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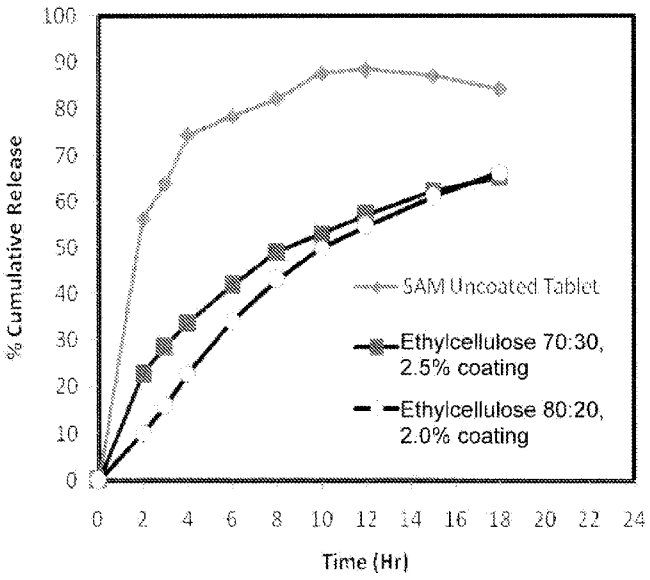
(54) Title: EXTENDED RELEASE PHARMACEUTICAL FORMULATIONS OF S-ADENOSYLMETHIONINE

Figure 1



(57) Abstract: Extended release formulations of S-methyladenosylmethionine (SAMe) are provided, as are methods of treating various disorders using extended release SAMe formulations. The extended release formulations may be used to treat a variety of disorders, including liver disorders, psychiatric disorders and joint disorders. Thus, extended release SAMe formulations may be used to treat alcoholic liver disease, fatty liver disease, hepatitis, generalized anxiety disorder, obsessive compulsive disorder, post traumatic stress disorder, panic disorder, and depressive disorders such as depression (e.g. major clinical depression) and dysthymia.

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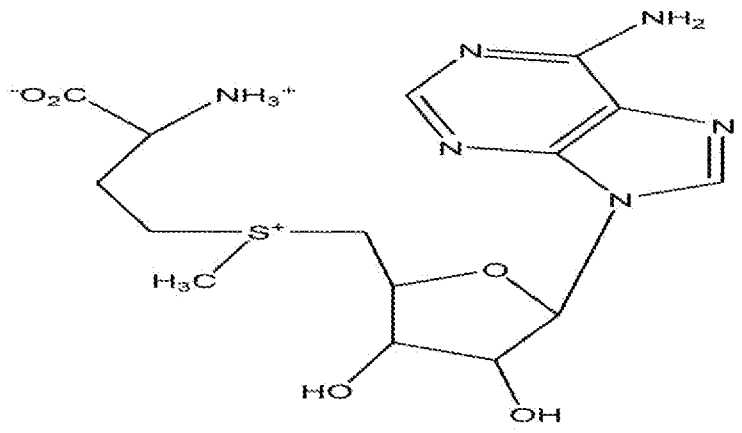
EXTENDED RELEASE PHARMACEUTICAL FORMULATIONS OF S-ADENOSYLMETHIONINE

CROSS-REFERENCE TO RELATED APPLICATIONS AND CLAIM TO PRIORITY

[0001] This application claims priority from United States patent application serial number 12/182,036, filed July 29, 2008, which application is a continuation-in-part of our prior Patent Application Serial Number 12/175,432 filed July 17, 2008, which is a continuation-in-part of prior Patent Application Serial Number 12/024,059 filed January 31, 2008, and claims priority to United States Provisional Patent Application Serial Number 60/887,565, filed January 31, 2007, all incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] 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 (e.g. in the production of polyamines, such as spermidine and spermine, from putrescine). SAMe is thus involved in the biosynthesis of numerous biological molecules including hormones and neurotransmitters. Although the metabolic processes in which SAMe is involved occur throughout the body, most SAMe is produced in the liver.



S-adenosyl-L-methionine
(SAMe)

[0003] In the body, SAMe is synthesized from an amino acid, methionine, and a triphosphate nucleotide, ATP. In fact, aside from water, SAMe is considered the second most common metabolic molecule – ATP being the most common – in the body. Unfortunately, SAMe biosynthesis appears to decrease with age; and decreased SAMe production has been linked to

aging, dementia, liver disease, alcoholism and depression. Indeed, SAMe has been subjected to numerous clinical trials for the treatment of various ailments, including arthritis, liver disease and depression.

[0004] 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 disulfate tosylate, the butanedisulfonate salt of SAMe, the di-p-toluene sulfonate disulfate of SAMe, the tri-p-toluene sulfonic acid salt of SAMe). Stable salts of SAMe are described in United States Patent Numbers 3,954,726 and 4,057,686, each of which is incorporated herein by reference in its entirety. Numerous clinical trials have suggested the suitability of SAMe for treating a variety of conditions, such as liver disease, depression and arthritis. Enteric coated SAMe has been developed as a nutritional supplement for sale in the United States and other countries; and SAMe has also been available in Europe as a prescription drug for decades. However, the use of extended release SAMe has not heretofore been reported, nor has the use of extended release SAMe for the treatment of disease been previously reported.

SUMMARY OF THE INVENTION

[0005] Some embodiments herein provide a method of treating a disorder selected from the group consisting of osteoarthritis, rheumatoid arthritis, fibromyalgia, a psychiatric disorder, an inflammatory condition, a central nervous system (CNS) disorder, a pain disorder, a liver disorder, a neurological disorder, a gastrointestinal disorder, a cardiovascular disorder, a disorder induced in whole or in part by oxidative or free-radical damage, and a cancer, comprising administering to the patient an extended release dosage comprising a therapeutically effective amount of SAMe, wherein the extended release dosage provides a quotient $Q = (([SAMe]_T-[SAMe]_0)/C_{max})$, wherein $C_{max} = [SAMe]_{Max}-[SAMe]_0$ and $[SAMe]_{Max}$ is a maximum blood plasma concentration of SAMe in a patient population after administration of SAMe to the patient population, $[SAMe]_0$ is a blood plasma concentration of SAMe immediately prior to administration of SAMe to the patient population and $[SAMe]_T$ is a blood plasma concentration of SAMe at time T after administration of SAMe to the patient population):

(a) Q is about 0.4 to about 0.95 when T is about 2 hours; Q is about 0.5 to about 1.0 when T is about 4 hours; Q is about 0.5 to about 1.0 when T is about 6 hours; Q is about 0.3 to about 0.9 when T is about 8 hours; and Q is about 0.15 to about 0.6 when T is about 12 hours;

(b) Q is about 0.4 to about 0.95 when T is about 2 hours; Q is about 0.5 to about 1.0 when T is about 4 hours; Q is about 0.5 to about 1.0 when T is about 6 hours; Q is about 0.3 to about 0.9 when T is about 8 hours; and Q is about 0.15 to about 0.6 when T is about 12 hours;

(c) Q is about 0.4 to about 0.95 when T is about 2 hours; Q is about 0.5 to about 1.0 when T is about 4 hours; Q is about 0.5 to about 1.0 when T is about 6 hours; Q is about 0.3 to about 0.9 when T is about 8 hours; and Q is about 0.15 to about 0.6 when T is about 12 hours;

(d) Q is about 0.6 to about 0.95 when T is about 2 hours; Q is about 0.65 to about 0.95 when T is about 4 hours; Q is about 0.9 to about 1.0 when T is about 6 hours; Q is about 0.7 to about 0.95 when T is about 8 hours; and Q is about 0.3 to about 0.65 (especially about 0.5 to about 0.6) when T is about 12 hours;

(e) Q is about 0.9 to about 1.0 when T is about 4 hours; Q is about 0.3 to about 0.5 when T is about 8 hours; Q is about 0.2 to about 0.4 when T is about 12 hours;

(f) Q is about 0.9 to about 1.0 when T is about 4 hours; Q is about 0.3 to about 0.5 when T is about 8 hours; Q is about 0.2 to about 0.4 when T is about 12 hours;

(g) Q is about 0.9 to about 1.0 when T is about 4 hours; Q is about 0.3 to about 0.5 when T is about 8 hours; Q is about 0.2 to about 0.4 when T is about 12 hours ;

(h) Q is about 0.7 to about 0.9 when T is about 2 hours; Q is about 0.7 to about 0.9 when T is about 4 hours; Q is about 0.9 to about 1.0 when T is about 6 hours; Q is about 0.4 to about 0.6 when T is about 8 hours; and Q is about 0.25 to about 0.45 when T is about 12 hours;

(i) Q is about 0.4 to about 0.6 when T is about 2 hours; Q is about 0.8 to about 1.0 when T is about 4 hours; Q is about 0.4 to about 0.8 when T is about 6 hours; Q is about 0.2 to about 0.7 when T is about 8 hours; and Q is about 0.2 to about 0.7 when T is about 12 hours;

(j) Q is about 0.5 to about 0.8 when T is about 2 hours; Q is about 0.8 to about 1.0 when T is about 4 hours; Q is about 0.8 to about 1.0 when T is about 6 hours; Q is about 0.3 to about 0.7 when T is about 8 hours; and Q is about 0.3 to about 0.7 when T is about 12 hours. In some embodiments Q is about 0.3 to about 0.7 at about 24 hours;

(k) Q is about 0.4 to about 0.6 when T is about 2 hours; Q is about 0.5 to about 0.7 when T is about 4 hours; Q is about 0.6 to about 0.8 when T is about 6 hours; Q is about 0.8 to about 1.0 when T is about 8 hours; and Q is about 0.5 to about 0.7 when T is about 12 hours. In some embodiments Q is about 0.5 to about 0.7 at about 24 hours; or

(l) Q is 0 to about 1.0 at time T of about 4 hours, Q is about 0.5 to about 1.0 at time T about 8 hours, and Q is about 0.5 to about 0.8 at time T of about 12 hours.

In some embodiments, the disorder is a liver disorder selected from the group consisting of alcoholic liver disease, fatty liver disease and hepatitis. In some embodiments, the disorder is

a gastrointestinal disorder such as inflammatory bowel disease (IBD), Crohn's disease or ulcerative colitis (UC). In some embodiments, the disorder is a psychiatric disorder selected from the group consisting of depressive disorders, eating disorders, bipolar disorder, abuse disorders, dependence disorders, Axis II disorders, psychosis and anxiety disorders. In some embodiments, the psychiatric disorder is an anxiety disorder selected from the group consisting of generalized anxiety disorder, post traumatic stress disorder, panic disorder and obsessive compulsive disorder. In some embodiments, the psychiatric disorder is a depressive disorder. In some embodiments, the depressive disorder is major depressive disorder, minor depression, brief recurrent depression, dysthymia or depression NOS. In some embodiments, the psychiatric disorder is an eating disorder selected from the group consisting of bulimia nervosa, anorexia nervosa, binge eating disorder, obesity, or eating disorder NOS. In some embodiments, the psychiatric disorder is bipolar disorder, an abuse disorder or a dependence disorder. In some embodiments, the psychiatric disorder includes abuse of, or dependence on, alcohol, cocaine, codeine, oxycodone, hydrocodone or other opiates. In some embodiments, the psychiatric disorder is an Axis II disorder selected from borderline personality disorder. In some embodiments, the disorder is a CNS disorder such as Parkinson's syndrome or Alzheimer's disease. In some embodiments, the disorder is an inflammatory disorder selected from the group comprising systemic lupus erythematosis, Reye's syndrome, rheumatic fever, allergic rhinitis, myasthenia gravis, temporal arteritis, vasculitis, psoriasis, atopic dermatitis, rosacea, eczema, alopecia universalis, scleroderma, pemphigus, contact dermatitis, ankylosing spondylitis, dermatomyositis, polymyositis, celiac sprue, Guillain-Barré syndrome, multi-infarct dementia, post cerebral vascular accident reperfusion damage, Addison's disease, Hashimoto's thyroiditis, asthma, upper respiratory inflammation symptoms, chronic bronchitis, atherosclerosis, pernicious anemia, autoimmune hepatitis, prostatitis, pelvic inflammatory disease, Goodpasture's syndrome, Wegener's granulomatosis, chronic nephritis, Sjogrens syndrome, or allergic conjuntivitis. In some embodiments, the etiology of the disorder may include oxidative or free-radical damage, and is selected from the group comprising chronic fatigue syndrome, temporal arteritis, vasculitis, multi-infarct dementia, chronic emphysema, or chronic nephritis. In some embodiments, the disorder is a cancer selected from the group consisting of cancers occuring in one or more of the liver, colon, rectum, ovaries, urethra, testicles, bladder, breast, stomach, esophagus, pancreas, head and neck, and adenocarcinomas. In some embodiments, the T_{max} is at least about 6 hours after administration of the extended release dosage. In some embodiments, the T_{max} is about 4 to about 12 hours after administration of the extended release dosage. In some embodiments,

the dose is administered in 1 to 4, 1 to 5 or 1 to 6 discrete dosage units. In some embodiments, the patient is fed prior to administration of the SAMe. In some embodiments, the method further comprises administering to the patient one or more additional active compounds. In some embodiments, the one or more additional compounds comprise vitamin B12 (B12), folate (folic acid or a biologically acceptable salt thereof), or both. In some embodiments, at least a portion of the SAMe is contained within an extended release matrix, an osmotic extended release core or a pulsatile release formulation. Some embodiments described herein provide a kit for treatment in a patient a disorder as described herein, which comprises an extended release SAMe formulation as described herein, optionally in combination with one or more additional components.

{0006} Some embodiments described herein provide an extended release SAMe dosage, or a method of treating in a patient a disorder selected from the group consisting of osteoarthritis, rheumatoid arthritis, fibromyalgia, a psychiatric disorder, an inflammatory condition, a central nervous system (CNS) disorder, a pain disorder, a liver disorder, a neurological disorder, a gastrointestinal disorder, a cardiovascular disorder, a disorder induced in whole or in part by oxidative or free-radical damage, and a cancer, comprising administering to the patient an extended release dosage comprising a S-adenosyl methionine (SAMe), or a pharmaceutically acceptable salt thereof, wherein the extended release dosage provides a blood plasma concentration versus time curve for SAMe in a patient population as follows: blood plasma concentration of SAMe of 0 to 200 nmol/L at about 2 hours, blood plasma concentration of SAMe of about 100 to 400 nmol/L at about 4 hours, and a SAMe C_{max} of from 100 to 400 nmol/L that occurs at a time T_{max} at least about 4 hours after administration of the extended release dosage. In some embodiments, the disorder is a liver disorder selected from the group consisting of alcoholic liver disease, fatty liver disease and hepatitis. In some embodiments, the disorder is an inflammatory disorder such as inflammatory bowel disease (IBD), Crohn's disease or ulcerative colitis (UC). In some embodiments, the disorder is a psychiatric disorder selected from the group consisting of depressive disorders, eating disorders, bipolar disorder, abuse disorders, dependence disorders, Axis II disorders, psychosis and anxiety disorders. In some embodiments, the psychiatric disorder is an anxiety disorder selected from the group consisting of generalized anxiety disorder, post traumatic stress disorder, panic disorder and obsessive compulsive disorder. In some embodiments, the psychiatric disorder is a depressive disorder. In some embodiments, the depressive disorder is major depressive disorder, minor depression, brief recurrent depression, dysthymia or depression NOS. In some embodiments, the psychiatric disorder is an eating disorder selected from the group consisting of bulimia

nervosa, anorexia nervosa, binge eating disorder, obesity, or eating disorder NOS. In some embodiments, the psychiatric disorder is bipolar disorder, an abuse disorder or a dependence disorder. In some embodiments, the psychiatric disorder includes abuse of, or dependence on, alcohol, cocaine, codeine, oxycodone, hydrocodone or other opiates. In some embodiments, the psychiatric disorder is an Axis II disorder selected from borderline personality disorder. In some embodiments, the disorder is a CNS disorder such as Parkinson's syndrome or Alzheimer's disease. In some embodiments, the disorder is an inflammatory disorder selected from the group comprising systemic lupus erythematosis, Reye's syndrome, rheumatic fever, allergic rhinitis, myasthenia gravis, temporal arteritis, vasculitis, psoriasis, atopic dermatitis, rosacea, eczema, alopecia universalis, scleroderma, pemphigus, contact dermatitis, ankylosing spondylitis, dermatomyositis, polymyositis, celiac sprue, Guillain-Barré syndrome, multi-infarct dementia, post cerebral vascular accident reperfusion damage, Addison's disease, Hashimoto's thyroiditis, asthma, upper respiratory inflammation symptoms, chronic bronchitis, atherosclerosis, pernicious anemia, autoimmune hepatitis, prostatitis, pelvic inflammatory disease, Goodpasture's syndrome, Wegener's granulomatosis, chronic nephritis, Sjogrens syndrome, or allergic conjuntivitis. In some embodiments, the etiology of the disorder may include oxidative or free-radical damage, and is selected from the group comprising chronic fatigue syndrome, temporal arteritis, vasculitis, multi-infarct dementia, chronic emphysema, or chronic nephritis. In some embodiments, the disorder is a cancer selected from the group consisting of cancers occuring in one or more of the liver, colon, rectum, ovaries, urethra, testicles, bladder, breast, stomach, esophagus, pancreas, head and neck, and adenocarcinomas. In some embodiments, the T_{max} is at least about 6 hours after administration of the extended release dosage. In some embodiments, the T_{max} is about 4 to about 12 hours after administration of the extended release dosage. In some embodiments, the dose is administered in 1 to 4, 1 to 5 or 1 to 6 discrete dosage units. In some embodiments, the patient is fed prior to administration of the SAMe. In some embodiments, the method further comprises administering to the patient one or more additional active compounds. In some embodiments, the one or more additional compounds comprise vitamin B12 (B12), folate (folic acid or a biologically acceptable salt thereof), or both. In some embodiments, at least a portion of the SAMe is contained within an extended release matrix, an osmotic extended release core or a pulsatile release formulation. Some embodiments described herein provide a kit for treatment in a patient a disorder as described herein, which comprises an extended release SAMe formulation as described herein, optionally in combination with one or more additional components

[0007] Some embodiments described herein provide an extended release SAMe formulation, or a method of treating a disorder selected from the group consisting of osteoarthritis, rheumatoid arthritis, fibromyalgia, a psychiatric disorder, an inflammatory condition, a central nervous system (CNS) disorder, a pain disorder and a liver disorder, in a patient, comprising administering to the patient an extended release dosage comprising a therapeutically effective amount of SAMe, wherein blood plasma concentrations of SAMe ($[SAMe]_T$, wherein T is a time after administration of the SAMe to a patient population) provided by the extended release dosage, at time points T of about 2 hours, about 4 hours, about 6 hours and about 8 hours after administration of the extended release dosage to the patient, are about 40 to 100 percent of the C_{Max}. In some embodiments, the disorder is a liver disorder selected from the group consisting of alcoholic liver disease, fatty liver disease and hepatitis. In some embodiments, the disorder is an inflammatory disorder such as inflammatory bowel disease (IBD), Crohn's disease or ulcerative colitis (UC). In some embodiments, the disorder is a psychiatric disorder selected from the group consisting of depressive disorders, eating disorders, bipolar disorder, abuse disorders, dependence disorders, Axis II disorders, psychosis and anxiety disorders. In some embodiments, the psychiatric disorder is an anxiety disorder selected from the group consisting of generalized anxiety disorder, post traumatic stress disorder, panic disorder and obsessive compulsive disorder. In some embodiments, the psychiatric disorder is a depressive disorder. In some embodiments, the depressive disorder is major depressive disorder, minor depression, brief recurrent depression, dysthymia or depression NOS. In some embodiments, the psychiatric disorder is an eating disorder selected from the group consisting of bulimia nervosa, anorexia nervosa, binge eating disorder, obesity, or eating disorder NOS. In some embodiments, the psychiatric disorder is bipolar disorder, an abuse disorder or a dependence disorder. In some embodiments, the psychiatric disorder includes abuse of, or dependence on, alcohol, cocaine, codeine, oxycodone, hydrocodone or other opiates. In some embodiments, the psychiatric disorder is an Axis II disorder selected from borderline personality disorder. In some embodiments, the disorder is a CNS disorder such as Parkinson's syndrome or Alzheimer's disease. In some embodiments, the disorder is an inflammatory disorder selected from the group comprising systemic lupus erythematosis, Reye's syndrome, rheumatic fever, allergic rhinitis, myasthenia gravis, temporal arteritis, vasculitis, psoriasis, atopic dermatitis, rosacea, eczema, alopecia universalis, scleroderma, pemphigus, contact dermatitis, ankylosing spondylitis, dermatomyositis, polymyositis, celiac sprue, Guillain-Barré syndrome, multi-infarct dementia, post cerebral vascular accident reperfusion damage, Addison's disease,

Hashimoto's thyroiditis, asthma, upper respiratory inflammation symptoms, chronic bronchitis, atherosclerosis, pernicious anemia, autoimmune hepatitis, prostatitis, pelvic inflammatory disease, Goodpasture's syndrome, Wegener's granulomatosis, chronic nephritis, Sjogrens syndrome, or allergic conjuntivitis. In some embodiments, the etiology of the disorder may include oxidative or free-radical damage, and is selected from the group comprising chronic fatigue syndrome, temporal arteritis, vasculitis, multi-infarct dementia, chronic emphysema, or chronic nephritis. In some embodiments, the disorder is a cancer selected from the group consisting of cancers occuring in one or more of the liver, colon, rectum, ovaries, urethra, testicles, bladder, breast, stomach, esophagus, pancreas, head and neck, and adenocarcinomas. In some embodiments, the T_{max} is at least about 6 hours after administration of the extended release dosage. In some embodiments, the T_{max} is about 4 to about 12 hours after administration of the extended release dosage. In some embodiments, the dose is administered in 1 to 4, 1 to 5 or 1 to 6 discrete dosage units. In some embodiments, the patient is fed prior to administration of the SAMe. In some embodiments, the method further comprises administering to the patient one or more additional active compounds. In some embodiments, the one or more additional compounds comprise vitamin B12 (B12), folate (folic acid or a biologically acceptable salt thereof), or both. In some embodiments, at least a portion of the SAMe is contained within an extended release matrix, an osmotic extended release core or a pulsatile release formulation. Some embodiments described herein provide a kit for treatment in a patient a disorder as described herein, which comprises an extended release SAMe formulation as described herein, optionally in combination with one or more additional components.

[0008] Some embodiments described herein provide an extended release, oral dosage for administration of SAMe to a patient, comprising a therapeutically effective amount of SAMe, wherein the oral dosage is not enterically coated, and wherein dissolution of the oral dosage in a USP II dissolution apparatus in aqueous HCl having an initial pH of about 1 provides less about 70% release of SAMe after about 2 hours, less than about 80% release of SAMe after about 3 hours and less than about 100% release of SAMe after about 4 hours.

[0009] Some embodiments described herein provide an extended release, oral dosage for administration of SAMe to a patient, comprising a therapeutically effective amount of SAMe, wherein dissolution of the oral dosage in a USP II dissolution apparatus in aqueous buffer at an initial pH of about 6.8 provides less about 70% release of SAMe after about 2 hours, less than about 80% release of SAMe after about 3 hours, less than about 100% release of SAMe after about 4 hours, and at least about 50% release after about 8 hours.

