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Review Article

Formulation Challenges: Multiple Vitamins and Minerals Dosage Forms

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Abstract:

Formulating multiple vitamin and mineral (MVM) dietary supplements presents significant challenges in ensuring stability, bioavailability, and consumer safety. The development of MVM dosage forms-such as tablets, capsules, and powders—requires precise balancing of active ingredients due to the distinct stability and solubility profiles of vitamins and minerals. Incompatibilities, such as those between vitamin C and iron, may result in degradation and reduced product efficacy. Certain vitamins necessitate specific pH conditions or protective coatings to maintain stability and effectiveness. Bioavailability is influenced by particle size, crystalline structure, and excipient selection. Achieving uniformity in multi-component blends is particularly challenging, as variations in density can lead to segregation, impacting dosage consistency. Regulatory requirements further complicate formulation, with varying limits on permissible dosages and combinations. Advances in excipient development, controlled-release technologies, and encapsulation methods are helping to address these formulation challenges. Ultimately, producing high-quality MVM supplements demands a nuanced approach that accounts for ingredient compatibility, stability optimization, and efficient delivery systems to ensure safe and effective products for consumers.

Keywords: formulation challenges; multiple vitamins; minerals; dosage forms; bioavailability; stability; encapsulation; excipients; uniformity; and regulatory requirement

Introduction

In the early 1960s vitamin and mineral formulations were products of major pharmaceutical companies. Products like Theragran, Unicaps, and various products intended for use by children and pregnant women were thought of as quasi-drug products and were routinely prescribed by physicians. Decavitamin tablets and capsules were the subject of a United States Pharmacopoeia (USP) monograph where test methods and acceptance standards were set. In the late 1960s or early 1970s, these products in multiple-ingredient form were no longer subjects of USP monographs. Very soon thereafter the market was flooded with every possible combination of vitamin and mineral products, including some containing herbals.

Regulatory agencies and consumer advocate groups began to sample and test these products, only to discover and disclose that many of them did not meet label declarations. Many of the small garage-type operations did not know the complexity of creating a stable formula that contained multiple ingredients. Some of the larger and more technologically sophisticated firms may have had the expertise to formulate a tablet or capsule, but could not still create a stable formulation, containing multiple formulations having unique characteristics.

Since most of the studies in this text are dedicated to the basics of formulation technology and the necessary mechanical properties of the dosage form components, this the study will address, what is believed to present the most significant challenge formulation of stable vitamin or vitamin/mineral combination products. The formulation of pharmaceutical quality vitamin products having adequate physical and chemical stability as well as suitable taste, odor, color, and freedom from bacterial contamination can entail numerous problems arising from different physical forms, stability, and solubility characteristics of the individual vitamins.

For liquid preparations, the inclusion of the optimal pH is a crucial factor. Interactions between some of the vitamins and between vitamins and other product constituents must also be considered. Successful development of vitamin products requires knowledge of the fundamental aspects of the physical and chemical properties of the various forms of the vitamins available, the use of adequate techniques of manufacture, and the addition of suitable manufacturing overages based on critical stability studies.

Elements That Affect Vitamin Stability

1. The stability characteristics of the individual vitamins.
2. Factors that enhance vitamin stability.
3. Formulation of vitamin products.
4. Industry experience with predicting vitamin stability, both from long-term and accelerated aging studies.
5. Stability-indicating assays are also a critical element, but will not be addressed in this Study

In the development of a multiple vitamin preparation one needs to be concerned with the stability characteristics of the individual vitamins, the interaction of the vitamins among themselves and the effects upon formulations of those factors. The factors that affect vitamin stability are: Solubility, pH, moisture, light, heat, and formulation additives (diluents and excipients).

Solubility Characteristics

Vitamins may be divided into two well-known groups, namely fat soluble and water soluble vitamins. The fat-soluble group includes:

1. Vitamin A
2. Vitamin D
3. Vitamin E
4. Vitamin K

Combinations of one or more of these fat-soluble vitamins in the same formula as water-soluble vitamins require the use of efficient emulsifying agents such as polysorbates to produce homogeneous and stable liquids. In tablet formulations, moisture is a major issue when combining fat-soluble and water-soluble vitamins.

The water-soluble group includes:

1. Vitamin B1–Thiamin
2. Vitamin B2–Riboflavin; Riboflavin 5 Phosphate Sodium
3. Vitamin B6–Pyridoxine
4. Vitamin B12–Cyanocobalamin
5. Vitamin C–Ascorbic acid; Sodium Ascorbate
6. Pantothenic acid; Calcium Pantothenate
7. Niacin; Niacinamide
8. Folic acid
9. Biotin

The water-soluble vitamins respond to a wide range of solubility parameters. Each one of these differences have a significant impact on tablet or capsule formulations, where water or moisture is a critical factor

Table summarizing the solubility profiles of various vitamins at 25°C:

Vitamin	Solubility (mg/mL)
Thiamin Hydrochloride	1000
Thiamin Mononitrate	27
Niacinamide	1000
Panthenol	Freely Soluble
Calcium Pantothenate	356
Ascorbic Acid	333
Sodium Ascorbate	620
Pyridoxine Hydrochloride	220
Cyanocobalamin	12.5
Biotin	0
Riboflavin	0.066 to 0.33
Riboflavin 5 Phosphate Sodium	43 to 112

Some other important stability characteristics of the individual vitamins under various conditions of stress are affected by:

1. Air
2. Heat
3. Light
4. PH
5. Oxidizing or reducing agents.

These conditions require special consideration when formulating vitamin products. Some of the vitamins are classified as stable or relatively stable and present no real problems regarding stability in multiple vitamin products. These include:

1. Vitamin E
2. Riboflavin
3. Niacinamide
4. Pyridoxine
5. Biotin

The vitamins that usually present problems of stability are:

1. Vitamin A
2. Vitamin D
3. Thiamin
4. Pantothenate
5. Vitamin B12
6. Folic acid
7. Vitamin C

The Stability Characteristics of The Individual Vitamins

Vitamin A

1. Sensitive to air oxidation especially in the alcohol form.
2. Oxidation is catalyzed by trace metals notably iron and copper.
3. Vitamin A is inactivated by ultraviolet light.
4. It isomerizes at acid pH.
5. It is stable in alkali with stability increasing with increasing pH

Vitamin D

Diet D is similar to diet A in balance traits, but extra solid.

Vitamin E

1. unfastened tocopherol is touchy to air oxidation, particularly in alkali.
2. Its miles oxidation catalyzed by hint minerals, considerably copper and iron.
3. The acetate ester may be very strong. Diet ok
1. Nutrition okay is stable to air and acid.
2. Its miles risky in sturdy alkali.
3. Its miles decomposed by using daylight. Riboflavin (diet B2)
1. Diet B2 is touchy to light, mainly in alkaline solution.
2. it's far stronger in acid solution and comparatively unaffected by using pH modifications in the acid variety.
3. It is sensitive to decreasing retailers.
4. it's far decomposed by decreasing sugars.

