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(54) Titre : COMPOSITIONS SOLIDES DESTINEES A L'ADMINISTRATION PAR VOIE ORALE COMPRENANT DES SELS NON HYGROSCOPIQUES DE L-CARNITINE ET ALCANOYL-L-CARNITINE AVEC UN ACIDE 2-AMINOETHANESULFONIQUE

(54) Title: SOLID COMPOSITIONS SUITABLE FOR ORAL ADMINISTRATION COMPRISING NON HYGROSCOPIC SALTS OF L-CARNITINE AND ALKANOYL-L-CARNITINE WITH 2-AMINO-ETHANESULFONIC ACID

(57) Abrégé/Abstract:

Stable and non hygroscopic salts of L-carnitine or lower alkanoyl-L-carnitine with 2-aminoethanesulfonic acid are disclosed suitable for preparing solid compositions useful as dietary/nutritional supplements for human use and as fodder supplement for veterinary purposes.



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(21) International Application Number: PCT/IT98/00060 (22) International Filing Date: 19 March 1998 (19.03.98) (30) Priority Data: RM97A000184 1 April 1997 (01.04.97) IT (71) Applicant (for all designated States except US): SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A. [IT/IT]; Viale Shakespeare, 47, I-00144 Rome (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): SCAFETTA, Nazareno [IT/IT]; Via Siena, 10, I-00040 Pavona di Albano (IT). TINTI, Maria, Ornella [IT/IT]; Via Ernesto Basile, 81, I-00182 Rome (IT). (74) Common Representative: SIGMA-TAU INDUSTRIE FAR- MACEUTICHE RIUNITE S.P.A.; Viale Shakespeare, 47, I-00144 Rome (IT).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>	
(54) Title: SOLID COMPOSITIONS SUITABLE FOR ORAL ADMINISTRATION COMPRISING NON HYGROSCOPIC SALTS OF L-CARNITINE AND ALKANOYL-L-CARNITINE WITH 2-AMINOETHANESULFONIC ACID		
(57) Abstract Stable and non hygroscopic salts of L-carnitine or lower alkanoyl-L-carnitine with 2-aminoethanesulfonic acid are disclosed suitable for preparing solid compositions useful as dietary/nutritional supplements for human use and as fodder supplement for veterinary purposes.		

**Solid compositions suitable for oral administration comprising
non hygroscopic salts of L-carnitine and alkanoyl-L-carnitine
with 2-aminoethanesulfonic acid.**

The present invention relates to stable, non-hygroscopic,
5 pharmacologically acceptable salts of L-carnitine and lower alkanoyl-L-
carnitines which favourably lend themselves to the preparation of solid,
orally administrable compositions. The present invention also relates to
such compositions.

Various therapeutic uses of L-carnitine and alkanoyl derivatives
10 thereof are already known. For instance, L-carnitine is used in the
cardiovascular field for the treatment of acute and chronic myocardial
ischaemia, angina pectoris, heart failure and cardiac arrhythmias.

In the nephrological field, L-carnitine is administered to chronic
uraemics undergoing regular haemodialytic treatment to combat
15 myasthenia and the onset of muscular cramps.

Other therapeutic uses relate to the normalization of the
HDL:LDL + VLDL ratio and total parenteral nutrition.

It is also known that the salts of L(-)-carnitine and its alkanoyl
derivatives present the same therapeutic or nutritional activities as those
20 of the so-called inner salts and can, therefore, be used in their place,
provided these salts are "pharmacologically acceptable", i.e. they do not
present unwanted toxic or side effects.

In practice, then, the choice between an "inner salt" and a true
L(-)-carnitine or alkanoyl-L(-)-carnitine salt will depend essentially on
25 availability, economical and pharmacy considerations rather than on
therapeutic or nutritional considerations.

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The present invention provides stable and non-hygroscopic salts of L-carnitine and lower alkanoyl-L-carnitines which are endowed with an enhanced therapeutical and/or nutritional efficacy with respect to their inner salt counterparts.

5 It should, therefore, be clearly understood that the utility of the salts of the present invention is not confined to their lack of hygroscopicity and higher stability compared to the corresponding inner salts, but also resides in the contribution to the overall therapeutic and/or nutritional value of the salt in its entirety provided by their
10 anionic moiety. This value is, therefore, no longer to be attributed exclusively to the "carnitine" moiety of the salt.