[0010] Some embodiments described herein provide an extended release, oral dosage for administration of SAMe to a patient, comprising a therapeutically effective amount of SAMe, wherein the oral dosage is not enterically coated, and wherein dissolution of the oral dosage in a USP II dissolution apparatus in aqueous HCl having an initial pH of about 1 provides less about 70% release of SAMe after about 2 hours, less than about 80% release of SAMe after about 3 hours and less than about 100% release of SAMe after about 4 hours, and at least about 70% release after about 8 hours. In some embodiments, dissolution of the extended-release oral dosage for administration SAMe in a USP II dissolution apparatus in aqueous buffer having an initial pH of about 6.8, provides: (a) less than about 50% release of SAMe after about 2 hours; less than about 80% release of SAMe after about 4 hours; at least about 50% release after about 8 hours; and at least about 80% release after about 12 hours; (b) less than about 70% release of SAMe after about 2 hours; less than about 80% release of SAMe after about 4 hours; at least about 40% release after about 8 hours; and at least about 90% release after about 12 hours. In some embodiments, dissolution of the extended-release oral dosage for administration SAMe in a USP II dissolution apparatus in aqueous HCl having an initial pH of about 1 provides: (a) less than about 50% release of SAMe after about 2 hours; less than about 80% release of SAMe after about 4 hours; at least about 50% release after about 8 hours; and at least about 80 % release after about 12 hours; or (b) less than about 70% release of SAMe after about 2 hours; less than about 80% release of SAMe after about 4 hours; at least about 40% release after about 8 hours; and at least about 90% release after about 12 hours.

[0011] Some embodiments described herein provide an extended release, oral dosage for administration of SAMe to a patient, comprising a therapeutically effective amount of SAMe, liquid paraffin, magnesium aluminometasilicate and 0-6% of an extended release coating, which optionally comprises a pore former.

[0012] Some embodiments described herein provide a kit for administration of SAMe to a patient, comprising at least a first dosage form and a second dosage form, wherein said first dosage form is an immediate release dosage optionally comprising an enteric coating; and the second dosage form is an extended release dosage form. In some embodiments, the kit comprises an extended release, oral dosage for administration of SAMe to a patient, comprising a therapeutically effective amount of SAMe, wherein dissolution of the oral dosage in a USP II dissolution apparatus in aqueous buffer having an initial pH of about 6.8 provides less about 70% release of SAMe after about 2 hours, less than about 80% release of SAMe after about 3 hours and less than about 100% release of SAMe after about 4 hours. In

some embodiments, the kit comprises an extended release, oral dosage for administration of SAMe to a patient, comprising a therapeutically effective amount of SAMe, wherein the oral dosage is not enterically coated, and wherein dissolution of the oral dosage in a USP II dissolution apparatus in aqueous HCl having an initial pH of about 1 provides less about 70% release of SAMe after about 2 hours, less than about 80% release of SAMe after about 3 hours and less than about 100% release of SAMe after about 4 hours. In some embodiments, the kit comprises an extended release, oral dosage for administration of SAMe to a patient, comprising a therapeutically effective amount of SAMe, wherein dissolution of the oral dosage in a USP II dissolution apparatus in aqueous buffer at an initial pH of about 6.8 provides less about 70% release of SAMe after about 2 hours, less than about 80% release of SAMe after about 3 hours, less than about 100% release of SAMe after about 4 hours, and at least about 50% release after about 8 hours. In some embodiments, the kit comprises an extended release, oral dosage for administration of SAMe to a patient, comprising a therapeutically effective amount of SAMe, wherein the oral dosage is not enterically coated, and wherein dissolution of the oral dosage in a USP II dissolution apparatus in aqueous HCl having an initial pH of about 1 provides less about 70% release of SAMe after about 2 hours, less than about 80% release of SAMe after about 3 hours and less than about 100% release of SAMe after about 4 hours, and at least about 70% release after about 8 hours. In some embodiments, dissolution of said first dosage form and said second dosage form in a USP II dissolution apparatus in aqueous buffer having an initial pH of about 6.8, provides: (a) less than about 50% release of SAMe after about 2 hours; less than about 80% release of SAMe after about 4 hours; at least about 50% release after about 8 hours; and at least about 80% release after about 12 hours; or (b) less than about 70% release of SAMe after about 2 hours; less than about 80% release of SAMe after about 4 hours; at least about 40% release after about 8 hours; and at least about 90% release after about 12 hours. In some embodiments, dissolution of said first dosage form and said second dosage form in a USP II dissolution apparatus in aqueous HCl having an initial pH of about 1, provides: (a) less than about 50% release of SAMe after about 2 hours; less than about 80% release of SAMe after about 4 hours; at least about 50% release after about 8 hours; and at least about 80% release after about 12 hours; or (b) less than about 70% release of SAMe after about 2 hours; less than about 80% release of SAMe after about 4 hours; at least about 40% release after about 8 hours; and at least about 90% release after about 12 hours. In some embodiments, the kit comprises an extended release, oral dosage for administration of SAMe to a patient, comprising a therapeutically effective amount of SAMe, liquid paraffin, magnesium

aluminometasilicate and 0-6% of an extended release coating, which optionally comprises a pore former.

[0013] Given the promising therapeutic profile of SAMe, it is considered that an extended release formulation of SAMe would provide advantageous pharmacokinetic properties for the use of SAMe in the treatment of a variety of psychiatric, neurological and other medical conditions, symptoms and disease states. However, as noted above, extended release SAMe has not been previously reported. There is thus a need for extended release formulations of SAMe, as well as therapeutic methods of using the extended release formulations for the treatment of one or more psychiatric or neurological conditions, such as depression. Embodiments of the present invention address this need and provide related advantages as well.

[0014] The foregoing and further objects are addressed by embodiments of the present invention, which provide a method of treating in a patient a disorder selected from the group consisting of osteoarthritis, rheumatoid arthritis, fibromyalgia, a psychiatric disorder, an inflammatory condition, a central nervous system (CNS) disorder, a pain disorder, a liver disorder, a neurological disorder, a gastrointestinal disorder, a cardiovascular disorder, a disorder induced in whole or in part by oxidative or free-radical damage, and a cancer, comprising administering to the patient an extended release dosage comprising a therapeutically effective amount of SAMe. In some embodiments, the extended release dosage provides:

(a) A blood plasma concentration of SAMe as follows: 0 to 200 nmol/L from 0 to 2 hours, 200 to 1000 nmol/L from 2 to 4 hours, and a Cmax of from 300 to 2000 nmol/L that occurs at a time Tmax at least about 4 hours after administration of the extended release dosage. In some specific embodiments of the invention, Tmax is at least about 7 hours after administration of the extended release dosage. In some embodiments, Tmax is about 5 to about 12 hours after administration of the extended release dosage;

(b) A ratio [SAMe]/[SAMe]max in blood plasma after administration of the extended release dosage as follows: 0 to 0.95 from 0 to 4 hours, 0.25 to 1.0 from 4 to 8 hours, and 0.25 to 1.0 from 8 to 12 hours after administration of the extended release dosage;

(c) Approximately 0 to 60 percent of the therapeutically effective amount 0 to 4 hours after administration, approximately 20 to 80 percent of the therapeutically effective amount 4 to 8 hours after administration, and approximately 30 to 100 percent of the therapeutically effective amount 8 to 36 (e.g. about 8 to 12 or 8 to 24) hours after administration;

(d) blood plasma concentrations of SAMe, over a period of from 0 to 24 hours after administration of the extended release dosage to the patient, or approximate 15 to 85 percent of the CMax for a non-extended release formulation of SAMe. In some such embodiments, the CMax of SAMe provided by the extended release dosage is in the range of about 15 to about 55 percent of the CMax for a non-extended release formulation of SAMe;

(e) approximately 0 to 60 percent of the therapeutically effective amount of SAMe (AUC) 0 to 4 hours after administration, approximately 20 to 80 percent of the therapeutically effective amount of SAMe 4 to 8 hours after administration, and approximately 25 to 100 percent of the therapeutically effective amount SAMe 8 to 36 (e.g. 8 to 12 or 8 to 24) hours after administration; or

(f) an in vitro extended release profile in an aqueous solution wherein: 0 to 60 percent of the therapeutically effective amount is released into the aqueous solution 0 to 4 hours after introduction of the extended release dosage to the aqueous solution, approximately 20 to 80 percent of the therapeutically effective amount is released into the aqueous solution 4 to 8 hours after introduction of the extended release dosage to the aqueous solution, and approximately 25 to 100 percent of the therapeutically effective amount is released into the aqueous solution 8 to 36 (e.g. 8 to 12 or 8 to 24) hours after introduction of the extended release dosage to the aqueous solution.

[0015] It is contemplated that extended release S-adenosylmethionine (as compared to immediate release SAMe) may be characterized by a more rapid onset of action and thus may reduce the risk of suicidal behavior, suicide attempts or successful suicide in psychiatric patients, by increasing the rate of response to SAMe therapy. In addition, it is contemplated that treatment with extended release SAMe may be characterized by decreased side effects, especially gastrointestinal side effects normally associated with high doses of SAMe. Thus, treatment of psychiatric conditions with extended release SAMe according to the present invention may result in a reduction in suffering and a more rapid improvement in functioning.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0017] Figure 1 is a graph comparing dissolution profiles of SAMe monolithic cores coated with ethylcellulose/pore former coating (70:30 and 80:20 of polymer : pore former ratio);

[0018] Figure 2 is a graph comparing dissolution profiles of tablets coated with ethylcellulose polymer mixed with pore former in ratios of 70:30 and 60:40 (polymer : pore former.);

[0019] Figure 3 is a graph comparing the dissolution profiles of various prototype extended release SAMe tablets in pH 6.8 buffer and 1 N HCl;

[0020] Figure 4 is a graph showing dissolution profiles of monolithic extended release tablets coated with ethylcellulose 60:40 with 2.0%, 2.5%, and 4.0% in 0.1 N HCl;

[0021] Figure 5 is a graph showing the plasma concentration versus time plots for immediate release, enteric coated SAMe. Each patient was administered 4×400 mg tablets (1600 mg total) of SAMe;

[0022] Figure 6 is a graph showing plasma concentration versus time for a monolithic extended release core (0% coated), and 2%, 4%, and 6% coated monolithic cores, wherein the coating is ethylcellulose mixed with pore former in a ration of ethylcellulose to pore former of 60:40. Each patient was administered 4×400 mg tablets (1600 mg total) of SAMe;

[0023] Figure 7 is a graph showing the plasma concentration versus time plots for immediate release, enteric coated SAMe, a monolithic extended release core (0% coated), and 2%, 4%, and 6% coated monolithic cores, wherein the coating is ethylcellulose mixed with pore former in a ration of ethylcellulose to pore former of 60:40. Each patient was administered 4×400 mg tablets (1600 mg total) of SAMe;

[0024] Figure 8 is a graphical comparison of area under the plasma concentration (AUC) calculations for immediate release, enteric coated SAMe, a monolithic extended release core (0% coated), and 2%, 4%, and 6% coated monolithic cores, wherein the coating is ethylcellulose mixed with pore former in a ration of ethylcellulose to pore former of 60:40;

[0025] Figure 9 is a graph showing the plasma concentration versus time plots for enteric coated SAMe, a monolithic extended release core (0% coated), and 2%, 4%, and 6% coated monolithic cores, wherein the coating is ethylcellulose mixed with pore former in a ration of ethylcellulose to pore former of 60:40, in reference to two commercial immediate release SAMe formulations. Each patient was administered 4×400 mg tablets (1600 mg total) of SAMe;

[0026] Figure 10 is a graph showing the plasma concentration versus time plots for a first hypothetical extended-release SAMe composition configured for initially delayed SAMe

release and for sustained elevated release of SAMe for an 8 to 24-h post-dosing period, in reference to the release profiles of the two commercial immediate-release SAMe formulations shown in Figure 9;

[0027] Figure 11 is a graph showing the plasma concentration versus time plots for a second hypothetical extended-release SAMe composition configured for initial SAMe release comparable to an immediate release SAMe formalation and for sustained elevated release of SAMe for a 24-h period, in reference to the release profiles of the two commercial immediate release SAMe formulations shown in Figure 9; and

[0028] Figure 12 is a graph showing the plasma concentration versus time plots for a third hypothetical extended-release SAMe composition configured for bi-phasic initial SAMe pulsatile release and for sustained elevated release of SAMe for a 24-h period, in reference to the release profiles of the two commercial immediate release SAMe formulations shown in Figure 9.

INCORPORATION BY REFERENCE

[0029] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE INVENTION

[0030] The present invention is directed to extended release formulations of SAMe and methods of using the same, e.g. for the treatment of depression in a once-a-day (q.d.) formulation. As used herein the term "SAMe" refers to S-adenosyl-L-methionine (or, more simply, "S-adenosylmethionine"). As can be seen in the structural formula above, SAMe appears as a charged species, having two positive and one negative center in physiologic solution. In its solid form, SAMe is always present as a salt. While the net charge of SAMe would suggest that it could form a salt with a single, negatively charged species, such as chloride, it is more common to find SAMe in a stable salt form, e.g. with p-toluenesulfonic acid as the negative counter ion, alone or in combination with one or more additional salt-forming substances (e.g. mineral or organic acids and/or amino acids). (See US 3,893,999, incorporated herein by reference in its entirety). Other stable SAMe salts are described in, for example, US 5,128,249, which teaches particular stable salts of SAMe. Thus, as used herein SAMe refers both to the stable salts of SAMe and to the ionic form of SAMe when present in

vivo. When a mass, weight, concentration (e.g. wt.-%) or other mass-dependent unit (that is a unit of measurement that includes mass of SAMe in the numerator or denominator) is used in reference to SAMe herein, unless otherwise specified, it relates to the mass of the SAMe cation exclusive of the counter-anion. Where the mass of the SAMe salt in intended, this is specifically stated.

[0031] In some embodiments, the invention provides a method of treating in a patient a disorder selected from the group consisting of osteoarthritis, rheumatoid arthritis, fibromyalgia, a psychiatric disorder, an inflammatory condition, a central nervous system (CNS) disorder, a pain disorder, a liver disorder, a neurological disorder, a gastrointestinal disorder, a cardiovascular disorder, a disorder induced in whole or in part by oxidative or free-radical damage, and a cancer, comprising administering to the patient an extended release dosage comprising a therapeutically effective amount of SAMe, wherein the extended release dosage provides a blood plasma concentration of SAMe as follows: 0 to 200 nmol/L from 0 to 2 hours, 200 to 1000 nmol/L from 2 to 4 hours, and a Cmax of from 300 to 2000 nmol/L that occurs at a time Tmax at least about 4 hours after administration of the extended release dosage. In some embodiments, the disorder is a liver disorder selected from alcoholic liver disease, fatty liver or hepatitis. In some embodiments, the disorder is a psychiatric disorder selected from depressive disorders (e.g. depression or dysthymia) and anxiety disorders. In some more specific embodiments, the disorder is an anxiety disorder selected from generalized anxiety disorder, post traumatic stress disorder, panic disorder and obsessive compulsive disorder. In some specific embodiments, the psychiatric disorder is a depressive disorder, such as depression (e.g. major clinical depression) or dysthymia. In some embodiments, the Tmax is at least about 7 hours after administration of the extended release dosage. In some embodiments, Tmax is about 4 to about 12 hours after administration of the extended release dosage.

[0032] In some embodiments, the invention provides a method of treating in a patient a disorder selected from the group consisting of osteoarthritis, rheumatoid arthritis, fibromyalgia, a psychiatric disorder, an inflammatory condition, a central nervous system (CNS) disorder, a pain disorder, a liver disorder, a neurological disorder, a gastrointestinal disorder, a cardiovascular disorder, a disorder induced in whole or in part by oxidative or free-radical damage, and a cancer, comprising administering to the patient an extended release dosage comprising a therapeutically effective amount of SAMe, wherein the extended release dosage provides a ratio [SAMe]/[SAMe]max in blood plasma after administration of the extended release dosage as follows: 0 to 0.95 from 0 to 4 hours, 0.23 to 1.0 from 4 to 8 hours,

and 0.25 to 1.0 from 8 and 12 hours after administration of the extended release dosage. In some embodiments, the disorder is a liver disorder selected from alcoholic liver disease, fatty liver or hepatitis. In some embodiments, the disorder is a psychiatric disorder selected from depressive disorders (e.g. depression or dysthymia) and anxiety disorders. In some more specific embodiments, the disorder is an anxiety disorder selected from generalized anxiety disorder, post traumatic stress disorder, panic disorder and obsessive compulsive disorder. In some specific embodiments, the psychiatric disorder is a depressive disorder, such as depression (e.g. major clinical depression) or dysthymia.

[0033] In some embodiments, the invention provides a method of treating in a patient a disorder selected from the group consisting of osteoarthritis, rheumatoid arthritis, fibromyalgia, a psychiatric disorder, an inflammatory condition, a central nervous system (CNS) disorder, a pain disorder, a liver disorder, a neurological disorder, a gastrointestinal disorder, a cardiovascular disorder, a disorder induced in whole or in part by oxidative or free-radical damage, and a cancer, comprising administering to the patient an extended release dosage comprising a therapeutically effective amount of SAMe, wherein the dosage provides: approximately 0 to 60 percent of the therapeutically effective amount 0 to 4 hours after administration, approximately 20 to 80 percent of the therapeutically effective amount 4 to 8 hours after administration, and approximately 30 to 100 percent of the therapeutically effective amount 8 to 36 (e.g. about 8 to 12 or 8 to 24) hours after administration. In some embodiments, the disorder is a liver disorder selected from alcoholic liver disease, fatty liver or hepatitis. In some embodiments, the disorder is a psychiatric disorder selected from depressive disorders (e.g. depression or dysthymia) and anxiety disorders. In some more specific embodiments, the disorder is an anxiety disorder selected from generalized anxiety disorder, post traumatic stress disorder, panic disorder and obsessive compulsive disorder. In some specific embodiments, the psychiatric disorder is a depressive disorder, such as depression (e.g. major clinical depression) or dysthymia.

[0034] In some embodiments, the invention provides a method of treating in a patient a disorder selected from the group consisting of osteoarthritis, rheumatoid arthritis, fibromyalgia, a psychiatric disorder, an inflammatory condition, a central nervous system (CNS) disorder, a pain disorder, a liver disorder, a neurological disorder, a gastrointestinal disorder, a cardiovascular disorder, a disorder induced in whole or in part by oxidative or free-radical damage, and a cancer, comprising administering to the patient an extended release dosage comprising a therapeutically effective amount of SAMe, wherein blood plasma concentrations of SAMe provided by the extended release dosage, over a period of from 0 to

24 hours after administration of the extended release dosage to the patient, are approximate 15 to 85 percent of the CMax for a non-extended release formulation of SAMe. In some embodiments, the disorder is a liver disorder selected from alcoholic liver disease, fatty liver or hepatitis. In some embodiments, the disorder is a psychiatric disorder selected from depressive disorders (e.g. depression or dysthymia) and anxiety disorders. In some more specific embodiments, the disorder is an anxiety disorder selected from generalized anxiety disorder, post traumatic stress disorder, panic disorder and obsessive compulsive disorder. In some specific embodiments, the psychiatric disorder is a depressive disorder, such as depression (e.g. major clinical depression) or dysthymia.

[0035] In some embodiments, the invention provides a method of treating and/or prophylaxis in a patient a disorder selected from the group consisting of osteoarthritis, rheumatoid arthritis, fibromyalgia, a psychiatric disorder, an inflammatory condition, a central nervous system (CNS) disorder, a pain disorder, a liver disorder, a neurological disorder, a gastrointestinal disorder, a cardiovascular disorder, a disorder induced in whole or in part by oxidative or free-radical damage, and a cancer, wherein the CMax of SAMe provided by the extended release dosage is in the range of about 15 to about 55 percent of the CMax for a non-extended release formulation of SAMe. In some embodiments, the disorder is a liver disorder selected from alcoholic liver disease, fatty liver or hepatitis. In some embodiments, the disorder is a psychiatric disorder selected from depressive disorders (e.g. depression or dysthymia) and anxiety disorders. In some more specific embodiments, the disorder is an anxiety disorder selected from generalized anxiety disorder, post traumatic stress disorder, panic disorder and obsessive compulsive disorder. In some specific embodiments, the psychiatric disorder is a depressive disorder, such as depression (e.g. major clinical depression) or dysthymia.

[0036] In some embodiments, the invention provides a method of treating in a patient a disorder selected from the group consisting of osteoarthritis, rheumatoid arthritis, fibromyalgia, a psychiatric disorder, an inflammatory condition, a central nervous system (CNS) disorder, a pain disorder, a liver disorder, a neurological disorder, a gastrointestinal disorder, a cardiovascular disorder, a disorder induced in whole or in part by oxidative or free-radical damage, and a cancer, comprising administering to the patient a therapeutically effective amount of SAMe by providing: approximately 0 to 60 percent of the therapeutically effective amount of SAMe 0 to 4 hours after administration, approximately 20 to 80 percent of the therapeutically effective amount of SAMe 4 to 8 hours after administration, and approximately 30 to 100 percent of the therapeutically effective amount SAMe 8 to 36 (e.g.

about 8 to 12 or 8 to 24) hours after administration. In some embodiments, the disorder is a liver disorder selected from alcoholic liver disease, fatty liver or hepatitis. In some embodiments, the disorder is a psychiatric disorder selected from depressive disorders (e.g. depression or dysthymia) and anxiety disorders. In some more specific embodiments, the disorder is an anxiety disorder selected from generalized anxiety disorder, post traumatic stress disorder, panic disorder and obsessive compulsive disorder. In some specific embodiments, the psychiatric disorder is a depressive disorder, such as depression (e.g. major clinical depression) or dysthymia.

[0037] In some embodiments, the invention provides an extended release dosage for the treatment of a disorder in a patient, comprising a therapeutically effective amount of SAMe, wherein the dosage provides 0 to 60 percent of the therapeutically effective amount (AUC) 0 to 4 hours after administration to a subject, approximately 20 to 80 percent of the therapeutically effective amount 4 to 8 hours after administration to the subject, and approximately 25 to 100 percent of the therapeutically effective amount 8 to 36 (e.g. 8 to 12 or 8 to 24) hours after administration to the subject. The extended release SAMe dosage is useful for treating a variety of disorders, such as osteoarthritis, rheumatoid arthritis, fibromyalgia, psychiatric disorders, pain disorders and liver disorders. In some embodiments, the disorder is a liver disorder selected from alcoholic liver disease, fatty liver or hepatitis. In some embodiments, the disorder is a psychiatric disorder selected from depressive disorders (e.g. depression or dysthymia) and anxiety disorders. In some more specific embodiments, the disorder is an anxiety disorder selected from generalized anxiety disorder, post traumatic stress disorder, panic disorder and obsessive compulsive disorder. In some specific embodiments, the psychiatric disorder is a depressive disorder, such as depression (e.g. major clinical depression) or dysthymia.

[0038] In some embodiments, the invention provides an extended release dosage for the treatment of a disorder in a patient, comprising a therapeutically effective amount of SAMe, wherein the dosage provides an in vitro extended release profile in an aqueous solution wherein: 0 to 60 percent of the therapeutically effective amount is released into the aqueous solution 0 to 4 hours after introduction of the extended release dosage to the aqueous solution, approximately 20 to 80 percent of the therapeutically effective amount is released into the aqueous solution 4 to 8 hours after introduction of the extended release dosage to the aqueous solution, and approximately 25 to 100 percent of the therapeutically effective amount is released into the aqueous solution 8 to 36 (e.g. about 8 to 12 or 8 to 24) hours after introduction of the extended release dosage to the aqueous solution. In some embodiments,

the disorder is selected from the group consisting of fibromyalgia, psychiatric disorders (such as depressive disorders and anxiety disorders), pain disorders and liver disorders. In some embodiments, the disorder is a liver disorder selected from alcoholic liver disease, fatty liver or hepatitis. In some embodiments, the disorder is a psychiatric disorder selected from depressive disorders (e.g. depression or dysthymia) and anxiety disorders. In some more specific embodiments, the disorder is an anxiety disorder selected from generalized anxiety disorder, post traumatic stress disorder, panic disorder and obsessive compulsive disorder. In some specific embodiments, the psychiatric disorder is a depressive disorder, such as depression (e.g. major clinical depression) or dysthymia.

