United States Patent Office 2,939,820 Patented June 7, 1960

2,939,820

AQUEOUS VITAMIN AND MINERAL COMPOSITIONS

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No Drawing. Filed June 11, 1956, Ser. No. 590,790

10 Claims. (Cl. 167—81)

This invention is concerned with aqueous vitamin and mineral compositions containing vitamin B_{12}, ascorbic acid, and a pharmaceutically acceptable form of iron such as ferrous gluconate, ferrous sulfate, ferric ammonium citrate, peptonized iron, ferric glycerophosphate, and reduced iron. These substances are normally incompatible in aqueous preparations and heretofore have not been provided in a single composition of this type.

Vitamin B_{12} is a highly useful substance which has proven particularly necessary in the nutrition of animals including humans. However, this vitamin and the related compounds having vitamin B_{12} activity, that is vitamin B_{12}, B_{12b}, B_{12c}, and other related substances are normally unstable and particularly when combined in solution with ascorbic acid or with iron-containing components. Furthermore, the decomposition of ascorbic acid is known to be catalyzed by metals including iron in various forms. This has been a troublesome problem in the art for some time since it is often highly desired to prepare multivitamin and mineral compositions containing each of these substances.

The preparation of such compositions has been possible to some extent, although not without complications, in the case of solid pharmaceutical preparations by effecting physical separation of the incompatible components. This has ordinarily been accomplished by coating the particles with inert materials, such as ethyl cellulose or magnesium stearate, but this has the disadvantage of reducing, in some instances, the physiological availability of the active components.

The incompatibility of ascorbic acid and iron with vitamin B_{12} active substances is particularly notorious in aqueous solution. This has militated against the preparation of liquid compositions wherein these ingredients are present in solution because no pharmaceutically acceptable non-aqueous solvents for these materials are known. This difficulty has been circumvented to a limited degree by resort to suspensions in non-solvent vehicles for the vitamin B_{12}, ascorbic acid and the iron compound. However, suspensions have obvious disadvantages from the standpoint of convenience and ease of administration, and in addition the danger is ever-present that inadequate mixing before use will result in failure to obtain the proper balance of ingredients.

As a result of the present invention stable liquid compositions containing vitamin B_{12} active materials with ascorbic acid and iron in various forms are provided by employing as a vehicle a liquid containing a minor proportion of water say up to about 30% and a major proportion of a polyol which in addition to being highly water soluble has a water binding capacity. The polyols are aliphatic hydrocarbon derivatives in which two or more carbon atoms bear hydroxyl groups. This water-binding capacity is possessed by a variety of polyols such as glycerol, trimethylene glycol, propylene glycol, and the hexitols such as sorbitol which are derived from the hexoses by reduction. Gums such as carboxymethyl cellulose and guar gum, and gelatin have a water binding capacity and are also useful components of the vehicles employed in the compositions of this invention. Sugar syrups which contain reducing sugars are not satisfactory for this use despite their water binding capacity. This is thought to be due to the incompatibility of the vitamin B_{12} active substances with the reducing sugars.

A preferred vehicle for the compositions of the present invention comprises sorbitol of from about 50% to 75% concentration. Sorbitol is a preferred vehicle for the above use, not only because of its high water solubility and its stabilizing effect on the vitamin B_{12} activity, but also because it has a sweet taste. Other polyols may of course be employed so long as they are pharmaceutically acceptable, have a high aqueous solubility, and have this water binding activity referred to above.

The lower polyols such as glycerol and propylene glycol alone are not suitable as vehicles for oral use because of their poor taste and palatability and for parenteral use because of their irritating propensities. Polyols containing from about five to seven carbon atoms are in general preferred. The anhydropolyols such as the hexitans and hexides are also satisfactory. The most critical limitation on the selection of the polyol solvent is that it contain at least about five carbon atoms and that it contain no reducing group such as the aldehyde or ketone group. The addition of soluble gums such as carboxymethyl cellulose or guar gum referred to above to the polyol vehicles appreciably assists in obtaining compositions having highly desirable properties in some instances. Ethanol can also be advantageously employed in the vehicle of this invention. In addition to its solvent power which makes it useful in the incorporation of other solutes, its use is also convenient for viscosity control.

