

[54] **TWO COMPARTMENT ONE UNIT
CONSECUTIVELY INJECTABLE LIQUID
VITAMIN PACKAGE**

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Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 384,995, Aug. 2, 1973, abandoned.

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[51] Int. Cl.² **A61K 31/59**

[58] Field of Search 424/237, 255, 280, 344

[56] **References Cited**

UNITED STATES PATENTS

2,811,483	10/1957	Aterno et al.	424/344
2,823,167	2/1958	Newark et al.	424/201

2,835,627	5/1958	Conine et al.	424/280
2,846,352	8/1958	Bryant	424/280
2,914,446	11/1959	MacDonald	424/280
2,939,821	6/1960	Freedman et al.	424/280
2,939,829	6/1960	Gerber et al.	424/280
2,959,520	11/1960	Kawasiri	424/255
3,168,440	2/1965	Meyer	424/104
3,626,065	12/1971	Maerawa et al.	424/280

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[57] **ABSTRACT**

A stable liquid multivitamin preparation in injectable form contains thiamine (B₁), riboflavin (B₂), niacinamide, pyridoxine (B₆), B₁₂ (cyanocobalamin), and optionally biotin and dexpantenol in one phase at pH 4.5 to 5.5; and in a second phase, at pH 6.8 to 7.6, sodium ascorbate (C), folic acid, and niacinamide, and optionally Vitamins A, D₂ and E so that storage incompatible vitamin components are held in separate compartments of a syringe, in separate phases, for consecutive administration from a two compartment syringe; thereby minimizing loss of potency on storage.

5 Claims, 3 Drawing Figures

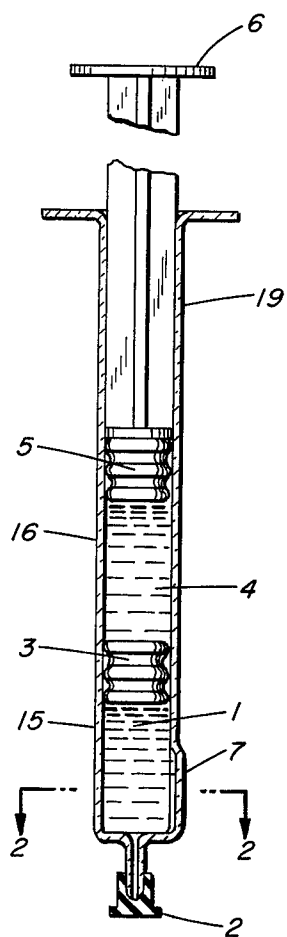


FIG. 1

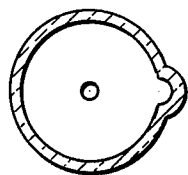


FIG. 2

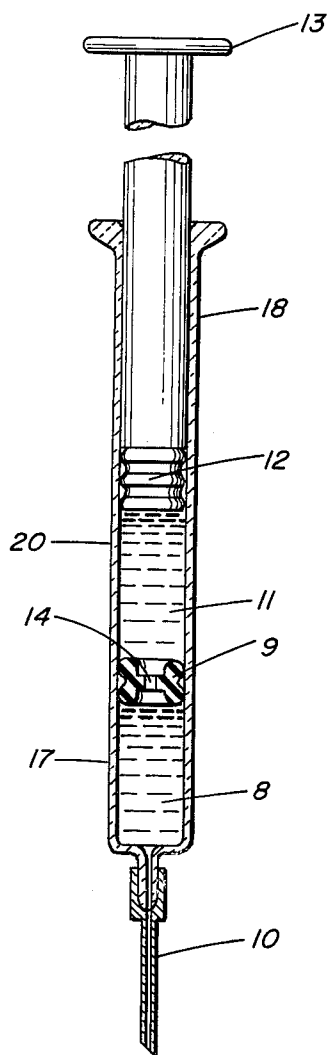


FIG. 3

TWO COMPARTMENT ONE UNIT CONSECUTIVELY INJECTABLE LIQUID VITAMIN PACKAGE

This application is a continuation-in-part of copending application Ser. No. 384,995, filed Aug. 2, 1973, and now abandoned.

