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(73) Patenthaver: **Gnosis S.p.A., Piazza Filippo Meda 3, 20121 Milano, Italien**

(72) Opfinder: **GIOVANNONE, Daniele, Viale Mazzini, 120, I-03100 Frosinone, Italien**
DE ANGELIS, Carlo, Via Roma 8, 1-03035 Fontana Liri (FR), Italien

(74) Fuldmægtig i Danmark: **Plougmann Vingtoft A/S, Strandvejen 70, 2900 Hellerup, Danmark**

(54) Benævnelse: **Faste orale sammensætninger baseret på S-adenosyl-methioninsalt og fremgangsmåde til opnåelse deraf**

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DESCRIPTION

[0001] S-adenosyl methionine (SAMe) is a physiological donor of methyl groups present in all living organisms and is involved in enzyme transmethylation reactions.

[0002] This substance therefore has a very important biological role and is essentially used in clinical practice as an antidepressant.

[0003] By "SAMe" is meant both the racemic mixture and the individual diastereoisomers (RS)-(+)-S-adenosyl-L-methionine [(RS)-(+)-SAMe)] and (SS)-(+)-S-adenosyl-L-methionine [(SS)-(+)-SAMe)], as well as mixtures other than the racemic mixture.

[0004] The difficulty of using S-adenosyl methionine as a drug and/or dietetic is however known because it is extremely unstable at temperatures above 0°C or in the presence of moisture, through both degradation of the active ingredient, understood to be the sum of the two diastereoisomers, and through the conversion of active (SS)-(+)-S-adenosyl-L-methionine to inactive (RS)-(+)-S-adenosyl-L-methionine (racemisation of the substance).

[0005] Prior methodology is thought to describe a process for the preparation of pharmaceutically acceptable salts of (SS,RS)-S-adenosyl-L-methionine with quantities of inactive diastereoisomer (RS)-(+)-S-adenosyl-L-methionine of 3% or less with respect to the active diastereoisomer (SS)-(+)-S-adenosyl-L-methionine of 97% or more. The same applies with regard to the need to use racemic mixtures with a high percentage of the active S,S diastereoisomer as this is the only one which is pharmacologically active. However, the patent confirms that although more than 97% of active S,S diastereoisomer is obtained at ambient temperature, the racemic mixture is unstable over time, with conversion of the (SS)-(+)-S-adenosyl-L-methionine into (RS)-(+)-S-adenosyl-L-methionine in a relatively short time.

[0006] Prior known methods are thought to describe a method for stabilising pharmaceutically acceptable salts of S-adenosyl methionine comprising S-adenosyl methionine paratoluene sulphonate, S-adenosyl methionine-1,4-butene disulphonate, S-adenosyl methionine sulphate, S-adenosyl methionine tosylate with a group of substances comprising chitosan, dextrin, carboxymethylcellulose, fumaric acid, azelaic acid and tryptophan. In particular the first of these patents indicates that it is important to have a product with the highest amount of S,S diastereoisomer which is the most stable possible over time because the R,S diastereoisomer is not only inactive but has a pharmacological effect which opposes that of the S,S. However, prior known methods are thought to describe methods for stabilising S-adenosyl methionine salts using the abovementioned substances in a percentage by weight with respect to the active ingredient which is very much higher than 50%, and adding them in reconstituted aqueous solution to S-adenosyl methionine salts, with final lyophilisation. This gives rise to high production costs and very low yields because the % of ions in the final product falls from approximately 50% to approximately 25%.

[0007] Racemisation of the S-adenosyl methionine is linked to three basic parameters:

1. 1. The nature of S-adenosyl-L-methionine salt formation.
2. 2. The residual moisture content in the powder after drying.
3. 3. The temperature at which the product is stored.

[0008] The rate of racemisation of SAMe as a salt of S-adenosyl methionine paratoluene sulphonate differs from the racemisation of SAMe in the form of S-adenosyl methionine-1,4-butene disulphonate salt, or S-adenosyl methionine sulphate or as S-adenosyl methionine tosylate.

[0009] Although they have different pH for the same residual moisture content, these four salts have very different stabilities and racemisation. The reason for this has to be sought in the mechanisms of diastereoisomer degradation and conversion in the various salts.

[0010] It is known that the drier the starting material the more stable the product will be.

[0011] The same consideration applies to rate of racemisation. Theoretically, with zero moisture content, the conversion rate of the S,S diastereoisomer at a given storage temperature is at a minimum.

[0012] It is also known that the rate of degradation and therefore also racemisation is associated with the thermal energy of the material. This is reflected in the fact that the higher the storage temperature for the material, the more rapidly it degrades and racemises.

[0013] If not formulated on the basis of specific procedures and using specific measures, formulations based on S-adenosyl methionine reflect the abovementioned instability and racemisation of the active ingredient, (conversion of the active S,S diastereoisomer into the inactive R,S diastereoisomer), with obvious adverse repercussions for the preservation and storage of the material, even for short periods of time.

[0014] United States Patents US3954726 and US4057686 describe relatively stable salts of S-adenosyl methionine, that is up to 25°C and 45°C, respectively. United States Patent US4465672 also describes stable salts of S-adenosyl methionine with 5 mols of a sulphonic acid with a pK of less than 2.5.

[0015] In this latter United States patent, the process of preparing the product comprises preparation of a concentrated aqueous solution of an impure salt of SAMe, purification of the solution and its elution with a dilute aqueous solution of the preselected sulphonic acid, titration of the resulting eluate, concentration and lyophilisation or spraying. Because of the high instability of SAMe and its derivatives the use of an aqueous environment makes the limitations of this process obvious, and even if residual moisture content is successfully contained it is still unsuitable because of the properties of the inactive ingredient.

[0016] Also these patents do not describe the rate of conversion of the active S,S enantiomer at various operating and storage temperatures for the product. Up to now no methods for stabilising the active (SS)-(+)-S-adenosyl-L-methionine diastereoisomer in acceptable percentages in solid oral formulations, particularly tablets, are known. The only known concept is the need to keep moisture content, impurities and the active (SS)-(+)-S-adenosyl-L-methionine diastereoisomer under strict control, protecting the tablets by either compression or film-forming.

[0017] NADH is an active ingredient normally used as an energising agent and antioxidant. Currently known compositions based on NADH, such as those for example described in United States Patents US5332727 and US7034011 are based on stabilising the active ingredient through association with other antioxidants.

[0018] The International patent application WO00/18259 relates to nutritional and pharmaceutical compositions, which due to the presence of an efflorescent component may be unstable and prone to decomposition and/or spoilage. The problem is overcome by incorporating one or more anhydrous compounds into the composition in an amount capable of sequestering any water which may be released from one or more water containing components. The preferred anhydrous compounds are anhydrous or calcined MgSO4 and CaO.

[0019] The International patent application WO2005/027932 refers to solid preparations obtained by formulating of 5-aminosalicylic acid or its salt and a discoloration preventive agent into medical preparations, which solid preparations exhibit in CIELAB color space a color difference of 10.5 or less brought about by storage at 80 DEG C for one week. The above discoloration preventive agent is characterized by containing at least one member selected from the group consisting of a thiol compound, a sulfide compound, an acid anhydride and hygroscopic compounds

[0020] The International patent application WO2005/084670 describes compositions which stabilize an active pharmaceutical ingredient in polymorph form susceptible to degradation or interconversion into other polymorph forms, wherein the stabilizing substance is selected among silicon dioxide, silicified microcrystalline cellulose, magnesium oxide and polyethylene glycol.

[0021] The United States of America patent US3012943 relates to vitamin C or ascorbic acid and, more particularly, to a method for the concentrating of vitamin C from acerola cherries and to the novel vitamin C concentrates thereby produced.

[0022] The International patent application WO03/043608 describes a process for the preparation of tablets comprising S-adenosylmethionine which comprises blending S-adenosylmethionine with calcium sulfate and/or phosphate, calcium and/or magnesium carbonate, glycerol behenate and or palmitostearate and silica and compressing the resulting mixture. EP0162323A1 relates to new stable sulpho-adenosyl-L-methionine (SAMe) salts, in particular it relates to salts deriving from the reaction between SAMe and disulphonic acids, their production process, and pharmaceutical compositions which contain them as active principles. US4465672A discloses a new class of S-adenosylmethionine (SAM) salts which are highly

stable at elevated temperatures and for practically indefinite time periods.

[0023] US3954726 relates to double salts of S-adenosyl methionine (SAMe) with sulphuric acid and para-toluene sulphonic acid, such as di-sulphate di-p-toluenesulphonate salt and the di-sulphate mono-p.toluenesulphonate salt of SAMe.

