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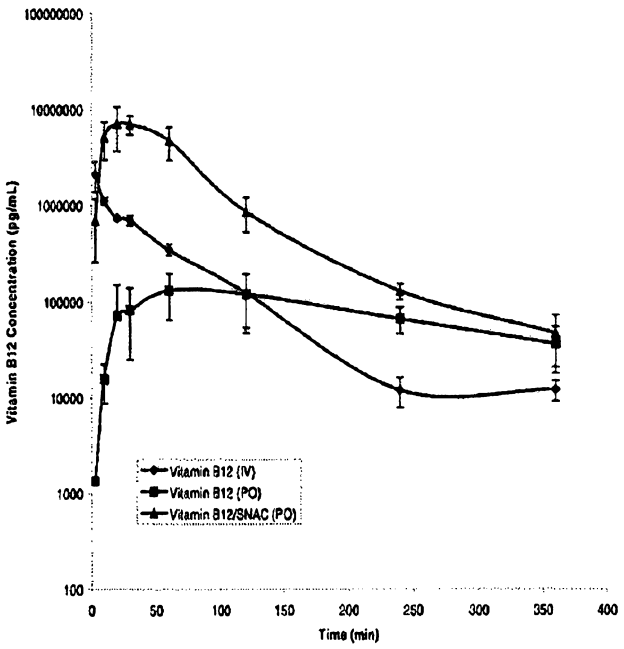
(54) Title: METHOD OF TREATING VITAMIN B12 DEFICIENCY



(57) Abstract: A method and composition for treating vitamin B12 deficiency in mammals that fail to respond to oral vitamin B12 therapy, including preparing a pharmaceutical composition for oral administration containing vitamin B12 and at least one substance selected from the group consisting of N-[8-(2-hydroxybenzoyl) amino]caprylic acid and its pharmaceutically acceptable salts, then administering the pharmaceutical composition to a subject to effectively treat the vitamin B12 deficiency.

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Method of Treating Vitamin B_{12} Deficiency

FIELD OF THE INVENTION

[0001] The present invention relates generally to methods of treating vitamin B_{12} deficiency and pharmaceutical compositions for such treatment.

BACKGROUND OF THE INVENTION

[0002] Vitamin B_{12} is important for the normal functioning of the brain and nervous system and for the formation of blood. It is involved in the metabolism of every cell of the body, especially affecting the DNA synthesis and regulation but also fatty acid synthesis and energy production. Its effects are still not completely known.

[0003] Cyanocobalamin is the most stable and widely used form of vitamin B_{12}. It is bound to plasma proteins and stored in the liver. Vitamin B_{12} is excreted in the bile and undergoes some enterohepatic recycling. Absorbed vitamin B_{12} is transported via specific B_{12} binding proteins, transcobalamin I and II, to the various tissues. The liver is the main organ for vitamin B_{12} storage.

[0004] Vitamin B_{12} deficiency can potentially cause severe and irreversible damage, especially to the brain and nervous system. Oral tablets containing vitamin B_{12} have been developed to treat vitamin B_{12} deficiency. However, many patients with vitamin B_{12} deficiency do not respond to oral vitamin B_{12} treatment. There is a need to develop a treatment for these patients.

[0004a] In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

BRIEF SUMMARY OF THE INVENTION

[0010] One aspect of the invention is directed to a method for treating vitamin B_{12} deficiency in a subject, comprising the steps of (a) preparing a pharmaceutical composition for oral administration containing (1) vitamin B_{12} and (2) at least one substance selected from the group consisting of *N*-[8-(2-hydroxybenzoyl) amino]caprylic acid and its pharmaceutically acceptable salts; and (b) administering the pharmaceutical composition to the subject to effectively treat said vitamin B_{12} deficiency.

[0011] Another aspect of the invention is directed to a pharmaceutical composition for treating vitamin B_{12} deficiency in a subject, comprising (1) vitamin B_{12} and (2) at least one substance selected from the group consisting of *N*-[8-(2-hydroxybenzoyl) amino]caprylic acid and its pharmaceutically acceptable salts; wherein said subject had failed to respond to existing oral vitamin B_{12} treatment.