BACKGROUND OF THE INVENTION

This invention is concerned with an improved injectable multivitamin package having two storage incompatible liquid mixtures of vitamins separately maintained in sterile injectable condition and capable of being administered consecutively by intramuscular injection. The mixture may also be injected through a rubber stopper into an intravenous feeding bottle without compromising sterility.

Prior to the development of this invention, the commercial means of providing a mixture of vitamins A, B₁, B₁₂ and C and others in an injectable form was to prepare certain of the vitamins in liquid form while the balance of the vitamins were prepared as a dried powder; or as two liquids in separate packages, usually consisting of an ampul and a vial. Just prior to administration, the powder was dissolved in the liquid and the combination was then injected into the host. This cumbersome method was necessitated by the incompatibility of the various vitamin components. If all of these components were combined in one liquid form, the product would be unstable. If the solution pH of certain of the vitamin components was adjusted to alkaline or acid conditions in order to improve stability, the result was a product which caused irritation at the site of injection, or in which at least some of the vitamins were not storage stable.

Now, for the first time, an injectable multivitamin preparation containing vitamins A, B₁, B₁₂ and C and others in liquid form has been developed which is stable, non-irritating and which, because of its unique mode of maintenance, provides an easy and safe one step method of administering said vitamins.

The advantage of the two component injectable liquid system within one package unit set forth herein, rather than two package injectable units, offers a great convenience to the administrator and danger of contamination is practically eliminated. Current packaging of a product of this type consists of a two package unit, i.e., vial and ampul or two vials. One unit requires reconstitution with the other or withdrawal from each prior to administration. This is considered tedious and sometimes a dangerous practice. The latter involves possible contamination of sample when a common needle used to withdraw from one unit is also used to withdraw from the second, and the danger of glass fragments when one package unit consists of an ampul.

U.S. Pat. No. 3,626,065, Maekawa and Egawa, is concerned with a stable aqueous multivitamin preparation in which vitamin B₁ is isolated from vitamins A and C and nicotinamide. This patent points out that it is known that vitamin B₁, vitamin C and vitamin A are unstable together in aqueous multivitamin preparations. U.S. Pat. No. 3,626,065 states that vitamins B₁ and C are stable against hydrolysis in different pH regions, below pH 4.0 for vitamin B₁ and pH 5.0 to 7.0 for vitamin C.

The U.S. Pat. No. 3,626,065 notes that, in general, the pH of the aqueous multivitamin preparations on the

market is adjusted to stabilize either vitamin B₁ or C, or alternatively, the pH is maintained at pH 4.0-5.0. These methods are unsatisfactory since the former sacrifices one or more vitamins to a specific vitamin and the latter is only a compromise.

Said U.S. Pat. No. 3,626,065 is concerned with a stable aqueous multivitamin preparation stored in a two compartment bottle-type container wherein the two liquid vitamins, vitamin B₁ containing and vitamin A, C, and nicotinamide containing, are admixed together before use. According to said U.S. Pat. No. 3,626,065, the pH of the vitamin A, C, and nicotinamide preparation is maintained at about pH 6, and the pH of the vitamin B₁ preparation below pH 4, at about pH 3.0. Said U.S. Pat. No. 3,626,065 does not disclose consecutive or serial injection of the two separately held vitamin preparations into a host. It is concerned solely with storage and admixture immediately prior to use. Moreover, as will be pointed out herein, the pH of the vitamin B₁ preparation of the present invention is maintained at a pH above 4 in contrast to the U.S. Pat. No. 3,626,065 disclosure of below pH 4.0 (Col. 1, line 32) and at about pH 3.0 (Col. 4, Line 69).

Numerous patents are concerned with and point up the problem of maintaining stable liquid vitamin preparations, for example, U.S. Pat. Nos. 2,939,821; 2,846,352; 2,939,820; 3,168,440; 2,823,167; 2,835,627; 2,914,446; and 2,959,520. However, no art is known which discloses the claimed aqueous multivitamin package or its claimed method of administration.

SUMMARY OF THE INVENTION

The invention here lies in the concept of an injectable, two compartment, one unit, liquid-liquid preparation of vitamins A, B₁, B₁₂ and C and others, maintained separately because of incompatibility and capable of being administered to a host in one step.

