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Stability of Vitamins in Pharmaceutical Preparations- A Review

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Abstract: ***Vitamins are one of the few groups of food constituents in which it is possible to demonstrate quantitatively deterioration in content over a period. The rate of this reduction in vitamin content is influenced by a number of factors. The stability of the more commonly used vitamins in vitamin concentrates and multivitamin preparations for oral administration has been studied in a variety of basic aqueous solvent mixtures of practical significance under normal storage conditions. The overage required for each vitamin under various conditions and in different formulations has been indicated in order to determine the excess of each vitamin necessary to maintain label declarations for normal storage periods. In general, many physical and chemical factors can have a negative effect on stability of vitamins. Water-soluble vitamins are prone to degradation in solutions, particularly when exposed to light. In the present study, the interaction of vitamins in all conventional formulations is discussed.***
Key words: Vitamins, Stability, Formulations, Interaction, Degradation

I. INTRODUCTION

In Multivitamin preparations, Vitamins are known to lose their potency during storage even though most of the individual Vitamins are stable and prepared in to reasonable stable dosage forms by themselves. Some of the factors which are generally responsible for the instability of Vitamins in Multivitamin preparations are as follows :

The pH of the medium
The presence of certain Metals like Iron, Copper, Calcium and stabilizers like Antioxidants, Metal Binders, Proteins, Amino acids etc.,
The nature of the base and the concentration of water present in the preparation
The conditions of storage such as the container, light, temperature, humidity etc.,
Incompatibility of Vitamins.

Interaction of Vitamins may be found in all conventional formulations including compressed Tablets, dry filled and oil filled Gelatin Capsules, Liquid Oral and Liquid Parenteral products. Sometimes even inert formulations additives and diluents may be involved because they supply moisture, introduce reactive contaminations including trace metals and alter the pH.

A. Vitamin " A"

Vitamin A Esters are more stable than Vitamin A itself. Stability of Vitamin A is effected by heat, light, and air, the most important factor being oxidation which is catalyzed by traces of metals such as Iron and Copper. The oxidation may be inhibited to a large extent by the addition of Antioxidants such as Alpha Tocopherol , Hydroquinone, Propyl Gallate and especially by the combinations of these Antioxidants. For example, the stability of Vitamin A dissolved in Liquid Paraffins, Ethyl Stearate, Ethyl Oleate and Arachis Oil is greatly enhanced by the addition of 0.05 % Propyl Gallate as Antioxidant. Vitamin A is stable when heated in an inert atmosphere at moderate temperature in the dark. On exposure to ultra violet light , the typical absorption band at 325 nm – 328 nm is destroyed and biologically inactive products are formed. Vitamin A dissolved in oil having a low peroxide content is stable for 3 months when kept in a well filled bottles. Vitamin A Esters under similar conditions are more stable than Vitamin A. The difference becomes appreciable under unfavorable storage conditions. Solutions of Vitamin A Acetates are more stable than Vitamin A Alcohol. The stability is enhanced by the addition of Antioxidants.
Aqueous solutions of Vitamin A are not stabilized by Alpha Tocopherol, if the concentration of Antioxidant is below 0.5 %. The best stabiliser is found to be a mixture of 3 % solution of Alpha Tocopherol, 0.01 % solution of Nordihydro Quairetic Acid, 0.2 %

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Solution of Sodium Edetate and 0.1 % Solution of Ascorbic Acid.

In Multivitamin preparations, Casein Hydrolysate alone or in combination with Cysteine Hydrochloride gives good protection to Vitamin A. Amino acids such as Asparagine, Glycine. Cysteine, Methionine, Glutamic Acid, Tryptophan do not give good stability to the shelf life of Vitamin A.

The stability of Vitamin A depends upon the nature and pH of the suspending medium and on the Concentration of Thiamine in oral liquid formulations. The optimum pH value for Vitamin A is 6.0

Sorbitol – Propylene Glycol – Glycerol – Ethyl Alcohol (2 : 1 : 1 : 1), Sugar Syrup – Glycerol – Water (2 : 2 : 1) and Sugar Syrup – Glycerol (1 : 1) combinations retained 70 % of Vitamin A during 5 months of storage.

B. Thiamine Mononitrate / Hydrochloride

In order to compensate for decomposition of Thiamine, an excess of 50 – 100 % of the vitamin should be included in multivitamin formulations. About 20 % of the vitamin activity is lost when Thiamin Concentrates are stored for 2 years in their original containers. Thiamin can be made more stable in multivitamin capsules with pigmented shells containing no added materials by adding a special Yeast medium. In such capsules no loss of vitamin is noticed even after several years of storage at room temperature. The capsules can be kept for about 2 years under tropical conditions with very little loss of Thiamin activity.

Thiamin is not stable in honey. Its stability is considerabily improved in the presence of Riboflavine.Decomposition products of Thiamine accelerates the destruction of Cyanocobalamin in a solutioncontaining Thiamine, Cyanocobalamin and other B Vitamins. In such solutions, Ferric Ions can protectthe destruction of Cyanocobalamin without having an appreciable effect on the stability of Thiamine.

The stability of Thiamin is maximum at pH 2.0 and decreases with increase in pH. The stability of an aqueous solution of the vitamin at pH 2.0 after storage for 6 months at 37 deg. Cent. Is 100 %. At pH 4.0 – 5.0 80 % Glycerol solution in water or 10 – 80 % Glycerol in syrup is found to be the best carrier. In the presence of Nicotinamide, Riboflavine and Pyridoxine and 0.1 % Cysteine Hydrochloride, the stability was found to be 100 % after 8 months storage at 37 deg. Cent. Cane sugar syrup (60 %) is a better carrier than Glycerol. The degradation of Thiamine in solution is accelerated by Sodium Hydro Sulphite, Potassium Metabisulphite and Sodium Sulphite.