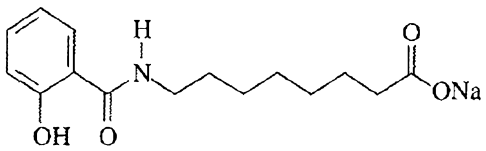
[0012] The contents of the patents and publications cited herein and the contents of these documents cited in these patents and publications are hereby incorporated herein by reference to the extent permitted.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] Fig. 1 is a graph of serum vitamin B_{12} concentration as a function of time.

DETAILED DESCRIPTION

[0014] As used herein, the term "SNAC" means Sodium-N-salicyloyl-8-aminocaprylate, Monosodium 8-(N-salicyloylamino) octanoate, N-(salicyloyl)-8-aminooctanoic acid monosodium salt, monosodium N-{ 8-(2 phenoxybenzoyl)amino}octanoate, E414 monosodium salt or sodium 8-[(2-hydroxybenzoyl)amino]octanoate. It has the structure



"*N*-[8-(2-hydroxybenzoyl) amino]caprylic acid " has an empirical formula $C_{15}H_{21}NO_4$.

[0015] The term "Vitamin B_{12}" means any member of a group of cobalt-containing compounds known as cobalamins which include, but is not limited to cyanocobalamin, hydroxocobalamin, methylcobalamin, and 5-deoxyadenosylcobalamin.

[0016] The term "treatment" or "treating" means any treatment of a disease or disorder in a mammal, including: preventing or protecting against the disease or disorder, that is, causing the clinical symptoms not to develop; inhibiting the disease or disorder, that is, arresting or suppressing the development of clinical symptoms; and/or relieving the disease or disorder, that is, causing the regression of clinical symptoms. The term "mammal" include human subjects.

[0017] The terms "carrier, excipient, emulsifier, stabilizer, sweetener, flavoring agent, diluent, coloring agent, solubilizing agent" are as defined in the Handbook of Pharmaceutical Excipients (fourth edition) by Raymond C. Rowe, Paul J. Sheskey and Paul J. Weller, the content of which is herein incorporated by reference.

[0018] The term "intrinsic factor protein" means is a glycoprotein produced by the parietal cells of the stomach. It is necessary for the absorption of vitamin B_{12} later on in the terminal ileum.

[0019] In a preferred embodiment, the treatment is directed to subjects that had failed to respond to existing oral vitamin B_{12} treatment. Preferably, tablets are used for the treatment. Such tablets contain from about 0.01mg to about 25 mg of vitamin B_{12} and from about 1 mg to about 600 mg of SNAC each, preferably from about 0.02 mg to about 25 mg of vitamin B_{12} and more preferably from about 0.1 mg to about 20 mg of vitamin B_{12} and the most preferably from about 0.5 mg to 10 mg of vitamin B_{12} and from about 10 mg to about 200 mg of SNAC in each tablet.

[0020] The preferred weight ratio of vitamin B_{12} and SNAC in the tablet is from about 2:1 to about 1:700, more preferably from about 1:2 to about 1:600 or from about 1:3 to about 1:20 and the most preferably from about 1:4 to about 1:10.

[0021] In a preferred embodiment, the pharmaceutical composition is in the form of tablets. Preferrably, each tablet contains from about 0.01mg to about 25 mg of vitamin B_{12} and from about 50 mg to about 600 mg of SNAC. More preferably, each tablet contains from about 0.02 mg to about 20 mg of vitamin B_{12}. More preferably, each tablet contains from about 0.1 mg to about 10 mg of vitamin B_{12}. The most preferably, each tablet contains about 15 to 20 mg of vitamin B_{12} and about 50 to 100 mg of SNAC, or about 0.1 to 1.5 mg of vitamin B_{12} and about 25 to 150 mg of SNAC.

[0022] In another preferred embodiment, the tablet further contains at least one of a carrier, excipient, emulsifier, stabilizer, sweetener, flavoring agent, diluent, coloring agent, solubilizing agent or combinations thereof.