Thiamine (B₁), riboflavin (B₂), niacinamide, pyridoxine (B₆), B₁₂ (cyanocobalamin), and optionally biotin and dexpantenol are dissolved in a clear aqueous solution in one phase at a pH of 4.5 to 5.5. In a second phase, at pH 6.8 to 7.6, sodium ascorbate (C), folic acid, and niacinamide, and optionally Vitamins A, D₂ and E are similarly dissolved in a clear aqueous solution. These solutions are consecutively placed, in a conventional manner, in a two compartment syringe, the pH 4.5 to 5.5 phase in one compartment and the pH 6.8 to 7.6 in the other compartment. The purpose of the two compartment syringe is to consecutively, sequentially or serially deliver the two incompatible vitamin preparations which have been separated until the moment of administration.

Surprisingly, at these pH values, the cyanocobalamin (B₁₂) and the thiamine (B₁) are both sufficiently stable for satisfactory shelf life. As taught by Maekawa, et al., the thiamine would be more stable at a more acid pH, but the B₁₂ would be less stable. A small amount of ferrous citrate may be used to control oxidation-reduction so as to permit storage stability.

Because vitamins are characteristically very reactive under body conditions, and catalyze reactions in the host, it is to be expected that they can react with each other and other components, so the formulation of compatible storage stable compositions containing as many different vitamins as can be packaged together has been the subject of much research in the industry.

The type of two compartment syringe is not critical so long as it is capable of maintaining the two liquids separately and administering the two liquids consecutively, sequentially or serially. Suitable two compartment syringes are the two compartment syringe with a conventional by-pass valve such as is manufactured by Becton-Dickenson. Another suitable two compartment syringe is that with a separator valve such as those sold by Century Laboratories, Inc., Turnersville, New Jersey.

Two component syringes with a by-pass are shown in Brown, U.S. Pat. No. 2,717,601, Sept. 13, 1955 and Visser, et al., U.S. Pat. No. 3,330,282, July 11, 1967. A valved free piston in a two-compartment syringe is shown by McConnaughey and Cohen, U.S. Pat. No. 3,091,240, May 28, 1963.

One aspect of the present invention is a stable aqueous multivitamin preparation consisting of two incompatible aqueous vitamin preparations each held in a separate compartment of a two compartment syringe capable of consecutively, or sequentially or serially injecting said preparations into a host, one of which is at a pH of 6.8 to 7.6 containing vitamin A, D, E, C, niacinamide and folic acid; and the other of which is at a pH above 4.5 to 5.5 containing vitamins B₁, B₂, B₆, B₁₂, dextranthenol and niacinamide.

A further aspect of the present invention is the method of administering the above aqueous vitamin preparations to a host serially through a single needle at a single injection.

BRIEF DESCRIPTION OF THE DRAWING

The advantages of the invention as well as specific embodiments and use thereof may be seen by referring to the following description and the accompanying drawing, in which:

FIG. 1 is a by-pass type syringe, with the tip cover in place, capable of maintaining, and upon removal of the tip cover and replacement with a needle for injection, administering the aqueous multivitamin preparations according to this invention.

FIG. 2 is a cross-section across 2—2 in FIG. 1 to more clearly show the by-pass aspect of the syringe of FIG. 1.

FIG. 3 is a separator valve type of syringe capable of maintaining and administering the aqueous multivitamin preparations according to this invention, with the tip cover removed and a needle for injection in place.

DESCRIPTION OF THE INVENTION

With reference to FIG. 1, the aqueous pH 4.5 to 5.5 (vitamin B₁, B₁₂, etc.) preparation is placed in lower chamber 1, in a conventional manner, and is separately retained or maintained therein by container wall 15 of syringe 19, tip cap 2 and divider plug 3. The aqueous pH 6.8 to 7.6 (vitamin C, folic acid, etc.) preparation is placed in upper chamber 4, in a conventional manner, and is separately retained or maintained therein by container wall 16 of syringe 19, divider plug 3 and plunger plug 5.