Because of their lack of hygroscopicity these salts can be easily compounded, particularly with a view of preparing solid, orally administrable compositions.

15 As is well known to experts in pharmacy, the processing of hygroscopic products entails the use of controlled-humidity chambers both for storage and for the processing itself.

Moreover, the finished products must be packed in hermetically sealed blisters in order to avoid unpleasant consequences due to
20 humidity.

All this involves extra costs both for the storage of raw materials and for their processing and packaging.

Among the populations of the industrialised countries there is an increasingly widespread use of food supplements or "nutraceuticals"
25 both by sportsmen (amateurs or professionals) and by people in good health.

The former use L-carnitine or food supplements containing L-carnitine because it facilitates the oxidation of fatty acids and makes a larger amount of energy available to skeletal muscle, thus allowing enhanced performance and giving rise to less accumulation of lactic acid
5 in the athletes' muscles.

People in good health use these food supplements as health foods, i.e. for the purposes of favouring a reduction in serum fat levels and normalisation of the ratio between the various cholesterol fractions in order to prevent diseases related to lipid metabolism disorders.

10 It has been estimated that the amount of L-carnitine and its derivatives sold for non-ethical purposes is twice that sold for ethical purposes.

The US market for food supplements or nutraceuticals amount to approximately 250 billion dollars, whereas the estimated figure for the
15 European market is approximately 500 billion dollars (Food Labeling News, 1994, "Nutraceuticals" Market said to be a vast one, March, Vol. 2, n° 25; King Communications Group Inc., 1993, "Nutraceuticals" Foods, Drink in Global Market. Food and Drink Daily, April, Vol. 3, n° 503).

20 Some non-hygroscopic salts of L-carnitine are already known.

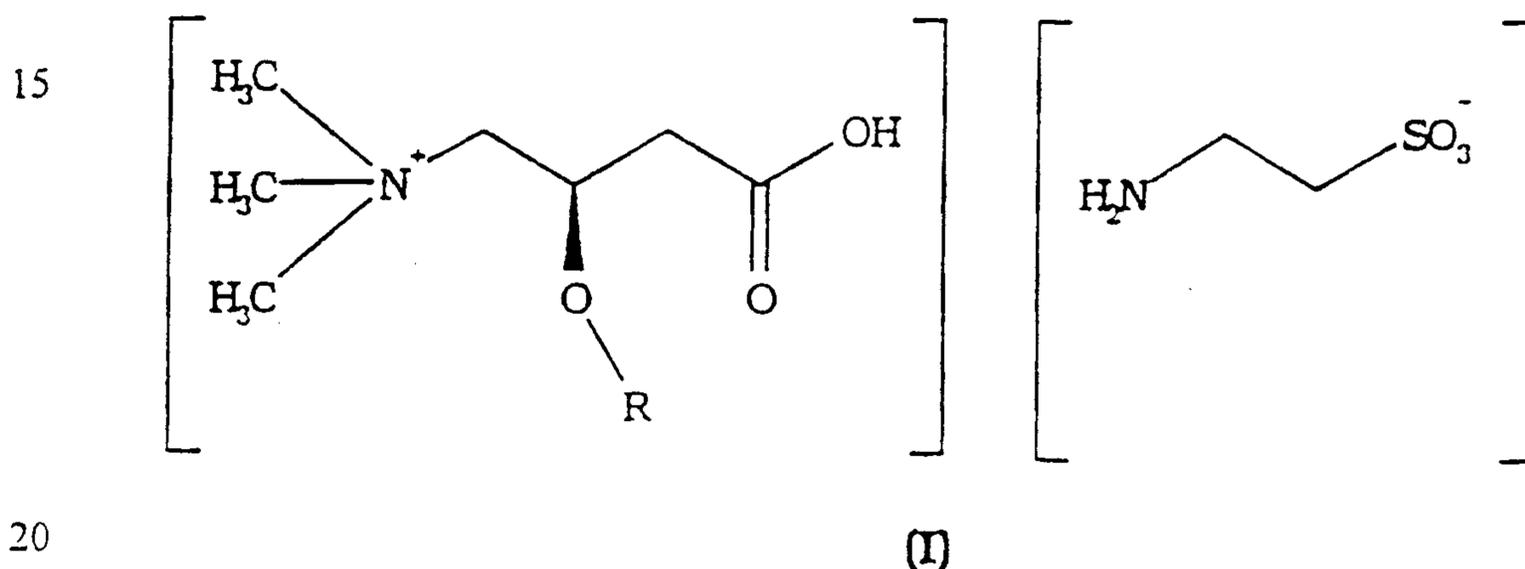
For instance EP 0 434 088 (LONZA) filed December 21, 1990 discloses the use of the non-hygroscopic L(-)carnitine L(+)tartrate (2:1) (the preparation and physico-chemical characterization of which were, however, described by D. Müller and E. Strack in Hoppe Seyler's Z.
25 Physiol. Chem 353, 618-622, April 1972) for the preparation of solid forms suitable for oral administration.