DISORDERS AND DISEASES TO BE TREATED WITH EXTENDED RELEASE SAMe

[0039] The extended release SAMe formulations of the present invention are expected to provide relief from one or more symptoms of a variety of physiological disorders and disease states, such as a mental or psychiatric disorder (*e.g.* psychotic or non-psychotic mental disorders exemplified by depression and substance abuse disorders, respectively), a nervous system disease/disorder (*e.g.* a central nervous system disease exemplified by Alzheimer's), other neurological disease/disorders (*e.g.* headaches and sleep disorders), conditions associated with injury to the central nervous system, a liver disease/disorder (*e.g.* alcoholic liver disease), a cancer (*e.g.* solid and blood-borne cancers), a joint disease/disorder (*e.g.* arthritis), an inflammatory disease/disorder (*e.g.* ulcerative colitis), an autoimmune disease/disorder (*e.g.* systemic lupus erythematosis and rheumatoid arthritis), a degenerative disease/disorder (*e.g.* Amyotrophic Lateral Sclerosis), a soft-tissue disease/disorder (*e.g.* a fibromyalgia disorder), a pain disease/disorder, a genetic disorder related to hyper- or hypo-methylation, a gastrointestinal disease/disorder, a cardiovascular disease/disorder, and a disorder induced in whole or in part by oxidative or free-radical damage.

[0040] Some embodiments of the present invention relate to therapeutic use of the exemplary compositions disclosed herein for treatment of a mental or psychiatric disorder selected from the group consisting of anxiety disorders, depressive disorders, eating disorders, bipolar disorder, abuse disorders, dependence disorders, Axis II disorders, and psychosis. In some exemplary embodiments, the mental or psychiatric disorder is an anxiety disorder selected from the group consisting of generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, panic disorder, Schizophrenia and obsessive compulsive disorder. In some exemplary embodiments, the mental or psychiatric disorder is a depressive disorder selected from the group consisting of major depressive disorder, multi-infarct dementia, minor

depression, postpartum or late-life depression (and the like), HIV-associated depression, brief recurrent depression, dysthymia or depression NOS (Not Otherwise Specified). In some exemplary embodiments, the mental or psychiatric disorder is an eating disorder selected from the group consisting of bulimia nervosa, anorexia nervosa, binge eating disorder, obesity, or eating disorder NOS. In some exemplary embodiments, the mental or psychiatric disorder is bipolar disorder, an abuse disorder or a dependence disorder, including abuse of, or dependence on, alcohol, nicotine, cocaine, codeine, oxycodone, hydrocodone or other opiates. In some exemplary embodiments, the mental or psychiatric disorder is an Axis II disorder selected from borderline personality disorder.

[0041] In some exemplary embodiments, the disorder is a nervous system disorder, including a central nervous system (CNS) disorder such as Parkinson's disease, Alzheimer's disease, Angelman Syndrome (genetic disorder), Multiple Sclerosis (MS) and pre-dementia and/or cognitive impairment.

[0042] In some exemplary embodiments, the disorder is a result of an injury to the CNS such as spinal cord injury or brain damage, memory loss, cognitive impairment and/or learning disability.

[0043] In some exemplary embodiments, the disorder is a liver disorder selected from the group consisting of alcoholic liver disease, fatty liver disease (non-alcoholic) hepatitis (both viral and non-viral), liver cancer, oxidative liver disease, HISS-dependent insulin resistance, cholestasis and cirrhosis.

[0044] In some exemplary embodiments, the disorder is a cancer selected from the group consisting of cancers occurring in one or more of the liver, colon, rectum, ovaries, urethra, testicles, bladder, breast, stomach, esophagus, pancreas, head and neck, lung, blood, skin (such as actinic keratosis, basal cell cancer, superficial basal cell cancer, squamous cell cancer, and malanoma) and adenocarcinomas.

[0045] In some exemplary embodiments, the disorder is a joint disorder such as, for example, arthritis and osteoarthritis.

[0046] In some exemplary embodiments, the disorder is an inflammatory disorder selected from the group comprising systemic lupus erythematosis, Reye's syndrome, rheumatic fever, allergic rhinitis, myasthenia gravis, temporal arteritis, vasculitis, psoriasis, atopic dermatitis, rosacea, eczema, alopecia universalis, scleroderma, pemphigus, contact dermatitis, ankylosing spondylitis, dermatomyositis, polymyositis, celiac sprue, Guillain-Barré syndrome, multi-

infarct dementia, post-cerebral vascular accident reperfusion damage, Addison's disease, Hashimoto's thyroiditis, asthma, upper respiratory inflammation symptoms, chronic bronchitis, atherosclerosis, pernicious anemia, autoimmune hepatitis, prostatitis, pelvic inflammatory disease, Goodpasture's syndrome, Wegener's granulomatosis, chronic nephritis, Sjogrens syndrome, or allergic conjunctivitis.

[0047] In some exemplary embodiments, the disorder is a gastrointestinal disorder such as inflammatory bowel disease (IBD), Crohn's disease or ulcerative colitis (UC).

[0048] In some exemplary embodiments, the disorder is a soft tissue disease such as fibromyalgia.

[0049] In some exemplary embodiments, the disorder is a pain disorder such as fibromyalgia, chronic headaches, shingles, reflex sympathetic dystrophy and polyneuropathy.

[0050] In some exemplary embodiments, the disorder is a cardiovascular disorder which is related to hyper- or hypo-homocysteinemia such as coronary heart disease, stroke, peripheral vascular disease and atherosclerotic disease.

[0051] In some exemplary embodiments, the disorder is related to a genetic or medical condition related to a deficiency of the methylation pathway such as methylenetetrahydrofolate reductase deficiency.

[0052] In some exemplary embodiments, the etiology of the disorder may include oxidative or free-radical damage, and is selected from the group comprising chronic fatigue syndrome, temporal arteritis, vasculitis, multi-infarct dementia, chronic emphysema, or chronic nephritis.

[0053] Among the advantages provided by extended release SAMe formulations of the invention, there may be mentioned the convenience and concomitant improved patient compliance due to once-a-day dosing, an improved side-effect profile (such as decreased stomach irritation and potentially decreased tendency to induce mania in manic depressive patients or patients at risk for manic episodes) and other side effects associate with or caused by the relatively high doses of SAMe (typically about 400 to about 3200 mg/day, more typically about 800 to about 1600 mg/day) necessary to achieve a therapeutic effect.

[0054] As used herein, the term "therapeutic effect" and its grammatical variants (e.g. "therapeutically effective") includes ameliorating at least one symptom of a physiological disorder or disease state in a patient, typically a human patient, and more typically an adult human patient (although in some embodiments human pediatric patients are not excluded). Various symptoms of specific physiological disorders and disease states which are

contemplated as being treatable within the context of the present invention are set forth in detail below. However, it is to be recognized that the understanding of various disease states by those of skill in the art is not static. Thus, though the following description is intended to be illustrative of the various disorders, disease states and symptoms that may be treated using the extended release SAMe formulations according to the present invention, the person skilled in the art will be expected to apply such knowledge as is generally possessed by the skilled clinician in diagnosing and treating specific disorders and disease states with the extended release SAMe formulations of the invention. In particular, unless otherwise specified, a symptom that one of skill in the art would normally associate with one of the enumerated disorders and disease states is not excluded from the present disclosure merely because it is not specifically mentioned herein.

OSTEOARTHRITIS

[0055] SAMe has been marketed as a nutritional supplement for the treatment of osteoarthritis and several clinical trials have been completed, in which it has been found that SAMe is an effective therapeutic agent for the treatment of OA. Thus, the present invention contemplates treatment of OA using an extended release SAMe formulation of the present invention. As SAMe has been shown to induce chondrocyte-mediated production of new cartilage, it is contemplated that extended release SAMe of the invention may be useful in the treatment of rheumatoid arthritis and other disorders and diseases affecting the joints. Whereas aspirin and other non-steroidal anti inflammatory drugs (NSAIDs) tend to suppress proteoglycan synthesis, and thus inhibit production of new cartilage and synovial fluid, SAMe has the opposite effect. Moreover, whereas NSAIDs have negative gastrointestinal effects in some patients, SAMe has been shown to have some gastrointestinal protective effects. Thus, the extended release SAMe formulations of the present invention are expected to be useful either in the palliation of the negative effects of aspirin, ibuprofen or other NSAID, or in the prevention of such negative effects, either in serial or combination therapy. Consequently, in some embodiments of the invention, the extended release SAMe compositions may include a therapeutically effective amount of an NSAID drug, such as aspirin or ibuprofen, for the treatment of osteoarthritis or other joint disorder. In other embodiments, SAMe may be co-administered with one or more doses of NSAID to treat osteoarthritis or another joint disorder.

[0056] SAMe has proven effective in the treatment of osteoarthritis and other joint diseases in clinical trials. Thus, it is expected that the extended release SAMe formulations of the

invention will also be effective in treating osteoarthritis and other joint diseases. Contemplated dosages of extended release SAMe formulations for the treatment of osteoarthritis and other joint diseases are from about 400 to about 3200 mg/day given on a once a day (or at most twice a day) basis.

PSYCHIATRIC DISORDERS

[0057] Psychiatric disorders (depressive disorders or anxiety disorders): A number of psychiatric and psychological conditions have been identified, which are contemplated as being amenable to treatment with the extended release SAMe formulations of the present invention. Among these, depression is a currently preferred indication; however other indications, especially dysthymia, generalized anxiety disorder, post traumatic stress disorder, panic disorder and obsessive compulsive disorder, are contemplated as indications for the extended release SAMe formulations according to the present invention. It is thus expected that the person skilled in the art will be able to treat one or more psychiatric disorder with the extended release SAMe formulations according to the invention. It is contemplated that doses of about 400 to about 3200 mg/day of SAMe, given on a once a day basis (or at most twice a day), will provide therapeutic benefit to a patient suffering from a psychiatric disorder, such as a depressive disorder (e.g. clinical depression or dysthymia) or an anxiety disorder (such as generalized anxiety disorder, post traumatic stress disorder, panic disorder and obsessive compulsive disorder). In some currently preferred embodiments, the dose of extended release SAMe is about 800 to about 1600 mg/day, given on a once a day basis.

DEPRESSIVE DISORDERS

[0058] Depressive disorders can include clinical depression (e.g. major clinical depression) and dysthymia. These disorders are discussed in more detail below. It is contemplated that doses of about 400 to about 3200 mg/day of SAMe, given on a once a day basis (or at most twice a day), will provide therapeutic benefit to a patient suffering from a depressive disorders, such as clinical depression and dysthymia. In some currently preferred embodiments, the dose of extended release SAMe is about 800 to about 1600 mg/day, given on a once a day basis.

DEPRESSION (CLINICAL DEPRESSION; MAJOR CLINICAL DEPRESSION)

[0059] The extended release SAMe according to the present invention may be administered to a patient in need thereof: i.e. a patient who is either currently undergoing or is deemed to be in danger of undergoing a depressive episode, including a patient who has a history of

depression or who is deemed to be at risk for depression. The pharmaceutically effective dose of SAMe administered to the patient may be in the range of about 400 mg/day to about 4000 mg/day, with common doses being about 400, 800, 1200, 1600, 2000 and 3200 mg/day. The effective dose of SAMe will relieve one or more symptoms of depression listed above, thereby partially or completely: lightening the patient's mood; restoring the patient's ability to experience pleasure; normalizing the patient's tendency to gain or loose weight; restoring the patient's normal sleep patterns; restoring the patient's normal psychomotor function; relieving the patient of fatigue; restoring the patient's feelings of self-worth; improving the patient's ability to concentrate and/or think clearly; or alleviating the patient's obsession with death. In particular, the extended release SAMe dosage form of the present invention is expected to lighten the patient's mood, restore the patient's ability to feel pleasure; and/or restore the patient's normal psychomotor function. In some specific embodiments of the invention, administration of the extended release SAMe formulation of the invention results in improvement in one or more symptoms of depression for a period starting within 1-4 weeks of administration It is contemplated that extended release S-adenosylmethionine may be characterized by 1. a more rapid onset of action; 2. higher adherence due to reduced frequency of dosing; 3. higher adherence due to reduced side-effects (see below); 4. higher percentage of patients gaining beneficial therapeutic effect due to 1, 2, and 3, as well as an independent effect of a more steady and sustained blood level of SAMe; and 5. reduced rate of induction of manic or other psychiatric or neurological symptoms due to 4. Thus it is contemplated the extended release formulation may decrease morbity due to reasons 1,2,3,4, and 5, and reduce the risk of suicidal behavior, suicide attempts or successful suicide due to reasons 1,2,3,4, and 5. Consistent with above, it is contemplated that the steadier blood-level achieved by extended-release SAMe may be characterized by decreased side effects, especially side effects normally associated with high doses of SAMe, such as gastrointestinal effects (e.g. nausea, diarrhea, gas, constipation, anorexia (loss of appetite)) as well as head-ache, anxiety, insomnia, spasms, fatigue, hypomania and unmasking of mania.

DYSTHYMIA

[0060] Because SAMe has proven effective in the treatment of other depressive disorders, such as depression (e.g. major clinical depression), it is expected that the extended release SAMe formulations of the invention will be effective in treating dysthymia. Contemplated dosages of extended release SAMe formulations for the treatment of dysthymia are from about 400 to about 3200 mg/day given on a once a day (or at most twice a day) basis.

ANXIETY DISORDERS

[0061] The extended release SAMe formulations of the invention are contemplated for treatment of psychiatric disorders such as anxiety disorders. Among the anxiety disorders contemplated as being indicated for the extended release SAMe formulations of the present invention, there may be mentioned generalized anxiety disorder, post traumatic stress disorder, panic disorder or obsessive compulsive disorder. Because SAMe has proven effective in the treatment of other psychiatric disorders, such as depression, it is expected that the extended release SAMe formulations of the invention will be effective in treating anxiety disorders such as generalized anxiety disorder, post traumatic stree disorder, panic disorder and obsessive compulsive disorder. Contemplated dosages of extended release SAMe formulations for the treatment of anxiety disorders are from about 400 to about 3200 mg/day given on a once a day (or at most twice a day) basis.

PAIN AND SOFT TISSUE DISORDERS

[0062] There are a number of pain disorders of diverse (and in many cases unexplained) etiology, having a common element of pervasive or persistent pain. Such pain disorders include chronic lower back pain, chronic headaches, fibromyalgia, shingles, reflex sympathetic dystrophy and polyneuropathy. Chronic lower back pain may be mechanical, biochemical or psychogenic. Whatever its etiology, chronic lower back pain may in some instances be treated with an analgesic, such as aspirin, acetaminophen, hydrocodone or a combination of a non-NSAID drug and an opioid, such as hydrocodone or oxycodone.

[0063] Because SAMe has proven effective in the treatment of other disorders, such as depression, and in particular other pain disorders, such as osteoarthritis, it is expected that the extended release SAMe formulations of the invention will be effective in treating fibromyalgia, chronic headaches, shingles, reflex sympathetic dystrophy and polyneuropathy . Contemplated dosages of extended release SAMe formulations for the treatment of fibromyalgia are from about 400 to about 3200 mg/day given on a once a day (or at most twice a day) basis.

LIVER DISEASE

[0064] A variety of liver disorders have been identified, which are expected to respond positively to extended release SAMe therapy, including alcoholic liver disease, fatty liver (also known as non-alcoholic fatty liver) and hepatitis. Hepatitis (inflammation of the liver) can be cause by a number of etiological agents, including viral and chemotoxic agents. SAMe has been tested extensively for efficacy in the treatment of liver disease; and it is expected

that an extended release SAMe formulation according to the present invention will provide relief from one or more symptoms of liver disease.

[0065] Because SAMe has proven effective in the treatment of liver disorders, it is expected that the extended release SAMe formulations of the invention will also be effective in treating liver disorders including but not limited to alcoholic liver disease, hepatitis, fatty liver disease, and liver cancer. Contemplated dosages of extended release SAMe formulations for the treatment of liver disorders are from about 400 to about 3200 mg/day given on a once a day (or at most twice a day) basis.

INFLAMMATORY CONDITIONS

[0066] There are a number of inflammatory conditions of diverse (and in many cases unexplained) etiology, having a common element of pervasive or persistent inflammation and associated pain and/or discomfort. The inflammatory response involves many components, two of which are cytokines and eicosanoids. SAMe has been shown to help cells return to baseline conditions are cytokine-induced damage. SAMe also interferes with the eicosanoid system, inhibiting edema and pleurisy, as well as prostaglandin-type materials, which are responsible for fever, vasodilation, and pain. In numerous studies, SAMe has been found to be equally effective in reducing pain and increasing range of motion in osteoarthritis as traditional anti-inflammatory drugs such as ibuprofen. Consequently, those skilled in these arts will understand that exogenous administrations of SAMe are likely to be useful therapies for any disease that has an inflammatory component.

GASTROINTESTINAL DISORDERS

[0067] Inflammatory bowel disease (IBD) comprises diseases exemplified by Crohn's disease and ulcerative colitis, and generally describes a group of inflammatory diseases of the large or small intestine. It has been shown that reactive oxygen species and homocysteine are often increased in IBD, while folate and vitamin B12 deficiencies are common as well. SAMe has been found to provide protection against induced colitis in a mouse model. It is also known to help lower levels of homocysteine and increase levels of folate and vitamin B12, by stabilizing the one-carbon cycle, which all of these molecules are part of. Furthermore, SAMe levels have been found to be significantly decreased in patients with severe IBD (either Crohn's Diesease or colitis forms) as compared to those with moderate IBD or controls.

CARDIOVASCULAR DISORDERS

[0068] Atherosclerosis and thrombosis are cardiovascular conditions thought to be associated at least in part with elevated levels of homocysteine, a molecule in the SAMe cycle. It has been shown that abnormalities in the SAMe cycle can lead to elevated plasma and tissue homocysteine levels, and that high homocysteine levels are associated with the risk of severe coronary atherosclerosis. SAMe has been shown to have significant beneficial effects on homocysteine metabolism, and therefore is useful for lowering homocysteine in patients with high levels of homocysteine, thereby lowering the risk of occurrence of associated cardiovascular disorders.

[0069] It is well-known that high triglyceride levels are also associated with cardiovascular disease. SAMe has been shown to decrease levels of hepatic triglycerides and therefore, exogenous administrations of SAMe are likely to be useful therapies for reducing plasma triglyceride levels.

OXIDATIVE STRESS INJURY

[0070] There are a number of disorders induced in whole or in part by oxidative or free-radical damage. These disorders include chronic fatigue syndrome, temporal arteritis, vasculitis, rheumatoid arthritis, multi-infarct dementia, post cerebral vascular accident reperfusion damage, chronic bronchitis/emphysema, and chronic nephritis. SAMe has been shown to have anti-oxidant properties, and to reduce induced oxidative stress in both renal and hepatic tissues in rate. SAMe maintains glutathione concentration, which is a key antioxidant which serves to inactivate free radicals, thus reducing damage.

CANCERS

[0071] There are certain cancers in which SAMe has been shown to have a beneficial effect. In colon cancer cells, SAMe has been shown to reduce mitogenic signaling, which leads to cell division and growth of the cancer. SAMe has also been found to inhibit development of liver cancer cells induced by treatment with a carcinogen. In patients with colorectal cancer, lower levels of folate and vitamin B12 were found that in controls, while high levels of folate were associated with a lower risk for cancer. SAMe is known to increase the levels of these two substances in vivo. DNA hypomethylation is also associated with an increased risk of adenoma, and nonsignificantly increased risk of cancer. As the body's main methyl donor, SAMe could have a beneficial effect in adenomas and in cancers related to hypomethylation, which include liver, colon, rectum, ovaries, urethra, testicles, bladder, breast, stomach, esophagus, pancreas, head and neck, lung, blood, skin (such as actinic keratosis, basal cell

cancer, superficial basal cell cancer, squamous cell cancer, and melanoma) and adenocarcinomas..

[0072] SAMe might also be useful as a "rescue" strategy after antimetabolite chemotherapy. Since the widely used chemotherapy agent methotrexate inhibits DHFR from converting DHF to THF. Since one THF function is to serve as a methyl donor, increased levels of SAMe increases THF stores for thymine synthesis, alleviating the primary toxic effect of methotrexate or any other treatment leading to a decrease in THF.

EXTENDED RELEASE SAMe FORMULATIONS

[0073] The present invention provides extended release SAMe compositions for twice a day (b.i.d.) or in some preferred embodiments once a day (q.d.) administration. A variety of methods have been used to prepare extended release compositions of various drugs; and it is contemplated that at least one of these methodologies can be used to prepare extended release SAMe compositions according to the present invention. For example, US Patent No. 6,759,395 (incorporated herein in its entirety) provides gelatin capsules capable of being adapted to provide extended release of SAMe, e.g. by including within the gelatin capsules granules of SAMe coated with a controlled-release coating, optionally including a pore former, such as sodium alginate and/or a fatty acid, such as stearic acid, or another water-soluble pore former. The types of extended release SAMe compositions that are contemplated within the scope of the present invention include osmotic dosage forms, extended release matrices, pulsatile release formulations and extended release formulations coated with one or more enteric coatings. In some embodiments, an extended release matrix (monolithic core) containing SAMe may be coated with an extended release coating, which may optionally include a pore former (such as sodium alginate, stearic acid or both). Thus, an ER formulation of SAMe according to the invention will include any formulation that has, as a substantial part of that formulation, an extended release component comprising SAMe – that is a component that releases SAMe over a period of more than about 2 hours, particularly about 2 to 24, 3 to 24 or 4 to 24 hours. As SAMe is sensitive to oxidation, in some embodiments it is considered necessary to coat the SAMe with a coating that will protect the SAMe from oxidation. The coating may be applied directly to SAMe granules (e.g. by spraying an oxygen impermeable coating, which may be an enteric coating, an immediate release coating, an extended release coating or a combination thereof, onto SAMe granules in a fluidized bed) or may be applied to the outside of a tablet, capsule or other dosage form, e.g. by spraying or dipping a tablet or capsule core containing SAMe. In some embodiments, the dosage form is a tablet or caplet containing SAMe in a matrix or osmotic core and the oxygen

impermeable layer is applied by spraying the oxygen impermeable layer onto the outside of the matrix or osmotic core or by dipping the matrix or osmotic core into a solution containing the oxygen impermeable layer material. In some embodiments, the oxygen impermeable layer is an enteric coating. In some embodiments, the oxygen impermeable layer, e.g. an immediate release layer, is applied before an enteric coating is applied to the outside of the dosage form, either by spraying the enteric coating onto the dosage form or dipping the core into the coating material. It is contemplated that a method of coating that results in an oxygen impermeable layer being interposed between the SAMe and the outside of the dosage form will produce a suitable result.

[0074] Granulation of SAMe: In some embodiments, SAMe is granulated before incorporating it into the dosage form. Granulation may be used to form particulates of suitable size and consistency for further processing, which may include coating of the particulates, compaction of the particulate into tablets, combination of the particulates with one or more excipients, including matrix formers, diluents, glidants, lubricants, anti-caking materials, etc.

[0075] In some embodiments, the granulation method is a wet-granulation method. In some embodiments, for example, a water soluble salt of SAMe is dissolved in a suitable solvent, such as water, and is sprayed into a drying environment, e.g. a heated stream of dry air. Other embodiments are also possible. In some embodiments, granulation of SAMe may also be accomplished by one or more dry granulation methods. In some such embodiments, the dry granulation method is a slugging method. Slugging is a dry granulation method in which SAMe, optionally in combination with one or more excipients, is first compressed to form a slug and is then milled to form particulates suitable for further processing. In some embodiments, the granulation method is roller compaction method, in which powder size enlargement is accomplished by feeding SAMe, optionally in combination with one or more wet or dry excipients (e.g. binders), through a roller apparatus, followed by drying (if necessary), milling and sizing the compacted SAMe mixture to form granules having the desired size.