To use the unit shown by FIG. 1, rubber tip cap 2 is removed, a sterile needle for injection is attached, intravenous infusion or intramuscular penetration is made in the host, and as plunger 6 of syringe 19 is acti-

vated, the host receives an initial injection of the vitamin B₁, B₁₂, etc. preparation from lower chamber 1 followed, as divider plug 3 reaches by-pass valve 7, by a consecutive or sequential or serial injection of the vitamin C, folic acid etc. preparation from upper chamber 4. In such a manner the host conveniently receives, with a maximum of safety, the entire multivitamin preparation contents of the syringe in one step. The storage-incompatible vitamin components, which cause stability problems, are maintained separately and yet the administration of the total vitamin content can be made without irritation to the host in one easy step, obviating the need for mixing components prior to administration.

The order of the multivitamin preparations can be reversed in the two chambers without departing from the scope of the invention.

By serially injecting, the components are injected into a subject at the time any mixing occurs, or for intravenous feeding, are diluted into the intravenous bottle, so as to minimize interaction. In a package system which requires mixing before administration, there is always a chance that the user will mix the components and keep the mixture an undesirably long time. With sequential injection, this misuse by the ultimate user is prevented.

With reference to FIG. 3, the aqueous pH 4.5 to 5.5 (vitamin B₁, B₁₂, etc.) preparation is placed in lower chamber 8, in a conventional manner, and is separately retained or maintained therein by container wall 17 of syringe 18, needle 10 and separator valve 9. The aqueous pH 6.8 to 7.6 (vitamin C, folic acid, etc.) preparation is placed in upper chamber 11, in a conventional manner, and is separately retained or maintained therein by container wall 20 of syringe 18, plunger plug 12 and separator valve 9. Separator valve 9 is made of rubber, or the like, with slit 14 centrally located therein which opens under pressure from plunger 13 permitting the contents of upper chamber 11 to pass through slit 14 into lower chamber 8. Slit 14 in separator valve 9 is closed when not under pressure thereby sealing off upper chamber 11 from lower chamber 8.

To use the unit shown in FIG. 3, intravenous infusion or intramuscular penetration is made with needle 10 in the host, and as plunger 13 of syringe 18 is activated, the host receives an initial injection of the vitamin preparation from lower chamber 8 followed, as plunger 13 moves toward the separator valve 9, and as the contents of lower chamber 8 are emptied, by a consecutive, sequential or serial injection of the vitamin preparation from upper chamber 11. Thus, again, in such a manner the host conveniently receives with a maximum of safety, the total multivitamin content of the syringe in one easy step.

Here again, the order of the multivitamin preparations can be reversed in the two chambers.

The concentrations of the vitamins in the two compartments is in part limited by solubility considerations, but is more controlled by therapeutic considerations. In general, two components of one milliliter each can provide the therapeutically preferred dose for most patients. For special deficiencies, either additional components may be added, or the patient treated with mas-

sive doses for a particular syndrome — but for general usage the following formulation is preferred for a complete multivitamin preparation:

COMPLETE MULTIVITAMIN FORMULA FOR PARENTERAL ADMINISTRATION		
Phase A	Per syringe of 1 milliliter	
vitamin A (as palmitate)	2500 —	10,000 units
vitamin D ₂ crystalline	200 —	500 units
vitamin E	3 —	30 units
ascorbic acid USP as sodium salt)(C)	90 —	500 units
folic acid U.S.P.	0.1 —	1.0 mg.
niacinamide U.S.P.	20 —	35 mg.
polysorbate 80 U.S.P.	50 —	100 mg.
benzyl alcohol - reagent	10 —	15 mg.
propylene glycol	50 —	100 mg.
water for injection U.S.P. qs to pH 6.8 to 7.6	100%	
Phase B	Per syringe of 1 milliliter	
thiamine (as HCl U.S.P.) (B ₁)	1 —	10 mg.
riboflavin USP(as 5'-phosphate, sodium, 70%) (B ₂)	1 —	10 mg.
niacinamide U.S.P.	55 —	65 mg.
pyridoxine (as HCl U.S.P.) (B ₆)	1 —	15 mg.
cyanocobalamin U.S.P.	5 —	25 mcg.
biotin	0 —	100 mcg.
dexpanthenol	0 —	10 mg.
ferrous citrate reagent	0.046	mg.
benzyl alcohol reagent	10 —	15 mg.
water for injection U.S.P. qs to pH 4.5 — to 5.5	100%	

Benzyl alcohol is present in both components. Its function as a preservative and local anaesthetic is well recognized. The polysorbate 80 and propylene glycol serve to insure solubility of the constituents. Ferrous citrate serves to stabilize the vitamin B₁₂. Both biotin and dexpanthenol (D-pantothenyl alcohol) may be considered as vitamins, and are advantageously added to insure completeness of the vitamin dosage. Because vitamin deficiencies may be so varied, and because an excess of vitamins are usually so innocuous, it is generally desirable to administer doses large enough to be sure of adequacy, rather than attempt to use minimum dosages.