Thiamin (vitamin B1)

1. Thiamin is an increasing number of unstable as pH rises.
2. it is touchy to oxidize and reduce sellers.
3. The HCl shape is extra hygroscopic than the mononitrate form. Niacin or Niacinamide
4. Niacin and niacinamide are fairly solid compounds and have demonstrated no balance problems.
5. It isn't always suffering from adjustments in pH in the acid pH range.

Pantothenic Acid

1. Pantothenic acid is hygroscopic, mainly dl-calcium pantothenate.
2. its miles unstable in acid pH.
3. Its miles decomposed through hydrolysis.
4. Stability is maximized at pH 6–7.

Panthenol

1. Panthenol is more solid than pantothenic acid compounds.
2. Its miles stable inside pH stages 5–7.

Folic Acid (Pteroylglutamic Acid)

1. Folic acid is volatile in acid pH at tiers lower than five.
2. It is decomposed via sunlight
3. It is unstable in solution (Better suspension stability).
4. Vitamin B1, B12, oxidizing and reducing agents cause decomposition when in
5. liquid products.
6. Folic acid works best when formulated as a solid dosage product.

Cyanocobalamin (Vitamin B12)

1. Vitamin B12 is slightly unstable in acid or alkaline solution.
2. Its optimal pH is 4 to 5.
3. It is decomposed by reducing agents.
4. Ascorbic acid and Thiamin accelerates decomposition.
5. Vitamin B12 is sensitive to light in very dilute solutions.

Ascorbic Acid (Vitamin C)

1. Ascorbic acid is stable to air when dry.
2. It is readily oxidized in a solution.
3. Copper and Iron act as catalysts to promote decomposition.
4. It is most unstable at pH 4 when in the presence of metallic ions.
5. In open systems, Vitamin C stability increases as pH varies from 4.2.

Biotin

1. Biotin is stable to air in neutral pH.
2. It is slightly unstable in alkaline conditions.
3. Multiple vitamin solutions should be made to pH 5–7 for best stability.

Pyridoxine Hydrochloride (Vitamin B6)

1. Vitamin B6 is a relatively stable compound.
2. It is relatively unaffected in the normal acid pH range.
3. It is light-sensitive when in solution.

Stability Problems Relative to pH

As already noted, stability relative to pH is most critical in liquid preparations. High pH gives good stability for all vitamins except B1 and results in odor development. A pH

around 4 creates excess pressure which affects vitamin stability. A pH of 3.5 offers the best compromise and provides the best test to use.

An example of a pH relationship is demonstrated between thiamin and calcium pantothenate in an acid solution. The pH affects the relation rate of destruction of calcium pantothenate and thiamin (B1 HCL) in 0.1% solutions. Both were subjected to 15 minutes

In an autoclave at 15 pounds of pressure. In contrast to thiamin, calcium pantothenate shows good stability at pH 6–7, but its stability decreases or increases when moved from this range (Fig. 1).

In tablet or capsule formulations pH becomes a factor if too much moisture is present, allowing for the solubilization of some of the more labile and moisture-sensitive vitamins. High moisture content will cause degradation of Vitamin B1, thiamin, and Vitamin C in the presence of metallic ions

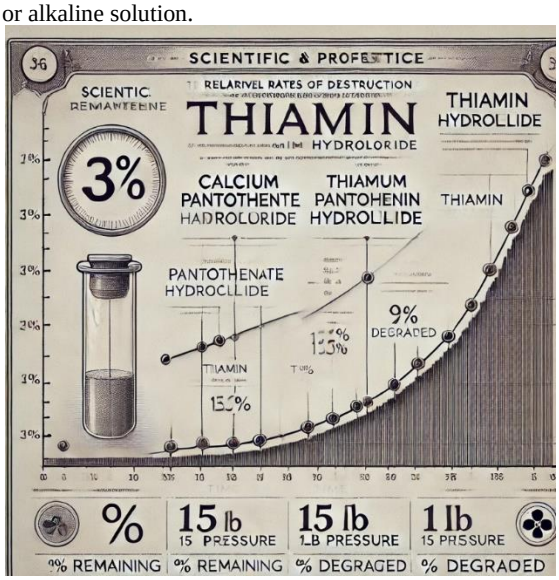


Figure 1: Relative rates of destruction of calcium pantothenate and thiamin hydrochloride in acid solution: (*) 0.1% solution of calcium pantothenate; (~) 0.1% solution of thiamin hydrochloride. All solutions were run in an autoclave at 15lb. Pressure for fifteen minutes. Source: From Ref. 9.

Comparative Stability Data for Panthenol and Pantothenate about pH

Another example of a pH stability-indicating relationship is shown in Figure 2, which describes the comparative stability data for panthenol and pantothenates in relationship to pH. There is a rapid decrease in stability for both the panthenol and the salt forms (pantothenates) in acid pH. Maximum stability is achieved around pH 6–7.

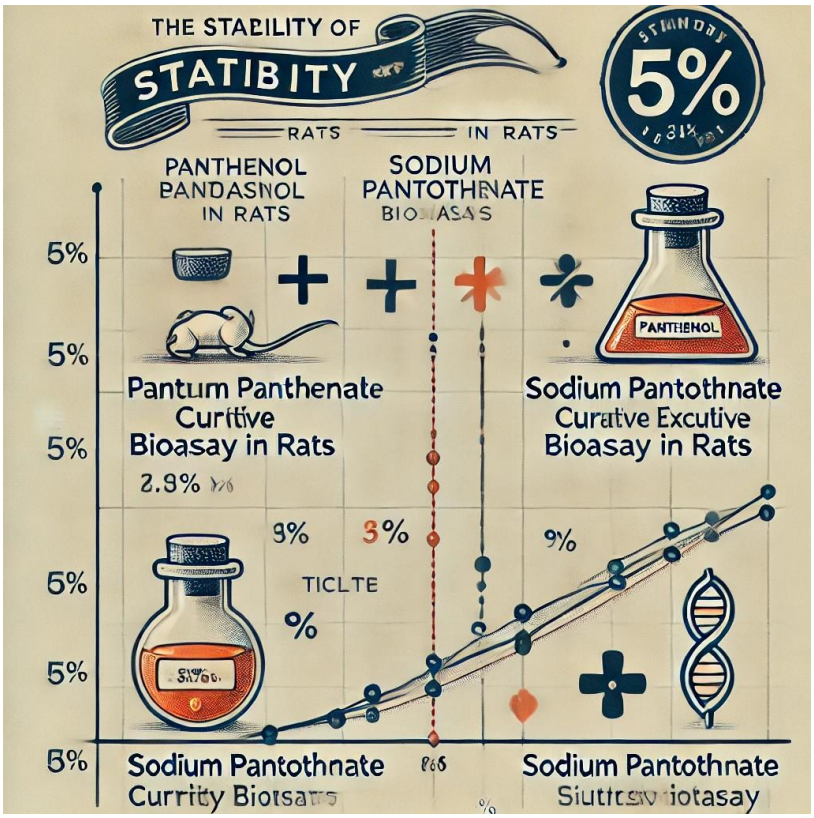
Ascorbic acid degradation is also pH-dependent. In aqueous solutions, assays for both reduced ascorbic acid and dehydroascorbic acid showed maximum loss of Vitamin C at pH 4.2. Excessive pressure development in multivitamin liquids can be a serious problem when the pH is close to 4.2.