[0023] In another preferred embodiment, the tablet optionally contains from about 1 to 25 mg of Capmul PG-8 and optionally contains from about 0.5 to 10 mg of providone. Preferably, Capmul PG-8 is in an amount from about 2 to 20 mg and

Providone is in an amount from about 1 to 8 mg. Preferably, Capmul PG-8 is in an amount from about 5 to 15 mg and the Providone is in an amount from about 1.5 to 5 mg. More preferably, Capmul PG-8 is in an amount from about 5 to 10 mg and Providone is in an amount from about 1.5 to 5 mg.

[0024] Without intending to be bound by any particular theory of operation, it is believed that gastrointestinal absorption of vitamin B_{12} depends on the presence of sufficient intrinsic factor protein, secreted from gastric parietal cells. The average diet supplies about 10 mcg/day of vitamin B_{12} in a protein-bound form that is available for absorption after normal digestion. Vitamin B_{12} is bound to intrinsic factor during transit through the stomach; separation occurs in the terminal ileum, and vitamin B_{12} enters the mucosal cell for absorption via a receptor mediated process. It is then transported by the transcobalamin binding proteins. A small amount (approximately 1% of the total amount ingested) is absorbed by simple diffusion, but this mechanism is adequate only with very large doses. It is also believed that SNAC will allow B_{12} to bypass its usual receptor mediated process.

[0025] The following examples are given as specific illustrations of the invention. It should be understood, however, that the invention is not limited to the specific details set forth in the examples. All parts and percentages in the examples, as well as in the remainder of the specification, are by weight unless otherwise specified.

[0026] Further, any range of numbers recited in the specification or paragraphs hereinafter describing or claiming various aspects of the invention, such as that representing a particular set of properties, units of measure, conditions, physical states or percentages, is intended to literally incorporate expressly herein by reference or otherwise, any number falling within such range, including any subset of numbers or ranges subsumed within any range so recited. The term "about" when used as a modifier for, or in conjunction with, a variable, is intended to convey that the numbers and ranges disclosed herein are flexible and that practice of the present invention by those skilled in the art using concentrations, amounts, contents, carbon numbers, and properties that are

outside of the range or different from a single value, will achieve the desired result, namely, effective treatment of a subject with vitamin B_{12} deficiency which failed to respond to existing oral vitamin B_{12} tablets as well as pharmaceutical compositions for such treatment.

Example 1. Preparation of *N*-[8-(2-hydroxybenzoyl) amino]caprylic acid and SNAC

[0027] The preparation method for *N*-[8-(2-hydroxybenzoyl) amino]caprylic acid and SNAC involves the following steps: The starting material is salicylamide, which is converted to form Carsalam. The second step involves the alkylation of Carsalam. The penultimate step is a hydrolysis to cleave the ethyl protection group at the end of the alkyl chain and spring open the heterocyclic ring forming the free acid of SNAC. In the final step, the sodium salt of the SNAC free acid is formed by reaction with a 1% excess stoichiometric amount of sodium hydroxide base. Upon cooling the precipitated product is isolated by centrifugation and vacuum dried prior to packaging. The in-process controls for the synthetic scheme are given in Table I.

Table I. In-process controls for SNAC Manufacturing Process.

Step	Reaction	Desired Product	Specification	In-Process Control
1	Carsalam	Carsalam	<10% salicylamide	HPLC
2	Alkylation	Alkylated Carsalam	<8% Carsalam	HPLC
3	Hydrolysis	SNAC Free acid	<0.5%	LOD
4	Sodium Salt	SNAC Sodium salt	95-105%	HPLC

Example 2. Preparation of vitamin B_{12} tablets.