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This salt presents, however, some drawbacks, such as e.g. the release, after prolonged storage, of traces of trimethylamine which give the product an unpleasant fishy odour. Moreover, L(-)-carnitine L(+)-tartrate (2:1) becomes deliquescent at relative humidity slightly exceeding 60%. Furthermore, L-(+)-tartaric acid is unable to give non-hygroscopic salts with the alkanoyl-L-carnitines, such as e.g. acetyl-L-carnitine.

The present invention provides novel, stable and non-hygroscopic pharmacologically acceptable salts of both L-carnitine and lower alkanoyl-L-carnitines wherein the anion moiety contributes to the therapeutic and/or nutritional value of the salt, is achieved by the salts of formula (I) wherein the salt anion is the anion of 2-aminoethanesulfonic acid (or taurine):



wherein R is hydrogen or straight or branched lower alkanoyl, having 2-5 carbon atoms.

The preferred salts are those wherein R is selected from the group comprising acetyl, propionyl, butyryl, valeryl and isovaleryl.

Taurine or 2-aminoethanesulphonic acid is one of the most

plentiful amino acids in the body and is to be found in the central nervous system and skeletal muscles as well as being concentrated in the brain and heart.

It has long been known to be an essential nutrient during mammalian growth and development, and is, in fact, present in mother's milk and is especially important for the development of the cerebellum and retina.

Taurine also performs a very important metabolic function: in the bile, the bile acids bind with taurine to form glycocholic and taurocholic acid, respectively.

The salts of bile acids possess the important property of lowering the surface tension of solutions. For this reason they are excellent emulsifiers and perform an important function in the uptake and digestion of lipids in the bowel.

These important metabolic and nutritional characteristics enable taurine, when bound to L-carnitine, to perform a complementary task to that performed by the latter.

In fact, taurine, by favouring the emulsification and digestion of fatty acids, exerts an activity which is complementary to the subsequent metabolic activity exerted by L-carnitine, i.e. the oxidation of fatty acids for the production of energy.

This complementarity of the metabolic action of the two salt moieties (i.e. L-carnitine and taurine) is particularly useful in human or animal nutrition both in physiological conditions, i.e. in state of good health, and in the malabsorption syndrome occurring in children and adults.

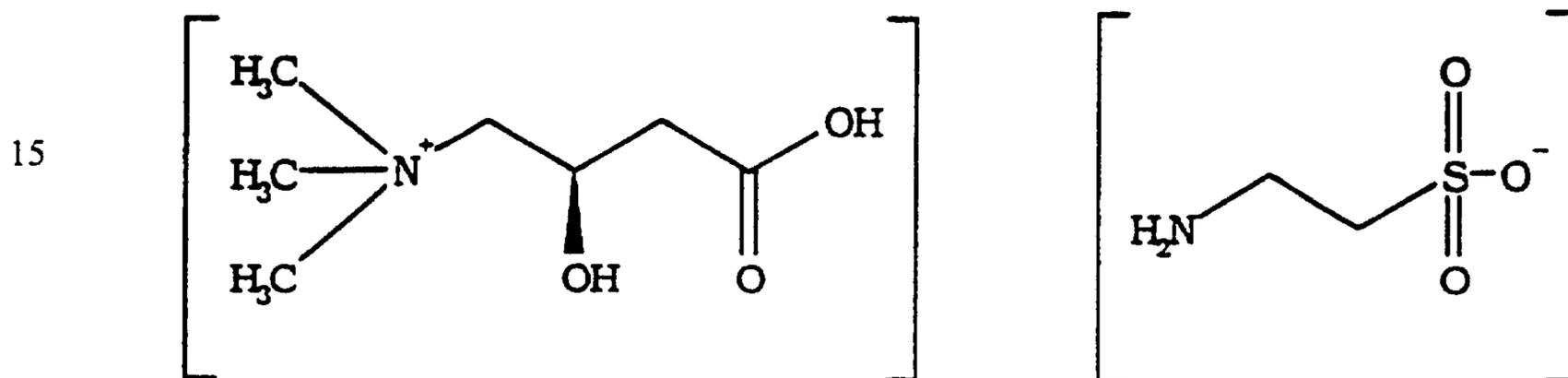
The new salts prove particularly useful as food supplements for sportsmen (amateur or professionals) also by virtue of the additional energy output facilitated by taurine. In people in good health they act as health food because they promote the digestion of fats and prevent diseases related to lipid metabolism disorders.