Effects of moisture and Humidity on Vitamin Preparations

The pH effects and the interaction of vitamins can occur only in the presence of water. In liquid preparations the decomposition of vitamins is kept at a minimum level by selecting the optimum pH and replacing the water to the maximum degree with glycols and sugars wherever possible. In solid dosage forms, further stabilization is possible through the use of special forms of vitamins and by keeping the moisture content at the lowest practical level.

An impression of the effect of moisture in solid vitamin mixtures is shown in Figures 3 and 4. In Figure 3, the effects of free water on the stability of Vitamin C are noted in mixtures with or without Silica Gel stored for 3 weeks at 45˚C. The loss is directly related to the free water.

In Figure 4, the water content is varied at two levels of silica gel. Utilizing equal amounts of ascorbic acid 300 mg in each test, and varying the amount of silica gel in one



(~) Sodium pantothenate, curative bio assay in rats; (~) Sodium pantothenate, microbioassay. Source: From Ref. 2. FIGURE 2 Comparative stability of panthenol and sodium pantothenate:

(*) Panthenol, curative bioassay in rats;

(*) Panthenol, excretion bioassay in rats;

(~) Sodium pantothenate, curative bias

Test, 80 g of silica gel was used, and in the other test, 640 mg of silica gel was used. The higher level exerts a protective effect indicating some binding of water by the silica gel takes place.

This work showed that silica gel binds a certain fraction of the water present and that the loss of ascorbic acid is directly proportional to the amount of unbound or free water in the system. Sodium ascorbate is even more sensitive to water than ascorbic acid (1).

Figure 5: shows the effect of moisture in a calcium pantothenate and Vitamin C mixture. The percentage of retention after 1 month at 45˚C varies from 98% with no added water to about 34% retention with 3% added water.

In another study, the moisture-relative stability of calcium pantothenate in a multiple-vitamin tablet mix and a chewable multiple-vitamin tablet mix was demonstrated.

The study demonstrated how the percentage of moisture contributes to vitamin

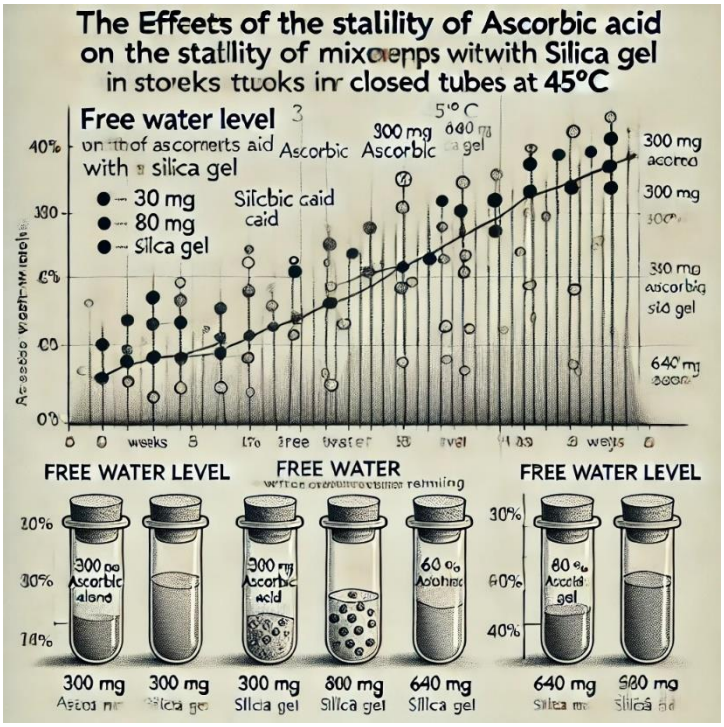


Figure 3: Effects of free water level on stability of ascorbic acid in mixtures with or without silica gel: storage in closed tubes for three weeks at 45˚C. Key: (*) 300 mg, ascorbic acid alone: (*) 300 mg, ascorbic acid + 80 or 640 mg silica gel. Source: From Ref. 1

Effect of Silica Gel on Stability of Ascorbic Acid

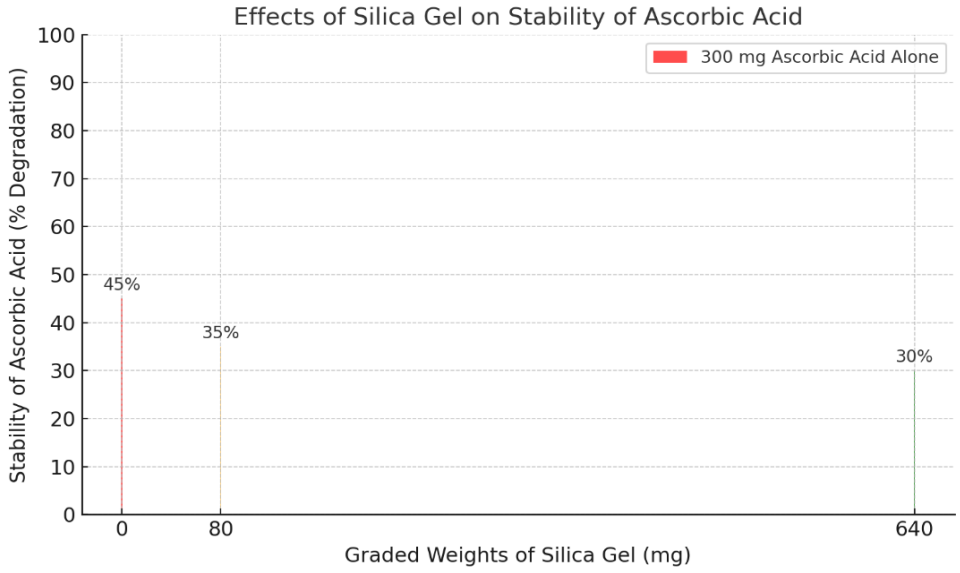


Figure 4: Effects of silica gel on the stability of ascorbic acid with graded weights of water added.

Mixtures were stored in closed tubes for three weeks at 45˚C. Key: (*) 300 mg ascorbic acid alone, (*) 300 mg ascorbic acid + 80 mg silica gel, ( ) 300 mg ascorbic acid + 640 mg silica gel. Source: From Ref. 1.

Degradation. Three percent moisture for 3 months held at 45˚ for 3 months resulted in 45% degradation in the chewable vitamin as compared to 35% for the for the multiple vitamin mix which absorbed less moisture.

Chewable products as a rule contain more water-soluble ingredients and tend to absorb more moisture. The data also showed that the decomposition of the calcium pantothenate increases with time.