[0024] There has therefore hitherto been felt a need to identify a simple and economic process which will make it possible to obtain a product based on SAMe with the removal of moisture and low hygroscopic properties, with as a consequence increased stability in terms of both the active ingredient and reduced racemisation in favour of stabilisation of the reduced (S,S) enantiomer.

[0025] Surprisingly it has been found that the addition of calcium oxide brings about improved stability of both the SAMe, regarded as the sum of the two S,S and R,S diastereoisomers, and the (S,S) diastereoisomer through reducing the water content of the SAMe and by reducing its hygroscopic properties, further favouring synergistic antidepressant action through the provision of calcium.

[0026] Calcium oxide directly mixed with atomised SAMe or with solid formulations based on SAMe are successful in removing water through a chemical reaction with the powder or the preparation itself.

[0027] In fact no other excipients which succeed in removing moisture in direct mixture with the powder and/or preparations of SAMe over time at relatively lower temperatures (15 - 20°C), reaching values of close to zero, are known.

[0028] The main reason is due to the highly hygroscopic nature of the SAMe which is even greater than that of substances which are well known as excellent desiccants such as silica gel, calcium chloride and others. This means that by mixing SAMe with excipients having a moisture content of close to zero, the residual water in mixtures and/or preparations based on SAMe is the same in absolute terms as that present in the initial SAMe powder. As a consequence there is only a percentage reduction in moisture content in the preparations through the dilution effect, but the same percentage by weight of water with respect to the weight of SAMe used. For this reason, in a direct mixture and/or SAMe preparations, it has never hitherto been possible to achieve higher stability of the active ingredient, and therefore a reduced racemisation rate, than that of the starting material, but at the limit this stability can be achieved.

[0029] Calcium oxide is instead a natural desiccant with very high reactivity in relation to water. It reacts with it and changes to a calcium hydroxide, eliminating it permanently in preparations.

$$CaO + 2H_2O \rightarrow Ca(OH)_2$$

[0030] Figure 1 shows the rate of absorption of H_2O with different absorbent substances

including calcium oxide.

[0031] It will be seen that calcium oxide absorbs slowly but constantly up to 28% of its weight.

[0032] Figure 2 shows the absorption capacity for water vapour of various desiccants as the environmental humidity (RH) varies.

[0033] In this case it will be seen that calcium oxide absorbs approximately 28% of water in a highly reactive way in an environment with a very low relative humidity.

[0034] Table 1 summarises the absorbent capacities of various desiccants under different relative humidity and temperature conditions.

Table 1:

Properties of adsorbents

Property	Molecular sieve	Silica gel	Montmorillonite clay	CaO	$CaSO_4$
Adsorption capacity at low concentrations of H_2O	Excellent	Poor	Slight	Excellent	Good
Absorption ratio	Excellent	Good	Good	Poor	Good
Capacity for water @77° F. 40% RH	High	High	Medium	High	Low
Separation by molecular dimensions	Yes	No	No	No	No
Adsorption capacity at high temperatures	Excellent	Poor	Poor	Good	Good

[0035] Specifically the shape of the two Figures 1 and 2 and the summary values in Table 1 demonstrate that calcium oxide is the only substance which is consistently capable of removing the very small quantities of residual moisture content of SAMe (approximately 1 - 1.5 % K.F. /approximately 5 - 7 % K.F.) by chemical conversion purely by physical contact, reducing it to values close to zero.

[0036] This therefore reduces the second instability factor in SAMe, or its salts, because of the high rate of racemisation of its active S,S diastereoisomer.

[0037] Table 2 provides moisture content values for five lots of starting material of SAMe (S-adenosyl methionine paratoluene sulphonate) with its corresponding analysis prior to mixing with calcium oxide and storage at 20°C for 21 days, and the relative accelerated stability at 53°C for 5 days.

Table 2:									
stress test 5 days at 53 °C									
Lot	Moisture content % K.F. t=0	Moisture content % K.F. t= 21days at 20 °C	% S,S t=0	SAMe titre % t=0	Total impurities % t=0	Moisture content% K.F.	% S,S	SAMe titre %	Total impurities %
001	1.15	1.13	80.87	52.96	0.66	1.09	56.21	51.19	5.17
002	1.08	1.05	80.02	51.98	0.73	1.05	56.31	50.84	5.54
003	1.06	1.03	80.21	52.76	1.03	1.03	56.12	50.11	4.55
004	1.09	1.09	79.82	52.23	0.94	0.99	55.79	49.58	4.34
005	1.04	1.12	81.54	52.29	1.04	1.00	55.28	49.99	5.02

[0038] Table 3 shows moisture content values for five lots of starting material of SAMe (S-adenosyl methionine paratoluene sulphonate) with its corresponding analysis after mixing with calcium oxide and storage at 20°C for 21 days, and the relative accelerated stability at 53°C for 5 days.

Table 3:									
Stress test 5 days at 53 °C									
Lot	Moisture content % K.F. t=0	Moisture content % K.F. t= 21days at 20 °C	% S,S t=0	SAMe titre % t=0	Total impurities % t=0	Moisture content% K.F.	% S,S	SAMe titre %	Total impurities %
001	0.98	0.63	80.67	50.22	0.66	0.43	66.47	50.09	3.17
002	1.16	0.55	80.32	50.02	0.73	0.41	65.43	50.00	2.78
003	1.00	0.70	80.11	50.16	1.03	0.39	66.56	49.81	2.65
004	1.04	0.59	79.99	50.23	0.94	0.35	65.79	49.98	2.89
005	0.95	0.61	81.23	50.19	1.04	0.38	67.25	49.87	3.02

[0039] Table 4 shows moisture content values for five lots of starting material of SAMe (S-adenosyl methionine-1,4-butene disulphonate) with corresponding analysis prior to mixing with calcium oxide and storage at 20°C for 21 days, and the relative accelerated stability at 53°C for 5 days.

Table 4:

Stress test 5 days at 53 °C

Lot	Moisture content % K.F. t=0	Moisture content % K.F. t= 21 days at 20 °C	% S,S t=0	SAMe titre % t=0	Total impurities % t=0	Moisture content% K.F.	% S,S	SAMe titre %	Total impurities %
001	2.03	2.03	84.58	51.34	0.44	2.09	59.43	50.94	4.06
002	2.01	2.31	85.34	51.54	0.56	2.21	60.02	50.93	4.23
003	1.98	1.99	83.89	52.34	0.45	2.00	60.32	51.03	4.05
004	1.89	1.99	84.82	52.02	0.67	1.96	59.49	51.72	4.63
005	1.94	2.02	85.34	51.78	0.64	1.93	58.98	50.79	4.47

[0040] Table 5 shows moisture content values for five lots of starting material of SAMe (S-adenosyl methionine-1,4-butene disulphonate) with corresponding analysis after mixing with calcium oxide and storage for 23°C for 21 days, and the relative accelerated stability at 53°C for 5 days.

Table 5:

Stress test 5 days at 53 °C

Lot	Moisture content % K.F. t=0	Moisture content % K.F. t= 21 days at 20 °C	% S,S t=0	SAMe titre % t=0	Total impurities % t=0	Moisture content % K.F.	% S,S	SAMe titre %	Total impurities %
001	1.94	1.33	84.21	50.01	0.49	0.78	70.34	50.00	2.03
002	1.89	1.45	85.02	49.78	0.50	0.87	70.02	50.01	1.98
003	1.87	1.27	83.49	50.12	0.49	0.93	71.32	49.89	2.00
004	1.80	1.38	84.54	50.34	0.57	0.81	71.89	50.04	2.13
005	1.84	1.40	85.25	50.08	0.53	0.88	70.94	50.00	1.35

[0041] From the data shown in Tables 2, 3, 4, 5 it will be seen that the mixture of calcium oxide in combination with SAMe (S-adenosyl methionine paratoluene sulphonate and S-adenosyl methionine-1,4-butene disulphonate) causes the stability of the material at 53°C for 5 days to increase with permanent removal of approximately 40% of the moisture content when the mixture is stored for 21 days at 20°C, and approximately 60% after the stress test at 53°C for 5 days.

[0042] Thus, one object of this invention relates to compositions comprising S-adenosyl methionine sulphate paratoluene sulphonate or S-adenosyl methionine-1,4-butane disulphonate

in association with calcium oxide and optionally pharmaceutically acceptable excipients.