The salts of formula (I) are non-hygroscopic and highly stable to prolonged storage.

The following non-limiting examples show the preparation of some non-hygroscopic salts according to the present invention.

10 EXAMPLE 1

Preparation of L-carnitine 2-aminoethanesulfonate (ST 1290)



L-carnitine inner salt (3.2 g; 0.02 moles) and taurine (2.5 g; 0.02 moles) were dissolved in water (final volume 100 mL). The resulting solution was concentrated under vacuum.

The residue was taken up with isobutanol and the resulting mixture concentrated under vacuum to remove water. The raw reaction product was suspended in acetone, the resulting mixture kept under stirring at room temperature overnight and then filtered.

5.6 g of a solid, non-hygroscopic solid were obtained.

M.P. = 170°C (dec.)

$$[\alpha]_D^{25} = -15.9 \text{ (c = 1\%, H}_2\text{O)}$$

5

HPLC:

Stationary phase: SGE-SAX (5 μ m) 250 x 4.0 mm, t = 25°C

Eluant: CH₃CN/KH₂PO₄ 50 mM 72/28 pH 5.6

Flow-rate: 0.75 mL/min

10 R_t L-carnitine: 11.9 min 51.3%

R_t taurine: 9.7 min 44.3%

H₂O (K.F. method): 5.7%

Elementary analysis for C₉H₂₁N₂O₆S

	C%	H%	N%
15 Calculated (with 5.7% H ₂ O):	35.72	7.63	9.25
Found:	35.32	8.31	9.10

NMR D₂O δ 4.4(m, 1H, CHOH); 3.3(4H, m, N⁺CH₂; NH₂CH₂);

3.1-3.0(13H, d+s, (CH₃)₃N⁺; CH₂SO₃); 2.2(2H, d, CH₂COO)

EXAMPLE 2

20 Preparation of acetyl L-carnitine 2-aminoethanesulfonate (ST 1294)

Acetyl L-carnitine 2-aminoethanesulfonate was prepared as described in Example 1.

A solid, non-hygroscopic compound was obtained.

M.P. = 140°C (dec.)

25

$$[\alpha]_D^{25} = -15.06 \text{ (c = 1\%, H}_2\text{O)}$$

HPLC:

Stationary phase: Spherisorb SCX (5 μ m) 250 x 4 mm, t = 25°C

Eluant: CH₃CN/NH₄H₂PO₄ 50 mM 60/40 pH 4

Flow-rate: 0.75 mL/min

5 R_t acetyl L-carnitine: 12.08 min 54%

R_t taurine: 4.711 min 41%

H₂O: 6.4%

Elementary analysis for C₁₁H₂₄N₂O₇S

	C%	H%	N%
10 Calculated (with 6.4% H ₂ O):	37.65	7.61	7.98
Found:	36.86	7.45	7.92

NMR D₂O δ 5.6(1H,m,CHOCO); 3.9-3.4(2H,m,N⁺CH₂);
 3.4(2H,t,NH₂CH₂); 3.3-3.1(2H,t,CH₂SO₃); 9H,s,(CH₃)₃N⁺;
 2.4-2.5(2H,m,CH₂COO); 2.1(3H,s,COCH₃)

15 The compounds of the foregoing examples are non-hygroscopic and highly stable.

The present invention also relates to compositions comprising as active principle(s) at least one of the aforesaid non-hygroscopic pharmacologically acceptable salts and, optionally, one or more
 20 pharmacologically acceptable excipients and active ingredients which are well-known to the experts in pharmacy and food technology.