[0028] The tablet die and punches are checked to ensure that they are clean and that their surfaces are dusted with magnesium stearate powder. Vitamin B_{12}, SNAC, carrier, excipient, emulsifier, stabilizer, sweetener, flavoring agent, diluent, coloring agent, solubilizing agent are screened through a #35 sieve and transferred into a sealed

containers. 50 mg of Vitamin B_{12} is weighed and mixed thoroughly with 11 grams of a carrier, excipient, emulsifier, stabilizer, sweetener, flavoring agent, diluent, coloring agent and/or solubilizing agent. 100 vitamin B_{12} tablets are made, with each tablet containing 0.5 mg of Vitamin B_{12} and 110 mg of a carrier, excipient, emulsifier, stabilizer, sweetener, flavoring agent, diluent, coloring agent and/or solubilizing agent. These tablets are used as a control.

Example 3. Preparation of Vitamin B_{12} and SNAC tablets

[0029] 50 mg of Vitamin B_{12}, 1 gram of SNAC are weighed and thoroughly mixed with 10 grams of a carrier, excipient, emulsifier, stabilizer, sweetener, flavoring agent, diluent, coloring agent and/or solubilizing agent. 100 vitamin B_{12} tablets are made, with each tablet containing 0.5 mg of Vitamin B_{12}. 10 mg of SNAC and 100 mg of a carrier, excipient, emulsifier, stabilizer, sweetener, flavoring agent, diluent, coloring agent and/or solubilizing agent. The process is repeated to make tablet batches containing 1.0 mg, 0.8 mg, 0.6 mg, 0.4 mg and 0.2 of Vitamin B_{12}, respectively. These tablets have the following specifications for release of SNAC component:

Tests	Specification	Analytical Method
Appearance	White to light-tan powder with pink hue	AM001
Identification Test for Sodium FTIR	 Confirms presence of Sodium Conforms to reference standard	 USP <191> USP <197K>
Melting Range/Temperature	193 – 203 °C with a range not to exceed 5°C	USP <741>
Water Content	NMT 3.0 %	USP <921> Method I
Heavy Metals	< 20 ppm	USP <231> Method II
Sodium Content	6.9 to 8.4 %	AM017
Residual Solvents Ethanol Heptane	 Less than 4000 ppm Less than 500 ppm	 AM008 AM008
Assay as SNAC Sodium salt (As Is)	90.0 – 110.0 % w/w	AM016

Example 4. Preparation of Tablets for Testing on Rats

[0030] Tablets with four types of different ingredients were made as follows: (1) 8.8 mg of vitamin B_{12}, 35 mg of SNAC were weighed, thoroughly mixed and made into a tablet for dosing on rat; (2) 8.8 mg of vitamin B_{12}, 35 mg of SNAC and 5 mg of Capmul PG-8 were weighed, thoroughly mixed and made into a tablet; (3) 8.8 mg of vitamin B_{12}, 35 mg of SNAC and 0.9 mg of Providone were weighed, thoroughly mixed and made into a tablet. Each of the four proceeses was repeated to produce more tablets.

Example 5. Dosing Sprague-Dawley Rats

[0031] Male Sprague-Dawley rats (325-350g) were dosed with vitamin B_{12} intravenously (0.5 mg/kg) alone, or orally with the tablets made in Example 4 at a dose of 50 mg/kg vitamin B_{12} alone or in combination with SNAC at 200 mg/kg. Blood samples were collected at 0, 3, 10, 20, 30, 60, 120, 240 and 360 minutes post dosing. Plasma samples were analyzed for B12 by RIA. The model independent PK metrics obtained following B12-SNAC combination were compared to those obtained following B12 alone. The testing results are shown in Table 1.

Table 1. Comparative Testing Results for Vitamin B_{12} Absorption

Group (N=5)	*Cmax (ug/mL)*		*Tmax (min)*		*AUC (ug*min/mL)*		Mean Bioavailability
	Mean	S.D	Mean	S.D	Mean	S.D	%
0.5mg/kg Vitamin B_{12} (IV)	2.15	0.64	4.4	3.13	65.84	11	
50mg/kg Vitamin B_{12} alone (PO)	0.14	0.07	52	17.9	28.72	13	0.42
50mg/kg Vitamin B_{12} + 200mg/kg SNAC (PO)	7.99	2.41	24	5.48	522.37	179	7.93