Mutual Interactions of Vitamins In Combination With Each Other

Thiamin–Riboflavin

An incompatibility between thiamin and riboflavin in aqueous Vitamin B complex solutions has been reviewed. The oxidative action of riboflavin and thiamin leads to the formation and precipitation of the chrome. Subsequently, chloroflavin the reduction product of riboflavin may also precipitate. In the Vitamin B complex solutions containing ascorbic acid, thiochrome formation is not observed.

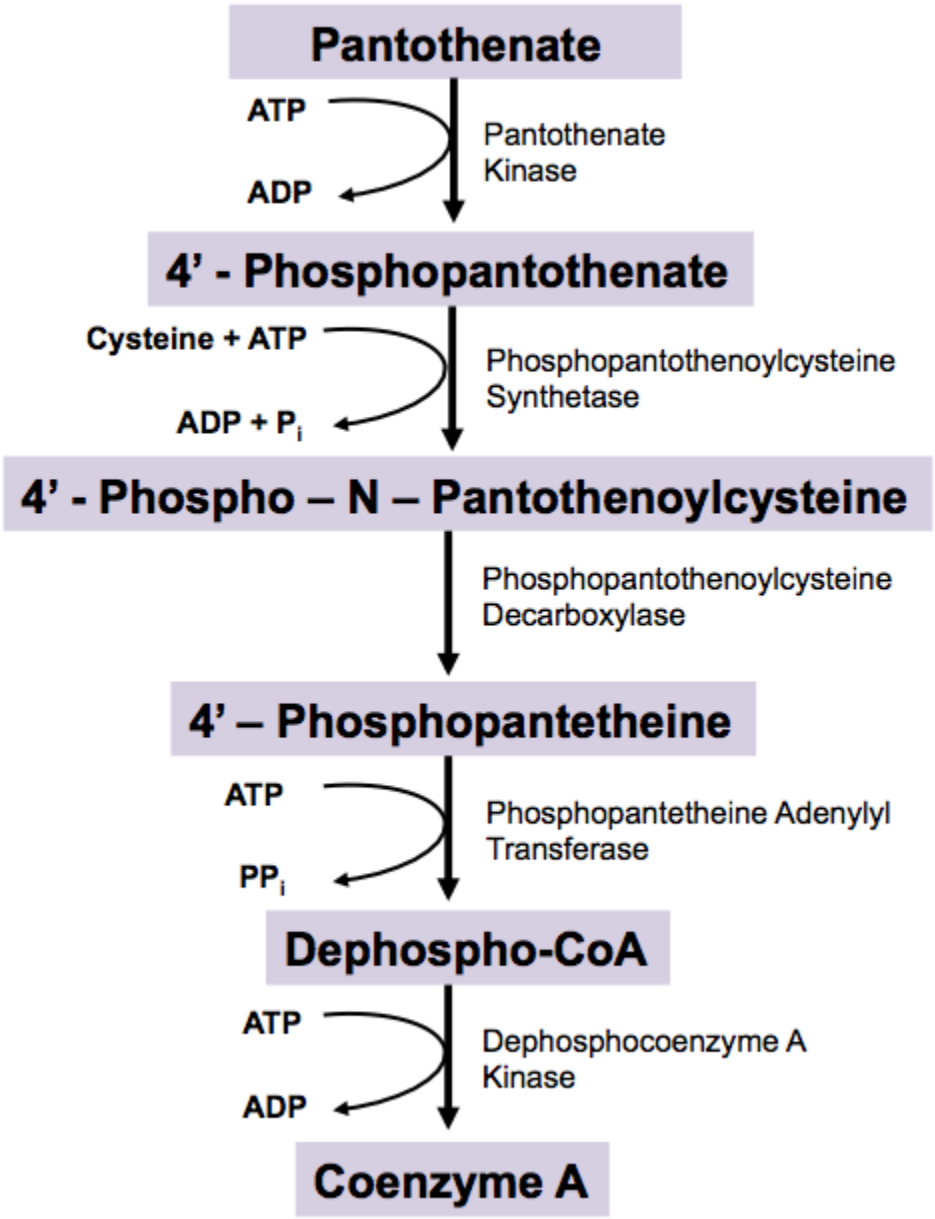


Figure 5: Slater et al, 1979 (3). Calcium pantothenate effect of moisture in a calcium pantothenicnate and Vitamin C mixture; 98% potency retention with no water added decreasing to approx. 30% with 3% water added.

Thiamin–Folic Acid

Thiamin causes considerable decomposition of Folic acid at pH 5.9 and 6.9 in aqueous buffered solutions. The breakdown of Folic acid is accelerated by the presence of decomposition products of thiamin. The key element was the hydrogen sulfide produced during the breakdown process. Thiamin–Cyanocobalamin The combination of thiamin and niacinamide in the presence of moisture causes the decomposition of cyanocobalamin Low levels of thiamin from 1 to 10 mg per dose showed considerably fewer losses than when higher levels of thiamin were used. Accelerated conditions enhance the decomposition process. Riboflavin–Niacinamide The presence of niacinamide increases the solubility of riboflavin due to the formation of a soluble complex formation. This condition takes place when the concentration of niacinamide is greater than 1% of the total matrix. Riboflavin–Folic Acid The combination of light and water with riboflavin has a deleterious effect on the stability of folic acid. It increases rapidly at pH 6.5. Protection from air and light retards the process but does not eliminate it. Riboflavin–Ascorbic Acid Riboflavin catalyzes the photochemical decomposition of ascorbic acid when exposed to light and air. Ascorbic Acid and Cyanocobalamin There is an incompatibility between ascorbic acid and cyanocobalamin with losses of Cyanocobalamin is at least at pH 1 and increasing to a maximum at pH 7. Copper ions greatly enhance the destructive action of ascorbic acid on cyanocobalamin. Ascorbic Acid–Vitamin D (ergocalciferol) Ergocalciferol in powder preparations is readily isomerized by ascorbic acid, folic acid, thiamin hydrochloride, and pyridoxine hydrochloride but not by niacinamide or calcium pantothenate.

Factors That Enhance Vitamin Stability

Reduction of Water Content

The most common protective measure for improving vitamin stability is the reduction of water content. This is true for liquid formulations as well as solid dosage forms. Water is generally substituted with glycerin and

propylene glycol to enhance stability. Drying powders to reduce the water content in solid formulations goes a long way to promote Product stability. In those cases where granulation is necessary to render a tablet formula compressible, moisture content becomes a critical process control.

Antioxidants

The stability of vitamins sensitive to oxidation decomposition can be increased by the addition of antioxidants. Vitamin A and Cholecalciferol are decomposed by exposure to air and are generally stabilized in concentrates are well as dietary supplement products by the addition of small amounts of antioxidants. Some commonly used antioxidants that are added to fat-soluble vitamins are tocopherol, butylated hydroxyanisole, butylated hydroxyl toluene, propylgallate, and ascorbyl palmitate.