[0043] According to this disclosure, by "SAMe" is meant both the racemic mixture and the individual (RS)-(+)-S-adenosyl-L-methionine [(RS)-(+)-SAMe)] and (SS)-(+)-S-adenosyl-L-methionine [(SS)-(+)-SAMe)] diastereoisomers, including the mixtures other than the racemic mixture. In particular, the compositions according to this invention contain S-adenosyl methionine sulphate paratoluene sulphonate or S-adenosyl methionine-1,4-butane disulphonatein a quantity varying from 30 and 90% by weightwith respect to the weight of the composition,preferably from 50 to 85% by weight with respect to the weight of the composition.. Preferably, in the composition according to the invention the calcium oxide is present in a quantity varying from 1 to 40% by weight with respect to the weight of the composition, preferably from 2 to 20% by weight with respect to the weight of the composition.

[0044] Preferably the said SAMe, or its salts, is S-adenosyl methionine sulphate paratoluene sulphonate or S-adenosyl methionine-1,4 butane disulphonate. The pharmaceutically acceptable excipients used according to this invention are preferably selected from calcium sulphate hemihydrate and/orglucono-delta-lactone.

[0045] Compositions according to this invention may optionally comprise at least one further active ingredient, preferably selected from 1-melatonin, 1-theanine and/or 1-tryptophan and/or 5-hydroxytryptophan or their mixtures. The compositions according to this invention may be in the form of a direct mixture, tablets, capsules, granules and/or powder. In this invention by direct mixture is meant a mixture of atomised powder of SAMe or their salts, in association with calcium oxide without the addition of other excipients.

[0046] Preferably, the compositions according to this invention are in the form of tablets, more preferably in the form of ordinary, coated, film-coated and/or gastroresistant tablets.

[0047] In this invention, by ordinary tablet is meant a tablet obtained by direct compression or compression after granulation without coating; by coated tablet is meant a tablet coated with non-gastroresistant substances; by film-coated tablet is meant a coated tablet which is further covered with water-based varnishes, which varnishes may have a gastroresistant action.

[0048] Thus, the compositions according to this disclosure may be film-coated with water-based varnishes preferably selected from gum Lac (Shellac™) and/or its salts, methacrylic acid, cellulose acetophthalates, titanium dioxide, talc, triethyl citrate, PVP K30, curcumin, lutein, hydroxypropylcellulose, hydroxypropylmethylcellulose and/or mixtures thereof.

[0049] By gastroresistant tablets according to this invention are meant tablets capable of passing unchanged through the gastric barrier.

[0050] The said film coating with varnishes, when provided through Shellac™, salts, cellulose acetophthalates and/or other coatings which are insoluble in an acid environment, may render the compositions according to the invention resistant to passage through the stomach. The varnishes according to this disclosure may be present in a quantity varying from 1.0 to 1.98% by

weight with respect to the composition.

[0051] The compositions according to this disclosure have approximately 60% less moisture content (KF) than the compositions based on SAMe known hitherto and are approximately 12 times less hygroscopic than shown in Table 6 above.

Table 8

Known tablets based on SAMe SAMe 400 mg tablets	Known tablets based on SAMe SAMe 400 mg tablets	SAMe/CaO tablets (Example 1)	SAMe/CaO tablets (Example 1)
KF% T=0	KF% T=24h*	KF% T=0	KF% T=24h*
Lot 01 1.24	3.76	0.45	0.76
Lot 02 1.21	3.87	0.51	0.68
Lot 03 1.10	3.98	0.52	0.70
Lot 04 1.33	3.75	0.43	0.64
Lot 05 1.39	3.76	0.57	0.74
at 40°C. -75Rh KF (moisture content according to the Karl Fischer method) T = time			

[0052] The compositions according to this disclosure are preferably intended for the treatment of depressive states.

[0053] A further object of this invention is a process for the preparation of tablets according to the invention, comprises the following stages:

1. a) mixing S-adenosyl methionine sulphate paratoluene sulphonate or S-adenosyl methionine-1,4-butane disulphonate with calcium oxide and pharmaceutically acceptable excipients,
2. b) precompression and subsequent granulation of the mixture obtained in stage a),
3. c) mixing of the granulate obtained in stage b) with pharmaceutically acceptable excipients such as calcium sulphate hemihydrate, xylitol, malic acid, glutamic acid, magnesium oxide, hydrogenated fatty acids, precipitated silica, magnesium stearate, saccharose, glycerol behenate,
4. d) compression of the mixture obtained in stage c), with the optional addition of sweeteners and/or flavourings,
5. e) optional coating of the tablet obtained in stage d) with hydrogenated fatty acids,
6. f) optional aqueous phase film-forming on the tablet obtained in stage e).

[0054] The process according to this disclosure is carried out in an environment in which the relative humidity lies below 20% and the temperature is held between 18 and 25°C, preferably around 20°C.

[0055] Granulation according to this disclosure is preferably carried out using a rotating blade granulator fitted with a stainless mesh having holes of between 1.2 mm and 3.2 mm in diameter.

[0056] SAMe, or its salts, is used in a quantity varying from 30 to 90% by weight, preferably from 50 to 85% by weight, with respect to the weight of the composition.

[0057] In particular, the pharmaceutically acceptable excipients used in the process are preferably selected from calcium sulphate hemihydrate, magnesium oxide, calcium carbonate, malic acid, glutamic acid, xylitol, saccharose, anhydrous microcrystalline cellulose, hydrogenated fatty acids, magnesium stearate, glycerol behenate, precipitated silica.

[0058] More particularly, in step a) the active ingredient is preferably mixed with calcium oxide from approximately 1.0 to approximately 10% by weight and/or magnesium stearate from approximately 0.5 to approximately 5% by weight and/or precipitated silica from approximately 0.5 to approximately 2.0% by weight calculated with respect to the active ingredient.

[0059] In stage c), the granulate obtained in b) is preferably mixed with magnesium hydroxide from approximately 1.0 to 10.0% by weight and/or microcrystalline cellulose from approximately 1.0 to approximately 20.0% by weight and/or hydrogenated fatty acids from approximately 1.0 to approximately 10% by weight and/or malic acid from approximately 1 to approximately 10% by weight and/or glutamic acid from approximately 1 to approximately 10% by weight and/or glucono-delta-lactone from approximately 1 to approximately 10% by weight, magnesium stearate from approximately 0.5 to approximately 5% by weight and/or glycerol behenate from approximately 1.0 to approximately 5.0% calculated with respect to the active ingredient.

[0060] Optionally, in said stage c) of the process according to the invention at least one further active ingredient preferably selected from 1-melatonin, 1-theanine and/or 1-tryptophan and/or 5-hydroxytryptophan and/or their mixtures may be added to the mixture.

[0061] At stage e) coating with hydrogenated fatty acids, preferably molten hydrogenated vegetable fatty acids, may be performed using conventional processes known in the art, with if appropriate the addition of surfactants which are miscible in the oily liquid.

[0062] According to this invention the coating mentioned in stage e) is applied using hydrogenated fatty acids, in a quantity of between 0.4 and 1.5% by weight with respect to the weight of the tablet.

[0063] Preferably in the process according to the present invention the aqueous phase film-forming mentioned in stage f) is performed using a varnish preferably selected from gum Lac and/or its salts (Shellac™), methacrylic acid, cellulose acetophthalates, titanium dioxide, talc, triethyl citrate, PVP K30, curcumin, lutein, hydroxypropylcellulose, hydroxypropylmethylcellulose and/or mixtures thereof.

[0064] In particular the said film-forming may be carried out using substances preferably

selected from gum Lac (Shellac™) and/or its salts.

[0065] A further object of this invention is the use of S-adenosyl methionine sulphate paratoluene sulphonate or S-adenosyl methionine-1,4-butane disulphonate in association with calcium oxide for the preparation of a composition for the treatment of depressive states.

[0066] Preferably in said compositions magnesium oxide is further added to the said calcium oxide.

[0067] A further object are compositions obtained through the process of the present invention.

[0068] Yet a further object of this invention is a method for stabilising a composition based on S-adenosyl methionine sulphate paratoluene sulphonate or S-adenosyl methionine-1,4-butane disulphonate comprising the use of the mixture of S-adenosyl methionine sulphate paratoluene sulphonate or S-adenosyl methionine-1,4-butane disulphonate with calcium oxide.

[0069] A preferred object is a method in which S-adenosyl methionine sulphate paratoluene sulphonate or S-adenosyl methionine-1,4-butane disulphonate is present in a quantity of between 30 and 90% by weight calculated in relation to the weight of the composition, preferably between 50 and 85% by weight calculated in relation to the weight of the composition. Preferably in said method the calcium oxide is present in a quantity which varies from 1 to 40% by weight with respect to the weight of the composition, preferably from 2 to 20% by weight with respect to the weight of the composition.