[0076] In some embodiments, the granulated SAMe may then be coated by spraying the SAMe with a coating material, such as an oxygen-impermeable coating material, an enteric coating material, a coating that retards release of SAMe from the granule, or a combination of two or more thereof, and then incorporated into a suitable dosage form. For example, granulated SAMe may be spray coated first with an oxygen-impermeable layer and then an

enteric coating and introduced into a gelatin capsule of appropriate size or may be further combined with one or more excipients (e.g. one or more binders, matrix formers, diluents, anti-caking agents, etc.) and compacted into tablets, caplets or cores for osmotic extended release formulations. As another example, granulated SAMe may be spray coated with an extended release layer and introduced into a gelatin capsule of appropriate size or may be further combined with one or more excipients (e.g. one or more binders, matrix formers, diluents, anti-caking agents, etc.) and compacted into tablets, caplets or cores for osmotic extended release formulations. In other embodiments, granulated SAMe may be spray coated with an oxygen-impermeable layer, then incorporated into an extended release matrix, which, after compaction to form a tablet or caplet, may then be coated with an enteric coating, an immediate release coating, a slow-release coating or some combination of two or more thereof. In other embodiments, the granulated SAMe may be incorporated into an extended release matrix to form a core, which is then coated with a coating, such as an immediate release coating that also serves as an oxygen-impermeable layer. The coated core then may be coated with an enteric coating, or in some embodiments, may be used as-is. In other embodiments, the granulated SAMe may be incorporated into an extended release matrix to form a core, which may then be coated with an enteric coating that is also oxygen-impermeable.

[0077] In some embodiments, the granules of SAMe obtained from wet- or dry- compaction methods, may be divided into two populations, one of which receives a first coating and a second of which receives a second coating having different properties from the first coating. The different properties of the coatings are due to differences in chemical properties, physical properties or both. In terms of chemical properties, the coatings may differ in terms of composition (e.g. one coating could be an extended release coating having a first composition and the second could be an extended release coating having a different composition), in terms of physical properties (e.g. one coating can be thicker than the other) or both. In terms of physical properties, the mass of a coating in relation to the final mass of the population of granules ("relative mass") may be easily calculated and a difference in coating thickness between two populations of particles may be inferred where the populations have substantially the same particle size distribution and the two coatings have substantially the same composition. In some embodiments, the first and second coatings are different in terms of their thickness and/or relative weights. In some embodiments, the first and second coatings have the same composition, but differ in terms of their thickness and/or relative weights. I some embodiments, the first and second coatings are both of the same or similar thickness

and/or relative weights, but differ in composition. In some embodiments, the first and second coatings are both delayed release coatings (which optionally may also be oxygen-impervious), but differ in thickness and/or relative weights. In some embodiments, the two populations of granules may then be introduced into a capsule (e.g. a gel capsule) or may be compacted into a tablet or caplet. In some specific embodiments, the first population of granules is coated with a first thickness of an extended-release or controlled-release coating and the second population of granules is coated with a second thickness of the same or different extended-release or controlled-release coating; then the two populations of granules are combined with one or more excipients, such as binders, diluents, anti-caking agents, etc., and then compacted to form tablets, tablet cores or caplets. Tablet cores may be further coated, for example with an enteric coating, an osmotic coating (which may also contain pore-formers and/or a laser-drilled hole), an anti-oxidant coating, a protective coating or other coating. The proportion of the first population of granules to the second population of granules in the single dosage form (tablet, core, caplet, capsule, etc.) may be adjusted to achieve a desired release profile. In some embodiments, the proportion of the first population of granules to the second population of granules is in the range or 1:20 to 20:1 (by SAMe weight). In some embodiments, the two populations of granules may be combined with a third, coated or uncoated, population of granules. The coating on the third population of granules, if present, will be different from those of the first and second populations of granules. In some such embodiments, the ratios of first and second, second and third and first and third populations of granules will be 1:20 to 20:1, 1:20 to 20:1 and 1:20 to 20:1 (by SAMe weight), respectively.

[0078] In some embodiments, the granules of SAMe obtained from wet- or dry- compaction methods, may be divided into two populations, one of which is further coated and the other of which is not, before the two populations of granules are combined in a single dosage form. The coated population receives a coating and is then combined in a capsule (e.g. a gel capsule) or may be compacted into a tablet, tablet core or caplet. In forming a tablet, core or caplet, the two populations of granules are optionally combined with one or more excipients, such as binders, diluents, anti-caking agents, etc.; then the granules, optionally admixed with excipients, are compacted to form tablets, tablet cores or caplets. Tablet cores may be further coated, for example with an enteric coating, an osmotic coating (which may also contain pore-formers and/or a laser-drilled hole), an anti-oxidant coating, a protective coating and/or other coating. The proportion of the first population of granules to the second population of granules in the single dosage form (tablet, core, caplet, capsule, etc.) may be adjusted to achieve a desired release profile. In some embodiments, the proportion of the first population

of granules to the second population of granules is in the range or 1:20 to 20:1 (by SAMe weight).

[0079] Extended Release Matrices: Matrix tablet systems incorporating active ingredients, fillers, binders and various other types of excipients have been employed with various active pharmaceutical ingredients (APIs) to provide extended release dosage forms. For example, hydroxypropyl cellulose (HPMC) has been used together with other matrix constituents, such as ethylcellulose, methylcellulose, sodium carboxymethyl cellulose, etc., to form controlled release delivery systems. (See: US 4,601,894; US 4,687,757; and US 4,695,591, each incorporated herein by reference.) Hydroxypropyl cellulose and a carboxy vinyl polymer have also been used. (See US 4,680,323, incorporated herein by reference). A hydrophilic matrix comprising a free-flowing directly compressible granulation useful as a controlled release pharmaceutical excipients a heteropolysaccharide and a polysaccharide material capable of cross-linking the heteropolysaccharide. (See US 4,994,276, incorporated herein by reference.) Indeed, various extended release matrices have been prepared using one or more alkylated cellulose derivatives, such as methyl cellulose, ethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, etc. (See: US 4,389,393; US 4,525,345; US 4,556,678; US 4,692,337; US 4,756,911; US 5,073,380; US 4,968,509; US 5,462,747; US 5,543,154; US 5,439,687; US 5,264,446, each of which is incorporated herein by reference in its entirety.) In some embodiments, SAMe is combined with a matrix former and optionally one or more hydrophobic barrier forming agents and/or one or more anti-caking agents (e.g. micronized silicon dioxide and/or magnesium aluminum silicate). In some embodiments, SAMe is combined with magnesium aluminometasilicate and optionally one or both of light liquid paraffin and/or magnesium stearate, subjected to granulation (e.g. slugging or roller compaction, as described herein), combined with one or more excipients (e.g. one or more anti-caking agents) and then compacted to form tablets or tablet cores. In some specific embodiments, SAMe is combined with appropriate amounts of magnesium aluminometasilicate, light liquid paraffin and magnesium stearate; then the mixture is slugged and combined with additional magnesium stearate; finally the mixture is compacted to form tablets or tablet cores.

OSMOTIC FORMULATIONS

[0080] Osmotic type extended release tablets are externally similar in appearance to conventional tablets. However, the interior of the osmotic formulation includes an osmotically active drug core surrounded by a semipermeable membrane. The core is divided

into two layers: an "active" layer containing the drug, and a "push" layer containing pharmacologically inert (but osmotically active) components. The membrane surrounding the tablet is permeable to water but not to drug or osmotic excipients. As water from the gastrointestinal is imbibed into the tablet, pressure increases in the osmotic layer and "pushes" against the drug layer, resulting in the release of drug through a small, laser-drilled orifice in the membrane on the drug side of the tablet. Drug delivery is essentially constant as long as the osmotic gradient remains constant, and then gradually falls to zero. The biologically inert components of the tablet remain intact during GI transit and are eliminated in the feces as an insoluble shell.

[0081] Osmotic formulations comprising two layers and coated with an extended release coating having an aperture therein have been used to provide zero-order release. In general, the formulations are prepared by preparing a first, osmotic layer, which is overlayed with a second, matrix layer comprising the API and at least one matrix component. The two layers are then coated with a semi-permeable coating. (The semi-permeable coating is permeable to water, but not the API). The first semi permeable coating may be coated with a second semi-permeable coating, in which case the inner semi-permeable coating may incorporate a pore forming component, which is gradually dissolved, thereby permitting increased rate of water ingress over time. An aperture is then formed through the water-permeable coating or coatings, which permits egress of the API under osmotic influence of the water imbibed through the water-permeable coating or coatings. (See for example US 2005/0158382)

[0082] Other osmotic release compositions are formed by mixing an API with an insoluble swelling agent and forming an osmotic core, about which is press formed a semi-permeable coating having an aperture therein. (See US 6,365,185, incorporated herein by reference.)

[0083] Enteric Coating: Due to the relative instability of SAMe in gastric fluids (pH ~ 1-4), in some embodiments it may be necessary to coat the extended release SAMe compositions of the present invention with an enteric coating. In general, the enteric coating may be any pharmaceutically acceptable coating that is insoluble in the stomach (pH ~ 1-4), but is soluble at the prevailing pH of the intestines (pH ~ 6-8). The enteric coating should also be inert with respect to the portion of the tablet that it coats. In this regard, it is considered possible to coat the extended release core with an intermediate coating, such as an immediate release coating, and then to coat the intermediate coating with an enteric coating. Thus the intermediate coating (e.g. the immediate release coating) can, in some embodiments of the contemplated invention, provide an inert barrier between the enteric coating and the extended release core.

This type of structure may be used, whether the extended release core is of the matrix type or the osmotic core type. Indeed, US 2005/0158382 describes both osmotic and matrix-type extended release cores which may be spray or dip coated with either an enteric coating that does not react with the extended release core, or with an immediate release coating that is coated with an enteric coating.

PULSATILE RELEASE

[0084] In some embodiments, the formulation of the present invention may comprise a controlled-release pharmaceutical composition comprising SAMe that is capable of delivering therapeutic amounts of SAMe to the proximal small bowel, distal small bowel or colonic regions of the gastrointestinal tract of an animal. In some embodiments, the present invention provides a controlled-release pharmaceutical composition comprising SAMe which may comprise the following components, each of which includes SAMe: (A) an immediate-release (IR) component of SAMe which is released within about 1 hour after administration; and (B) a delayed-release (DR) component comprising of SAMe which is released in the body over a period of time of about 2 hours to about 24 hours, about 3 to about 24 hours or about 4 to about 24 hours after administration. In some embodiments, the invention contemplates a multiparticulate controlled-release composition having a first component comprising a first population of SAMe-containing particles and a second component comprising a second population of SAMe-containing particles. The first component may be an immediate-release component, a controlled-release component or a delayed-release component having a first release profile. The active ingredient-containing particles of the second component may be coated with a controlled-release coating or may be provided in a controlled-release matrix material. In embodiments in which the SAMe-containing particles of the second component are coated with a controlled-release coating, the coating applied to the second population of particles causes a delay between the release of SAMe from the first population of particles and the release of SAMe from the second population of particles. Similarly, the presence of a controlled-release matrix material in the second population of particles causes a delay between the release of SAMe from the first population of particles and the release of SAMe from the second population of particles. The duration of the delay may be varied by altering the composition and/or the amount of the controlled-release coating and/or altering the composition and/or amount of controlled-release matrix material utilized. Thus, the duration of the delay can be designed to achieve a desired plasma profile. Following oral delivery, the

composition in operation is capable of delivering the active ingredient or active ingredients in a pulsatile manner.

[0085] As discussed in more detail above, multiparticulate compositions may comprise two or more populations of granules. A first population of granules may be coated with a first coating and a second population of granules may be coated with a second coating or may lack any coating. In any case, the first population and the second population differ from one another in terms of the physical, chemical or physico-chemical properties of their respective coatings. In some embodiments, dissolution of a first population of granules may be delayed by a first delay period by coating the granules with a delayed-release or controlled-release coating, while dissolution of the second population of granules may be delayed by a lesser delay period (including no delay) by coating the second population of granules with a faster-dissolving coating, a thinner layer of coating or no coating. In some embodiments, a dissolution profile of a dosage comprising more than one population of granules at pH 6-8 will demonstrate a multimodal dissolution profile over time. In some embodiments, a dissolution profile of a dosage comprising more than one population of granules at pH 1-4 (e.g. pH 1) will demonstrate a multimodal dissolution profile over time. In some embodiments, a blood plasma concentration curve for SAMe obtained after administration of a dosage comprising more than one population of granules will be multimodal over time. In some embodiments, a blood plasma concentration curve for SAMe obtained after administration of a dosage comprising more than one population of granules will demonstrate a blood plasma concentration curve for SAMe that is essentially flat – i.e. it varies less than about 10%, 15%, 30% or 40% (above baseline) over a period of at least about 6, 8, 10 or 12 hours.

[0086] The multiparticulate controlled-release composition of the invention may further comprise one or more additional active ingredients that are compatible with SAMe and, if more than one additional active ingredient, each other. In some embodiments, the multiparticulate controlled-release composition of the invention may comprise a therapeutically effective amount of the controlled-release form of SAMe of the present invention in combination with B12, folate or both. In some exemplary embodiments, the SAMe particulates may be coated separately from particulates containing B12 and/or folate in order to prevent interaction between SAMe and/or folate. The B12 and/or folate may be incorporated into an immediate-release or controlled-release formulation, e.g. by coating particulates containing B12 and/or folate with an appropriate immediate-release or controlled-release coating.

[0087] Because the plasma profile produced by the multiparticulate controlled-release formulation of the invention upon administration is substantially similar to the plasma profile produced by the administration of two or more immediate-release dosage forms given sequentially, the multiparticulate controlled release composition of the present invention is particularly useful for administering active ingredients for which such plasma profiles are desired. It is contemplated that the controlled-release composition will support q.d. dosing, although in some embodiments, b.i.d. dosing is also contemplated.

[0088] The present invention also provides solid oral dosage forms of SAMe comprising a composition according to the invention. The solid oral dosage forms of the present invention may further comprise B12, folate or both.

[0089] The time release characteristics for the release of the SAMe from each of the components may be varied by modifying the composition of each component, including modifying any of the excipients or coatings which may be present. In particular, the release of SAMe may be controlled by changing the composition and/or the amount of the controlled-release coating on the particles, if such a coating is present. If more than one controlled-release component is present, the controlled-release coating for each of these components may be the same or different. Similarly, when controlled-release is facilitated by the inclusion of a controlled-release matrix material, release of the SAMe may be controlled by the choice and amount of controlled-release matrix material utilized. The controlled-release coating may be present, in each component, in any amount that is sufficient to yield the desired delay time for each particular component. The controlled-release coating may be preset, in each component, in any amount that is sufficient to yield the desired time lag between components.

[0090] The delay for the release of the SAMe from each component may also be varied by modifying the composition of each of the components, including modifying any excipients and coatings which may be present. For example, the first component may be an immediate-release component from which the SAMe is released substantially immediately upon entry into the small intestine. The second component may be, for example, an extended-release component in which the SAMe is released in a controlled fashion over an extended period of time.

[0091] As will be appreciated by those skilled in the art, the exact nature of the plasma concentration curve will be influenced by the combination of all of the aforementioned factors. In particular, the delay between the delivery (and thus also the onset of action) of the SAMe in each component may be controlled by varying the composition and coating, if

present, of each of the components. Thus, by variation of the composition of each component and by variation of the delay, numerous release and plasma profiles may be obtained. Depending on the duration of the delay between the release of SAMe from each component and the nature of the release from each component (i.e. immediate release, sustained release etc.), the pulses in the plasma profile may be well separated and clearly defined peaks (e.g. when the delay is long) or the pulses may be superimposed to a degree (e.g. in when the delay is short).

[0092] In another embodiment, the multiparticulate controlled-release composition according to the present invention has an immediate-release component and at least one controlled-release component, the immediate-release component comprising a first population of SAMe-containing particles and the controlled-release components comprising second and subsequent populations of SAMe-containing particles. The second and subsequent controlled-release components may comprise a controlled-release coating. Additionally or alternatively, the second and subsequent controlled-release components may comprise a controlled-release matrix material. In operation, administration of such a multiparticulate controlled-release composition having, for example, a single controlled-release component results in characteristic pulsatile plasma concentration levels of the SAMe in which the immediate-release component of the composition gives rise to a first peak in the plasma profile and the controlled-release component gives rise to a second peak in the plasma profile. Embodiments of the invention comprising more than one controlled-release component give rise to further peaks in the plasma profile.

[0093] A multiparticulate controlled-release composition according to the present invention may be incorporated into any suitable dosage form that facilitates release of the active ingredient in a pulsatile manner. For example, the dosage form may be a blend of the different populations of active ingredient containing particles which make up the immediate-release and the controlled-release components, the blend being filled into suitable capsules, such as hard or soft gelatin capsules. Alternatively, the different individual populations of active ingredient containing particles may be compressed (optionally with additional excipients) into mini-tablets which may be subsequently filled into capsules in the appropriate proportions. Another suitable dosage form is that of a multilayer tablet, in which the first component of the multiparticulate controlled-release composition may be compressed into one layer, with the second component being subsequently added as a second layer of the multilayer tablet.

[0094] Preferably, in operation, the composition of the invention and the solid oral dosage forms containing the composition release the active ingredient such that substantially all of the active ingredient contained in the first component is released prior to release of the active ingredient from the second component. When the first component may comprise an immediate release component, for example, it is preferable that release of the active ingredient from the second component is delayed until substantially all the active ingredient in the immediate release component has been released. Release of the active ingredient from the second component may be delayed as detailed above by the use of a controlled-release coating and/or a modified release matrix material.

DOSING WITH MULTIPLE DOSAGE UNITS

[0095] In some embodiments, the present invention provides for treatment in a patient of one or more diseases selected from the group consisting of osteoarthritis, rheumatoid arthritis, fibromyalgia, a psychiatric disorder, an inflammatory condition, a central nervous system (CNS) disorder, a pain disorder, a liver disorder, a neurological disorder, a gastrointestinal disorder, a cardiovascular disorder, a disorder induced in whole or in part by oxidative or free-radical damage, and a cancer, comprising administering to the patient an extended release dosage comprising a therapeutically effective amount of S-adenosyl methionine (SAMe), or a pharmaceutically acceptable salt thereof. In some particular embodiments, the therapeutically effective dose is administered on a once-a-day basis. In some embodiments, the once-a-day dose may be administered in a single dosage unit – e.g. a single tablet, capsule, caplet, etc. In other embodiments, the dose may be administered as multiple tablets, capsules or caplets. In some embodiments, for instance, a dosage of 400 to 3200 mg of SAMe per day may be divided into two, three, four or more tablets, capsules or caplets of 100 to 1600 mg of SAMe per unit dose. In some preferred embodiments, the daily dose is two, three or four tablets, capsules or caplets of 100 to 800 mg of SAMe per dose. Particular dosage regimens that may be mentioned are: four units of 200, 400 or 800 mg SAMe per unit; three units of 100, 150, 200, 300, 400, 600, 800 or 1,000 mg of SAMe per unit; two units of 200, 400, 800 or 1600 mg per unit. In each case, the form of the dosage unit may be a capsule, a tablet, a caplet or other suitable extended release dosage unit.

[0096] In some embodiments, the extended release SAMe may be divided between multiple daily doses. In some particular embodiments, the extended release SAMe may be divided into two daily doses. Each dose may be administered as a single dosage unit – e.g. a single tablet, capsule or caplet – or may be divided into multiple dosage units. In some

embodiments, a twice-daily dose of from about 100 to about 1600 mg of SAMe per dose may be divided into one to four dosage units of from about 100 to about 800 mg of SAMe per unit. In each case, the form of the dosage unit may be a capsule, a tablet, a caplet or other suitable extended release dosage unit.

FED vs. FASTED DOSING

[0097] In some embodiments of the invention, it may be advantageous to ensure that the patient is either fed or fasted (e.g. overnight for at least about 6, especially about 8, hours). It is considered that food or a carbonated beverage administered at the same time, immediately (i.e. less than about 30, especially less than about 15 minutes) before or soon (e.g. less than about 10 minutes) after the extended release SAMe formulation of the invention is administered to the patient may increase the rate of gastric emptying, thus increasing the rate of uptake of SAMe from the extended release formulation. Thus, in some embodiments, the invention contemplates administering the extended release SAMe formulation of the invention with food or a carbonated beverage. In such cases, it is considered that the onset of action of SAMe will be hastened without significantly affecting the long-acting characteristics of the extended release SAMe formulation.

COMBINATIONS OF SAMe WITH OTHER ACTIVE INGREDIENTS

[0098] Some exemplary embodiments of the present invention relate to combinations of SAMe with one or more active ingredients that are commonly prescribed or used for treating and/or prophylaxis in a subject a disease or disorder selected from the group consisting of, but not limited to, a mental or psychiatric disorder (*e.g.* psychotic or non-psychotic mental disorders such as depression and substance abuse disorders, respectively), a nervous system disease/disorder (*e.g.* a central nervous system disease such as Alzheimer's), other neurological disease/disorders (*e.g.* headaches and sleep disorders), conditions associated with injury to the central nervous system, a liver disease/disorder (*e.g.* alcoholic liver disease), a cancer (*e.g.* solid and blood-borne cancers), a joint disease/disorder (*e.g.* arthritis), an inflammatory disease/disorder (*e.g.* ulcerative colitis), an autoimmune disease/disorder (*e.g.* systemic lupus erythematosis and rheumatoid arthritis), a degenerative disease/disorder (*e.g.* Amyotrophic Lateral Sclerosis), a soft-tissue disease/disorder (*e.g.* a fibromyalgia disorder), a pain disease/disorder, a genetic disorder related to hyper or hypo methylation, a gastrointestinal disease/disorder, a cardiovascular disease/disorder, and a disorder induced in whole or in part by oxidative or free-radical damage, comprising administering to said subject

an exemplary composition of the present invention which improves the pharmacokinetic profile of a physiologically effective amount of exogenous SAMe.

[0099] In some exemplary embodiments of the present invention relate to combinations of SAMe with one or more active ingredients that are commonly prescribed or used for treatment of and/or prophylaxis of mental or psychiatric disorders in a subject include, but are not limited to, 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, commonly used antidepressant augmenters such as lithium, triple reuptake inhibitors,.

[0100] In some exemplary embodiments of the present invention relate to combinations of SAMe with one or more device therapies that are commonly prescribed or used for treatment of and/or prophylaxis of mental or psychiatric disorders in a subject include, but not limited to ECT (electro convulsive therapy) and electric shock therapy.

[0101] In some exemplary embodiments of the present invention relate to combinations of SAMe with one or more active ingredients that are commonly prescribed or used for treatment of and/or prophylaxis of a nervous system disease/disorder in a subject include, but are not limited to anticonvulsants such as pregabalin, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists, methylphosphonate (NMPA) receptor antagonists, histamine receptor antagonists, nitric oxide (NO) modulators, glutamate receptor antagonists, acetylcholinesterase inhibitors, dopamine agonists, N-methyl-d-aspartate (NMDA) receptor antagonists such as memantine, cholinesterase inhibitors such as donepezil, neuroprotectants, nootropic agents, CNS modulators, antiamyloidogenics.

[0102] In some exemplary embodiments of the present invention relate to combinations of SAMe with one or more active ingredients that are commonly prescribed or used for treatment of and/or prophylaxis of a liver disorder in a subject include, but are not limited to, antiviral medication such as alpha interferon, ribavirin, lamivudine, steroids, antibiotics and zinc acetate.

[0103] In some exemplary embodiments of the present invention relate to combinations of SAMe with one or more active ingredients that are commonly prescribed or used for treatment of and/or prophylaxis of a cancer in a subject include, but are not limited to, chemotherapeutic agents, drug resistance modulators, monoclonal antibodies, cytokines (*e.g.* interferons and interleukins), immunocytokines, growth factors, chemoprotectants, vaccines and other biological response modifiers.