A similar preparation may be prepared with the B

B COMPLEX		
Phase A	Per syringe of 1 milliliter	
ascorbic acid U.S.P.(as sodium salt) (C)	90 —	500 mg.
folic acid U.S.P.	0.1 —	1.0 mg.
niacinamide U.S.P.	20 —	35 mg.
benzyl alcohol reagent	10 —	15 mg.
water for injection U.S.P. qs to pH 6.8 to 7.6	100%	
Phase B	Per syringe of 1 milliliter	
thiamine (as HCl U.S.P.)(B ₁)	1 —	10 mg.
riboflavin USP(as 5'-phosphate, sodium 70%) (B ₂)	1 —	10 mg.
niacinamide U.S.P.	55 —	65 mg.
pyridoxine (as HCl U.S.P.) (B ₆)	1 —	15 mg.
cyanocobalamin U.S.P.(B ₁₂)	5 —	25 mcg.
biotin	0 —	100 mcg.
dexpanthenol	0 —	10 mg.
ferrous citrate reagent	0.046	mg.
benzyl alcohol reagent	10 —	15 mg.
water for injection U.S.P. qs to pH 4.5 — to 5.5	100%	

In filling these formulations, an overage should be provided. That is, the syringe package should be filled so as to deliver 1 milliliter of each component — which, depending on the dead space in the syringe can require from about 1.1 to 1.25 milliliter per component per syringe. Preferably, the solutions are sterilized by sterile filtration techniques, and the syringes are aseptically assembled. Such packaging procedures are conventional in the industry.

The invention is illustrated by the following examples:

EXAMPLE 1

FORMULA I		
Phase A	Per syringe of 1 milliliter	
ascorbic acid USP (as sodium salt)	300	mg.
folic acid U.S.P.	1	mg.
niacinamide U.S.P.	20	mg.
benzyl alcohol-reagent grade	10	mg.
water for injection U.S.P. qs to	1	milliliter
Phase B		
thiamine HCl U.S.P.	10	mg.
riboflavin USP(as 5'-phosphate, sodium, 70%)(B ₂)	10	mg.
niacinamide U.S.P.	55	mg.
dexpanthenol	10	mg.
pyridoxine HCl U.S.P.	15	mg.
cyanocobalamin U.S.P.	15	mcg.
ferrous citrate - reagent	0.046	mg.
benzyl alcohol - reagent	10	mg.
water for injection U.S.P. qs to	1	milliliter

The thiamine, riboflavin, pyridoxine, cyanocobalamin, dexpanthenol, and a portion of the total amount of niacinamide (Phase B) are put into aqueous solution sterile filtered and filled aseptically into the lower chamber of a syringe such as shown in FIGS. 1 and 3, in a conventional manner, so as to discharge the above amounts per syringe. The vitamin C, folic acid and the balance of the total amount of niacinamide (Phase A) are put into aqueous solution, sterile filtered and aseptically filled in the upper chamber of a syringe such as shown in FIGS. 1 and 3, in a conventional manner so as to obtain the above amounts per syringe. All filling is done using sterile techniques. The pH of Phase A is a natural pH of from 6.8 to 7.6 and that of Phase B a natural pH of from 4.5 to 5.5.

In detail, Phase A is prepared under an atmosphere of nitrogen. Fresh water for injection representing 60% of the final formulation volume is added to a glass or stainless steel container and brought to 60°C. with nitrogen sparging. The sodium ascorbate is added and dissolved. The solution is reduced to room temperature. The folic acid and niacinamide are mixed together using only enough water to produce a heavy, homogeneous slurry. This slurry is added to the bulk solution and dissolved. The benzyl alcohol is added and mixed. The solution is brought to final volume with water for injection and possesses a natural pH of from 6.8 to 7.6. It is sterile filtered through an 0.2μm membrane into a sterile container under a nitrogen atmosphere.