[0070] Preferably, said method comprises the addition of pharmaceutically acceptable excipients.

EXAMPLES

EXAMPLE 1

TABLETS OF 400 mg SAMe ion/tablet

[0071] Composition based on SAMe sulphate p-toluene sulphonate

A. SAMe sulphate p-toluene sulphonate	800.00 mg
B Calcium oxide	70.00 mg
C. Magnesium hydroxide	80.00 mg
D. Saccharose	100.00 mg
E. Calcium carbonate	80.00 mg

F. Magnesium stearate	20.00 mg
G. Malic acid	40.00 mg
E. Hydrogenated fatty acid	50.00 mg
Total weight of core	1240.00 mg
F. Hydrogenated vegetable fatty acids	4.00 mg
G. Shellac®	30.00 mg
H. PVP K 30	6.0 mg
I. Titanium dioxide	5.00 mg
L. Talc	10.00 mg
M. Triethyl citrate	5.00 mg
N. Curcumin	0.050 mg
Total weight of tablet	1300.50 mg

1.1. Mixing

[0072] The working environment was conditioned to a temperature of 20°C and a relative humidity value of approximately 20% RH. A, B, C, D, E and G and 50% of F were then transferred to the mixer in the quantities indicated above, leaving them with stirring for approximately 30 minutes. At the end of this operation the resulting mixture was transferred to dry containers, always controlling moisture content and temperature.

1.2. Precompression

[0073] Precompression of the mixture was effected using a rotary machine equipped with round punches of 25.0 mm. The hardness of the tablets produced had to be regulated to subsequently produce a granulate having good flow characteristics.

1.3 Granulation

[0074] The tablets produced during the first processing stage were granulated on a 1000-1500 µm mesh, again in a humidity-controlled environment.

1.4 Mixing

[0075] The granulate obtained in stage 1.3 was transferred into the mixer, adding magnesium

stearate and leaving it with stirring for approximately 30 minutes. At the end of this operation the resulting mixture was transferred into dry containers.

1.5 Compression

[0076] Final compression of the granulate was carried out using a rotary machine equipped with oblong punches of 21.0 × 9.8 mm adjusting the weight to 1240 mg/tablet and the compression force to at least 25 KP. The tablets produced had a hardness of between 25 and 35 Kp.

[0077] Friability: ≤ 1.0%; disaggregation time: ≤ 15 minutes (measured using the method described in U.S.P. 24th ed.)

[0078] Moisture content according to K.F. ≤ 1.50%

[0079] Stability tests on uncoated tablets were performed at only 40°C and 75% RH for six months and for a single lot because this is not a finished product. The samples were stored in alu/alu blisters.

Table 9

Lot 001 - cores of 400 mg ion/tablet (qualitative/quantitative composition in Example 1)					
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]
001 (20/0)	0.66	79.9	0.21	0.43	409.98
001A (40/1)	0.56	75.7	0.33	0.67	409.58
001B (40/3)	0.44	72.5	0.54	0.78	407.02
001C (40/6)	0.35	70.3	0.76	0.98	404.78
Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; SAMe sulphate p-toluene sulphonate (mg/tablet);					

[0080] The data in Table 9 show that the tablets have optimum stability.

1.6: Tablet coating

[0081] The tablets resulting from the preceding processing stages were coated in a bowl with a mixture of hydrogenated fatty acids (4.0 mg/tablet). Hydrogenated fatty acid melting at 70°C was placed in a glass container of 2.0 litres and the temperature of the mixture was raised to

approximately 75°C obtaining a homogeneous fused mass.

[0082] After the bowl had been preheated to approximately 65°C, approximately 250 kg of tablets were added and allowed to heat up to 60°C. The cores were then protected by causing the previously prepared fused mass to adhere to the moving tablets. The cores so treated were again left at 60°C for approximately 3 minutes, until the waxy layer had been completely cleaned from the basket of the bowl.

1.7: Film-forming on the tablets

[0083] Shellac™ and PVP were dissolved in a container of suitable size until a solution of 20% w/v was obtained, and triethyl citrate was added slowly with constant stirring.

[0084] In another steel container again fitted with a stirrer, talc, titanium dioxide and curcumin were dispersed in 4.0 1 of deionised water. The resulting suspension was poured into the Shellac™ solution, washing the container with approximately 1.0 l of deionised water, subsequently diluting with a further 4.0 l of deionised water.

[0085] During the first coating stage the temperature of the cores was held at 54°C for approximately 40 minutes, and this was then reduced in regular steps down to a value of 45°C in the final stage.

[0086] After coating of the protected cores was complete, they were allowed to dry for a further 10 minutes, again at 45°C. Finally reduction in the temperature to 42-43°C was awaited so that emptying of the bowl could begin, taking care to store the tablets in suitable envelopes which were impermeable to moisture. No increase in percentage water content was observed in the tablets produced in this way. All the checks specified by the quality specifications were also carried out on these.

EXAMPLE 2

TABLETS OF 400 mg SAMe ion/tablet

[0087] Compositions based on SAMe sulphate p-toluene sulphonate

A. SAMe sulphate p-toluene sulphonate	800.00 mg
B. L- melatonin	2.00 mg
C Calcium oxide	70.00 mg
D. Magnesium hydroxide	100.00 mg
E. Calcium sulphate hemihydrate	100.00 mg

F. Calcium carbonate	160.00 mg
G. Magnesium stearate	20.00 mg
H. Malic acid	40.00 mg
I. Hydrogenated fatty acid	40.00 mg
Total weight of core	1332.00 mg
L. Hydrogenated vegetable fatty acids	4.00 mg
M. Shellac®	30.00 mg
N. PVP K 30	6.0 mg
O. Titanium dioxide	5.00 mg
P. Talc	10.00 mg
Q. Triethyl citrate	5.00 mg
R. Curcumin	0.050 mg
Total weight of tablet	1302.50 mg

[0088] The quantities relate to the preparation of a standard industrial lot of 250.00 kg of tablets.

[0089] The tablets were prepared in the manner described in Example 1 using the components and quantities indicated above.

Table 10

Lot 002 - cores of 400 mg/ion/tablet (qualitative/quantitative composition in Example 2)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	L-melatonin mg
002 (20/0)	0.71	81.2	0.29	0.39	413.11	2.04
002A (40/1)	0.50	76.8	0.35	0.58	410.21	2.03
002B (40/3)	0.52	73.0	0.49	0.65	411.54	2.03
002C (40/6)	0.42	71.0	0.79	0.83	409.40	2.01
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

[0090] The data in Table 10 indicate that the tablets have optimum stability.

EXAMPLE 3

TABLETS OF 400 mg SAMe ion/tablet

[0091] Composition based on SAMe sulphate p-toluene sulphonate

A. SAMe sulphate p-toluene sulphonate	800.00 mg
B. L-theanine	200.00 mg
C Calcium oxide	70.00 mg
D. Magnesium hydroxide	100.00 mg
E. Xylitol	50.00 mg
F. Calcium carbonate	100.00 mg
G. Microcrystalline cellulose	60.00 mg
H. Magnesium stearate	20.00 mg
I. Malic acid	40.00 mg
L. Hydrogenated fatty acid	40.00 mg
Total weight of core	1480.00 mg
M. Hydrogenated vegetable fatty acids	4.00 mg
N. Shellac®	30.00 mg
O. PVP K 30	6.0 mg
P. Titanium dioxide	5.00 mg
Q. Talc	10.00 mg
R. Triethyl citrate	5.00 mg
S. Hydroxypropylmethylcellulose	10.00 mg
T. Curcumin	0.050 mg
Total weight of tablet	1550.05 mg

[0092] The quantities relate to the preparation of a standard industrial lot of 250.00 kg of tablets.

[0093] The tablets were prepared in the manner described in Example 1 using the components and quantities indicated above.

Table 11

Lot 003 - cores of 400 mg ion/tablet (qualitative/quantitative composition in Example 3)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	L-theanine
003 (20/0)	0.59	80.4	0.23	0.34	411.32	204.54

Lot 003 - cores of 400 mg ion/tablet (qualitative/quantitative composition in Example 3)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	L-theanine
003A (40/1)	0.53	76.6	0.32	0.61	410.54	203.54
003B (40/3)	0.45	73.4	0.45	0.72	410.02	203.01
003C (40/6)	0.37	71.3	0.69	0.88	407.56	201.92
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

[0094] The data in Table 11 show that the tablets have optimum stability.