[0104] In some exemplary embodiments of the present invention relate to combinations of SAMe with one or more active ingredients that are commonly prescribed or used for treatment of and/or prophylaxis of a joint or inflammatory disease/disorder in a subject include, but are not limited to, analgesics, non-steroidal anti-inflammatory drug compounds (NSAID), disease-modifying antirheumatic drugs (DMARDs), corticosteroids, anakinra (an interleukin-1 receptor antagonist), COX-2 inhibition, gamma-aminobutyric acid-B (GABAB) receptor agonists, such as baclofen, GABAA potentiating drugs, such as the benzodiazepines tumor necrosis factor (TNF)-inhibiting drugs, and other drugs that modify the immune response (immunosuppressive drugs).

[0105] In some exemplary embodiments of the present invention relate to combinations of SAMe with one or more active ingredients that are commonly prescribed or used for treatment of and/or prophylaxis of an autoimmune disease/disorder in a subject include, but are not limited to, DMARDs, corticosteroids, anakinra (an interleukin-1 receptor antagonist), TNF-inhibiting drugs, and other drugs that modify the immune response (immunosuppressive drugs).

[0106] In some exemplary embodiments of the present invention relate to combinations of SAMe with one or more active ingredients that are commonly prescribed or used for treatment of and/or prophylaxis of a degenerative disease/disorder in a subject include, but are not limited to, NSAIDs, COX-2 inhibition, GABAB receptor agonists, such as baclofen, and GABAA potentiating drugs, such as the benzodiazepines.

[0107] In some exemplary embodiments of the present invention relate to combinations of SAMe with one or more active ingredients that are commonly prescribed or used for treatment of and/or prophylaxis of a soft tissue disease/disorder in a subject include, but are not limited to, milnacipram, pregabalin, SNRIs, NSRIs, muscle relaxers, sedatives, painkillers, and NSAIDs.

[0108] In some exemplary embodiments of the present invention relate to combinations of SAMe with one or more active ingredients that are commonly prescribed or used for

treatment of and/or prophylaxis of a genetic disease/disorder related to hyper or hypo methylation in a subject include, but are not limited to methionine, MTA (5'-deoxy-5'-(methylthio) adenosine) and other SAMe metabolites.

[0109] In some exemplary embodiments of the present invention relate to combinations of SAMe with one or more active ingredients that are commonly prescribed or used for treatment of and/or prophylaxis of a gastrointestinal disease/disorder in a subject include, but are not limited to, 5-Aminosalicylic acid (5-ASA) medications, Corticosteroids (prednisone), immunomodulatory medications such as Azathioprine (Immuran), 6-Mercaptopurine (6-MP), Methotrexate and Cyclosporine (Sandimmune), commonly used antibiotics such as Metronidazole (Flagyl) and Ciprofloxacin (Cipro) and biologic agents such as Infliximab (Remicade).

[0110] In some exemplary embodiments of the present invention relate to combinations of SAMe with one or more active ingredients that are commonly prescribed or used for treatment of and/or prophylaxis of a cardiovascular disease/disorder in a subject include, but are not limited to, statins, angiotensin-converting enzyme (ACE) inhibitors, ASA, SAMe break down products such as methionine, MTA and folate, cardioprotectants, vasoprotectants, coagulation inhibitors.

[0111] In some exemplary embodiments of the present invention relate to combinations of SAMe with one or more active ingredients that are commonly prescribed or used for treatment of and/or prophylaxis of a disorder induced in whole or in part by oxidative or free-radical damage including, but are not limited to, antioxidants such as Vitamin A, Vitamin C, Vitamin E, polyphenols, flavonoids, selenium, carotenoids.

[0112] In some exemplary embodiments of the present invention relate to combinations of SAMe with one or more active ingredients that are commonly prescribed or used for treatment of and/or prophylaxis of a disorder induced in whole or in part by damage to the central nervous system such as brain injury or spinal cord injury including, but not limited to, neuroprotectants, nootropic agents, CNS modulators, analgesics, muscle relaxants, apoptosis inhibitors, bone modulators, antioxidants.

[0113] In some exemplary embodiments of the present invention relate to combinations of SAMe with methionine, MTA, folate, vitamin B6 and/or B12 as they are each correlated with lowering homocysteine production. Therefore, it is considered that combining SAMe with methionine, MTA, folate, vitamin B6 and/or B12 may result in increased supplementation of SAMe by enhancing the body's natural ability to make SAMe while at the same time

supplementing SAMe with exogenous SAMe exhibiting an improved pharmacokinetic profile.

[0114] In some embodiments, an exemplary improved pharmacokinetic SAMe dosage form according to the invention may be included in a kit with a separate dosage form containing at least one other active ingredient, exemplified by one or more compounds suitable for the treatment of or commonly prescribed or used for the treating and/or prophylaxis in a subject a disease or disorder selected from the group consisting of, but not limited to, a mental or psychiatric disorder (*e.g.* psychotic or non-psychotic mental disorders such as depression and substance abuse disorders, respectively), a nervous system disease/disorder (*e.g.* a central nervous system disease such as Alzheimer's), other neurological disease/disorders (*e.g.* headaches and sleep disorders), conditions associated with injury to the central nervous system, a liver disease/disorder (*e.g.* alcoholic liver disease), a cancer (*e.g.* solid and blood-borne cancers), a joint disease/disorder (*e.g.* arthritis), an inflammatory disease/disorder (*e.g.* ulcerative colitis), an autoimmune disease/disorder (*e.g.* systemic lupus erythematosis and rheumatoid arthritis), a degenerative disease/disorder (*e.g.* Amyotrophic Lateral Sclerosis), a soft-tissue disease/disorder (*e.g.* a fibromyalgia disorder), a pain disease/disorder, a genetic disorder related to hyper or hypo methylation, a gastrointestinal disease/disorder, a cardiovascular disease/disorder, and a disorder induced in whole or in part by oxidative or free-radical damage, comprising administering to said subject an exemplary composition of the present invention which improves the pharmacokinetic profile of a physiologically effective amount of exogenous SAMe.

[0115] In addition to combinations of SAMe with the one or more additional ingredients exemplified above or methionine, MTA, folate, vitamin B6 and/or B12, administration of the exemplary improved pharmacokinetic SAMe formulations of the invention may also augment the effects of other drugs or nutritional supplements being taken by the subject. Thus, some exemplary embodiments of the present invention relate to combinations of SAMe with drugs or nutritional compounds already employed for treating other diseases for increasing the activity of said drugs or nutritional compounds.

EXAMPLES

Example 1: Extended Release Monolithic Matrix Tablets

[0116] A formulation comprising SAMe, magnesium aluminometasilicate, light liquid paraffin and magnesium stearate was compounded by mixing the ingredients and compressing

them with a semi-automatic tablet press. Humidity was maintained at less than 30 % and temperature was maintained at 20-25 °C during the entire manufacturing process. The proportions of the ingredients are set forth in Table 1-1, below.

Table 1-1: Formulation of SAMe with Liquid Paraffin

Excipients	Mg/Tablet	% (wt.)
SAMe	400	72.7 %
Magnesium Aluminometasilicate (Neusilin US 2)	100	18.18
Light Liquid Paraffin	30	5.45
Magnesium Stearate NF	20	3.63
Total wt of uncoated tablet (mg)	**500**	

[0117] The formulation in Table 1-1 enabled manufacture of SAMe tablets with less than 30% total excipients. The granules used this formulation had good flow properties and demonstrated no sticking picking during compression.

Example 2: Slugging Procedure

[0118] In an effort to improve the compressibility of the SAMe formulation from Example 1, a granulation procedure (slugging) was employed. SAMe was mixed with liquid paraffin and magnesium aluminometasilicate. The resulting powder mixture was loaded into a V blender and mixed for 10 minutes at 50 RPM. Half the quantity of magnesium stearate (see Table 2-1, below), 2.97 g, was added to the V blender and mixed for another 10 minutes.

[0119] The resulting powder was passed through a 20 # sieve. The blend was compressed into 400-500 mg slugs with a hardness of about 8-9 kp. The slugs were then milled, passed through a 30 # sieve and mixed with the remaining magnesium stearate (2.97 g). The resulting mixture was then compressed to a hardness of 12-15 kp.

Table 2-1: Formulation for Manufacturing SAMe Tablet Core with Liquid Paraffin

Excipients	Mg/Tablet	% (wt)	Excipient Mass for 110 Tablets
SAMe	800	71.81	88.00
Magnesium aluminometasilicate	200	17.95	22.00
Liquid Paraffin	6.00	5.39	66.00
Magnesium Stearate	5.40	4.85	59.40
Total	114.00	100.00	122.54

[0120] Ethylcellulose coating was performed by third party vendors (Colorcon, Aqualon). The specific ethylcellulose coatings and their coating levels (percent weight gains upon coating) are shown in Table 2-2, below. Dissolution studies were performed in pH 6.8 PBS media using USP II dissolution apparatus and protocol.

Table 2-2: Ethylcellulose Based Coatings

Coating Material	Coating Level (% Weight Gain on Coating)
Surelease® by Colorcon	5, 6, 7, 8 and 9 %
Aquarius® by Aqualon	4, 5, 6 and 7%

[0121] Introduction of the slugging process increased density of the powder and improved flow properties. Both coating trials were successful with no reported tablet erosion, delamination or friability during coating.

Example 3: Coating Trials

[0122] Matrix core SAMe tablets as disclosed in Example 2, above, were coated with ethylcellulose coatings having various amounts of pore former (Nutrateric® pore former, a combination of sodium alginate and purified stearic acid). The ethylcellulose portion of the coating was a combination of purified water, Ethyocel 20 cP STD. Prem. ethylcellulose and 28% ammonium hydroxide. The coatings tested were 100:0 (ethylcellulose:pore former), 80:20 and 70:30 by weight. Tablets were either uncoated or coated with either 2.5% of 70:30 or 80:20 ethylcellulose composition. Dissolution was tested in pH 6.8 PBS buffer solution. The results are summarized in Table 3-1:

Table 3-1: Dissolution Results for Uncoated and Coated Tablets at pH 6.8

Time (hr)	Uncoated Core	Tablets Coated with Ethylcellulose 70:30*, 2.5%**	Tablet Coated with Ethylcellulose 80:20*, 2.0%**
2	56.36	22.72	10.17
3	64.00	28.72	15.99
4	74.21	33.78	22.73
6	78.27	41.92	34.09
8	82.00	49.19	43.22
10	87.53	53.11	49.95
12	88.22	57.32	54.68
15	86.96	62.29	61.15
18	84.08	65.26	66.48

*Ratio of ethylcellulose to pore former; ** Wt.% gain of Coating per Tablet

[0123] The results of this study are depicted graphically in Figure 1.

Example 4: Second Coating Trial

[0124] Tablets cores as described in Example 2 were coated with ethylcellulose coatings at a polymer to pore former ratio of 60:40 at various coating levels. The coating levels, as determined by weight gain, were 2.0, 2.5, 3.0, 3.5 and 4.0 % weight gain. Dissolution studies were performed in pH 6.8 (starting pH) PBS and 0.1 N HCl using USP II dissolution apparatus. The results of this study are summarized in Table 4-1 and in figures 2, 3 and 4. In Table 4-1, the ratio of polymer (ethylcellulose) to pore former is expressed as a ratio (e.g. 60:40, 70:30) and the coating level is expressed as wt.% weight gain over the uncoated core (e.g. 2.0%, 2.5%, 4%).

[0125] Table 4-1: Dissolution Results of Coated Tablets

Time (hr)	**Tablet coated with 60:40, 2.0%**	**Tablet coated with 60:40, 2.0%**	**Tablet coated with 60:40, 2.5%**	**Tablet coated with 60:40, 4%**	**Tablet coated with 70:30, 2.5%**
Dissolution Medium	**pH 6.8 PBS**	**0.1 N HCl**	**0.1 N HCl**	**0.1 N HCl**	**0.1 N HCl**
2	35.16	43.43	35.18	22.7	23.8
4	49.68	57.90	55.39	43.0	38.4
6	59.67	73.97	71.13	57.4	50.1
8	66.25	82.67	82.67	71.1	60.9
10	71.15	89.47	89.83	78.9	68.0
12	75.32			84.1	76.7
14	73.45			87.9	86.4
16	75.67			89.3	91.7
20	82.89			90.3	92.3

[0126] In pH 6.8 buffer, 70-75% of SAMe was released from the tablet coated with 2.0% of 60:40 polymer:pore former composition. It is considered that degradation of SAMe in the pH 6.8 solution may have led to degradation of the drug during the study, reducing the concentration of SAMe in the course of the study at pH 6.8. In order to test this hypothesis, parallel studies were conducted in pH 1 (0.1 N HCl) solution. Both 60:40, 4% and 70:30, 2.5% coatings provided dissolution profiles in pH 1 solution that were considered to meet extended-release criteria. Such compositions are considered suitable for advancement into *in vivo* studies in man or animal models.

Example 5: Human (*in vivo*) Administration of Extended-Release Coated Matrix Cores

[0127] In order to understand the *in vivo* release characteristics of coated and uncoated monolithic SAMe tablets, the SAMe cores having the composition set forth in Example 2 were coated with 0%, 2%, 4% or 6% ethylcellulose (60:40 polymer to pore former ratio) and administered to human volunteers in an unblinded, pharmacokinetic study. The results obtained with the monolithic cores were compared to those obtained with commercially available SAMe in an enterically coated formulation (Mood Plus®, 4×400 mg enterically coated, immediate release SAMe Nature Made®). Blood samples were collected immediately before administration of SAMe (to establish baseline values) and at the intervals stated in Tables 5-1 through 5-7, below. The results of the study are depicted graphically in Figures 5, 6 and 7.

Table 5-1: SAMe Monolithic Core, 0% Coating: 640 mg of SAMe Ion

Time (hrs)	N-1	N-2	N-3	N-4	Mean (ng/mL)	SD	N	Above Baseline (ng/mL)	C/Cmax	nmol/L
0	18.3	3.5	3.7	23.5	**12.3**	**10.2**	**4**	0	0.00	30.74
2	17.4	3.7	27.0	135.0	**45.8**	**60.3**	**4**	33.5	0.89	114.85
4	54.2	14.6	16.1	71.8	**39.2**	**28.5**	**4**	26.9	0.71	98.26
6	98.3	10.5	8.0	83.2	**50.0**	**47.5**	**4**	37.7	1.00	125.46
8	127.4	5.8	23.4	24.9	**45.4**	**55.4**	**4**	33.1	0.88	113.92
12	42.4	12.4	41.8	30.6	**31.8**	**14.1**	**4**	19.6	0.52	79.81
24	40.0	6.7	23.9	21.1	**22.9**	**13.6**	**4**	10.7	0.28	57.55

$C = [SAME]_T - [SAME]_0$

$Cmax = [SAME]_{max} - [SAME]_0$

Table 5-2: SAMe Monolithic Core, 0% Coating: 1600 mg of SAMe Ion

Time (hrs)	Z-1	Z-2	Z-3	Z-4	Z-5
0	19.5	18.0	12.4	19.4	20.5
2					196.2
4	133.2	105.2	53.5	59.4	139.5
8	56.3	74.0	29.9	53.0	37.4
12	31.8	66.7	23.9	28.9	43.9
24	23.4	35.8	17.6	28.5	22.3
32	24.4	57.4	21.0	21.2	27.7
48	23.9	24.8	16.7	16.4	27.0

Table 5-3: SAMe Monolithic Core, 2% Coating: 1600 mg of SAMe Ion

Time (hrs)	M2-1	M2-2	M2-3	Mean (ng/mL)	SD	N	Above Baseline (ng/mL)	C/Cmax	nmol/L
0	20.4	48.0	54.8	41.1	18.2	3	0	0.00	103.07
2	57.8	108.6	56.2	74.2	29.8	3	33.1	0.49	186.26
4	80.0	85.8	77.6	81.1	4.3	3	40.1	0.59	203.59
6	75.0	207.4	43.9	108.8	86.8	3	67.7	1.00	272.96
8	60.7	116.1	62.3	79.7	31.5	3	38.6	0.57	200.05
12	42.4	84.8	31.2	52.8	28.3	3	11.8	0.17	132.58
24	32.4	48.7	24.8	35.3	12.2	3	-5.8	-0.09	88.61

$C = [SAME]_T - [SAME]_0$

$Cmax = [SAME]_{max} - [SAME]_0$

Table 5-4 SAMe Monolithic Core, 4% Coating, 1600 mg of SAMe Ion

Time (hrs)	M4-1	M4-2	M4-3	Mean (ng/mL)	SD	N	Above Baseline (ng/mL)	C/Cmax	nmol/L
0	23.1	24.6	30.6	26.1	4.0	3	0	0.00	65.49
2	45.5	41.3	58.6	48.5	9.1	3	22.4	0.46	121.64
4	42.8	36.8	145.0	74.9	60.8	3	48.8	1.00	187.93
6	20.6	34.1	109.7	54.8	48.0	3	28.7	0.59	137.57
8	29.8	32.7	66.0	42.9	20.1	3	16.8	0.34	107.55
12	59.0	51.0	49.6	53.2	5.1	3	27.1	0.56	133.52
24	27.0	37.0	43.9	36.0	8.5	3	9.9	0.20	90.25

$C = [SAME]_T - [SAME]_0$

$Cmax = [SAME]_{max} - [SAME]_0$

Table 5-5: SAMe Monolithic Core, 6% Coating, 1600 mg of SAMe Ion

Time (hrs)	M6-1	M6-2	M6-3	M6-4	Mean (ng/mL)	SD	N	Above Baseline (ng/mL)	C/Cmax	nmol/L
0	38.0	32.4	40.5	36.2	36.8	3.4	4	0	0.00	92.34
2	61.9	41.2	42.2	92.4	59.4	24.0	4	22.6	0.68	149.16
4	98.3	65.4	49.0	67.2	70.0	20.6	4	33.2	1.00	175.58
6	65.0	91.6	56.8	59.0	68.1	16.0	4	31.3	0.94	170.89
8	65.2	50.4	58.3	44.2	54.5	9.2	4	17.7	0.53	136.83
12	81.8	33.3	47.3	53.6	54.0	20.4	4	17.2	0.52	135.55
24	47.7	37.0	42.6	40.6	42.0	4.5	4	5.2	0.16	105.34

$C = [SAME]_T - [SAME]_0$

$Cmax = [SAME]_{max} - [SAME]_0$

Table 5-6: Enteric Coated Monolithic (ER) Core, 1600 mg of SAMe Ion

	EM-1		EM-2		EM-3		Mean	Mean	C/Cmax
Time (hrs)	µmol/L	ng/ml	µmol/L	ng/ml	µmol/L	ng/ml	µmol/L	ng/ml	µmol/L
0	50.1	20.0	95.3	38.1	100.4	40.2	81.9	32.6	0.00
2	74.2	29.7	136.7	54.7	133.1	53.2	114.7	45.7	0.82
4	90.9	36.4	124.6	49.8	142.4	57.0	119.3	47.5	0.94
6	68.9	27.6	142.4	57.0	154.3	61.7	121.9	48.6	1.00
8	115.2	46.1	165.3	66.1	141.3	56.5	140.6	56.0	1.47
12	70.4	28.2	159.8	63.9	128.3	51.3	119.5	47.6	0.94
24	66.4	26.6	139.8	55.9	156.5	62.6	120.9	48.2	0.98

$C = [SAME]_T - [SAME]_0$

$Cmax = [SAME]_{max} - [SAME]_0$

Table 5-7: Enteric Coated Immediate Release (Nature Made®) Core, 1600 mg of SAMe Ion

	NM-1		NM-2		NM-3		NM-4		Mean	Mean	C/Cmax
Time (hrs)	µmol/L	ng/ml	µmol/L	ng/ml	µmol/L	ng/ml	µmol/L	ng/ml	µmol/L	ng/ml	
0	34.9	14.0	155.5	62.2	32.3	12.9	119.4	47.8	85.5	34.1	0.00
2	37.4	15.0	253.0	101.2	35.8	14.3	150.0	60.0	119.1	47.4	0.56
4	1427	570.9	501.2	200.5	28.0	11.2	149.5	59.8	526.5	209.8	0.64
6	939.4	375.8	577.7	231.1	1001.4	400.6	151.1	60.4	667.4	265.9	0.68
8	289.7	115.9	221.6	88.6	268.4	107.4	117.1	46.8	224.2	89.3	1.00
12	88.9	35.6	124.1	49.6	124.9	50.0	96.1	38.4	108.5	43.2	0.64
24	32.5	13.0	161.2	64.5	47.7	19.1	83.1	33.2	81.1	32.3	0.66

$C = [SAME]_T - [SAME]_0$

$Cmax = [SAME]_{max} - [SAME]_0$

[0128] As can be seen from Figures 5 through 7, the monolithic core in accordance with Example 2, provided extended increase in blood plasma concentrations of SAMe above baseline, whereas the enteric coated formulation provided a rapid rise in SAMe concentration in blood plasma, followed by precipitous decline. The blood concentration profiles set forth in Tables 5-1 through 5-4 are very flat, demonstrating little change between hours 2 and 4, hours 4 and 6, hours 6 and 8 and hours 8 and 12, whereas the enteric coated SAMe formulation showed a nearly 300% variance between hours 2 and 4, and a nearly 200% variance between hours 4 and 6. It is considered that the flat blood plasma concentration curves obtained in Tables 5-1 through 5-4 are desirable from the standpoint of providing a more even release of SAMe over time.

[0129] Using the data provided above, the area under the plasma concentration (AUC) values were calculated for the Immediate Release (Nature Made®), Extended Release (Monolithic) core, and the 60:40-coated Extended Release core (2%, 4% and 6%). The values are set forth in the following Table 5-7.

Table 5-7: AUC Values for Immediate Release and 0%, 2%, 4% and 6% Coated Monolithic Core

	Baseline	1600 mg	1600 mg	1600 mg	1600 mg	1600 mg
	No Tabs:Low Methionine	Nature Made	MSI-NakedCore (0%)	2%*	4%*	6%*
Average AUC	16.0	1052	782.1	526.1	407.5	334.2
sem	5.3	388	191.0	280.0	112.9	97.2

[0130] The data shown above are depicted graphically in Figure 8.

Example 6: Human (*in vivo*) Administration of Extended-Release Coated Matrix Cores

[0131] In order to further understand the *in vivo* release characteristics of coated and uncoated monolithic SAMe tablets, 1600-mg SAMe cores having the composition set forth in Example 2 were coated with 0%, 2%, 4%, 6% ethylcellulose (60:40 polymer to pore former ratio) and administered to human volunteers in an unblinded, pharmacokinetic study. The results obtained with the monolithic cores were compared to those obtained with two commercially available enterically coated SAMe formulations i.e.: (1) Mood Plus®, 4×400 mg enterically coated, immediate release SAMe distributed by Nature Made®, and (2) NSI® SAM-e, 2×400 mg enterically coated, immediate release SAMe distributed by NSI Inc. ("NSI" is a registered trademark of the Nature's Wealth Company Corp., Boynton Beach, FL, USA, 33426). Blood samples were collected immediately before administration of SAMe (to establish baseline values) and at the intervals stated in Tables 6-1 through 6-8, below. SAMe levels in each of the blood samples collected in this study were determined using a LCMS system. The results of the study are shown in Tables 6-1 through 6-8.