To summarize then, the unique liquid vehicles of the present compositions comprise a minor proportion of water, up to about 30%, and from about 50 to 75% of a polyvol or an anhydro derivative thereof containing five or more carbon atoms. Sorbitol and sorbitol containing minor proportions of glycerol, ethanol, propylene glycol, carboxymethyl cellulose, etc., are preferred vehicles. Ordinarily the maximum quantity of ethanol and/or lower polyol present is less than about half the volume of the final vehicle volume. When carboxymethyl cellulose is included as a component of the vehicle it is used in a very minor proportion, for example, less than about 5–10 mg./ml. Actually a vehicle comprising approximately 70% sorbitol and 30% water is satisfactory in most instances and the other components such as the lower polyols containing less than five carbon atoms, ethanol, and gums such as carboxymethyl cellulose are added only when they are needed to modify the physical properties of the vehicles such as viscosity, taste, palatability, and solvent power in the particular preparation at hand. The resulting compositions are viscous liquid preparations which may be administered readily to patients to furnish a suitable dosage of vitamin B_{12}, ascorbic acid, iron and other vitamins and minerals.

For preparations intended for oral use such as tonics, hematinics, etc. 0.05–3 g. of ascorbic acid per fluid ounce has been found to be a convenient concentration range to employ. Similarly, 10–50 mcg. of vitamin B_{12} activity per ounce and about 10–150 mg. of iron in a suitable form, such as one of those listed above, per ounce of composition is suitable for oral formulations. Of course, the amount of the iron compound employed will depend upon its solubility and the exact amount of iron contained therein. When ferrous gluconate serves as the iron-containing ingredient, 50–600 mg./oz. is used. For parenteral use the above components are generally employed at the higher concentrations listed. Somewhat higher concen-

trations may be employed, but this is not normally necessary.

In addition to the compositions containing only vitamins and minerals, other specific embodiments of this invention include compositions containing therapeutic agents such as hormones. In anti-inflammatory hormone therapy the incorporation of vitamins and minerals including vitamin B_{12}, ascorbic acid, and iron into oral preparations containing an anti-inflammatory steroid hormone, e.g. cortisone, hydrocortisone, prednisone, prednisolone, etc., has proven useful. Still further embodiments of this invention incorporating therapeutic components into nutritional supplements are geriatric preparations or tonics which contain a variety of products included for their gonadotropic, metabolic, and anti-depressant effect. Therapeutic components that have been used for the above purposes include androgens and estrogens such as methyltestosterone and ethinylestradiol, thyroxine for its stimulating effect on anabolism, and amphetamine salts for their stimulating effect on the central nervous system.

Specific examples of various embodiments of the sort just described appear hereinafter. While the compositions of this invention are usually administered orally, they are suitable for parenteral use as well. One reason for the predominance of oral use is that they are ordinarily taken on a daily basis by the patient at home. Oral administration of course is preferred for this type of regimen. Parenteral administrtion is preferred in instances where nausea or extreme debility is involved. For maximum stability, the viscosities are preferably greater than about 100 centipoises. Compositions having viscosities in the range of about 100 to 400 centipoises are syringeable.

A preferred procedure for preparing the compositions of this invention involves dissolving the iron salt, for example ferrous gluconate, ferrous ammonium citrate or ferrous sulfate in the sorbitol at an elevated temperature say 70 to 100° C. Other components that are stable at the elevated temperature such as riboflavin and niacin amide are then dissolved and then the mixture is cooled and the ascorbic acid and remaining vitamins are added. The vitamin B_{12} component is ordinarily added toward the end of the procedure. When it is desired to employ sodium carboxymethyl cellulose, guar gum or gelatin as a thickener, the thickener is first dissolved in glycerol and then this solution is added to the main batch. Certain materials are conveniently added by first dissolving in dilute alkali and then adding this solution to the main solution of the other materials in the polyol vehicle. Folic acid and thyroxin are examples of materials that are conveniently added in this fashion. When steroid materials are employed such as hydrocortisone, ethinylestradiol and methyltestosterone, these materials are added by first dissolving in the minimum quantity of ethanol and then adding this solution to the polyol vehicle containing the other components. D-amphetamine sulfate can also be added in this fashion. A final stage of the preparation involves adjusting the pH to approximately 4–5. This can be done with a concentrated solution of citric acid in 70% aqueous sorbitol in the case of alkaline mixtures and with sodium bicarbonate in the case of acidic mixtures. Specific examples of detailed preparations appear hereinafter.