EXAMPLE 4

TABLETS OF 400 mg SAMe ion/tablet

[0095] Composition based on SAMe sulphate p-toluene sulphonate

A. SAMe sulphate p-toluene sulphonate	800.00 mg
B Calcium oxide	70.00 mg
C. Magnesium hydroxide	100.00 mg
D. Calcium carbonate	150.00 mg
E. Magnesium stearate	20.00 mg
F. Malic acid	40.00 mg
G. Hydrogenated fatty acid	40.00 mg
Total weight of core	1220.00 mg
H. Hydrogenated vegetable fatty acids	8.00 mg
I. Hydroxypropylmethylcellulose	30.00 mg
L. PVP K 30	6.0 mg
M Titanium dioxide	5.00 mg
N. Talc	10.00 mg
O. Triethyl citrate	5.00 mg
P. Curcumin	0.050 mg
Total weight of tablet	1284.05 mg

[0096] The quantities relate to the preparation of a standard industrial lot of 250.00 kg of tablets.

[0097] The tablets were prepared in the manner described in Example 1 using the components and quantities indicated above.

EXAMPLE 5

TABLETS OF 400 mg SAMe ion/tablet

[0098] Composition based on SAMe sulphate p-toluene sulphonate

A. SAMe sulphate p-toluene sulphonate	800.00 mg
B. Folic acid	3.00 mg
C Calcium oxide	70.00 mg
D.Magnesium hydroxide	100.00 mg
E.Calcium carbonate	100.00 mg
F. Calcium sulphate	100.00 mg
G. Magnesium stearate	20.00 mg
H. Malic acid	40.00 mg
I. Hydrogenated fatty acid	40.00 mg
Total weight of core	1273.00 mg
L. Hydrogenated vegetable fatty acids	8.00 mg
M. Hydroxypropylmethylcellulose	30.00 mg
N. PVP K 30	6.0 mg
O Titanium dioxide	5.00 mg
P. Talc	10.00 mg
Q. Triethyl citrate	5.00 mg
R. Curcumin	0.050 mg
Total weight of tablet	1284.05 mg

[0099] The quantities relate to the preparation of a standard industrial lot of 250.00 kg of tablets.

[0100] The tablets were prepared in the manner described in Example 1 using the components and quantities indicated above.

Table 12

Lot 004 - cores of 400 mg ion/tablet (qualitative/quantitative composition in Example 5)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	Folic acid mg
004 (20/0)	0.59	80.11	0.33	0.23	410.89	3.23
004A (40/1)	0.53	75.4	0.45	0.55	410.43	3.24
004B (40/3)	0.45	72.8	0.55	0.67	409.76	3.21
004C (40/6)	0.37	69.6	0.79	0.99	408.67	3.19
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

[0101] The data in Table 12 indicate that the tablets have optimum stability.

EXAMPLE 6

TABLETS OF 400 mg SAMe ion/tablet

[0102] Composition based on SAMe sulphate p-toluene sulphonate

A. SAMe sulphate p-toluene sulphonate	800.00 mg
B. Folic acid	3.00 mg
C. Melatonin	2.00 mg
C Calcium oxide	70.00 mg
D.Magnesium hydroxide	100.00 mg
E.Calcium carbonate	100.00 mg
F. Calcium sulphate	100.00 mg
G. Magnesium stearate	20.00 mg
H. Malic acid	40.00 mg
I. Hydrogenated fatty acid	40.00 mg
Total weight of core	1275.00 mg

[0103] The quantities relate to the preparation of a standard industrial lot of 250.00 kg of tablets.

[0104] The tablets were prepared in the manner described in Example 1 using the components and quantities indicated above.

Table 13

Lot 005 - cores of 400 mg ion/tablet (qualitative/quantitative composition in Example 6).							
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	Folic acid mg	L-melatonin mg
005 (20/0)	0.53	81.3	0.29	0.40	415.12	3.12	2.21
005A (40/1)	0.50	76.2	0.38	0.59	414.21	3.03	2.12
005B (40/3)	0.41	73.2	0.51	0.73	413.34	3.02	2.04
005C (40/6)	0.29	69.2	0.83	1.09	412.21	3.00	2.08
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);							

[0105] The data in Table 13 reveal that the tablets have optimum stability.

DESCRIPTION OF COMPONENTS	**QUANTITY PER UNIT**	
Active ingredient		
A) NADH	mg	5.50
O) Triethyl citrate	mg	0.15
Overall weight of the coated tablets	**mg**	**52.85**
A) NADH	mg	5.50
O) Talc	mg	0.20
P) Triethyl citrate	mg	0.15
Overall weight of the coated tablets	**mg**	**52.85**

EXPERIMENTAL PART

Stability tests on the finished product

[0106] Stability at 40°C 75% RH (STRESS TEST) and at ambient temperature over a long period (SHELF LIFE) for the compositions in Examples 1, 2, 3, 4, 5, 6, obtained according to the

process according to the invention were evaluated for changes in appearance (essentially change in colour), titre of SAMe sulphate p-toluene sulphonate (mg/tablet), increase in degradation purities, moisture content (K.F.) and % of the active (SS)-(+)-S-adenosyl-L-methionine diastereoisomer; the presence of any degradation products, which can be substantially identified as adenosine and methylthioadenosine expressed as a percentage with respect to the mg of SAMe-toluene sulphonate per tablet was further checked by HPLC.

STRESS TEST

[0107] The tablets were prepared in stoppered glass bottles and enclosed in such a way as to reproduce the conditions of final packaging (generally aluminium/aluminium blister).

[0108] The samples so prepared were stored for six months in a stove thermostatted to a temperature of 40 ± 2°C and 75% RH.

[0109] Nine samples from three different lots were used for the 400 mg tablets (Examples 1, 2, 3, 4, 5, 6), and each sample from each lot was sampled after 0, 1, 3 and 6 months.

[0110] The following tables (14-31) report the results of the stress test.

Table 14

Lot 006- tablets of 400 mg ion/tablet (Example 1)					
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]
006 (20/0)	0.73	78.4	0.24	0.41	411.98
006 (40/1)	0.59	74.2	0.36	0.63	409.45
006B (40/3)	0.54	71.5	0.59	0.73	409.02
006C (40/6)	0.43	68.9	0.87	0.91	405.71
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);					

Table 15

Lot 007- tablets of 400 mg ion/tablet (Example 1)					
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]
007 (20/0)	0.61	79.2	0.31	0.55	412.32
007A (40/1)	0.62	75.4	0.39	0.69	411.88
007B (40/3)	0.57	73.1	0.52	0.72	410.67
007C (40/6)	0.49	70.1	0.77	0.89	408.65
[1]Temperature (°C)/time (months); adenosine; methylthioadenosine; SAMe sulphate p-toluene sulphonate (mg/tablet);					

Table 16

Lot 008- tablets of 400 mg ion/tablet (Example 1)					
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]
008 (20/0)	0.81	77.9	0.34	0.49	408.54
008A (40/1)	0.76	73.4	0.53	0.59	407.58
008B (40/3)	0.61	71.1	0.74	0.74	407.04
008C (40/6)	0.55	68.8	0.88	0.84	404.21
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);					

Table 17

Lot 009 - tablets of 400 mg ion/tablet (EXAMPLE 2)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	L-melatonin mg
009 (20/0)	0.54	80.3	0.34	0.33	412.13	2.02
009A (40/1)	0.50	77.4	0.39	0.45	410.54	2.01
009B (40/3)	0.43	72.5	0.54	0.67	410.01	2.00
009C (40/6)	0.32	70.3	0.84	0.93	408.44	1.98
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 18

Lot 010 - tablets of 400 mg ion/tablet (EXAMPLE 2)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	L-melatonin mg
010 (20/0)	0.61	80.0	0.52	0.53	410.54	2.03
010A (40/1)	0.57	75.4	0.55	0.58	408.65	2.03
010B (40/3)	0.51	72.3	0.67	0.69	408.56	2.00
010C (40/6)	0.48	70.0	0.86	0.98	406.98	1.95
[1] Temperature (°C)/time (months); adenosine; methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 19

Lot 011 - tablets of 400 mg ion/tablet (EXAMPLE 2)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	L-melatonin mg
011 (20/0)	0.75	78.3	0.24	0.34	412.21	2.00
011A (40/1)	0.55	75.8	0.35	0.55	410.29	2.02
011B (40/3)	0.50	73.1	0.44	0.77	409.65	1.98
011C (40/6)	0.47	71.3	0.75	0.97	407.65	1.95
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 20

Lot 012 - tablets of 400 mg ion/tablet (Example 3)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	L-theanine
012 (20/0)	0.66	80.3	0.34	0.54	414.43	205.65
003A (40/1)	0.61	75.4	0.43	0.66	413.43	203.54
012B (40/3)	0.58	72.2	0.54	0.76	411.32	203.32
012C (40/6)	0.43	70.2	0.64	0.89	410.98	202.46
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 21