Example 6. Preparation of Tablets for Testing on Human Subjects

[0032] Tablets were made from Cyanocobalamin, SNAC, Kollidon 90F, Anhydrous Emcompress USP/EP and Magnesium Stearate, NF/BP/EP/JP. Each tablet contains the followings:

Ingredients	mg/tablet
Cyanocobalamin, USP (Intragranular)	5.00
SNAC (Intragranular)	100.00
Kollidon 90F, NF/EP/JP (Providone K90; Intragranular)	2.00
Anhydrous Emcompress USP/EP (Diabasic Calcium Phosphate, Anhydrous; Intragranular)	70.00
Anhydrous Emcompress USP/EP (Diabasic Calcium Phosphate, Anhydrous; Extragranular)	21.00
Magnesium Stearate, NF/BP/EP/JP (extragranular)	2.00
Total Weight	200.0

Example 7. Dosing Human Subjects

[0033] Sixteen healthy male subjects were randomized to receive one of the following treatments:

(1) Treatment B: a single oral dose of cyanocobalamin/SNAC (5 mg cyanocobalamin/ 100 mg SNAC) administered in the fasted state as a tablet. (6 subjects);

(2) Treatment C: a single oral dose of cyanocobalamin alone (5 mg cyanocobalamin, VitaLabs, commercial) administered in the fasted state as a tablet. (6 subjects).

(3) Treatment D: a single intravenous dose of cyanocobalamin (1 mg cyanocobalamin) administered in the fasted state. (4 subjects). Each subject received a 1 mL intravenous injection of a 1 mg/mL (1000 μg/mL) solution resulting in a total dose of 1 mg cyanocobalamin.

The subjects were fasted overnight prior to dosing and had no liquids (including water) consumption for at least one hour before and after dosing. The oral forms of cyanocobalamin/SNAC tablets were administered in a single dose as tablets with 50 mL

of plain water. Twenty-five blood samples were drawn for cyanocobalamin analyses at the following time points: within 30 minutes pre-dose and at Minutes 2, 5, 10, 20, 30, 40, 50, and at Hours 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 20 and 24 post-dose.

Pharmacokinetic metrics was obtained following a model independent pharmacokinetic analysis of individual cyanocobalamin concentrations. Descriptive statistics was used to summarize the results.

Following 1 tablet of 5 mg B12/ 100 mg SNAC mean B12 peak concentration is 12847 ± 6613 pg/mL and occur within 1 hour post dose (mean tmax of 0.50 ± 0.21 hours). Mean AUClast (0-24) value is 54618 ± 16392 hr*pg/mL. The percent coefficient of variation (%CV) is 51.5% for Cmax and 30.0% for AUC.

Following a single oral dose of cyanocobalamin alone (5 mg cyanocobalamin, VitaLabs, commercial) mean B12 peak concentration is 1239 ± 450 pg/mL and occur between 3 to 10 hours post-dose (mean tmax of 6.8 ± 3.2 hours). Mean AUClast (0-24) value is 23131 ± 8343 hr*pg/mL. The percent coefficient of variation (%CV) is 36.3% for Cmax and 36.1% for AUC.

Following a single intravenous dose of cyanocobalamin (1 mg cyanocobalamin) administered in the fasted state (4 subjects). Mean B12 peak concentration is 221287 ± 80248 pg/mL and mean AUClast (0-24) value is 215391 ± 44602 hr*pg/mL. The percent coefficient of variation (%CV) is 36.3% for Cmax and 20.7% for AUC.

The mean bioavailability of 1 tablet of 5 mg vitamin B12 alone, 1 tablet of 5 mg vitamin B12/100 mg SNAC, and 2 tablets of 5 mg vitamin B12/ 100 mg SNAC are 2.15 ± 0.77%, 5.07 ± 1.52, and 5.92 ± 3.05 %, respectively. (Note: 2 tablets of 5 mg vitamin B12/ 100 mg SNAC were dosed previously in a pilot arm are designated Treatment A).

The mean tmax of 1 tablet of 5 mg vitamin B12 alone, 1 tablet of 5 mg vitamin B12/100 mg SNAC, and 2 tablets of 5 mg vitamin B12/ 100 mg SNAC are 6.8 ± 3.2 hours, 0.50 ± 0.21 hours, and 0.54 ± 0.32 hours, respectively.

