the amount of SAMe ion which is administered. For example, reference to a "400 mg SAMe tablet" of the SAMe tosylate disulfate would include the 400 mg of SAMe ion, another 370 mg of the counter-ions, and 200-300 mg of additional excipient to make up a final tablet weight of 1.0-1.1 grams. Thus, for example, a 1600 mg oral dose of SAMe which is generally reported in the art would typically be a dose of four such 1.0-1.1 gram tablets taken at one time. Alternatively, the same 1600 mg dose of SAMe ion may also be accomplished by administration of other combinations of multiple tablets such as, sixteen 100 mg or eight 200 mg tablets of SAMe ion taken at a given time. Conventional oral dosage forms of SAMe are most commonly

produced with about 400 mg of SAMe ion; above that, the larger dosage form becomes difficult for swallowing considering that even at 400 mg of SAMe ion the tablets are quite large at 1.0-1.1 grams.

[0006] Exogenous SAMe exposure may be measured by looking at multiple pharmacokinetic parameters, the most common being the C_{max}, T_{max} and AUC. After non-parenteral administration of SAMe, its concentration in the blood increases until it reaches a peak concentration, this measured in plasma is the C_{max}, and the time taken to reach the C_{max} is termed, T_{max}. The area under the (plasma concentration) curve, or AUC, is another useful measurement and represents the drug exposure in the systemic circulation over a period of time.

[0007] A few studies examining these pharmacokinetic parameters in humans have been recorded for SAMe. The role of intravenous (IV) versus oral administration of SAMe has been investigated to a small extent as well as the effect of repeat dosing over time. Giulidori et al., report plasma drug levels and half-lives of SAMe after a single, IV administered dose (Giulidori, P. et al., (1984) *Eur. J. Clin. Pharmacol.* 27:119.) Another group looked at SAMe plasma levels after a single, orally administered dose (Stramentinoli, G. (1987) *Am. J. Med.* 83:35.) A recent study examines SAMe pharmacokinetic parameters after one-day and five-day doses of orally and IV administered SAMe tosylate disulfate (Yang, J. et al (2009) *Clin. Therapeutics*, 31 (2): 311.) The prior art indicates that the half-life of oral SAMe is short and that AUC values of oral formulations are low.

[0008] There exists a need in the art to generate non-parenteral SAMe formulations with improved pharmacokinetic profiles compared to conventional prior art SAMe dosage forms. For example, those which have increased C_{max} and/or AUC values as well as those which are more potent and exhibit similar C_{max} and AUC values at low doses of SAMe. High C_{max} or AUC formulations may produce an increased biological response to SAMe supplementation and 'high potency' formulations would have the benefit of a lower pill count and potentially increased tolerability for desired C_{max} and/or AUC values.

SUMMARY OF THE INVENTION

[0009] The present inventors have discovered that the pharmacokinetic (PK) profile of exogenous SAMe can be significantly improved by designing dosage forms to release substantial amounts of SAMe within a particular "window" of dissolution. Formulations that release the vast majority of SAMe extremely early (*i.e.* those exhibiting an initial

"burst" of drug) and those that are slower in their drug release are unable to achieve improved *in vivo* PK profiles of SAMe. The investigators here identify compositions and methods that are designed to release SAMe within this unexpected "window" of preferred drug release levels. Thus, in some exemplified embodiments, compositions that exhibit improved SAMe PK profiles have targeted amounts of drug release within a defined dissolution "window" - this *in vitro* correlates to a specified time interval for preferred drug release and *in vivo* relates to transition through a specific region of the gastrointestinal tract.

[0010] In some embodiments of the invention improved *in vivo* PK profiles are generated when combining exogenous SAMe with suitable excipients and/or processing parameters that impart specific product characteristics such as, for example, thickness, water content, friability, hardness, disintegration or dissolution properties. Accordingly, exemplified embodiments of the present invention relate to non-parenteral compositions and methods which exhibit improved pharmacokinetic profiles, specifically high *in vivo* SAMe C_{max} values and/or increased AUC values, in comparison to conventional prior art SAMe dosage forms. In some exemplified embodiments, provided are improved PK SAMe compositions which exhibit a targeted amount of drug release over a desired range of locations within the gastrointestinal tract of a fasted individual. In certain embodiments, targeted drug release is achieved by use of one or more functional coatings such that the functional coating allows for extensive dissolution of the composition at the precise time interval *in vitro*. In some embodiments, targeted drug release formulations are identified *in vitro* using low pH dissolution profiles. Low pH dissolution studies are performed at below the standard of pH 6.8. Accordingly, the invention also provides an *in vitro* screening method which utilizes specific dissolution profiles of formulation candidates to identify products which yield improved pharmacokinetic values *in vivo*. Standard dissolution methods do not effectively distinguish these improved PK formulations from others. Obtaining dissolution profiles at low pH values (mimicking the pH of a specific location within the duodenum or upper small intestine where the formulations of the invention are targeted to release) in comparison to dissolution profiles at pH 6.8 (which best represents the pH of the distal small intestine) identifies rapid, yet targeted, dissolution formulations as leading to improved pharmacokinetic parameters *in vivo*.

[0011] In other exemplified embodiments, compositions which exhibit improved SAMe PK profiles are generated under conditions of very low relative humidity. It is generally known that SAMe should be manufactured under conditions of low humidity (less than about 35%)