Chelating Agents

Both ascorbic acid and pyridoxine hydrochloride have been stabilized by adding chelating agents to formulations. This practice is not popular in the Dietary Supplement industry where consumers are concerned with the concept of natural.

Coating and Encapsulation

Improving the stability of labile vitamins under stress conditions is an important function of coating agents. They are also useful for converting liquid vitamins into free-flowing dry powders, masking taste in chewable vitamins, and improving handling and tableting characteristics. It is also used for stabilizing the color of ascorbic acid tablets, which otherwise may develop a tan color on aging.

Adsorbate Preparations

Adsorption of fat-soluble vitamins on suitable adsorbents has been utilized as a means of conversion of the vitamin to dry, free-flowing powders as well as to enhance their stability. Vitamin A has been successfully adsorbed onto calcium silicate. Neutral or weakly alkaline carriers such as magnesium oxide tend to stabilize Vitamin A and

Cholecalciferol.

Ethanolamine and polyoxyethylene compounds are very effective in preventing the isomerization or ergocalciferol caused by surface acidity of excipients, both Vitamins A and D adsorbant products are commercially available and are commonly used in multiple vitamin tablets.

Lyophilization

In the pharmaceutical industry, lyophilization has been used to achieve improved stability in liquid preparations. This process has been applied in the preparation of multidose vials of Vitamin B complex vitamins for parenteral use. Lyophilization has proven useful to stabilize cyanocobalamin in the presence of ascorbic acid in liquid preparations.

Formulation of Vitamin Products

Liquid Formulations

Since liquid formulations are no longer popular in today‘s market, only a few problems regarding liquid products will be addresse

Liquid diet products have been prepared in the form of drops for infants, and a couple of nutrition syrups for the elderly and those who have tough swallowing tabwe could. Nutrients are also formulated as injectables for pharmaceutical use and the treatment of significant nutrition deficiencies.

The maximum not unusual issues with liquid merchandise are:

1. gasoline formation and strain,
2. readability and emulsion balance,
3. diet stability, particularly A, B1, C, and panthenol.

These issues can satisfactorily be resolved using:

1. selection of the right pH. High pH impacts B1 and creates excess gasoline. Adjusting pH to five or decrease offers the satisfactory consequences.
2. Glycols and tweens whilst used to form emulsions and to solubilize sure nutrients have to be adjusted to the proper stages. Glycols must be balanced to prevent oxidation of vitamin C and additionally to prevent emulsion separation.
3. Diet C is excellently formulated in beverages at tiers no better than 50 mg/0.6ml.
4. Right, overages should be established primarily based on critical stability research.

Capsules and tablet Formulations

The maximum not unusual styles of solid dosage bureaucracy for nutrition merchandise are pills and drugs (both 2-piece and smooth gelatin capsules). At the same time, stability troubles can be obvious from the foregoing examples of the steadiness problems with the individual vitamins and to a lesser diploma in combination with every different, it is going to be addressed in this segment as a part of the formula demanding situations.

The second factor of the system challenges for these products lies in the more than one active nutritional ingredients merchandise where homogeneity is a trouble. First, the ingredients need to be covered to decrease degradation after which be commingled to offer a mix to result in a dosage shape that meets label claims. Subsequently, patients need to be decided on for functionality and at the same time need to be like-minded with all of the product's lively components.

Protection to Enhance Stability

The fat-soluble vitamins A, E, D, and ok are normally incorporated into tablets and two-piece tablets inside the shape of dry stabilized lined merchandise or as adsorbates defined previously. These are commercially available from most nutrition ingredient producers.

The B complex vitamins, thiamin, riboflavin, niacinamide, and pyridoxine are normally lined if utilized in chewable capsules due to taste, in any other case they're introduced as is. The products synthetic for chewable capsules generally include 25–33% of the lively covered with fatty acids or mono and diglycerides of fatty acids which could be very effective in covering flavor and enhancing product stability.

Ascorbic acid is currently available at percentages from 90 to one hundred, with varying quantities of granulating excipients making up the distinction. A small percentage of ethyl cellulose and lactose are available as a granulation for direct compression, however, has the added gain of retarding discoloration of diet C. Most vitamin C products available these days can be utilized in immediately compressible Products

Folic acid, cyanocobalamin, and biotin are used in tablets and capsules in the form of triturates, adsorbates, or spray-dried powders containing 0.1–1.0% of the diet to facilitate distribution of the microgram quantities that might be typically used for those vitamins.

For the ones a couple of vitamin products that also incorporate more than one mineral, extra troubles are created because of reactions among some of the nutrients and minerals. Iron and copper are incompatible with several nutrients. In reaction to this example, there are covered mineral merchandise to be had to be used in these formulations. Minerals are additionally to be had as triturates at the tiers generally delivered to those formulas.

Homogeneity in mixing

In the dietary complement industry the maximum common merchandise is more than one vitamin and more than one mineral formulation. It isn't always uncommon to have at least 10 vitamins and 6 minerals in the same system to be dosed in one pill or pill. A method ought to comprise 6 mum of nutrition B12 and 500 mg of vitamin C. These activities may be combined with all of the B complicated vitamins in various quantities.

Minerals inside the equal various ratios can also be incorporated into this mixture.

There are two strategies of blending used in the dietary supplement industry: wet granulation and dry mixing. Dry mixing is commonly known as the "direct compression or direct encapsulation technique." earlier than choosing the proper approach of mixing the bodily residences of powders have to be evaluated. The parameters checked are flowability, particle size, particle form, and bulk density. Free-flowing powders are easy to combine. Sticky or cohesive powders generally tend to shape clumps and are harder to mix. Elements with excessive variation in particle length are also difficult to mix. Round powders are simpler to mix than fibrous solids or substances with needle-like debris. Elements with particles of similar densities mixture without problems, whilst substances with an extra of small particles will tend to upward thrust to the top of the mixture or come to be unmixed. Diet blends with multiple components vitamins may have components with multiple parameter versions.

The project of blending is likewise structured upon the kind of blending device to be used. Tumbler blenders (V-kind) or slant cones paintings differently from convection mixers (Ribbon mixers) and both require an experimental design that allows you to maximize the blending for efficiency and product high-quality.

The suggested mixing process for Direct Compression or Encapsulation

1. Test all energetic elements for identity and efficiency limits.
2. Take a look at all excipients for identification and physical properties. Together with drift characteristics, particle size distribution, and bulk density.
3. Buy components that have consistent particle length distribution or that have a narrow range or version.
4. When using a V-kind blender, add the ingredients via the exit valve. In case you need to upload them via the legs of the vessel, divide the ingredients into the same elements, and then upload one portion to at least one side and the other element to the other facet.
5. screen lumpy or cohesive elements as you upload them to the blender. It'll reduce agglomeration throughout the mixing
6. Always add a portion of the largest quantity of ingredient (usually an excipient)to the blender first. It will coat the blender and prevent lesser ingredients from sticking to the walls.
7. Before adding small-quantity active ingredients to the blend, gravimetrically dilute each one in several steps until the quantity reaches an amount that will facilitate a homogeneous blend.
8. Blending duration, intervals and the level of fill in the vessel play a critical role in determining the adequacy of blending. Parameters should be established during the development stages.
9. Test the blend for adequacy of mixing by taking adequate samples for testing. At a minimum sample should be taken from the top middle and bottom of the blender.