Particularly preferred are the solid, orally administrable compositions such as tablets, chewable tablets and capsules, which comprise a salt of L-carnitine or alkanoyl-L-carnitine of formula (I) in
 25 an amount corresponding to 50-2,000, preferably 100-1,000, mg of L-carnitine or alkanoyl-L-carnitine inner salt.

For instance, a composition for preparing tablets is the following:

	Non-hygroscopic L-carnitine salt of formula (I)	:	500	mg
	Starch	:	20	mg
5	Talc	:	10	mg
	Calcium stearate	:	1	mg
			<hr/>	
			531	mg

10 A composition suitable for preparing capsules is the following:

	Non-hygroscopic L-carnitine salt of formula (I)	:	500	mg
	Starch	:	20	mg
	Lactose	:	50	mg
15	Talc	:	5	mg
	Calcium stearate	:	2	mg
			<hr/>	
			577	mg

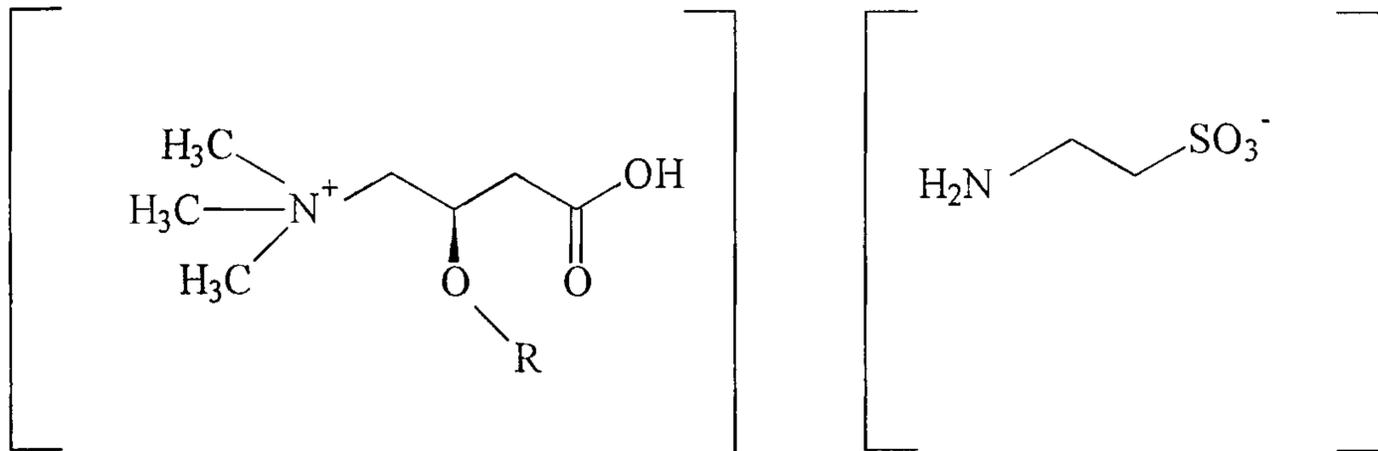
20 The compositions of the present invention may be used as dietary/nutritional supplements for human use or as fodder supplement for veterinary purposes.

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CLAIMS:

1. A salt of L-carnitine or an alkanoyl-L-carnitine with 2-aminoethanesulfonic acid of general formula (I):



5

(I)

wherein R is H, or a straight or branched lower alkanoyl having 2-5 carbon atoms.

2. The salt of claim 1, wherein R is selected from the group consisting of acetyl, propionyl, butyryl, valeryl and isovaleryl.

3. A pharmaceutical composition comprising, as the active ingredient, a salt as defined in claim 1 or 2, and a pharmacologically acceptable excipient.

4. The composition of claim 3, in the form of tablets, chewable tablets, capsules, granulates or powders.

5. The composition of claim 3 or 4, in unit dosage form comprising 50 to 2,000 mg of a salt as defined in claim 1 or 2.

6. The composition of claim 5, wherein the unit dosage form comprises 100 to 1,000 mg of a salt as defined in claim 1 or 2.

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7. The composition of any one of claims 3 to 6 as a dietary/nutritional supplement for human use.

8. The composition of claim 3 as a fodder supplement for veterinary use.

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