The stability of these preparations was demonstrated by a series of storage tests in which the compositions were stored at various temperatures and assayed at periodic intervals. It was found that at room temperature and below the preparations were highly stable for periods of at least six months. The stability of any particular preparation of course depends somewhat on the other components such as flavors, dyes, and other therapeutic agents contained therein in addition to the vitamin B_{12}, ascorbic acid, and the iron. In some instances a loss in B_{12} activity of as much as 20% was observed in 6 months, but a loss even of this size is neglibible compared to that ordinarily encountered in liquid compositions containing vitamin B_{12}, ascorbic acid, and iron, and can be provided for by using an excess or overage of the material beyond the dosage requirement under consideration. For comparison purposes, an aqueous solution containing in addition to ascorbic acid and vitamin B_{12}, sodium benzoate preservative was tested. This solution contained 1.67 mg. per ml. of ascorbic acid and 0.5 mcg./ml. of vitamin B_{12} at the outset. In less than 2 weeks the vitamin B_{12} activity had decreased to about .01 mcg./ml. or by a factor of roughly 50. In the same period the ascorbic acid activity had decreased to 1.13 mgm./ml. corresponding to a loss of about one-third. Within two and one-half weeks the mixture had darkened and there was vitrtually no remaining vitamin B_{12} or ascorbic acid activity. This is in startling contrast to the stability observed for the valuable compositions of the present invention which are given in detail hereinafter.

In the stability tests the vitamin B_{12} and ascorbic acid assays were carried out by standard assay procedures as described in the United States Pharmacopeia, vol. XV. The peroxide modification was employed in those samples containing ferrous salts to eliminate interference from them. This modification is described in "Vitamin Methods," volume I, Academic Press, New York (1950), by Paul Gyorgy. The vitamin B_{12} assay procedure was a microbiological method of the turbidimetric type employing *Lactobacillus leichmannii* as the test organism.

Various dyes, flavors, taste-masking substances, and sweetening agents can be employed in the above compositions to improve their palatability and appeal. Caramel, lemon, peach, menthol, cocoanut, apricot, pineapple, quince and mint flavors have been found to be particularly suitable. Suitable sweetening agents include for example sodium saccharin. Dyes which have been approved for drug use that have been employed include D & C red, No. 33; D & C red, No. 19; and D & C yellow, No. 10.

In many instances it is desirable to employ a preservative in the composition to prevent the growth of microorganisms. Molds are particularly troublesome if preservatives are not employed. It is preferred to avoid the use of red-ox type preservatives such as sodium bisulfite or phenolic types. Preferred preservatives include the parabens, sodium benzoate, sodium propionate and the quaternary ammonium types such as cetylpyridinium chloride and benzalkonium chloride. A small proportion of preservative is employed, generally less than about 5 mg./ml.

The following examples are given to further illustrate the invention and are not considered to be limiting thereof in any way.

EXAMPLE I

Hormone-tonic composition

A liquid composition was prepared containing the following materials. The amounts indicated are those contained in each fluid ounce of the finished composition.

Hydrocortisone	mg.	10
Thiamin	mg.	2
Riboflavin	mg.	0.1
Niacinamide	mg.	10
Pyridoxine	mg.	1
Ascorbic acid	mg.	50
Vitamin B_{12}	mcg.	15
Ferrous gluconate	mg.	100
Liver fraction No. 1, N.F.	mg.	300
70% aqueous sorbitol (weight basis)	ml.	20.25
Glycerol	ml.	6.75
Sodium carboxymethyl cellulose (Hercules Powder Company) Type 70–LV	mg.	135
Ethanol	ml.	3