Table 6-1: SAMe Monolithic Core, 0% Coating: 1600 mg of SAMe Ion*

Time (hrs)	AM-1	AF-1	AM-2	AM-3	AM4	Mean	C/Cmax
0	20.4	24.5	21.9	33.7	30.9	26.3	0.00
4	94.4	140.4	66.0	115.6	101.6	103.6	1.00
8	36.4	52.8	35.0	101.2	50.8	55.3	0.37
12	36.1	41.6	28.0	64.4	36.4	41.3	0.19
24	24.4	31.0	23.8	49.6	33.8	32.5	0.08

* Data values are ng/mL

$C = [SAME]_T - [SAME]_0$

$Cmax = [SAME]_{max} - [SAME]_0$

Table 6-2: SAMe Monolithic Core, 2% Coating: 1600 mg of SAMe Ion*

Time (hrs)	BM-1	BF-1	BM-2	BM-3	BM-4	BM-5	BM-6	BM-7	Mean	C/Cmax
0	20.0	28.2	21.7	33.6	25.4	22.3	24.8	18.4	24.3	0.00
2	56.8	95.2	74.8	127.2	63.6	85.6	82.4	70.0	82.2	0.87
4	52.4	86.8	62.8	97.2	87.6	71.6	87.2	71.2	77.6	0.80
6	44.8	252.4	51.2	66.8	50.4	56.0	63.2	136.4	90.9	1.00
8	32.5	110.4	42.8	54.8	36.8	37.3	46.0	147.2	64.5	0.60
12	23.7	58.8	36.8	40.8	29.6	34.0	42.4	26.7	38.1	0.21
24	18.0	31.2	27.7	37.1	28.8	28.2	29.2	24.5	31.1	0.10

* Data values are ng/mL

$C = [SAME]_T - [SAME]_0$

$Cmax = [SAME]_{max} - [SAME]_0$

Table 6-3: SAMe Monolithic Core, 4% Coating, 1600 mg of SAMe Ion*

Time (hrs)	M-3	C/Cmax
0	18.5	0.00
2	40.4	0.25
4	106.4	1.00
6	90.8	0.82
8	55.2	0.42
12	40.0	0.24
24	26.3	0.09

* Data values are ng/mL

$C = [SAME]_T - [SAME]_0$

$Cmax = [SAME]_{max} - [SAME]_0$

Table 6-4: SAMe Monolithic Core, 6% Coating, 1600 mg of SAMe Ion*

Time (hrs)	CM-1	CM-2	Mean	C/Cmax
0	20.3	26.7	23.5	0.00
2	23.6	90.4	58.0	1.00
4	32.8	79.2	58.0	1.00
6	33.3	53.2	46.3	0.66
8	46.4	52.0	53.2	0.86
12	31.7	37.5	40.6	0.50
24	23.8	23.5	35.6	0.35

* Dat values are ng/mL

$C = [SAME]_T - [SAME]_0$

$Cmax = [SAME]_{max} - [SAME]_0$

Table 6-5: Enteric Coated Monolithic (ER) Core, 1280 mg of SAMe Ion*

Time (hrs)	15 (M)	22 (M)	23 (F)	Mean	C/Cmax
0	20.6	23.5	25.2	23.1	0.00
2	36.8	29.8	28.8	31.8	0.51
4	28.6	32.2	43.2	34.7	0.68
6	32.0	30.7	55.6	39.4	0.96
8	39.4	26.5	54.4	40.1	1.00
12	29.0	31.4	42.4	34.3	0.66
24	21.0	25.9	29.0	25.3	0.13

* Data values are ng/mL

$C = [SAME]_T - [SAME]_0$

$Cmax = [SAME]_{max} - [SAME]_0$

Table 6-7: Enteric Coated Immediate Release (Nature Made®) Core, 1600 mg of SAMe Ion*

Time (hrs)	N-1	N-2	N-3	N-4	N-5	N-6	N-7	N-8	Mean	C/Cmax
0	22.4	22.7	19.6	24.4	21.3	29.9	26.2	27.2	24.2	0.00
2	26.0	29.8	33.2	65.6	25.7	452.0	524.0	230.4	173.3	0.31
4	28.5	30.2	1572.0	588.0	24.9	624.0	488.0	664.0	502.5	1.00
6	29.3	28.1	588.0	350.8	381.6	270.8	197.6	240.4	260.8	0.49
8	57.2	26.8	252.8	211.2	170.8	176.8	130.0	167.6	149.1	0.26

* Data values are ng/mL

$C = [SAME]_T - [SAME]_0$

$Cmax = [SAME]_{max} - [SAME]_0$

[0132] The C/Cmax data were derived from the blood plasma SAMe levels shown in Tables 6-1 through 6-8, and are graphically depicted in Figure 9. Data points for 10 h and 18 h after administration of the SAMe compositions, were extrapolated from the plotted curves generated from the derived C/Cmax data. Missing and/or not recorded 12-h and 24 data points

were also extrapolated from the plotted C/Cmax data to enable comparisons of the different compositions over a 24-h release period. The data demonstrate that coating SAMe monolithic cores with different thicknesses of the ethylcellulose coatings (i.e., at a polymer to pore former ratio of 60:40), affected the rates of SAMe release at different time periods after administration, and also provided considerably elevated levels of SAMe release 8 h and 12 h after administration when compared to the two commercial SAMe reference formulations.

Table 6-8: Enteric Coated Immediate Release (NSI® SAM-e) Core, 800 mg of SAMe Ion*

Time (hrs)	SP-1	SP-2	SP-3	SP-4	SP-5	SP-6	SP-7	SP-8	SP-9	SP-10	Mean	C/Cmax
0	26.4	27.5	20.9	20.2	22.0	25.7	20.3	24.9	27.4	21.6	23.7	0.00
2	1136.0	2132.0	378.4	432.0	3236.0	88.8	322.8	22.5	29.2	61.2	783.9	1.00
4	408.0	640.0	484.0	190.4	2296.0	928.0	564.0	24.7	26.5	772.0	633.4	0.80
6	164.4	255.2	197.6	201.2	648.0	333.2	196.0	25.5	35.9	277.2	233.4	0.28
8	92.8	115.6	104.4	67.6	232.4	161.6	82.0	26.8	31.8	123.2	103.8	0.11
12	37.9	180.4	564.0	27.0	60.8	54.8	33.5	25.2	32.0	38.8	105.4	0.11
24	384.0	116.8	45.2	436.0	274.8	28.4	504.0	432.0	2392.0	387.2	500.0	0.63

* Data values are ng/mL

$C = [SAME]_T - [SAME]_0$

$Cmax = [SAME]_{max} - [SAME]_0$

Example 7: Configuration of extended-release SAMe compositions

[0133] The data shown in Examples 5 and 6 demonstrate that selection of coating materials and coating thickness can significantly affect and elevate SAMe release profiles over a 24-h post-dosing period in reference to the release profiles of immediate-release SAMe compositions. Accordingly, those skilled in these arts will understand and appreciate that the exemplary embodiments disclosed herein can be suitably configured and adapted to produce extended-release SAMe compositions having desired 24-h post-dosing SAMe release profiles by selecting and manipulably coating two or more SAMe components such as those exemplified, among others, by monolithic cores, granules produced by wet granulation processes and granules produced dry granulations processes, with selected coatings. Each of these types of SAMe components may be controllably coated with coatings known to those skilled in these arts to provide osmotic dosage forms, extended release matrices, pulsatile release formulations and extended release formulations coated with one or more enteric coatings. In some embodiments, an extended release matrix (monolithic core) containing SAMe may be coated with an extended release coating, which may optionally include a pore former (such as sodium alginate, stearic acid or both). Thus, an ER formulation of SAMe according to the invention will include any formulation that has, as a substantial part of that formulation, an extended release component comprising SAMe – that is a component that releases SAMe over a period of more than about 2 hours, particularly about 2 to 24, 3 to 24 or 4 to 24 hours. As SAMe is sensitive to oxidation, it is suitable to coat the SAMe with a coating that will protect the SAMe from oxidation. The coating may be applied directly to SAMe granules (e.g. by spraying an oxygen impermeable coating, which may be an enteric coating, an immediate release coating, an extended release coating or a combination thereof, onto SAMe granules in a fluidized bed) or may be applied to the outside of a tablet, capsule or other dosage form, e.g. by spraying or dipping a tablet or capsule core containing SAMe. Alternatively, the dosage form may be a tablet or caplet containing SAMe in a matrix or osmotic core and the oxygen impermeable layer is applied by spraying the oxygen impermeable layer onto the outside of the matrix or osmotic core or by dipping the matrix or osmotic core into a solution containing the oxygen impermeable layer material. The oxygen impermeable layer may optionally be an enteric coating. For some applications, it may be suitable to apply an oxygen impermeable layer, e.g. an immediate release layer, before an enteric coating is applied to the outside of the dosage form, either by spraying the enteric coating onto the dosage form or dipping the core into the coating material. It is contemplated that a method of coating that results in an oxygen impermeable layer being interposed between the SAMe and the

outside of the dosage form will produce a suitable result. As SAMe is also sensitive to moisture, it is also suitable to optionally coat the SAMe with a water-impermeable coating (i.e. a moisture barrier coating). Suitable moisture barriers are exemplified by hydrophobic polymeric film-forming compounds such as ethylcellulose, methylcellulose, stearic acid monoglyceride, and the like. The moisture impermeability of such film-forming polymers may be augmented if so desired with additional hydrophobic compounds exemplified by polydimethylsiloxane and zein amoung others. The moisture barrier coating may be applied directly to SAMe granules (e.g. by spraying a moisture barrier coating onto SAMe granules in a fluidized bed) or may be applied to the outside of a tablet, capsule or other dosage form, e.g. by spraying or dipping a tablet or capsule core containing SAMe. Alternatively, the dosage form may be a tablet or caplet containing SAMe in a matrix or osmotic core and the moisture barrier layer is applied by spraying the moisture barrier layer onto the outside of the matrix or osmotic core or by dipping the matrix or osmotic core into a solution containing the moisture barrier layer material. The moisture barrier layer may optionally be an enteric coating. For some applications, it may be suitable to apply a moisture barrier layer, e.g. an immediate release layer, before an enteric coating is applied to the outside of the dosage form, either by spraying the enteric coating onto the dosage form or dipping the core into the coating material. It is contemplated that a method of coating that results in an moisture layer being interposed between the SAMe and the outside of the dosage form will produce a suitable result. It certain applications, it may be suitable to provide a moisture barrier layer overlaid or alternatively underlaid an oxygen-impermeable layer. It is also within the scope of the present invention to coat one or more different SAMe components with one or more selected coatings, and then mix together the coated SAMe components, and then to controllably coat the mixture with one or more additional selected coatings, in order to provide a desired SAMe release profile over a 24-h period.

[0134] It is suitable to contemplate a 24-h SAMe extended release profile as generally comprising four distinct time periods wherein the first time period is about 2 to 6 hours post-dosing, the second time period is about 4 to 10 hours post-dosing, the third time period is about 8 to 16 hours post-dosing, while the fourth period is about 10 to 24 hours post-dosing so that the amount of SAMe released during each of the third and fourth time periods is within a selected therapeutic target range, which for example could be at least 50% greater than the SAMe baseline at time 0. Those skilled in these arts will understand that suitable therapeutic targets for controllable SAMe release during the third and fourth time periods could be selected from the range of 10% to 100% greater that the SAMe baseline at time 0. It is suitable to adjust, if so desired, the duration of each time period so that it is controllably compressed or extended. It is

also suitable to configure the 24-h release profile as having three distinct time periods, e.g., wherein the first time period is about 2 to 6 hours post-dosing, the second time period is about 4 to 12 hours post-dosing and the third time period is about 10 to 24 hours post-dosing.

[0135] It is noted that the release profiles of the two commercial SAMe formulations referenced in Examples 5 and 6 reached their Cmax values during the first time period (i.e., within 6 hours post-dosing) after which their rates of SAMe release dropped considerably during the second time period (i.e., by 10-12 hours post-dosing) and then approximated the time 0 baseline during the third and fourth time periods (Figure 9). An exemplary SAMe release profile for a first contemplated SAMe formulation is shown in Figure 10, in reference to the two commercial SAMe formulations, wherein very little SAMe release occurs during the first time period, its Cmax occurs during the second time period (i.e., about 4 to 10 hours post-dosing), followed by a gradual decline in the rate of SAMe release during the third time period, to a baseline release profile during the fourth time period that is therapeutically elevated in comparison to the baseline at time 0. An exemplary SAMe release profile for a second contemplated SAMe formulation is shown in Figure 11, in reference to the two commercial SAMe formulations, wherein the initial SAMe release profile is similar to the two reference formulations and its Cmax is reached during the first time period post-dosing. The rate of SAMe release slowly declines to an elevated therapeutic baseline level during the fourth time period. An exemplary SAMe release profile for a third contemplated SAMe formulation is shown in Figure 12, in reference to the two commercial SAMe formulations, wherein the third contemplated SAMe formulation is configured with an immediate-release component to provide a first peak of SAMe release during the first time period, and a first controlled release component to provide a second and further elevated peak of SAMe release during the second time period, and at least a second controlled release component to provide a gradual decline in the rate of SAMe release during the third time period, and optionally at least a third release component to provide a therapeutically elevated rate of SAMe release during the fourth time period.

[0136] The SAMe release profiles of compositions configured and prepared as disclosed herein can be assessed and verified with *in vivo* testing as outlined in Examples 5 and 6. Blood plasma levels of SAMe may be assayed with a suitable method, such as high performance liquid chromatography (HPLC), mass spectrometry (MS) or a combination thereof (e.g. LC/MS). The person skilled in the art will recognize that plasma concentration (C) may be obtained from a population of one or more individuals. In addition, plasma concentrations may in some cases need to be interpolated from a graph of plasma concentration versus time. For example, in some

embodiments, a SAMe concentration-versus-time graph may be obtained by collecting plasma at times 0, 2, 4, 6, 8, 12 and 24 hours and deriving a best-fit curve from those data, e.g. by a regression analysis or interpolation method (such as splines). Other blood plasma concentration points (e.g. 10, 18 and/or 20 hours) can then be calculated, e.g. by interpolation or using a formula derived by a regression analysis method. Thus, as used herein, a SAMe blood plasma concentration, or a value derived from SAMe blood plasma concentrations, can represent either individual or population values, may be assayed using a suitable method, and may be actual or calculated (e.g. interpolated). In some embodiments, a value derived from SAMe blood plasma concentrations can include Q, which is the quotient of SAMe concentration above baseline at a particular time point divided by the maximum SAMe blood plasma concentration above baseline. Thus, the value of Q at a particular time (t) is represented by the formula:

$$Q = ([SAMe]_T - [SAMe]_{baseline}) / ([SAMe]_{Max} - [SAMe]_{baseline}) \quad (1)$$

which also may be rendered:

$$Q = C_T / C_{Max} \quad (2)$$

[0137] wherein $[SAMe]_T$ is the plasma concentration in a treated individual at time T after administration of SAMe; $[SAMe]_{baseline}$ is the plasma concentration of SAMe in an untreated population; $[SAMe]_{baseline}$ can also be represented as $[SAMe]_0$, especially where baseline SAMe concentrations are obtained immediately prior to administration of SAMe to the population; $[SAMe]_{Max}$ is the maximum blood plasma concentration of SAMe in a treated population; C_T is the blood plasma concentration of SAMe for the population above baseline at time T; C_{Max} is the maximum blood plasma concentration of SAMe above baseline for the population.

[0138] In some embodiments, $[SAMe]_{baseline}$ is measured in the same or similar population at the same times during the day as $[SAMe]_T$ and $[SAMe]_{Max}$; in some embodiments $[SAMe]_{baseline}$ is the blood plasma concentration of SAMe in a population immediately prior to administration of SAMe to the population. It is noted that the time at which $C_T = C_{Max}$ (i.e. $Q = 1$) is referred to as T_{Max}.

[0139] In some embodiments, the invention provides formulations and methods in which the formulation is adapted to provide a T_{Max} of at least about 6 hours, at least about 7 hours, at least about 8 hours, at least about 9 hours or at least about 10 hours.

[0140] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to

the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. An extended release SAMe formulation comprising a therapeutically effective amount of S-adenosyl-L-methionine (SAMe), or a method of treating in a patient a disorder, comprising administering to the patient said extended release SAMe formulation, wherein the extended release dosage provides a quotient $Q = (([SAMe]_T-[SAMe]_0)/C_{max})$, wherein $C_{max} = [SAMe]_{Max}-[SAMe]_0$ and $[SAMe]_{Max}$ is a maximum blood plasma concentration of SAMe in a patient population after administration of SAMe to the patient population, $[SAMe]_0$ is a blood plasma concentration of SAMe immediately prior to administration of SAMe to the patient population and $[SAMe]_T$ is a blood plasma concentration of SAMe at time T after administration of SAMe to the patient population), wherein:

(a) Q is about 0.05 to about 0.95 when T is about 2 hours; Q is about 0.5 to about 1.0 when T is about 4 hours; Q is about 0.4 to about 1.0 when T is about 6 hours; Q is about 0.2 to about 1.0 when T is about 8 hours; Q is about 0.1 to about 0.8 when T is about 12 hours; Q is about 0.1 to about 0.7 when T is about 18 hours; and Q is about 0.05 to about 0.6 when T is about 24 hours;

(b) Q is about 0.2 to about 1.0 when T is about 8 hours; Q is about 0.1 to about 0.8 when T is about 12 hours; Q is about 0.05 to about 0.6 when T is about 24 hours; or

(c) Q is about 0.05 to about 0.95 when T is about 2 hours; Q is about 0.5 to about 1.0 when T is about 4 hours; Q is about 0.4 to about 1.0 when T is about 6 hours; Q is about 0.2 to about 1.0 when T is about 8 hours; Q is about 0.1 to about 0.8 when T is about 12 hours; and Q is about 0.05 to about 0.7 when T is about 18 hours.

2. The formulation or method of claim 1, wherein:

(a) Q is about 0.05 to about 0.75, about 0.1 to about 0.75, about 0.2 to about 0.85, about 0.3 to about 0.85, about 0.4 to about 0.95, about 0.5 to about 0.95, about 0.6 to about 0.95, about 0.7 to about 0.95, about 0.4 to about 0.6, or about 0.6 to about 0.8, when T is about 2 hours;

(b) Q is about 0.5 to about 1.0, about 0.6 to about 1.0, about 1.0 when T is about 4 hours, or about 0.8 to about 1.0, when T is about 4 hours;

(c) Q is about 0.4 to about 1.0, about 0.5 to about 1.0, about 0.6 to about 1.0, about 0.7 to about 1.0, orabout 0.8 to about 1.0, when T is about 6 hours;

(d) Q is about 0.2 to about 1.0, about 0.3 to about 1.0, about 0.4 to about 1.0, about 0.5 to about 1.0, about 0.6 to about 1.0, about 0.7 to about 1.0, or about 0.4 to about 0.6, when T is about 8 hours;

(e) Q is about 0.2 to about 0.8, about 0.2 to about 0.7, about 0.3 to about 0.7, about 0.4 to about 0.8, about 0.5 to about 0.7, about 0.25 to about 0.45, or about 0.15 to about 0.6, when T is about 12 hours; or

(f) Q is about 0.05 to about 0.5, about 0.1 to about 0.5, about 0.15 to about 0.5, or about 0.2 to about 0.6 when T is about 24 hours.

3. The formulation or method of claim 1, wherein the disorder is a mental or psychiatric disorder (*e.g.* psychotic or non-psychotic mental disorders exemplified by depression and substance abuse disorders, respectively), a nervous system disease/disorder (*e.g.* a central nervous system disease exemplified by Alzheimer's), other neurological disease/disorders (*e.g.* headaches and sleep disorders), conditions associated with injury to the central nervous system, a liver disease/disorder (*e.g.* alcoholic liver disease), a cancer (*e.g.* solid and blood-borne cancers), a joint disease/disorder (*e.g.* arthritis), an inflammatory disease/disorder (*e.g.* ulcerative colitis), an autoimmune disease/disorder (*e.g.* systemic lupus erythematosis and rheumatoid arthritis), a degenerative disease/disorder (*e.g.* Amyotrophic Lateral Sclerosis), a soft-tissue disease/disorder (*e.g.* a fibromyalgia disorder), a pain disease/disorder, a genetic disorder related to hyper- or hypo-methylation, a gastrointestinal disease/disorder, a cardiovascular disease/disorder, and a disorder induced in whole or in part by oxidative or free-radical damage.

4. The formulation or method of claim 1, wherein:

(a) Q is about 0.05 to about 0.5 when T is about 2 hours; Q is about 0.5 to about 0.8 when T is about 4 hours; Q is about 0.7 to about 1.0 when T is about 6 hours; Q is about 0.5 to about 0.8 when T is about 8 hours; Q is about 0.15 to about 0.55 when T is about 12 hours; Q is about 0.1 to about 0.6 when T is about 18 hours; and Q is about 0.05 to about 0.5 when T is about 24 hours;

(b) Q is about 0.4 to about 0.95 when T is about 2 hours; Q is about 0.75 to about 1.0 when T is about 4 hours; Q is about 0.5 to about 1.0 when T is about 6 hours; Q is about 0.5 to about 0.9 when T is about 8 hours; Q is about 0.2 to about 0.7 when T is about 12 hours; Q is about 0.1 to about 0.6 when T is about 18 hours; and Q is about 0.1 to about 0.5 when T is about 24 hours;

(c) Q is about 0.4 to about 0.95 when T is about 2 hours; Q is about 0.6 to about 1.0 when T is about 4 hours; Q is about 0.7 to about 1.0 when T is about 6 hours; Q is about 0.7 to about 1.0 when T is about 8 hours; Q is about 0.1 to about 0.7 when T is about 12 hours; Q is about 0.1 to about 0.6 when T is about 18 hours; and Q is about 0.05 to about 0.5 when T is about 24 hours; or

(d) Q is about 0.4 to about 0.95 when T is about 2 hours; Q is about 0.6 to about 1.0 when T is about 4 hours; Q is about 0.7 to about 1.0 when T is about 6 hours; Q is about 0.7 to about 1.0 when T is about 8 hours; Q is about 0.25 to about 0.8 when T is about 12 hours; Q is about 0.2 to about 0.7 when T is about 18 hours; and Q is about 0.15 to about 0.6 when T is about 24 hours.

5. The formulation or method of claim 1, wherein:

(a) Q is about 0.2 to about 1.0, about 0.3 to about 1.0, about 0.4 to about 1.0, about 0.5 to about 1.0, about 0.6 to about 1.0, about 0.7 to about 1.0, or about 0.4 to about 0.6 when T is about 8 hours;

(b) Q is about 0.2 to about 0.8, about 0.2 to about 0.7, about 0.3 to about 0.7, about 0.4 to about 0.8, about 0.5 to about 0.7, about 0.25 to about 0.45, about 0.15 to about 0.45, or 0.15 to about 0.6, when T is about 12 hours; or

(c) Q is about 0.05 to about 0.5, about , 0.1 to about 0.5, about 0.15 to about 0.5, about 0.2 to about 0.6 when T is about 24 hours.

6. The formulation or method of claim 1, wherein:

(a) Q is about 0.5 to about 0.8 when T is about 8 hours; Q is about 0.15 to about 0.55 when T is about 12 hours; and Q is about 0.05 to about 0.5 when T is about 24 hours;

(b) Q is about 0.5 to about 0.9 when T is about 8 hours; Q is about 0.2 to about 0.7 when T is about 12 hours; and Q is about 0.1 to about 0.5 when T is about 24 hours;

(c) Q is about 0.7 to about 1.0 when T is about 8 hours; Q is about 0.1 to about 0.7 when T is about 12 hours; and Q is about 0.05 to about 0.5 when T is about 24 hours; or

(d) Q is about 0.7 to about 1.0 when T is about 8 hours; Q is about 0.25 to about 0.8 when T is about 12 hours; and Q is about 0.15 to about 0.6 when T is about 24 hours.