The test should be performed on several ingredients but should include the smallest quantity ingredient with results falling between 85% and 115 %.

S.N.	Ingredient	Claim	Overage (mg/tablet)	Mg per Tablet
1	Beta Carotene (as Betatab)	20%	5	7.5
2	Dry Vitamin A Acetate	500 IU	35	60
3	Vitamin D (as Vitamin D3)	100 CWS/HP	5	25
4	Vitamin E (as Dry Vitamin E Acetate)	950 NS	30 IU	5
5	Vitamin C (as Ascorbic Acid)	90% granulation	70	70
6	Vitamin B1 (as Thiamine Mononitrate USP)	1.5 mg	1.65	10
7	Vitamin B2 (as Riboflavin USP-FCC)	1.7 mg	1.87	10
8	Vitamin B6 (as Pyridoxine HCl)	2.0 mg	2.67	10
9	Vitamin B12 (as Cyanocobalamin)	0.1% SD	7.8	30
10	Folic Acid (as Folic Acid USP)	0.4 mg	0.5	25
11	Niacin (as Niacinamide)	20.0 mg	21	5
12	Biotin (as Bitrit-1)	30.0 mcg	3.75	25
13	Vitamin K1 (as Dry Phytonadione)	25.0 mcg	0.75	50
14	Pantothenic Acid (as d-Calcium Pantothenate)	10.0 mg	14.67	35
15	Iron (as Ferrous Fumarate)	18.0 mg	54.76	-
16	Copper (as Cupric Oxide)	2.0 mg	2.51	-
17	Zinc (as Zinc Sulfate)	15.0 mg	41.17	-
18	Manganese (as Manganese Sulfate Monohydrate)	2.5 mg	7.7	-
19	Iodine (as Potassium Iodide Stabilized)	0.15 mg	0.22	-
20	Potassium Chloride	40 mg	76.34	-
21	Magnesium (as Magnesium Oxide DC)	100.0 mg	166.67	-
22	Dicalcium Phosphate Anhydrous	135.0 mg (Calcium)	457.54	-
23	Crospovidone (as Polyplasdone XL)	-	7	-
24	Vitacei (Microcrystalline Cellulose/Calcium Carbonate)	30 mg	194.39	-
25	Avicel PH102 or Ex-Cell 102 (MCC)	-	80	-
26	Silicon (as Syloid 74)	2.0 mg	4.28	-
27	Stearic Acid	-	4	-
28	Magnesium Stearate	-	4	-

Examples Of Typical Vitamin and Mineral Tablet Formulations Utilizing Stability-Enhancing Components (A2)

The two formulations are being reproduced with compliments of DSM Nutritional products, formerly Hoffman-LaRoche, Inc.

The first formula is an example of a multiple vitamin with minerals where the formulator has taken into consideration the stability characteristics of the individual vitamins and made the best choices of minerals and excipients to provide a formulation that will sustain a two-year expiration date under proper storage conditions.

Noteworthy is the use of fat-soluble vitamins in adsorbate forms and Vitamin C, as a 90% granulation.

The minerals of choice were selected to minimize as much as possible, the tablet size. In particular, dicalcium phosphate was selected because it can function as a source of calcium and phosphorus as well as act as a filler. All other minerals were used to provide the highest concentrations of the elemental metal, selected again to minimize tablet size. Microcrystalline cellulose serves to absorb moisture and prolong the life of the moisture-sensitive vitamins as well as function as a dry binder and disintegration time enhancer.

In the second formulation, chewable multiple vitamins with minerals, the formulator utilizes the vitamins that have been well coated with fatty acids. These products were selected to mask taste and promote vitamin stability. Also, all of the minerals are coated to minimize reactions between the vitamins and minerals in a matrix that is prone to moisture absorption. The low-potency vitamins are added as triturations in order.

Multivitamin Mineral 2 Tablets Dry Vitamin E Acetate 950 NS (30 IU Vitamin E)

*TotalCalciumfromDicalPhosAnhydrousandVitacei¼162mg.

To facilitate adequate blending. Even though the best selections are being made to Facilitate blending efficiency, the formulator still utilizes geometric dilution to ensure blending adequacy.

Manfacturing Procedure

1. MixItems1–5withitem11for5minutes.SetasideasPartA.

2.Blenditems6–10withitems12–14. Screenthrougha#30or40meshsieve.Remix

for5minutesandsetasideasPartB.

3.Blenditems15–19withitem26.Screenthrough#30or40meshsieve.Remix for

5minutesandsetasideasPartC.

4. BlendPartsA, B, andCwithItems20*, 21, 22, 23, 24, and25 for10minutes.

Note: Screenanylumpymaterialsthrough#20meshbeforeaddingtomix.

5. Additems27and28asapremixwithaportionof the blend, screenthrough#30 mesh, combineandmixfor5minutes.

6. CompressonaManestyRotarytabletpressatappropriatepressurewith5/16 3=4 capsuleshapedpunchesat40RPM

Compression Force (lb)	Hardness Avg (sc)	Disintegration Time (min)
4100	22.2	2
5000	26.6	5
6100	30.8	10
7100	35.1	16
8000	38.3	20
9100	40.6	24

Key Observations

Compression pressure: because the compression pressure will increase, the average hardness of the pills additionally will increase. This suggests that higher compression results in denser and more difficult drugs.

Hardness: The average hardness stages from 22.2 to 40.6 trendy units (sc) across the exclusive compression forces. This shows that the capsules come to be substantially more difficult with elevated compression.

Disintegration Time: The disintegration time increases with better compression forces, ranging from 2 mins at 4100 lb to 24 mins at 9100 lb. This indicates that tougher drugs take longer to disintegrate, which might also affect the discharge of energetic substances.