Phase B is also prepared under an atmosphere of nitrogen. The niacinamide and riboflavin are dissolved in fresh water for injection representing 80% of the final formulation volume. The thiamine and pyridoxine are

added and dissolved. The dextranthenol is weighed in a container, a small quantity of water is added and the mixture is warmed to 50°C. on a steam bath. This mixture is added to the above solution of vitamins. The ferrous citrate is added and dissolved by mixing for 30 minutes. The cyanocobalamin is added and dissolved. The benzyl alcohol is added and mixed for 30 minutes. The solution is brought to volume with water for injection and mixed. This mixture possesses a natural pH of 4.5 to 5.5. It is sterile filtered through a 0.22 μm membrane into a sterile container under a nitrogen atmosphere.

EXAMPLE 2

Phase A	Per Syringe
vitamin A palmitate	10,000 Units
vitamin D ₂ crystalline	500 Units
d-Alpha tocopheryl acetate N.F.	30 Units
ascorbic acid USP	
(as sodium salt	300 mg.
folic acid U.S.P.	1 mg.
niacinamide U.S.P.	20 mg.
polysorbate 80 U.S.P.	10% w/v
benzyl alcohol - reagent	10 mg.
propylene glycol U.S.P.	100 mg.
water for injection U.S.P. qs to	1 milliliter

Phase B	
thiamine HCl U.S.P.	10 mg.
riboflavin USP(as 5'-phosphate, sodium, 70%) (B ₂)	10 mg.
niacinamide U.S.P.	55 mg.
dextranthenol	10 mg.
pyridoxine HCl U.S.P.	15 mg.
cyanocobalamin U.S.P.	15 mcg.
ferrous citrate - reagent	0.046 mg.
benzyl alcohol - reagent	10 mg.
water for injection U.S.P. qs to	1 milliliter

In a conventional manner similar to that of Example 1, Phase A and B are prepared and placed in a syringe such as shown in FIGS. 1 and 3. The pH of Phase A is a natural pH of from 6.8 to 7.6 and that of Phase B 4.5 to 5.5.

In detail, Phase A is prepared under an atmosphere of nitrogen. The benzyl alcohol is weighed into a container. The vitamin D₂ is added and dissolved. The vitamin A and d-alpha tocopheryl are added and mixed. The polysorbate 80 is added and the mixture is stirred thoroughly while heating to 50°C. on a steam bath. This mixture is added slowly with vigorous stirring to a mixture of propylene glycol and water. The sodium ascorbate is added and dissolved. (If turbidity occurs it will clarify later when brought to volume). The folic acid and niacinamide are mixed together with small increments of water to provide a thin paste. This paste is diluted with additional water and added to the above described vitamin solution. The solution is diluted to volume with water for injection and filtered through a sterile 0.2 μm membrane into a sterile container under a nitrogen atmosphere. The natural pH of this solution is 6.8 to 7.6.

Phase B formulation and preparation are exactly as described under Phase B of Example 1.

Following is a brief description of the filling process. The Phase B component is aseptically filled at 1.15 cc into presterilized and siliconized 3 cc syringes, containing tip caps at the needle end. These syringes are then fitted with a center divider plug (slit type, if the syringe

does not contain a by-pass valve, or solid type if a by-pass valve is present) by passing several (18) at a time held in a filling rack into a vacuum chamber. A sleeve containing the plugs is placed over the syringe rack and, under vacuum, a bar of insertion fingers displaces the plugs into the syringe barrel to a point slightly above the liquid surface. Vacuum pulls the plugs to or close to the liquid surface. The syringes are then recycled through the filling chamber. The Phase A component is filled at 1.15 cc into the upper chamber. The syringes are vacuum fitted with an upper, threaded plug. (The thread is for plunger rod insertion). The syringes are then removed from sterile conditions and packaged.

The same filling procedure may be conducted without the use of vacuum equipment by employing a hollow needle wire which is placed at the plug edge at the time of plug insertion, allowing the escape of trapped air. The syringes are recycled for the second chamber filling and the needle wire is again used to position the upper plug.