7. The formulation or method of claim 6, wherein:

(a) Q is about 0.05 to about 0.75, 0.1 to about 0.75, 0.2 to about 0.85, about 0.3 to about 0.85, about 0.4 to about 0.95, about 0.5 to about 0.95, about 0.6 to about 0.95, 0.7 to about 0.95, about 0.4 to about 0.6, claim 66, wherein Q is about 0.6 to about 0.8 when T is about 2 hours;

(b) Q is about 0.5 to about 1.0, about 0.6 to about, 0.6 to about 1.0 when, about 0.7 to about 1.0, or about 0.8 to about 1.0 T is about 4 hours;

(c) Q is about 0.4 to about 1.0, about 0.5 to about 1.0, about 0.6 to about 1.0, about 0.7 to about 1.0, about 0.8 to about 1.0, about 0.2 to about 1.0 when T is about 6 hours;

(d) Q is about 0.3 to about 1.0, about 0.4 to about 1.0, about 0.5 to about 1.0, Q is about 0.6 to about 1.0, about 0.7 to about 1.0, about 0.4 to about 0.6, about 0.1 to about 0.7, about 0.2 to about 0.7, when T is about 8 hours;

(e) Q is about 0.3 to about 0.7, about 0.7 to about 0.7, about 0.5 to about 0.7, Q is about 0.25 to about 0.45, about 0.7 to about 0.7, when T is about 12 hours; or

(f) Q is about 0.05 to about 0.5, 0.1 to about 0.5, about 0.15 to about 0.5, about 0.2 to about 0.5 when T is about 18 hours.

8. The formulation or method of claim 7, wherein: Q is about 0.05 to about 0.5 when T is about 2 hours; Q is about 0.5 to about 0.8 when T is about 4 hours; Q is about 0.7 to about 1.0 when T is about 6 hours; Q is about 0.5 to about 0.8 when T is about 8 hours; Q is about 0.15 to about 0.55 when T is about 12 hours; and Q is about 0.1 to about 0.6 when T is about 18 hours.

9. The formulation or method of claim 7, wherein: Q is about 0.4 to about 0.95 when T is about 2 hours; Q is about 0.75 to about 1.0 when T is about 4 hours; Q is about 0.5 to about 1.0 when T is about 6 hours; Q is about 0.5 to about 0.9 when T is about 8 hours; Q is about 0.2 to about 0.7 when T is about 12 hours; and Q is about 0.1 to about 0.6 when T is about 18 hours.

10. The formulation or method of claim 7, wherein: Q is about 0.4 to about 0.95 when T is about 2 hours; Q is about 0.6 to about 1.0 when T is about 4 hours; Q is about 0.7 to about 1.0 when T is about 6 hours; Q is about 0.7 to about 1.0 when T is about 8 hours; Q is about 0.1 to about 0.7 when T is about 12 hours; and Q is about 0.1 to about 0.6 when T is about 18 hours.

11. The formulation or method of claim 7, wherein: Q is about 0.4 to about 0.95 when T is about 2 hours; Q is about 0.6 to about 1.0 when T is about 4 hours; Q is about 0.7 to about 1.0 when T is about 6 hours; Q is about 0.7 to about 1.0 when T is about 8 hours; Q is about 0.25 to about 0.8 when T is about 12 hours; and Q is about 0.2 to about 0.7 when T is about 18 hours.

12. The formulation or method of one of claims 1-11, wherein T_{max} is at least about 6 hours after administration of the extended release dosage.

13. The formulation or method of one of claims 1-11, wherein T_{max} is about 4 to about 12 hours after administration of the extended release dosage.

14. The formulation or method of one of claims 1-13, wherein the dose is administered in 1 to 4, 1 to 5 or 1 to 6 discrete dosage units.

15. The formulation or method of one of claims 1-14, wherein the patient is fed.

16. The formulation or method of one of claims 1-15, further comprising administering to the patient one or more additional active compounds.

17. The formulation or method of one of claims 1-16, wherein at least a portion of the SAMe is contained within an extended release matrix, an osmotic extended release core or a pulsatile release formulation.

18. The formulation or method of one of claims 1-17 wherein the formulation is adapted for once-a-day (Q.D.) dosing.

19. formulation or method of one of claims 1-18, wherein Q is above 0.60 for at least 5 hours during a 24 hour period from one dose.

20. A kit for treatment in a patient a disorder selected from the group consisting of osteoarthritis, rheumatoid arthritis, fibromyalgia, a psychiatric disorder, an inflammatory condition, a central nervous system disorder, a pain disorder, a liver disorder, a neurological disorder, a gastrointestinal disorder, a cardiovascular disorder, an oxidative stress, and a cancer, comprising at least one dosage form comprising an extended-release oral dosage comprising a therapeutically effective amount of S-adenosyl-L-methionine (SAMe), wherein the extended release dosage provides a quotient $Q = (([SAMe]_T-[SAMe]_0)/C_{max})$, wherein $C_{max} = [SAMe]_{Max}-[SAMe]_0$ and $[SAMe]_{Max}$ is a maximum blood plasma concentration of SAMe in a patient population after administration of SAMe to the patient population, $[SAMe]_0$ is a blood plasma concentration of SAMe immediately prior to administration of SAMe to the patient population and $[SAMe]_T$ is a blood plasma concentration of SAMe at time T after administration of SAMe to the patient population), wherein: Q has a value set forth in any one of claims 1-19.

21. The kit of claim 20, wherein the kit further comprises at least one dosage form selected from the group consisting of an immediate release SAMe dosage and an enterically coated immediate release SAMe dosage.

22. An extended-release oral dosage for administration of S-adenosyl-L-methionine (SAMe) to a patient, said oral dosage comprising a therapeutically effective amount of SAMe, wherein dissolution of the oral dosage in a USP II dissolution apparatus in aqueous buffer having an initial pH of about 6.8, provides: less than about 50% release of SAMe after about 2 hours; less than about 80% release of SAMe after about 4 hours; at least about 50% release after about 8 hours; and at least about 80% release after about 12 hours.

23. An extended-release oral dosage for administration of S-adenosyl-L-methionine (SAMe) to a patient, said oral dosage comprising a therapeutically effective amount of SAMe, wherein the oral dosage is not enterically coated, and wherein dissolution of the oral dosage in a USP II dissolution apparatus in aqueous HCl having an initial pH of about 1, provides: less than about

50% release of SAMe after about 2 hours; less than about 80% release of SAMe after about 4 hours; at least about 50% release after about 8 hours; and at least about 80 % release after about 12 hours.

24. An extended-release oral dosage for administration of S-adenosyl-L-methionine (SAMe) to a patient, said oral dosage comprising a therapeutically effective amount of SAMe, wherein dissolution of the oral dosage in a USP II dissolution apparatus in aqueous buffer at an initial pH of about 6.8, provides: less than about 70% release of SAMe after about 2 hours; less than about 80% release of SAMe after about 4 hours; at least about 40% release after about 8 hours; and at least about 90% release after about 12 hours.

25. An extended-release oral dosage for administration of S-adenosyl-L-methionine (SAMe) to a patient, said oral dosage comprising a therapeutically effective amount of SAMe, wherein the oral dosage is not enterically coated, and wherein dissolution of the oral dosage in a USP II dissolution apparatus in aqueous HCl having an initial pH of about 1, provides: less than about 70% release of SAMe after about 2 hours; less than about 80% release of SAMe after about 4 hours; at least about 40% release after about 8 hours; and at least about 90% release after about 12 hours.

26. An extended-release oral dosage for administration of S-adenosyl-L-methionine (SAMe) to a patient, comprising a therapeutically effective amount of SAMe, liquid paraffin, magnesium aluminometasilicate and 0-6% of an extended-release coating, said extended-release coating optionally comprising a pore former.

27. A kit for administration of S-adenosyl-L-methionine (SAMe) to a patient, comprising at least a first dosage form provided with a first therapeutically effective amount of SAMe and a second dosage form provided with a second therapeutically effective amount of SAMe, wherein said first dosage form is an immediate release dosage optionally comprising an enteric coating, and the second dosage form is an extended release dosage form.

28. The kit of claim 27, wherein dissolution of said first dosage form and said second dosage form in a USP II dissolution apparatus in aqueous buffer having an initial pH of about 6.8, provides: less than about 50% release of SAMe after about 2 hours; less than about 80% release of SAMe after about 4 hours; at least about 50% release after about 8 hours; and at least about 80% release after about 12 hours.

29. The kit of claim 27, wherein dissolution of said first dosage form and said second dosage form in a USP II dissolution apparatus in aqueous HCl having an initial pH of about 1, provides:

less than about 50% release of SAMe after about 2 hours; less than about 80% release of SAMe after about 4 hours; at least about 50% release after about 8 hours; and at least about 80% release after about 12 hours.

30. The kit of claim 27, wherein dissolution of said first dosage form and said second dosage form in a USP II dissolution apparatus in aqueous buffer at an initial pH of about 6.8, provides: less than about 70% release of SAMe after about 2 hours; less than about 80% release of SAMe after about 4 hours; at least about 40% release after about 8 hours; and at least about 90% release after about 12 hours.

31. The kit of claim 27, wherein dissolution of said first dosage form and said second dosage form in a USP II dissolution apparatus in aqueous HCl having an initial pH of about 1, provides: less than about 70% release of SAMe after about 2 hours; less than about 80% release of SAMe after about 4 hours; at least about 40% release after about 8 hours; and at least about 90% release after about 12 hours.

32. The kit of claim 27, wherein the kit comprises an extended release, oral dosage for administration of SAMe to a patient, comprising a therapeutically effective amount of SAMe, liquid paraffin, magnesium aluminometasilicate and 0-6% of an extended-release coating, said extended-release coating optionally comprising a pore former.

Figure 1

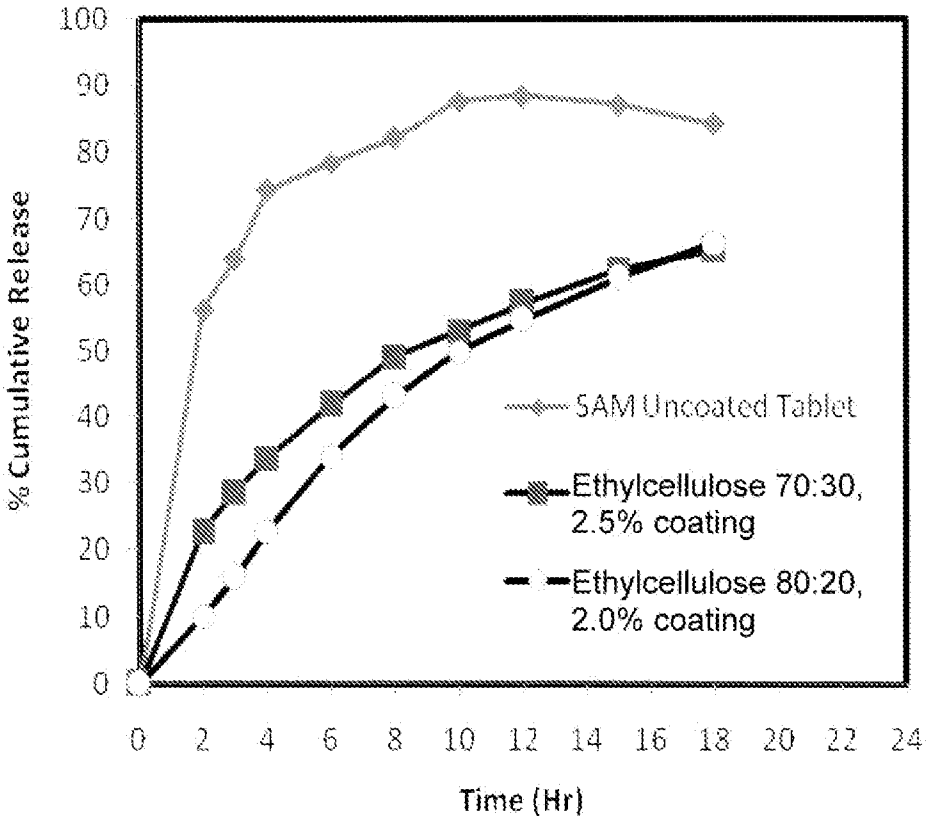

100
90
80
70
60
50
40
30
20
10
0
% Cumulative Release
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (Hr)
5AM Uncoated Tablet
Ethylcellulose 70:30, 2.5% coating
Ethylcellulose 80:20, 2.0% coating

Figure 2

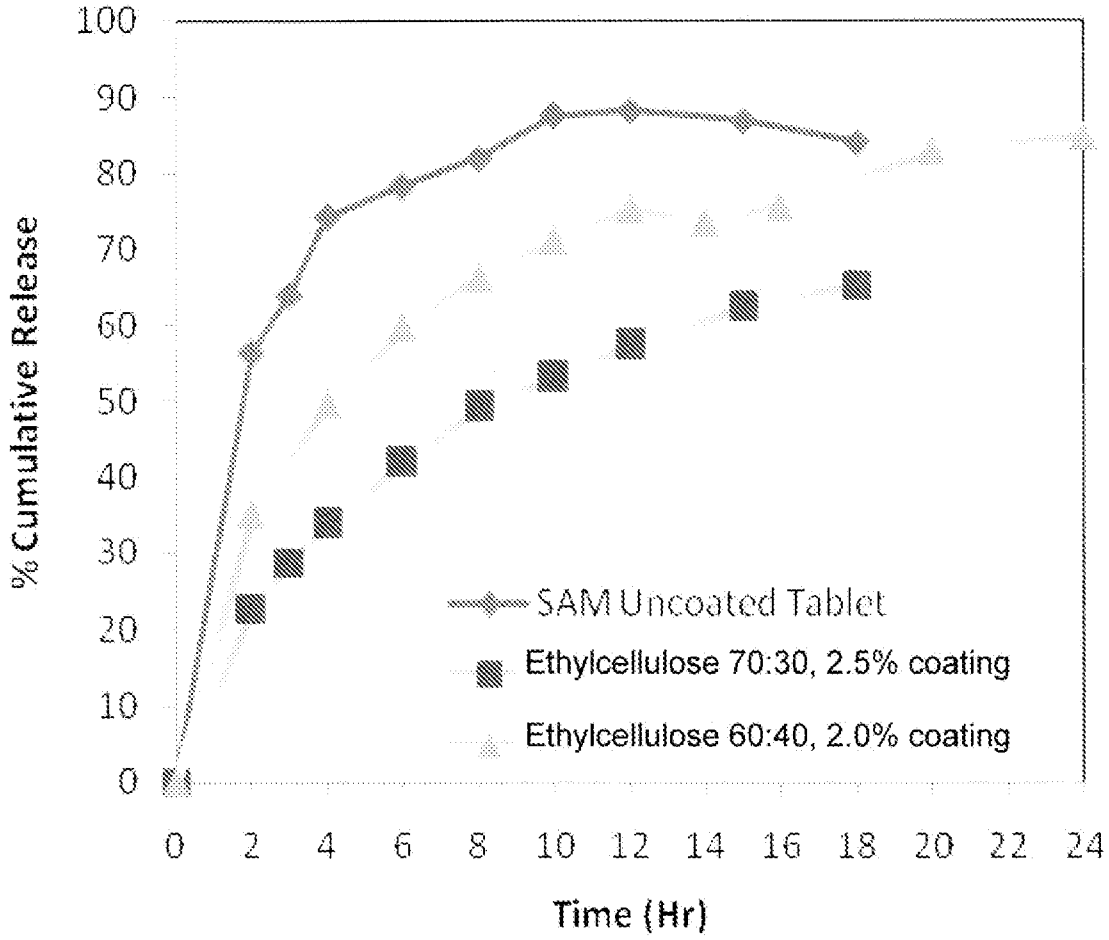

100
90
80
70
60
50
40
30
20
10
0
% Cumulative Release
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (Hr)
SAM Uncoated Tablet
Ethylcellulose 70:30, 2.5% coating
Ethylcellulose 60:40, 2.0% coating

Figure 3

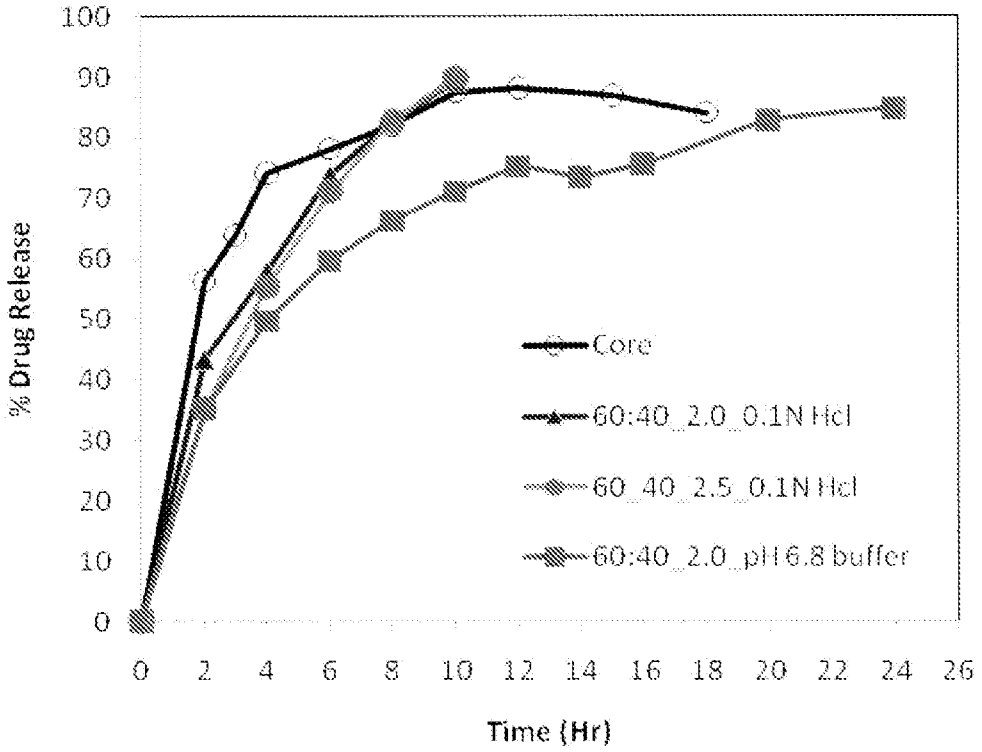

100
90
80
70
60
50
40
30
20
10
0
% Drug Release
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Time (Hr)
Core
60:40_2.0_0.1N Hcl
60_40_2.5_0.1N Hcl
60:40_2.0_pH6.8 buffer

Figure 4

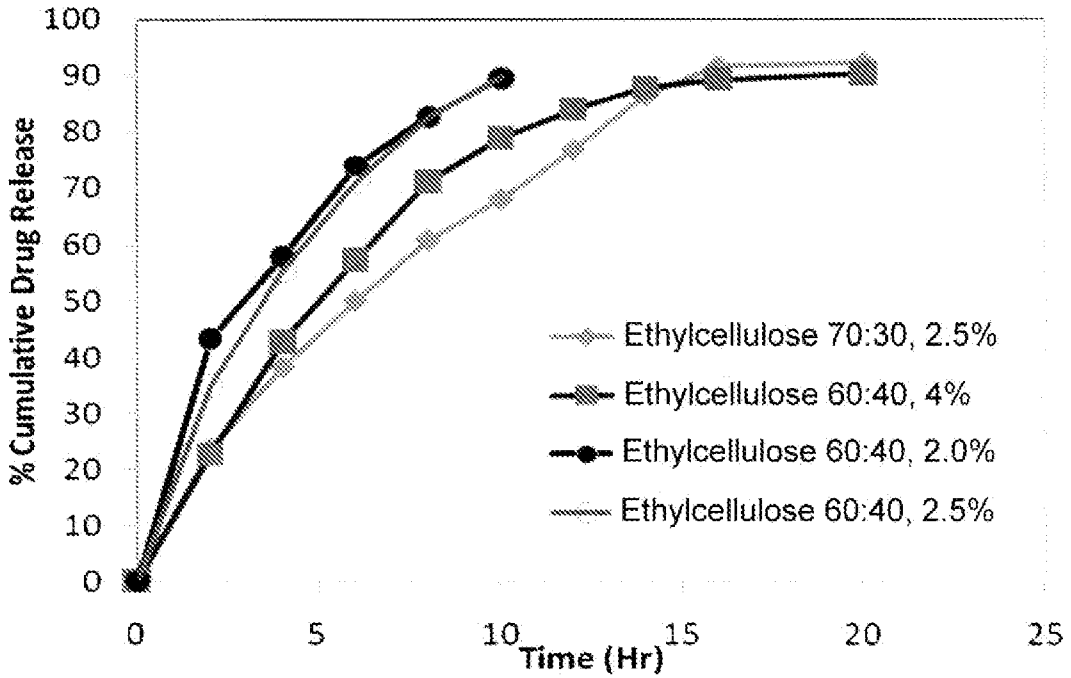

100
90
80
70
60
50
40
30
20
10
0
% Cumulative Drug Release
0
5
10
15
20
25
Time (Hr)
Ethylcellulose 70:30, 2.5%
Ethylcellulose 60:40, 4%
Ethylcellulose 60:40, 2.0%
Ethylcellulose 60:40, 2.5%

Figure 5

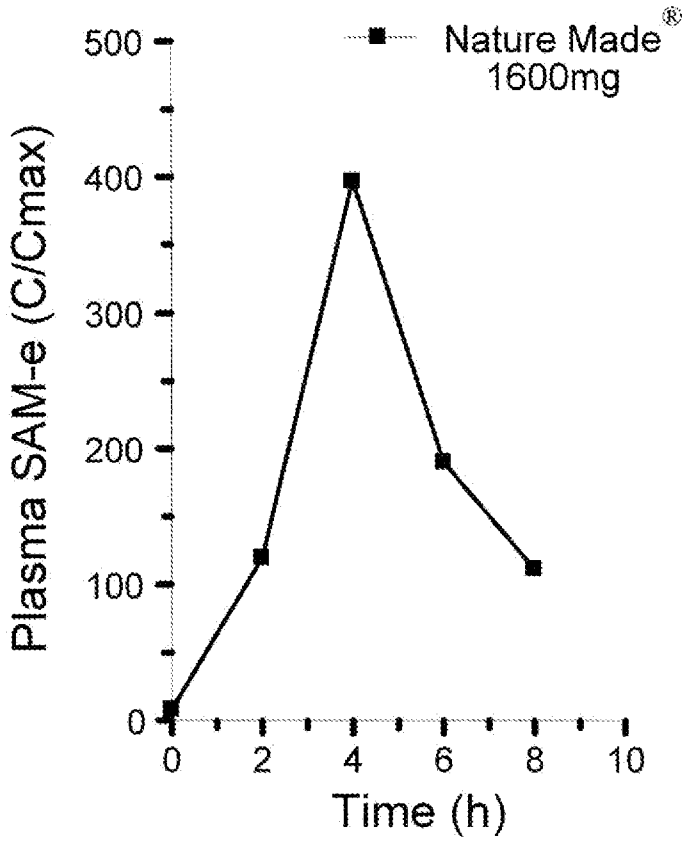

Nature Made®
1600mg
Plasma SAM-e (C/Cmax)
500
400
300
200
100
0
0
2
4
6
8
10
Time (h)