Formula 2

Ingredient	Label Claim	% Mg / Tablet	Average Actual mg/Tab
Vitamin A (as Palmabeads)	2000 IU	4.0	5.0
Beta Carotene (0.3 mg)	500 IU	12.50	15.63
Vitamin D3 (as Vitamin D3 Type 100 WS)	200 IU	2.0	2.50
Vitamin E (as Dry Vitamin E Acetate 50%)	15 IU	30.00	31.50
Vitamin C (as Sodium Ascorbate)	60 mg	22.23	23.35
	45 mg	5.00	47.25
Folic Acid	200 mcg	0.2	0.28
Vitamin B1 (as B1rocoats 33.3%)	0.75 mg	2.25	2.48
Vitamin B2 (as B2rocoats 33.3%)	0.85 mg	2.25	2.81
Niacinamide (as Niacinamide rocoats 33.3%)	10 mg	30.03	33.03
Vitamin B6 (as B6rocoats 33.3%)	1 mg	3.64	4.0

Ingredient	Label Claim	% Mg / Tablet	Average Actual mg/Tab
Vitamin B12 (as B12 0.1% SD)	3 mm	3.0	4.2
Biotin (as Bitrit-1)	25 mm	2.5	3.5
Pantothenic Acid (as Calcium Pantothenate SD)	5 mg	5.44	7.62
Vitamin K (as K1 1% SD)	5 mm	0.50	1.0
Calcium (as Calcium Carbonate 90 Aa)	100 mg	278.0	278
Magnesium (as Magnesium Oxide DC)	50 mg	83.00	83.0
Iron (as Iron Fumarate 60% Coated)	6 mg	30.30	30.30
Zinc (as Zinc Oxide)	5 mg	12.45	12.45
Copper (as Cupric Oxide)	0.5 mg	1.25	1.32
Manganese (as Manganese Sulfate 50% Coated) A Desmo Chemical b0E.Mendell	0.5 mg	2.75	2.75
Ingredient	**Label Claim**	**mg/Tablet**	**Average Actual mg/Tab**
Rose Hips	0.5 mg	0.5	0.5
Rutin	0.5 mg	0.5	0.5
Bioflavonoids	0.5 mg	0.5	0.5
Iodine (as Potassium Iodide)	37.5 mm	0.055	0.058

Theoretical Weight of Actives

Description	Weight (mg)
Theoretical Weight of Actives	**409.378 mg**

Inactive Ingredients

Inactive Ingredient	Weight (mg)
Starch 1500	125.00
Dipac Compressible Sugar	1241.472
Sugar 6 Powdered	50.0
Syloid 244	7.0
Microcel C	7.0
Citric Acid	50.0
Carrageenan	70.0
Prosweet Flavor Enhancer (Mm)	30.0
Natural Strawberry Flavor	100.0
Magnesium Stearate	13.0
Total Weight of Inactives	**2287.00 mg**

Manufacturing Procedure

Vitamin Premix

1. Mixfolicacid, VitaminB1, VitaminB2, biotin, VitaminB6, calcium pantothenate and Niacinamide in a suitable blender using geometric dilution when necessary.

2. skip through #30meshscreenor equivalent milling procedure and remix for 5 minutes.

3. Mixsodiumascorbate, VitaminE, ascorbicacid, c-ninety, betacarotene, VitaminB12, PalmabeadsType500, Vitamind 3 and Vitamin K using geometric dilution when necessary and let mix for 10 minutes or until a uniform blend is obtained.

4. Charge steps 2 and 3 in to a suitable blender and mix for 10 minutes or until a uniform blend is obtained.

Mineral Premix

1. MixpotassiumIodide, Rosehips, Rutin, Bioflavonoids, CupricOxide, manganese Sulfate, Zincoxideand Ferrousfumarate, using geometric dilution when necessary.

2. Passstep1througha#30mesh screen if necessary and remix for 5 minutes.

3. Add Calcium Carbonate and Magnesium Oxide to step 2 and mix for 5 minutes or Until a uniform blend is obtained.

Final Blend

1. Add the vitamin premix to them in eralpremix in a suitable blender and mix for 5 minutes or until a uniform blend is obtained.
2. Add Dipac, Starch 1500, Carrageenan, Citric acid, and Prosweet to step 1 and mix for 5 minutes or until a uniform combo is obtained.
3. Mix and display taste, Magnesium Stearate, Syloid 244 and Microcel C via #30 Mesh.
4. Upload steps 3 to 2 and mix for two to three minutes.
5. Keep the final combination in appropriate drums covered with polyethylene bags.

Compression

1. A part of the very last blend changed into compressed on a suitable tablet press equipped with 5/8 tooling and showed the following residences:

(a) Tablet Hardness, sturdy Cobb devices (SCU)*

(b) Tablet Friability (%)

2. A part of the very last blend turned into compressed with 3=4 tooling

(a) Tablet hardness

(b) Tablet Friability (%)

14

1.3

14

4

Nutritional supplement 2007 FDA exact production Practices necessities for Formulations effective August 25, 2007, all producers of dietary supplements, which includes vitamin and Mineral preparations may be required to conform to the new cGMPs for nutritional dietary supplements.

Identify 21 CRF element 211 require the subsequent.

Master production report

1. You should put together and follow a written master manufacturing report for each specific components of dietary supplements that you manufacture, and for every size, to make sure uniformity in the completed batch from batch to batch.

2. The grasp production file ought to:

A. pick out specs for the factors, steps, or stages within the manufacturing process, wherein management, is necessary to make sure the first-class the nutritional supplement and that the nutritional supplement is packaged and categorized as special within the master manufacturing record.

B. set up controls and tactics to ensure that every batch of dietary supplement that you manufacture meets the specifications identified according to paragraph (b) (1) of this bankruptcy. [Code of Federal Regulations, Title 21, Part III, Section E (b) (1)].

What does the master manufacturing report encompass?

The master manufacturing document must encompass:

1. The name of the dietary supplement to be manufactured and the electricity, concentration, weight, or measure of each nutritional component for every batch size;
2. 2. A complete tabulation of parts for use.
3. 3. A correct announcement of the load or quality of each phenomenon expected used.
4. 4. The correspondence and pressure or measure of each abstinence from food determinant so individual can be asserted
5. on the complement label and the similarity of all points in the manner expected asserted on
6. The additives list of the abstinence from food complement.
7. 5. A proclamation of any deliberate surplus size of a digestive element.
8. 6. A declaration of the hypothetical yield of a made-food supplement anticipated at
9. all phenomenon, step, or degree of bearing arrangement in which maneuver is desired to confirm
10. the excellent of the nutritional complement, and the expected yield when you finish man
11. manufacturing the digestive complement that involves the maximum and minimum possibilities
12. of the hypothetical yield further that a departure study of a batch is fault-finding
13. And material judgment is completed activity and an arrangement election is made.
14. 7. Description of the bundle and a representative label, or a go link accompanying the physical place of the real consultant label.
15. 8. Written education, in addition to the following:
16. a. specs each point, step, or stage inside the production device place
17. control is owned by confirming the excellent of the dietary complement to what the
18. about food, supplement is wrapped and top-secret as extraordinary within the grasp manufacring
19. Turing document.
20. b. methods for examining and a cross relates accompanying procedures for exams or
21. Examinations.
22. c. particular campaigns unavoidable to complete the activity and confirm points, steps, or ranges within the
23. result habit in what way survive is owned by making sure the outstanding of the
24. abstinence from food complements what the abstinence from food supplements is packaged and top-secret
25. as singular in the grasp result document:
26. i.
27. ii.
28. Such particular moves include proving the burden or degree of some
29. Determinant and verifying the adding of some issues.
30. For manual movements, the aforementioned moves should encompass:
31. A. person careful consideration and each human proving the weight or measure;
32. B. individual guy containing the facet and another guy or woman proving the adding;
33. C. singular notations and carefulness to be found;
34. D. healing motion pans are expected secondhand while a specification is due.
35. This recently announced very last rule has especially exchanged the necessities for compo
36. Composition of a master result report. This is the most natural tale of a contemporary accurate
37. result Practices standard that prescriptively spells aforementioned necessities as approach
38. Controls and texture evaluation or healing activity plans as a constituent a grasp report.
39. Supplementary strong scheme records
40. Eligible or diversified burden misfortune plan capsules had been fashioned by way of way of all moist granulation and dry granulation methods. Wettish granulation is achieved to a 5 secondary diploma, on account of the evidence most ingredients and excipients may be convinced assembly the tangible limits alive to
41. Plan pills and tablets. Dry granulation approaches are price-effective and show
42. Better complete merchandise by way of the removal of water. Alcoholic answers have additionally happened
43. favorably working to granulate minerals formulations, nevertheless, this form is similarly