No adverse events were observed during the given treatments. All formulations appear to be safe and well tolerated.

It was found surprisingly that the extent of B12 absorption, measured as Cmax and AUC, was significantly enhanced by the administration of the cyanocobalamin/SNAC combination. Vitamin B12 bioavailability was ~240 % greater for the 1 tablet of 5 mg

B12/ 100 mg SNAC compared to 5 mg B12 commercial formulation. Mean peak B12 concentrations following B12 commercial oral formulation occurred significantly later compared to that following the B12/SNAC combinations likely due to a different site of absorption between the two oral formulations. This is consistent with literature data describing intestinal absorption of B12 occurring in the distal section of the gastrointestinal tract in the absence of the carrier.

[0034] The principles, preferred embodiments, and modes of operation of the present invention have been described in the foregoing specification. The invention which is intended to be protected herein, however, is not to be construed as limited to the particular forms disclosed, since these are to be regarded as illustrative rather than restrictive. Variations and changes may be made by those skilled in the art, without departing from the spirit of the invention.

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The claims defining the invention are as follows:

1. A method for treating vitamin B_{12} deficiency in a subject in need thereof, comprising administering (1) vitamin B_{12} and (2) at least one substance selected from the group consisting of *N*-[8-(2-hydroxybenzoyl) amino]caprylic acid and its pharmaceutically acceptable salts to said subject.

2. A method according to claim 1, wherein said subject had failed to respond to existing oral vitamin B_{12} treatment.

3. A method according to claim 1 or 2, wherein (1) and (2) are administered as a pharmaceutical composition.

4. A method according to claim 3, wherein said pharmaceutical composition comprises from about 0.01mg to about 25 mg of vitamin B_{12} and from about 1 mg to about 600 mg of sodium *N*-[8-(2-hydroxybenzoyl) amino]caprylate.

5. A method according to claim 3, wherein said pharmaceutical composition comprises from about 0.02 mg to about 25 mg of vitamin B_{12}.

6. A method according to claim 3, wherein said pharmaceutical composition comprises from about 0.1 mg to about 20 mg of vitamin B_{12}.

7. A method according to claim 3, wherein said pharmaceutical composition comprises about 0.5 mg of vitamin B_{12} and about 17.5 mg of sodium *N*-[8-(2-hydroxybenzoyl) amino]caprylate.

8. A method according to any one of claims 1 to 7, wherein the weight ratio of vitamin B_{12} to sodium *N*-[8-(2-hydroxybenzoyl) amino]caprylate is from about 2:1 to about 1:700.

9. A method according to claim 8, wherein said weight ratio is from about 1:2 to about 1:600.

10. A method according to claim 8, wherein said weight ratio is from about 1:3 to about 1:20.

11. A method according to claim 8, wherein said weight ratio is about 1:4.

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12. A method according to claim 8, wherein said weight ratio is from about 1:500 to about 1:700.

13. A method according to any one of claims 3 to 12, wherein said pharmaceutical composition further comprises at least one of a carrier, excipient, emulsifier, stabilizer, sweetener, flavoring agent, diluent, coloring agent, solubilizing agent or combinations thereof.

14. A pharmaceutical composition comprising (1) vitamin B_{12} and (2) at least one substance selected from the group consisting of *N*-[8-(2-hydroxybenzoyl) amino]caprylic acid and its pharmaceutically acceptable salts.

15. A pharmaceutical composition according to claim 14, wherein said pharmaceutical composition is a tablet.

16. A pharmaceutical composition according to claim 15, wherein said tablet comprises from about 0.01mg to about 25 mg of vitamin B_{12} and from about 50 mg to about 600 mg of sodium *N*-[8-(2-hydroxybenzoyl) amino]caprylate.

17. A pharmaceutical composition according to claim 15, wherein said tablet comprises from about 0.02 mg to about 20 mg of vitamin B_{12}.

18. A pharmaceutical composition according to claim 15, wherein said tablet comprises from about 0.1 mg to about 10 mg of vitamin B_{12}.