As illustrative of the storage characteristics of the present compositions, solutions were prepared containing:

	Ingredient	milligrams per milliliters
	thiamine hydrochloride U.S.P.	12
	riboflavin USP(as 5'-phosphate, sodium, 70%) (B ₂)	12
	niacinamide U.S.P.	57.75
	dextranthenol	12
	pyridoxine hydrochloride U.S.P.	18
	cyanocobalamin U.S.P.	0.0225
	ferrous citrate reagent	0.046
	benzyl alcohol reagent	15
	water for injection U.S.P. qs ad	1 milliliter

The solution was separated into seven equal portions of approximately 400 ml each in 500 ml glass stoppered graduated cylinders under nitrogen. The pH of each fraction was adjusted as follows:

Fraction	Final pH	Ingredient Employed
A	4.52	none (no adjustment)
B	4.0	10.6 ml of 10% HCl
C	3.5	26.8 ml of 10% HCl
D	3.0	48.8 ml of 10% HCl
E	4.0	5.1 ml of lactic acid
F	3.5	22.7 ml of lactic acid
G	3.0	66 ml of lactic acid

All the solutions were diluted to 500 ml with additional water for injection. The solutions were passed through a 0.22 μm membrane filter and filled under nitrogen in a laminar flow hood into forty 10 ml vials and forty 2 ml syringes in an aseptic manner. The vials and syringes were stored at the following temperatures, 3°C., room temperature and 42°C. for varying periods of time. The vials and syringes were examined for signs of physical instability (precipitation, discoloration) prior to determining potency stability through appropriate assay means. Samples from solution D, in syringes and vials, precipitated but were assayed for Vitamins B₁, B₂, B₆ and B₁₂ nevertheless. The results appear in Tables I, II and III:

Table I

Storage Time	Conditions Temperature	Physical Stability in Vials and Syringes Solutions Adjusted w/HCl				Solutions Adjusted w/Lactic Acid		
		A(pH 4.5)	B(4.0)	C(3.5)	D(3.0)	E(4.0)	F(3.5)	G(3.0)
1 Week	42°C.	D ^a	L ^b	LT ^c	PPT ^d	L	D	D
	RT ^e	NC ^f	NC	NC	PPT	NC	NC	NC
2 Weeks	3°C.	NC	NC	NC	PPT	NC	NC	NC
	42°C.	D	L	LT	PPT	D	D	D
4 Weeks	RT	NC	NC	NC	PPT	NC	NC	NC
	3°C.	NC	NC	NC	PPT	NC	NC	NC
8 Weeks	42°C.	D	L	LT	PPT	D	D	D
	RT	NC	NC	NC	PPT	NC	NC	NC
	3°C.	NC	NC	NC	PPT	NC	NC	NC
	42°C.	D	L	LT	PPT	D	D	D
	RT	NC	NC	NC	PPT	NC	NC	NC
	3°C.	NC	NC	NC	PPT	NC	NC	NC

^aD = dark solution^bL = lighter solution than D^cLT = lightest solution (lighter than L)^dPPT = precipitate^eRT = room temperature^fNC = no change

Color fading is a sign of instability. Solution C(pH 3.5) precipitated when ejected from syringes in 8 week room temperature sample, and, hence, was unsatisfactory.

Table II

Stability in Vials as Percent of Initial After Storage for 1 Month at 42°C.				
Solution pH	B ₁	Vitamin Potency in %		
		B ₂	B ₆	B ₁₂
A 4.52	91	102	102	92
B 4.0	96	102	97	92
C 3.5	99	102	105	78
D 3.0	99	98	100	93
E 4.0	92	99	97	91
F 3.5	91	100	103	83
G 3.0	90	103	105	68

Table III

Stability in Syringes as Percent of Initial After Storage for 4 Month at Room Temperature				
Solution pH	B ₁	Vitamin Potency in %		
		B ₂	B ₆	B ₁₂
A 4.52	97	101	97	97
B 4.0	98	102	99	96
C 3.5	99	100	98	93
D 3.0	PPT ^a	PPT	PPT	PPT
E 4.0	97	100	99	95
F 3.5	98	102	99	86
G 3.0	98	102	98	76

^aPPT = precipitate

These results show conclusively that the Phase B, Vitamin B complex was physically unstable at pH 3.0 and 3.5 when adjusted with HCl, a mineral acid. The physical instability was noted by the formation of an unsightly precipitate.