Lot 013 - tablets of 400 mg ion/tablet (Example 3)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	L-theanine
013 (20/0)	0.73	79.5	0.25	0.53	412.45	203.01
003A (40/1)	0.64	76.1	0.38	0.64	412.01	202.83
013B (40/3)	0.55	72.5	0.65	0.72	410.52	202.01
013C (40/6)	0.47	69.9	0.79	0.96	409.74	201.21
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 22

Lot 014 - tablets of 400 mg ion/tablet (Example 3)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	L-theanine
014 (20/0)	0.62	79.2	0.35	0.44	412.22	202.01
003A (40/1)	0.60	76.4	0.45	0.55	411.01	201.43
014B (40/3)	0.57	72.9	0.67	0.76	410.52	200.01
014C (40/6)	0.47	70.7	0.85	0.93	409.44	198.21
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 23

Lot 015 - tablets of 400 mg ion/tablet (Example 4)					
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]
018 (20/0)	0.63	79.4	0.43	0.52	412.54
018A (40/1)	0.52	74.7	0.44	0.69	411.58
018B (40/3)	0.41	71.5	0.58	0.78	49.78
018C (40/6)	0.31	68.9	0.72	0.99	407.75
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);					

Table 24

Lot 016 - tablets of 400 mg ion/tablet (Example 4)					
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]
016 (20/0)	0.56	79.2	0.33	0.49	410.54
001A (40/1)	0.46	75.9	0.39	0.67	410.11
016B (40/3)	0.42	72.9	0.50	0.69	409.67
016C (40/6)	0.39	70.7	0.86	0.87	408.65
Temperature (°C)/time (months); [2] adenosine; methylthioadenosine; SAMe sulphate p-toluene sulphonate (mg/tablet);					

Table 25

Lot 017 - tablets of 400 mg ion/tablet (Example 4)					
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]
017 (20/0)	0.69	78.9	0.35	0.49	413.54
017A (40/1)	0.59	75.4	0.45	0.69	412.58

Lot 017 - tablets of 400 mg ion/tablet (Example 4)					
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]
017B (40/3)	0.56	72.9	0.59	0.79	409.02
017C (40/6)	0.49	71.7	0.87	0.96	407.59
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);					

Table 26

Lot 018 - tablets of 400 mg ion/tablet (Example 5)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	Folic acid mg
018 (20/0)	0.69	80.4	0.29	0.36	412.45	3.13
018A (40/1)	0.56	75.7	0.35	0.58	411.98	3.04
018B (40/3)	0.50	73.2	0.54	0.87	410.71	3.01
018C (40/6)	0.38	70.3	0.66	1.05	407.37	3.09
Temperature (°C)/time (months); adenosine; methylthioadenosine; SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 27

Lot 019 - tablets of 400 mg ion/tablet (Example 5)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	Folic acid mg
019 (20/0)	0.59	80.1	0.55	0.33	410.00	3.10
019A (40/1)	0.53	75.4	0.65	0.45	410.02	3.03
019B (40/3)	0.45	72.8	0.87	0.61	408.43	3.06
019C (40/6)	0.37	69.6	1.01	0.79	40627	3.07
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 28

Lot 020 - tablets of 400 mg ion/tablet (Example 5)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	Folic acid mg
020 (20/0)	0.49	80.8	0.23	0.33	414.89	3.00
020A (40/1)	0.50	75.8	0.37	0.51	412.29	2.89
020B (40/3)	0.37	72.3	0.51	0.63	409.76	2.98
020C (40/6)	0.28	69.1	0.63	0.87	408.63	2.78
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 29

Lot 021 - tablets of 400 mg ion/tablet (Example 6)							
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	Folic acid mg	L-melatonin mg
021 (20/0)	0.65	78.9	0.21	0.49	415.12	3.19	2.11
021A (40/1)	0.53	76.1	0.34	0.57	414.21	3.23	2.02
021B (40/3)	0.41	72.1	0.50	0.63	413.34	3.03	2.04
021C (40/6)	0.26	69.0	0.81	0.94	412.21	3.00	2.01
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);							

Table 30

Lot 022 - tablets of 400 mg ion/tablet (Example 6)							
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	Folic acid mg	L-melatonin mg
022 (20/0)	0.76	80.2	0.25	0.42	412.34	3.32	2.11
022A (40/1)	0.64	75.9	0.27	0.54	411.21	3.23	2.10
022B (40/3)	0.59	72.4	0.43	0.77	410.12	3.12	2.09
022C (40/6)	0.46	70.1	0.55	0.90	408.91	3.08	2.05

[1] Temperature (°C)/time (months); adenosine; [3] methylthioadenosine; SAMe sulphate p-toluene sulphonate (mg/tablet);

Table 31

Lot 023 - tablets of 400 mg ion/tablet (Example 6)							
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	Folic acid mg	L-melatonin mg
023 (20/0)	0.53	81.0	0.22	0.47	411.87	3.05	2.13
023A (40/1)	0.50	76.0	0.33	0.69	409.27	3.03	2.12
023B (40/3)	0.41	73.7	0.55	0.73	405.34	3.08	2.07
023C (40/6)	0.29	69.9	0.74	0.87	404.71	3.03	2.04

[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);

[0111] From the stability data at 40°C and 75% RH (STRESS TEST) it will be seen that all the lots examined after six months had suffered degradation equal to approximately 2.5% of both SAMe and the other active ingredients with a reduction of approximately 10% in the active (SS)-(+)-S-adenosyl-L-methionine diastereoisomers;

SHELF LIFE

[0112] The tablets were packed in stoppered glass bottles and enclosed in such a way as to reproduce the conditions of final packaging (generally aluminium/aluminium blister).

[0113] The samples were selected in the same way and in the same quantities as described for the stress test and kept in an environment thermostatted to a temperature of 25 ± 2°C and a humidity of 60% RH.

[0114] Nine samples originating from three different lots were used for the 400 mg tablets (Examples 1, 2, 3, 4, 5, 6) and each sample from each lot was sampled after 0, 3, 6, 12 months.

[0115] The following tables (38- 55) show the results for SHELF LIFE.

Table 38

Lot 024- tablets of 400 mg ion/tablet (Example 1)					
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]
024 (20/0)	0.65	79.4	0.32	0.28	413.48
024A (40/1)	0.56	75.3	0.44	0.34	413.23
024B (40/3)	0.52	72.5	0.59	0.65	411.89
024C (40/6)	0.44	69.9	0.83	0.79	409.76
Temperature (°C)/time (months); adenosine; methylthioadenosine; SAMe sulphate p-toluene sulphonate (mg/tablet);					

Table 39

Lot 025 - tablets of 400 mg ion/tablet (Example 1)					
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]
006 (20/0)	0.69	78.9	0.27	0.46	410.67
025 (40/1)	0.65	74.6	0.39	0.67	408.78
025B (40/3)	0.56	73.5	0.65	0.74	409.02
025C (40/6)	0.34	70.4	0.79	0.89	405.32
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);					

Table 40

Lot 026 - tablets of 400 mg ion/tablet (Example 1)					
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]
026 (20/0)	0.78	78.7	0.20	0.47	411.65
006 (40/1)	0.65	74.9	0.39	0.60	409.43
026B (40/3)	0.54	72.5	0.69	0.70	408.02
026C (40/6)	0.48	68.45	0.88	0.94	404.43
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);					

Table 41

Lot 027 - tablets of 400 mg ion/tablet (Example 2)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	L-melatonin mg
027 (20/0)	0.70	80.0	0.41	0.20	410.24	2.12
010A (40/1)	0.64	75.7	0.54	0.47	408.65	2.04
027B (40/3)	0.55	72.7	0.69	0.58	405.56	2.05

Lot 027 - tablets of 400 mg ion/tablet (Example 2)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	L-melatonin mg
027C (40/6)	0.43	70.4	0.83	0.85	406.58	1.99
Temperature (°C)/time (months); adenosine; [3] methylthioadenosine; SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 42

Lot 028 - tablets of 400 mg ion/tablet (Example 2)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD [3] (%)	SAMe[4]	L-melatonin mg
010 (20/0)	0.64	80.4	0.33	0.35	413.44	2.07
028A (40/1)	0.54	76.73	0.45	0.54	412.35	2.09
028B (40/3)	0.50	73.9	0.67	0.56	408.46	2.04
028C (40/6)	0.37	73.0	0.85	0.67	406.58	2.02
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 43