The sodium carboxymethyl cellulose was dissolved in the glycerol by heating to 110–115° C. under an atmos-

phere of nitrogen. The solution was then allowed to cool to room temperature and maintained in a nitrogen atmosphere until required below. Similarly, the hydrocortisone was dissolved in the ethanol and kept under an atmosphere of nitrogen until needed. The sorbitol vehicle was warmed to 100° C. wtih adequate precautions to prevent evaporation, and the ferrous gluconate dissolved in it with stirring. The mixture was cooled to 70° C. and the riboflavin and niacinamide added. Stirring and heating at 70° C. were continued until these materials were completely dissolved. The solution was then cooled to 20–25° and the ascorbic acid, pyridoxine, thiamin and vitamin B_{12} added consecutively in that order with stirring after each addition until the material had completely dissolved. The liver fraction was then dispersed in the solution and the formulation completed by adding the ethanolic hydrocortisone solution and the carboxymethylcellulose-glycerine solution prepared above. The pH of this preparation was approximately 5 and the viscosity in the range 300–400 centipoises. The specific gravity was about 1.3.

In a storage test the vitamin B_{12} and ascorbic acid activities of this composition were without loss after 6 months at room temperature.

A similar composition was prepared in which flavors were added to increase the palatability of the product. The following flavors were added to the above formula: imitation butter carmel flavor (Alva, No. 3261), 0.03 ml.; and imitation floral mint (Alva, No. 3236), 0.003 ml.

Other preparations were prepared substituting prednisone and prednisolone for the hydrocortisone. In each of these formulations 3.0 mg. of the hormone was used.

EXAMPLE II

Gariatric liquid tonic composition

A composition was prepared containing the following materials in each fluid ounce.

Ferrous gluconate	mg..	180
Ascorbic acid	mg..	300
D-amphetamine sulfate	mg..	3
Folic acid	mg..	100
Vitamin B_{12}	mcg..	15
Thyroxine	mg..	6
Ethinylestradiol	mcg..	6.0
Methyltestosterone	mg..	6.0
Liver fraction No. 1, N.F.	mg..	150

The vehicle employed consisted of ethanol, 3 ml.; a 70% sorbitol solution on a weight basis, 20.2 ml.; glycerol, 6.8 ml.; carboxymethylcellulose (Hercules Powder Company, Type 70–LV), 135 mg.

These materials were compounded in much the same fashion as in Example I. Stock solutions were first prepared of the carboxymethylcellulose in the glycerol; of the ethinylestradiol, methyltestosterone and D-amphetamine sulfate in the ethanol; and of the thyroxine and folic acid in a small volume of 0.1 N sodium hydroxide. The ferrous gluconate was then dissolved in the sorbitol at 70° C., the solution cooled to room temperature, and the ascorbic acid added followed by the sodium hydroxide solution of the thyroxine and folic acid, the vitamin B_{12}, and the liver fraction. The ethanolic solution of the ethinylestradiol, methyltestosterone, and D-amphetamine sulfate was then added, followed by the the glycerol solution of carboxymethyl cellulose. As a final step the pH was adjusted to 4.0–4.2 with a concentrated solution of citric acid in 70% aqueous sorbitol.

The following flavors were added in some batches to increase the palatability of the composition; menthol, U.S.P. 0.017 g.; cocoanut flavor (Dolco No. 5245), 0.084 ml.; apricot aroma (Polak), 0.033 ml.; pineapple flavor (Busch No. 4253), 0.033 ml.

In storage tests, the vitamin B_{12} activity was found to decrease by about 20% in 6 months at 37° C. These losses were compensated for by including a 20% excess of these materials in the composition over the normal requirement.

EXAMPLE III

Pediatric hematinic liquid preparation

A liquid composition containing the following materials in each fluid ounce was prepared.

Ascorbic acid	mg..	600
Vitamin B_{12}	mcg..	12
Ferrous gluconate	g..	0.518
70% aqueous sorbitol (weight basis)	ml..	30

The ferrous gluconate was dissolved in the 70% sorbitol at 70° C. with stirring. The mixture was then cooled to 25° and the ascorbic acid dissolved followed by the vitamin B_{12}. The pH of the composition was adjusted to 4.0 with sodium bicarbonate.