The solutions faded in color when adjusted below pH 4.0 with HCl, showing instability.

All of the solutions were stable with respect to Vitamins B₁, B₂ and B₆ but losses in Vitamin B₁₂ potency were observed when solutions were adjusted to pH values below 4. This degradation was accelerated by the presence of lactic acid, an organic acidulant.

Even though there is some loss of stability of B₁ at the pH of 4.52, this pH permits stability of Vitamin B₁₂.

The storage-stability of multivitamin preparation must be based on a series of compromises, and the present packages are uniquely satisfactory.

What is claimed:

1. A stable aqueous multivitamin preparation in sterile, storage-stable injectable form in a two compartment hypodermic syringe comprising two incompatible vitamin components each held in a separate compartment of said syringe, one of said components having a pH of 6.8 to 7.6 consisting essentially of:

vitamin A palmitate	0 -	10,000 units
vitamin D ₂	0 -	500 units
vitamin E	0 -	30 units
ascorbic acid	90 -	500 mg.
folic acid	0.1 -	1 mg., and
niacinamide	20 -	25 mg.

per milliliter as the vitamin ingredients thereof; in an aqueous carrier; and the other of said components having a pH of 4.5 to 5.5 consisting essentially of:

thiamine hydrochloride	1 -	10 mg.
riboflavin	1 -	10 mg.
niacinamide	55 -	65 mg.
pyridoxine hydrochloride	1 -	15 mg.
cyanocobalamin	5 -	25 mcg.
dexpantenol	0 -	10 mg., and
biotin	0 -	100 mcg.

per milliliter as the vitamin ingredients thereof, in an aqueous carrier.

2. The preparation of claim 1 in which the component having a pH of 6.8 to 7.6 consists essentially of:

ascorbic acid	90 -	500 mg.
folic acid	0.1 -	1 mg., and
niacinamide	20 -	35 mg.

per milliliter as the vitamin ingredients thereof; in an aqueous carrier.

3. The preparation of claim 1 in which the component having a pH of 6.8 to 7.6 consists essentially of:

vitamin A palmitate	2500 -	10,000 units
vitamin D ₂	200 -	500 units
vitamin E	3 -	30 units
ascorbic acid	90 -	500 mg.
folic acid	0.1 -	1 mg., and
niacinamide	20 -	35 mg.

per milliliter as the vitamin-ingredients thereof; in an aqueous carrier.

4. The preparation of claim 1 in which the component having a pH of 6.8 to 7.6 consists essentially of:

ascorbic acid	300 mg.
folic acid	1 mg., and
niacinamide	20 mg.

per milliliter as the vitamin ingredients thereof; in an aqueous carrier having 10-15 mg. of benzyl alcohol therein; and the other of said components having a pH of 4.5 to 5.5 consisting essentially of:

thiamine hydrochloride	10 mg.
riboflavin	10 mg.
niacinamide	55 mg.
dexpantenol	10 mg.
pyridoxine hydrochloride	15 mg., and
cyanocobalamin	15 mcg.

per milliliter as the vitamin ingredients thereof, in an aqueous carrier having therein 10-15 mg. of benzyl alcohol and 0.046 mg. of ferrous citrate.

5. The preparation of claim 1 in which the component having a pH of 6.8 to 7.6 consists essentially of:

vitamin A palmitate	10,000 units
vitamin D ₂	500 units
vitamin E	30 units

ascorbic acid
folic acid
niacinamide

300 mg.
1 mg., and
20 mg.

5 per milliliter as the vitamin ingredients thereof; in an aqueous carrier having 10-15 mg. of benzyl alcohol, 50-100 mg. of polysorbate 80, and 50-100 mg. of propylene glycol therein; and the other of said components having a pH of 4.5 to 5.5 consisting essentially of:

thiamine hydrochloride	10 mg.
riboflavin	10 mg.
niacinamide	55 mg.
dexpantenol	10 mg.
pyridoxine hydrochloride	15 mg., and
cyanocobalamin	15 mcg.

20 per milliliter as the vitamin ingredients thereof, in an aqueous carrier having therein 10-15 mg. of benzyl alcohol and 0.046 mg. of ferrous citrate.

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