Lot 029 - tablets of 400 mg ion/tablet (Example 2)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD [3] (%)	SAMe[4]	L-melatonin mg
029 (20/0)	0.64	78.7	0.33	0.45	408.43	2.13
029A (40/1)	0.57	75.3	0.34	0.54	407.55	2.12
029B (40/3)	0.51	72.5	0.54	0.56	404.45	2.05
029C (40/6)	0.39	71.2	0.67	0.76	403.23	1.99
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 44

Lot 030 - tablets of 400 mg ion/tablet (Example 3)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	L-theanine
030 (20/0)	0.71	79.76	0.22	0.34	413.49	209.35

Lot 030 - tablets of 400 mg ion/tablet (Example 3)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	L-theanine
030A (40/1)	0.61	74.7	0.33	0.46	412.33	203.54
030B (40/3)	0.55	73.2	0.51	0.66	410.32	202.32
030C (40/6)	0.49	71.4	0.69	0.79	404.98	200.32
[1] Temperature (°C)/time (months); adenosine; [3] methylthioadenosine; SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 45

Lot 031 - tablets of 400 mg ion/tablet (Example 3)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	L-theanine
031 (20/0)	0.62	80.4	0.37	0.43	412.43	205.21
031A (40/1)	0.56	74.4	0.40	0.54	410.45	204.54
031B (40/3)	0.58	71.2	0.50	0.65	407.78	203.23
031C (40/6)	0.49	68.5	0.61	0.79	407.21	201.34
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 46

Lot 032 - tablets of 400 mg ion/tablet (Example 3)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	L-theanine
032 (20/0)	0.63	81.5	0.44	0.24	409.99	203.65
032A (40/1)	0.65	75.5	0.43	0.46	406.78	202.45
032B (40/3)	0.59	73.4	0.64	0.56	406.54	203.00
032C (40/6)	0.50	70.0	0.84	0.75	404.21	201.23
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 47

Lot 033 - tablets of 400 mg ion/tablet (Example 4)					
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]
033 (20/0)	0.74	79.9	0.39	0.29	411.23
033A (40/1)	0.64	74.4	0.44	0.38	409.45
033B (40/3)	0.59	73.5	0.63	0.57	406.02
033C (40/6)	0.34	70.6	0.88	0.89	404.23
[1] Temperature (°C)/time (months); adenosine; methylthioadenosine; SAMe sulphate p-toluene sulphonate (mg/tablet);					

Table 48

Lot 034 - tablets of 400 mg ion/tablet (Example 4)					
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]
034 (20/0)	0.59	78.3	0.25	0.39	410.23
034A (40/1)	0.60	73.4	0.35	0.57	408.58
034B (40/3)	0.53	70.9	0.49	0.88	404.32
034C (40/6)	0.39	68.5	0.68	0.90	402.12
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);					

Table 49

Lot 035 - tablets of 400 mg ion/tablet (Example 4)					
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]
035 (20/0)	0.59	78.7	0.38	0.39	408.56
035A (40/1)	0.49	74.9	0.49	0.57	409.65
035B (40/3)	0.50	72.0	0.65	0.68	404.73
035C (40/6)	0.36	70.2	0.97	0.87	402.12
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);					

Table 50

Lot 036 - tablets of 400 mg ion/tablet (Example 5)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	Folic acid mg
036 (20/0)	0.70	80.4	0.47	0.37	413.00	3.05
036A (40/1)	0.58	74.4	0.56	0.40	410.45	3.03
036B	0.42	72.0	0.78	0.66	408.99	3.06

Lot 036 - tablets of 400 mg ion/tablet (Example 5)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	Folic acid mg
(40/3)						
036C (40/6)	0.39	69.8	0.89	0.72	404.67	3.01
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 51

Lot 037 - tablets of 400 mg ion/tablet (Example 5)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	Folic acid mg
037 (20/0)	0.69	78.7	0.49	0.39	411.30	3.05
037A (40/1)	0.63	74.5	0.64	0.55	408.57	3.01
037B (40/3)	0.59	71.8	0.81	0.67	405.98	3.00
037C (40/6)	0.48	69.2	1.00	0.89	402.56	2.89
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 52

Lot 038 - tablets of 400 mg ion/tablet (Example 5)						
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	Folic acid mg
038 (20/0)	0.70	81.2	0.52	0.31	410.99	3.11
038A (40/1)	0.63	75.4	0.60	0.43	407.32	3.08
038B (40/3)	0.58	73.2	0.76	0.68	405.89	3.03
038C (40/6)	0.49	70.6	0.80	0.93	401.34	3.01
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; [4] SAMe sulphate p-toluene sulphonate (mg/tablet);						

Table 53

Lot 039 - tablets of 400 mg ion/tablet (Example 6)							
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	Folic acid mg	L-melatonin mg
039 (20/0)	0.63	81.4	0.29	0.43	410.43	3.03	2.06
039A (40/1)	0.53	74.7	0.39	0.65	406.89	3.05	2.07
039B (40/3)	0.57	72.7	0.58	0.79	403.69	3.00	2.03
039C (40/6)	0.42	70.9	0.79	0.89	401.34	2.89	2.02
[1] Temperature (°C)/time (months); adenosine; methylthioadenosine; SAMe sulphate p-toluene sulphonate (mg/tablet);							

Table 54

Lot 040 - tablets of 400 mg ion/tablet (Example 6)							
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	Folic acid mg	L-melatonin mg
040 (20/0)	0.63	78.8	0.35	0.40	408.88	3.10	2.05
040A (40/1)	0.58	74.5	0.45	0.67	404.47	3.07	2.02
040B (40/3)	0.48	72.5	0.60	0.70	403.34	3.03	2.07
040C (40/6)	0.37	69.3	0.78	0.89	400.45	3.00	2.00
[1] Temperature (°C)/time (months); [2] adenosine; [3] methylthioadenosine; SAMe sulphate p-toluene sulphonate (mg/tablet);							

Table 55

Lot 041 - tablets of 400 mg ion/tablet (Example 6)							
Lot (T/t)[1]	Moisture content % (K.Fischer)	S,S %	AD[2] (%)	MTAD[3] (%)	SAMe[4]	Folic acid mg	L-melatonin mg
041 (20/0)	0.73	81.6	0.42	0.38	410.48	3.15	2.10
023A (40/1)	0.70	75.3	0.43	0.49	407.56	3.09	2.12
041B (40/3)	0.58	72.4	0.58	0.70	406.65	3.08	2.08
041C (40/6)	0.49	70.4	0.73	0.88	402.39	3.05	2.03

[1] Temperature (°C)/time (months); adenosine; methylthioadenosine; SAMe sulphate p-toluene sulphonate (mg/tablet);

[0116] From the stability data at 25°C and 60% RH (SHELF LIFE) it will be seen that all the lots examined after twelve months had suffered very little degradation of the SAMe with a reduction of approximately 10% in the active (SS)-(+)-S-adenosyl-L-methionine diastereoisomer;

REFERENCES CITED IN THE DESCRIPTION

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- US4057686A **[0014]**
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- US7034011B **[0017]**
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- WO03043608A **[0022]**
- EP0162323A1 **[0022]**

Patentkrav

1. Sammensætning omfattende S-adenosyl-methionin-sulfat-paratoluen-sulfonat eller S-adenosyl-methionin-1,4-butan-disulfonat sammen med calciumoxid og eventuelt farmaceutisk acceptable excipienser.

2. Sammensætning ifølge krav 1, hvor S-adenosyl-methionin-sulfat-paratoluen-sulfonatet eller S-adenosyl-methionin-1,4-butan-disulfonatet er til stede i en mængde der varierer fra 30 til 90 vægt% i forhold til sammensætningens vægt, fortrinsvis fra 50 til 85 vægt% i forhold til sammensætningens vægt.

3. Sammensætning ifølge krav 1, hvor calciumoxidet er til stede i en mængde der varierer fra 1 til 40 vægt% i forhold til sammensætningens vægt, fortrinsvis fra 2 til 20 vægt% i forhold til sammensætningens vægt.

4. Sammensætning ifølge krav 1, omfattende mindst et yderligere aktivstof fortrinsvis valgt fra I-melatonin, I-theanin og/eller I-tryptophan og/eller 5-hydroxytryptophan eller blandinger deraf.

5. Sammensætning ifølge krav 1, hvor mindst én af de farmaceutisk acceptable excipienser er calciumsulfat-hemihydrat og/eller glucono-delta-lacton.

6. Sammensætning ifølge et hvilket som helst af de foregående krav, i form af en direkte blanding, tablet, kapsel, granulat eller pulver, fortrinsvis i form af en tablet, mere foretrinsvis en ordinær, coatet, film-coatet og/eller gastroresistent tablet.