The following flavors can be added to the above composition to improve its palatability; imitation butter caramel flavor (Alva No. 3261), 0.03 ml.; imitation floral mint flavor (Alva No. 3236), 0.003 ml.; imitation lemon (Fritsche No. 23463), 0.0015 ml.

In storage tests at room temperature the vitamin B_{12} activity was found to be still stable and without change after 6 months. In 6 months at 37° C., the ascorbic acid activity decreased by about 25%. Considerably smaller decreases were observed at room temperature. This loss was generally provided for by including a 25% excess of ascorbic acid over the labeling statement.

What is claimed is:

1. A liquid pharmaceutical preparation comprising a vitamin B_{12} active substance, ascorbic acid, and a pharmaceutically acceptable form of iron in a vehicle comprising from about 50 to 75% of a substance selected from the group consisting of an aliphatic hydrocarbon polyol containing at least five carbon atoms, and the anhydro derivatives thereof, and up to about 30% of water, said vitamin B_{12} active substance, ascorbic acid, and iron being present in therapeutically effective amounts.

2. A liquid pharmaceutical preparation as claimed in claim 1 containing also a therapeutically effective amount of an anti-inflammatory steroid hormone.

3. A liquid pharmaceutical preparation as claimed in claim 1 containing also a therapeutically effective amount of an androgenic steroid hormone.

4. A liquid pharmaceutical preparation as claimed in claim 1 containing also a therapeutically effective amount of an estrogenic steroid hormone.

5. A liquid pharmaceutical preparation as claimed in claim 1 containing also a therapeutically effective amount of an anabolic steroid hormone.

6. A liquid pharmaceutical preparation comprising a vitamin B_{12} active substance, ascorbic acid, a pharmaceutically acceptable form of iron, and methyltestosterone in a vehicle comprising from about 50 to 75% of a substance selected from the group consisting of an aliphatic hydrocarbon polyol containing at least five carbon atoms and the anhydro derivatives thereof and up to about 30% of water, said vitamin B_{12} active substance, ascorbic acid, iron, and methyltestosterone being present in therapeutically effective amounts.

7. A liquid pharmaceutical preparation comprising a vitamin B_{12} active substance, ascorbic acid, a pharmaceutically acceptable form of iron, and ethinylestradiol in a vehicle comprising from about 50 to 75% of a substance selected from the group consisting of an aliphatic hydrocarbon polyol containing at least five carbon atoms and the anhydro derivatives thereof and up to about 30% of water, said vitamin B_{12} active substance, ascorbic acid, iron, and ethinylestradiol being present in therapeutically effective amounts.

8. A liquid pharmaceutical preparation comprising a vitamin B_{12} active substance, ascorbic acid, a pharmaceutically acceptable form of iron, and hydrocortisone

in a vehicle comprising from about 50 to 75% of a substance selected from the group consisting of an aliphatic hydrocarbon polyol containing at least five carbon atoms and the anhydro derivatives thereof and up to about 30% of water, said vitamin B_{12} active substance, ascorbic acid, iron, and hydrocortisone being present in therapeutically effective amounts.

9. A liquid pharmaceutical preparation comprising a preparation comprising a vitamin B_{12} active substance, ascorbic acid, a pharmaceutically acceptable form of iron, and prednisone in a vehicle comprising from about 50 to 75% of a substance selected from the group consisting of an aliphatic hydrocarbon polyol containing at least five carbon atoms and the anhydro derivatives thereof and up to about 30% of water, said vitamin B_{12} active substance, ascorbic acid, iron, and prednisone being present in therapeutically effective amounts.

10. A liquid pharmaceutical preparation comprising a vitamin B_{12} active substance, ascorbic acid, a pharmaceutically acceptable form of iron, and prednisolone in a vehicle comprising from about 50 to 75% of a substance selected from the group consisting of an aliphatic hydrocarbon polyol containing at least five carbon atoms and the anhydro derivatives thereof and up to about 30% of water, said vitamin B_{12} active substance, ascorbic acid, iron, and prednisolone being present in therapeutically effective amounts.

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