44. Curving into out of date on account of referring to practices or policies that do not negatively affect the environmental controls set on firms for solvent diffusions.
45. Capsules may be uncoated or contained accompanying the aid of film or added sugar strategies. Sugar coating of
46. vitamin pills is curving into archaic, by way of the reality pressure deficit program consumers, except that children decide upon not any more to have
47. Carbohydrate influenced to ability. Chewable products are usually constructed for the children‘s forum
    Sugar-coated vitamins had a shorter shelf life than the current film-coated tablets,

Due to the introduction of water and the faster drying times. Sustained released vitamin products have been a matter of interest, however very Little has been published on the technology and formulation of such products. The major Problem in formulating a sustained-release multivitamin product is achieving full Bioavailability of the vitamin in addition to sustained release for a significant number of Hours. Riboflavin is particularly troublesome in this regard due to its very low solubility in Water [2].

Shelf Life

The shelf life of a product is determined by the stability of its most unstable ingredient. In multiple vitamin products, there are usually three to five limiting ingredients, making it impossible to generate data at elevated temperatures and predict shelf life by the classical application of the Arrhenius plot. Accelerated testing has most often resulted in erroneous predictions due to excessive variations in analysis [3].

Suggested Methods for Predicting the Stability of Vitamin Products While the final rule “Good Manufacturing Practices Regulation for Dietary Supplements” does not include a requirement for expiration dating, it has become the industry standard imposed by customers and consumers alike. It is for this reason that expiration dating is not likely to go away despite what may become the final rule. More than likely, it will probably become a requirement in the future [8].

The Nutrition Health and Labeling Act on the other hand states that dietary supplements must maintain 100% of their labeled ingredients throughout their shelf life. Based upon this requirement, predicting product stability becomes a requirement by default. To meet these needs stability studies and expiration dating must be the topic for methods of Predicting shelf life. Since single-ingredient vitamin products can be tested by the classical stability Predicting method, popularized by the pharmaceutical industry, these products present the fewest of concerns. Also, ingredient products have always been topics of the USP, there are volumes of real-time stability data available to manufacturers, particularly from raw ingredient suppliers. Secondly, multiple vitamin combination product manufacturers are usually fast followers in the marketplace, who do not enjoy the luxury of product patents and proprietary information. The return on investment does not permit them to invest time and Money in waiting for long-term studies to be completed before launching a new product. Thus, product labels must bear an expiration date based on “best guess” and literature Searches. The following three suggested methods may provide some input to those manufactures who may be interested in utilizing the methodology that is currently being used for interim expiration dating. These methods are being utilized by some of the more responsible industry members who also do not have the resources to conduct real-time studies before launching a new product.

Suggested Methods to Collect Supporting Data for Interim Expiration Dating

1. New Products: A minimum of one batch in the commercial package held for 3 months at 40˚C/75% relative humidity with a documented commitment to test the product at labeled storage conditions at, 6 months, 1 year, and at the end of the declared shelf life and removed it from the market if it failed at any test interval. (Testing three batches under these conditions is preferred when the manufactured volumes and frequency of manufacture will permit.)
2. New Products with ingredients similar to existing products with real-time data. One batch minimum tested under accelerated conditions run side by side with the existing product. The excipient base must also be the same and in similar ratios. Commitment to long-term studies must be documented and completed as above
3. Existing products for which stability studies have not been conducted-Conduct stability test on at least three samples from retains, preferably unopened identical containers that have reached the expiration date. Place one additional new lot or batch Sample on stability annually to confirm test data. Test results from all of the above shall be termed interim expiration dating until long term data becomes available.

Research Method

Researching a diversified part of vitamins and minerals in drugs or other ingestible forms usually involves a combination of dramatization, expression development, and hands-on experiments. Researchers are looking at existing formulations to identify gross challenges and growth measures. This includes evaluating the stability, bioavailability, and efficacy of various nutritional sources and not organic combinations of indifferent parts of the drug or other ingestible forms to the degree of tablets, capsules, powders, and liquids.

Results

Findings show that a consistent diet often lacks essential foods, which outweighs the high demand for digestive supplements. Studies show that preparations must balance the safety of vitamins and minerals accompanying their bioavailability to ensure active inclusion in the framework. For example, some vitamins are sensitive to light and heat, which can shame their effectiveness, while others admit the possibility of requiring special excipients to embellish their cohesion and solubility.

Discussion

Formulating diversified vitamins and minerals presents different challenges. One important issue is the potency of individual vitamins, as many are forced to degrade when not protected into tangible determinants. For example, nutrient C is very sensitive to corrosion, while B vitamins can be affected by heat and liquid. In addition, the interaction between different vitamins and minerals can cause a decrease in productivity; extreme doses of calcium can prevent the incorporation of magnesium and zinc.

Another challenge is achieving the required amount of drug or other form of consumption that is acceptable to customers. Chewable tablets, gums, and liquid formulations are well-known among children and adults but often require additional spices and sweeteners, which can confuse the process of expression. In addition, it is necessary to guarantee that part of the drug or other edible form will be palatable, and at the same time, the determination of vital factors will be enforced.

Conclusion

The formulation of multivitamin and multimineral supplements is a complex process that demands careful consideration of multiple factors, including ingredient potency, bioavailability, and consumer preferences. Many vitamins are highly sensitive to environmental conditions such as heat, light, and moisture, necessitating protective strategies to prevent degradation. Additionally, interactions among different vitamins and minerals may compromise efficacy, requiring sophisticated formulation techniques to preserve product integrity. Formulators must also balance the sensory acceptability of products—particularly in chewable or liquid forms—without compromising stability or therapeutic value. Regulatory compliance, cost efficiency, and manufacturing feasibility further complicate the development process. Despite these challenges, continuous advancements in pharmaceutical technology are enabling the development of stable, effective, and consumer-friendly MVM products. Ongoing research and innovation remain crucial to addressing nutrient deficiencies and meeting evolving consumer health needs.

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Declaration of Interest:

I herewith acknowledge that:

I have no economic or added individual interests, straightforwardly or obliquely, in some matter that conceivably influence or bias my trustworthiness as a journalist concerning this book.

Conflicts of Interest:

The authors profess that they have no conflicts of interest to reveal.

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