7. Fremgangsmåde til fremstillingen af en tablet ifølge krav 6, omfattende følgende stadier at:

a) blande S-adenosyl-methionin-sulfat-paratoluen-sulfonatet eller S-adenosyl-methionin-1,4-butan-disulfonatet med calciumoxid og farmaceutisk acceptable excipienser,

b) forkompression og efterføkgende granulering af blandingen opnået i trin a),

c) blande granulatet opnået i trin b) med farmaceutisk acceptable excipienser såsom calciumsulfat-hemihydrat, xylitol, malinsyre, glutaminsyre, glucono-delta-lacton, magnesiumoxid, hydrogenerede fedtsyrer, præcipiteret silica, magnesiumstearat, saccharose, glycerolbehenat,

d) kompression af blandingen opnået i trin c), med den eventuelle tilsætning af sødestoffer og/eller aromastoffer,

e) eventuel coating af tabletten opnået i trin d) med hydrogenerede fedtsyrer,

f) eventuel vandig fase film-coating af tabletten opnået i trin e).

8. Fremgangsmåde ifølge krav 7, hvor i trin c) mindst ét yderligere aktivstof fortrinsvis valgt fra I-melatonin, I-theanin og/eller I-tryptophan og/eller 5-hydroxytryptophan og/eller blandinger deraf kan tilsættes til blandingen.

9. Fremgangsmåde ifølge krav 7, hvor coatingen nævnt i trin e) påføres under anvendelse af hydrogenerede fedtsyrer i en mængde på mellem 0,4 og 1,5 vægt% i forhold til tablettens vægt.

10. Fremgangsmåde ifølge krav 7, hvor den vandige fase film-dannelse nævnt i trin f) udføres under anvendelse af en lak fortrinsvis valgt fra gum Lac og/eller dens salte (Shellac™), methacrylsyre, celluloseacetophthalater, titaniumdioxid, talkum, triethylcitrat, PVP K30, curcumin, lutein, hydroxypropylcellulose, hydroxypropylmethylcellulose og/eller blandinger deraf.

11. Sammensætninger der kan opnås gennem fremgangsmåden ifølge kravene 7-10.

12. Anvendelse af S-adenosyl-methionin-sulfat-paratoluen-sulfonat eller S-adenosyl-methionin-1,4-butan-disulfonat sammen med calciumoxid til fremstillingen af en sammensætning til behandlingen af depressive tilstande.

13. Anvendelse ifølge krav 12 hvor magnesiumoxidet yderligere tilsættes til calciumoxidet.

14. Fremgangsmåde til stabilisering af en sammensætning baseret på S-adenosyl-methionin-sulfat-paratoluen-sulfonat eller S-adenosyl-methionin-1,4-butan-disulfonat omfattende anvendelse af blandingen af S-adenosyl-methionin-sulfat-paratoluen-sulfonat eller S-adenosyl methionin-1,4-butan-disulfonat med calciumoxid.

15. Fremgangsmåde ifølge krav 14, hvor S-adenosyl-methionin-sulfat-paratoluen-sulfonatet eller S-adenosyl-methionin-1,4-butan-disulfonatet er til stede i en mængde på mellem 30 og 90 vægt% beregnet i forhold til sammensætningens vægt, fortrinsvis mellem 50 og 85 vægt% beregnet i forhold til sammensætningens vægt.

16. Fremgangsmåde ifølge kravene 14-15, hvor calciumoxidet er til stede i en mængde der varierer fra 1 til 40 vægt% i forhold til sammensætningens vægt, fortrinsvis fra 2 til 20 vægt% i forhold til sammensætningens vægt.

17. Fremgangsmåde ifølge krav 16, omfattende tilsætningen af farmaceutisk acceptable excipienser.

DRAWINGS

Figure 1

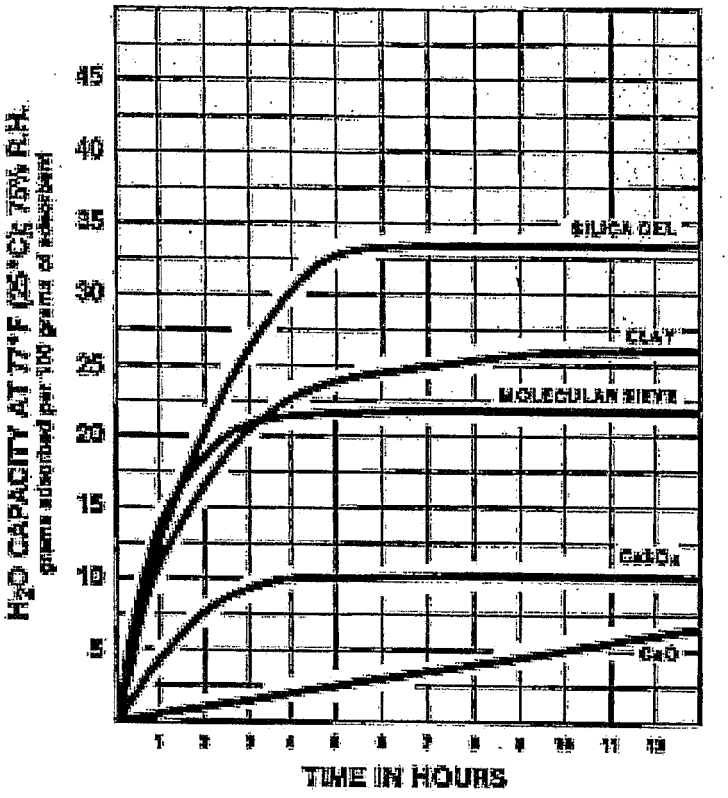

Figure 2

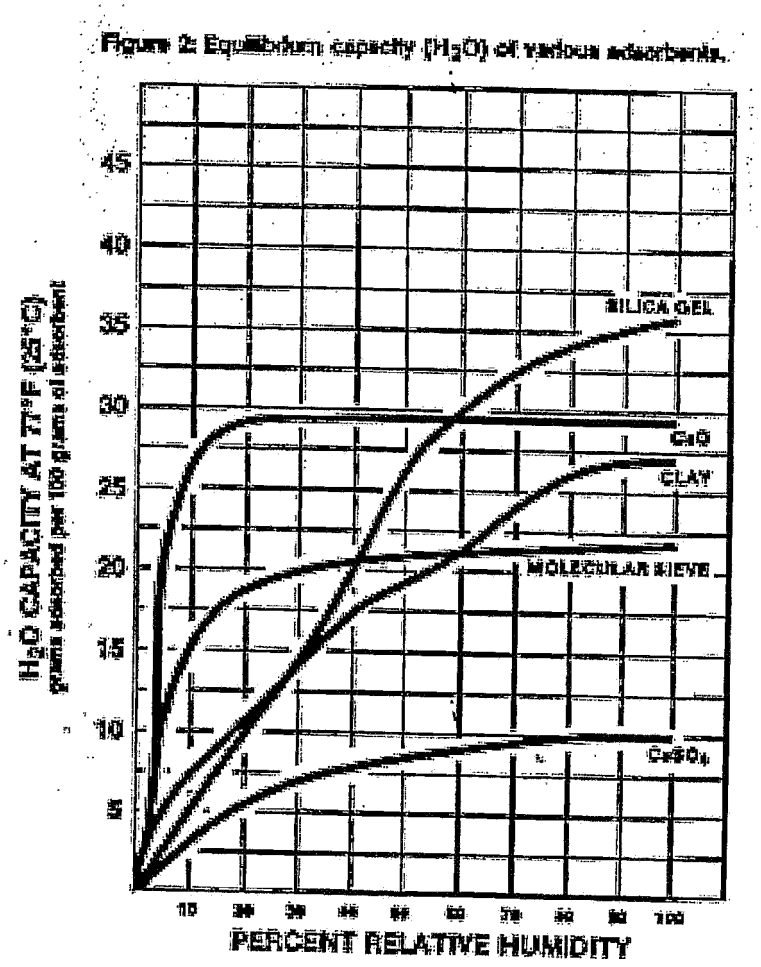
Figure 2: Equilibrium capacity (H_2O) of various adsorbents.
H_2O CAPACITY AT 77°F (25°C)
grams adsorbed per 100 grams of adsorbent
45
40
35
30
25
20
15
10
5
SILICA GEL
CaO
CLAY
MOLECULAR SIEVE
$CaSO_4$
10
20
30
40
50
60
70
80
90
100
PERCENT RELATIVE HUMIDITY