Figure 6

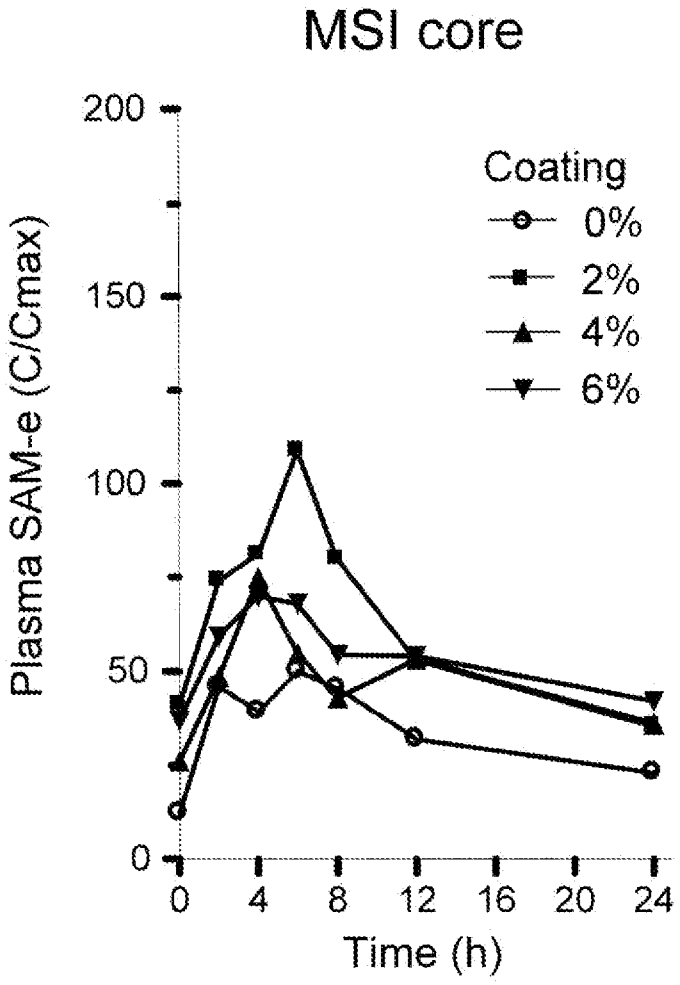

MSI core
Plasma SAM-e (C/Cmax)
200
150
100
50
0
0
4
8
12
16
20
24
Time (h)
Coating
0%
2%
4%
6%

Figure 7

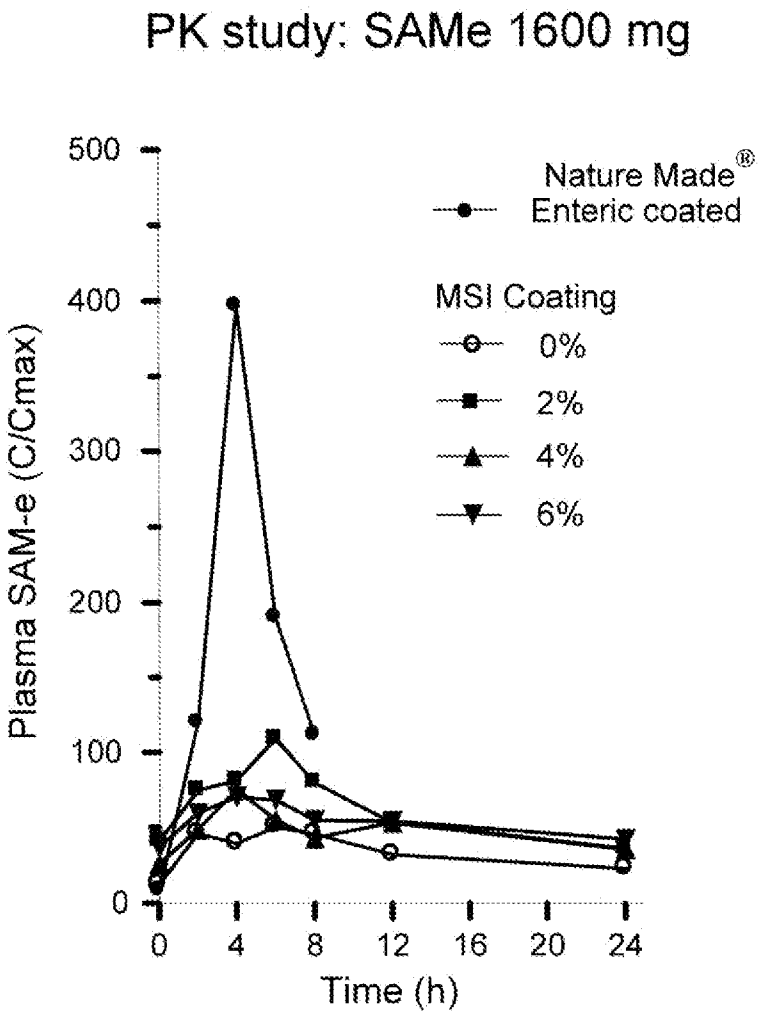
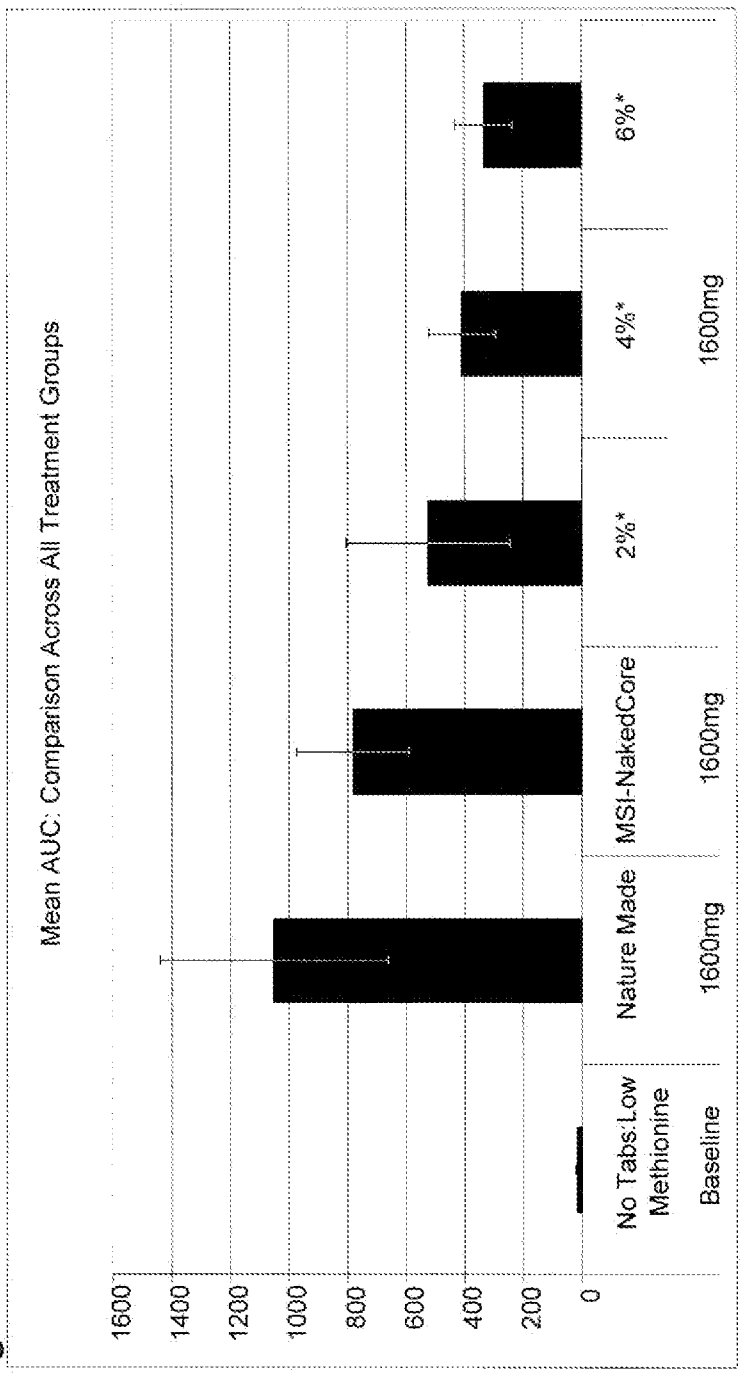

PK study: SAMe 1600 mg
Plasma SAM-e (C/Cmax)
500
400
300
200
100
0
0
4
8
12
16
20
24
Time (h)
Nature Made®
Enteric coated
MSI Coating
0%
2%
4%
6%

Figure 8


Mean AUC: Comparison Across All Treatment Groups
1600
1400
1200
1000
800
600
400
200
0
No Tabs:Low Methionine
Baseline
Nature Made
1600mg
MSI-NakedCore
1600mg
2%*
4%*
6%*
1600mg

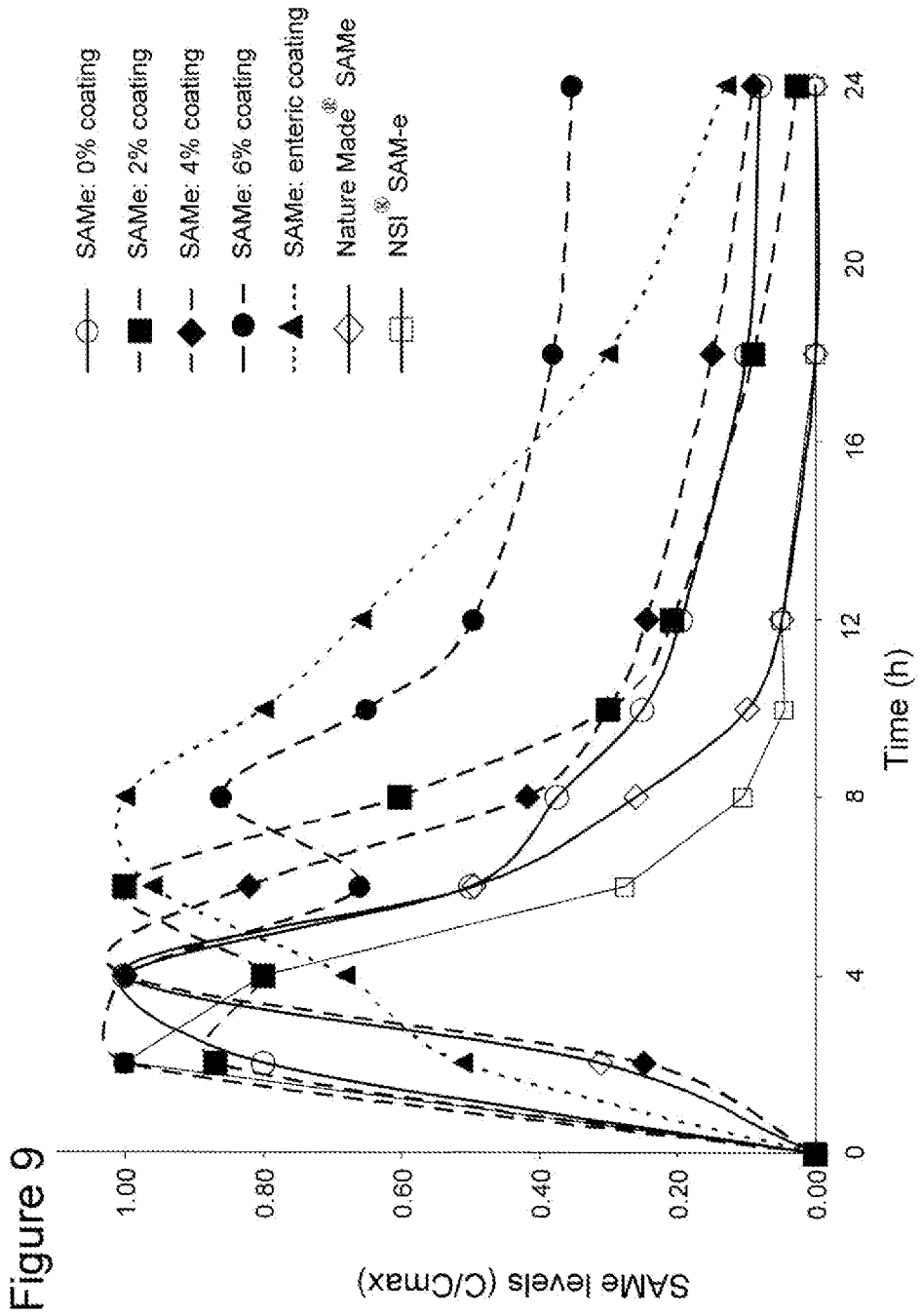

SAMe: 0% coating
SAMe: 2% coating
SAMe: 4% coating
SAMe: 6% coating
SAMe: enteric coating
Nature Made® SAMe
NSI® SAM-e
SAMe levels (C/Cmax)
1.00
0.80
0.60
0.40
0.20
0.00
0
4
8
12
16
20
24
Time (h)

Figure 9

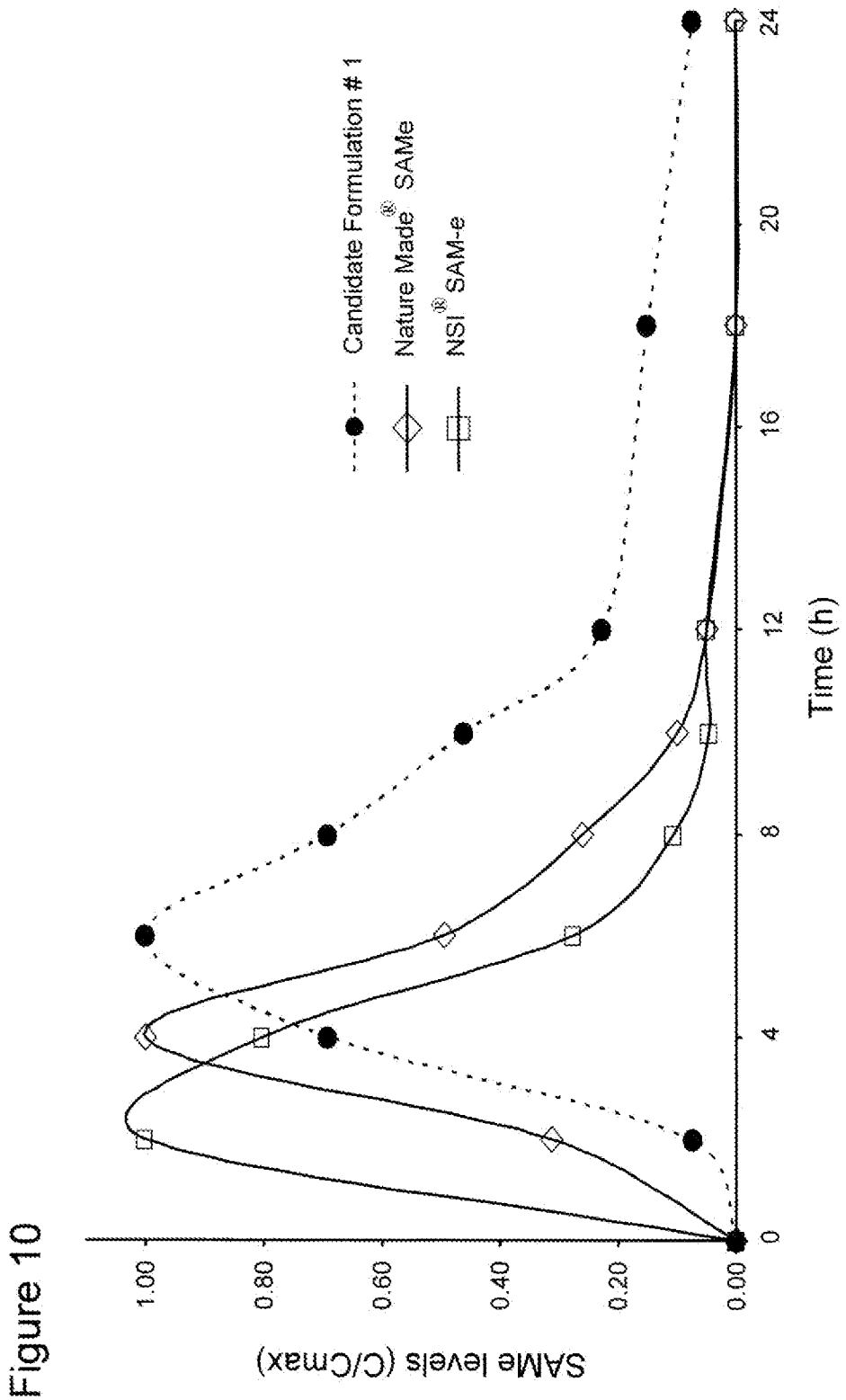

Candidate Formulation # 1
Nature Made® SAMe
NSI® SAM-e
SAMe levels (C/Cmax)
1.00
0.80
0.60
0.40
0.20
0.00
0
4
8
12
16
20
24
Time (h)

Figure 10

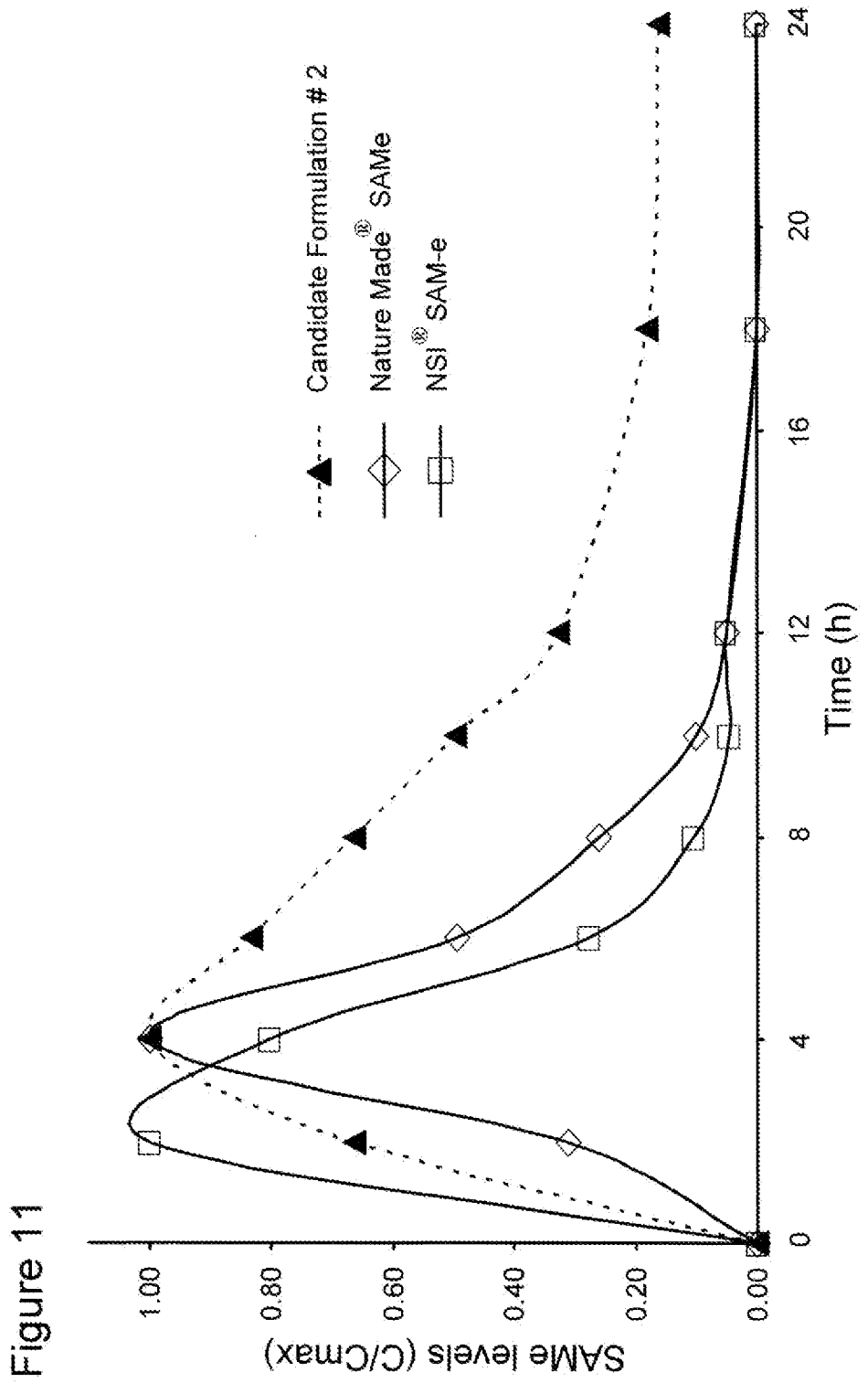

Candidate Formulation # 2
Nature Made® SAMe
NSI® SAM-e
SAMe levels (C/Cmax)
1.00
0.80
0.60
0.40
0.20
0.00
0
4
8
12
16
20
24
Time (h)

Figure 11

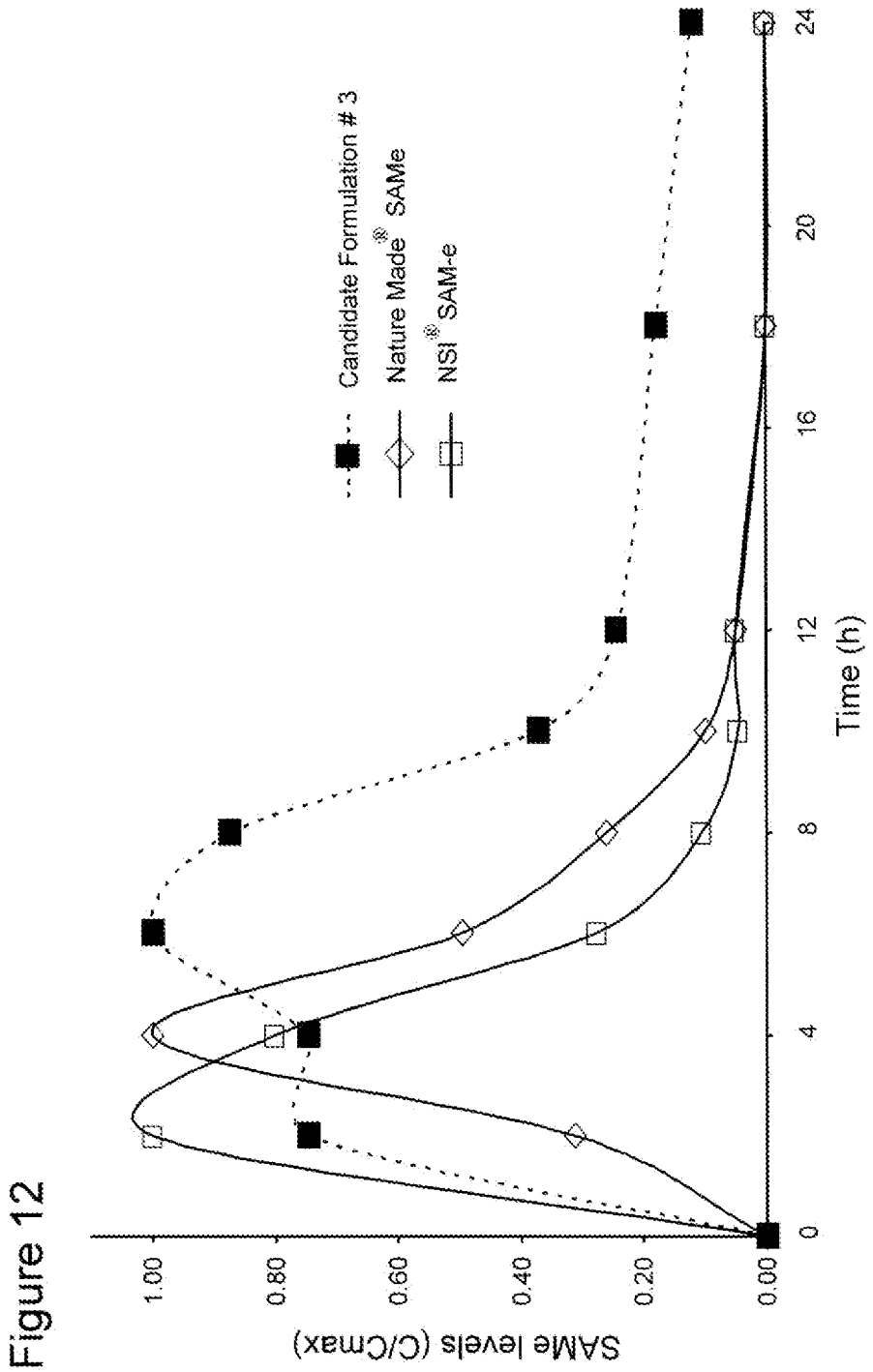

Candidate Formulation # 3
Nature Made® SAMe
NSI® SAM-e
SAMe levels (C/Cmax)
1.00
0.80
0.60
0.40
0.20
0.00
0
4
8
12
16
20
24
Time (h)

Figure 12