19. A pharmaceutical composition according to claim 15, wherein said tablet comprises about 1 to 15 mg of vitamin B_{12} and about 50 to 200 mg of sodium *N*-[8-(2-hydroxybenzoyl) amino]caprylate.

20. A pharmaceutical composition according to any one of claims 14 to 19, further comprising at least one of a carrier, excipient, emulsifier, stabilizer, sweetener, flavoring agent, diluent, coloring agent, solubilizing agent or combinations thereof.

21. A method according to any one of claims 3 to 13, wherein said pharmaceutical composition is a tablet.

22. A method according to any one of claims 1 to 13 and 21, wherein, upon oral administration of the pharmaceutical composition, the T_{max} of the vitamin B_{12} is decreased.

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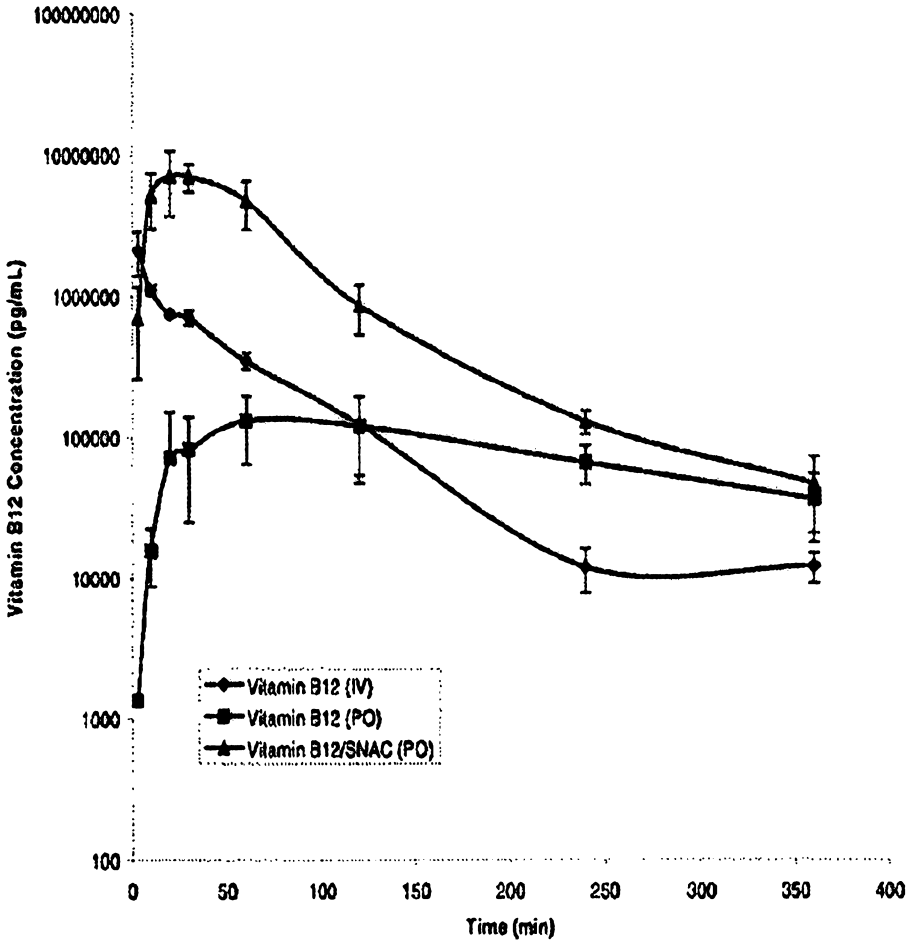
23. A pharmaceutical composition according to any one of claims 14 to 20, wherein, upon oral administration of the pharmaceutical composition, the T_{max} of the vitamin B_{12} is decreased.

Figure 1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1000
100
Vitamin B12 Concentration (pg/mL)
0
50
100
150
200
250
300
350
400
Time (min)
Vitamin B12 (IV)
Vitamin B12 (PO)
Vitamin B12/SNAC (PO)