The stability of Thiamin is decreased by increasing the water contents of multivitamin formulations prepared in a carrier containing 20 % of water with either 80 % Propylene Glycol or 40 % of Propylene Glycol and 40 % Glycerol. Thiamine Mononitrate is more stable in a carrier containing 80 % Propylene Glycol. Thiamine Hydrochloride is more stable in that contains 40 % each of Glycerol and Propylene Glycol. Its stability in the presence of Ascorbic acid is improved by the addition of 0.01 % Calcium Edetate.

During storage at 37 ^{0} Cin different carriers, the deterioration of Thiamin is least in the presence of Pyridoxine and loss of potency of Thiamine in the presence of Riboflavine depends upon the concentration of Nicotinamide present in the formulation. The shelf life of Thiamine in 12 different formulations of 15, 27 and 37 deg. Cent show that the stabilizing actions of the following compounds are in decreasing order as follows : Cysteine Hydrochloride, Propyl Gallate and Thiourea.

The colour of Thiamine Hydrochloride injections depends upon the quality of the raw material and on the pH of the solution. The temperature of sterilization (70 – 120 deg. Cent) affects the quality of Thiamine solutions to a lesser extent than does the presence of Oxygen in ampoules.

C. Riboflavine

At pH 6.8, a concentrated aqueous solution of Tryptophan dissolves Riboflavine to the extent of 4 mg/ml. This solubility of Riboflavine is increased markedly by the addition of Nicotinamide. At room temperature, these solutions are stable for at least 7 months and are suitable for injections.

The destruction of Riboflavine by Ascorbic acid is decreased by Glutathione and Thiourea. Calcium inactivates Riboflavine and Cyanocobalamin is inactivated by Thiamin.

Vitamin concentrates stored in air tight containers for 5 years at room temperature showed very little loss of activity. Similarly no significant loss of Riboflavine in multivitamin capsules during the storage at 37 deg. Cent for 1 year occurs.

D. Pyridoxine Hydrochloride

In mixed vitamin preparations, Pyridoxine is stable to the same extent as Nicotinic Acid and Riboflavine. It is unstable when it is irradiated at pH 6.8 or above in aqueous solutions. It is almost unaffected at pH 1.0.

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The vitamin is stable when heated to 100 deg. Cent in 5 M Sodium Hydroxide solution or 5 M Hydrochloric acid or Sulphuric acid. However the vitamin is unstable at 100 deg. Cent in Nitric acid due to the laters oxidizing effect.

E. Folic Acid

Aqueous solution of Folic acid in presence of Citrate – Phosphate buffers are stable between pH 6 and 9.8., below the pH 5.0, Folic acid is sparingly soluble and is decomposed rapidly. It is decomposed in presence of Thiamine and Riboflavine. Between pH 3 and 4, crystalline Folic acid Is almost insoluble and is table in presence of Thiamine, Riboflavine and other B group vitamins. Decomposition of Folic acid caused by light or the presence of Riboflavine is more pronounced between pH 4 and 6.5 and retarded by the addition of antioxidants or exclusion of air. About 18 % of the vitamin is lost in Folic acid solution with Riboflavine adjusted to pH 5.5 containing 0.05 % Ethyl Hydro Caffeate, 0.05 % Butylated Hydroxy Anisole or 0.02 % Nordihydro Guaiaretic acid and stored in amber glass bottles for 3 months in diffused day light at room temperature. The loss is increased in 35 % in 6 months under the same conditions.

A 0.5 % solution of Folic acid or Nicotinamde adjusted to pH 6 when heated to 75 deg. Cent remains stable in the presence of Nicotinamide and is discoloured when 10 % amino acetic acid is used. The solution with Nicotinamide is also stable in the presence of Cyanocobalamin.

Folic acid is stable in aqueous solutions of pH 5.0 – 8.0. Thiamine, Riboflavine., Ascorbic acid, Choline,

Calcium Hypophosphite and Manganese Sulphate are mainly responsible for the instability of Folic acid in multivitamin formulations.

Buffered carrier solutions containing Tween 80, alcohol, glycerine and propylene glycol retain most of the folic acid content at pH 6.0 – 6.6. The stability of folic acid is greatly affected by atmospheric oxygen, light, pH and temperature.

F. Cyanocobalamin

The instability of Cyanocobalamin in aqueous solution is mainly due to Dehydro Ascorbic acid which is the decomposition product of Ascorbic acid. Cyanocobalamin is alone stable even when exposed to light. Decomposition is caused by the presence of Riboflavine.

Nicotinamide accelerates photolysis of Cyanocobalamin which is inhibited by addition of the Antioxidants Thiourea and Ethyl Hydrocaffeate. About 5 % microbiological activity is lost at pH 4.5.

Hydroxycobalamin is less stable in presence of Ascorbic acid. The hydrated forms of Cyanocobalamin is stable alone or in dry triturations in sodium chloride, sucrose, dextrose, mannitol and maize starch. the anhydrous material is hygroscopic.

Sterile aqeous solutions are stable at room temperature. Talc quantitatively absorbs Cyanocobalamin from which it can not be eluted with water. Cyanocobalamin is converted to Hydrocobalamin Between pH 3.5 and 6.5 under the action of light. The reaction can be reversed or stopped by storing the solution in the dark.

Stable preparations of Cyanocobalamin with Ascorbic acid are obtained using equal volumes of Glycerol and Propylene Glycol after 6 months storage at room temperature no loss of Cyanocobalamin and 10 % loss of Ascorbic acid occurs.

Cyanocobalamin preparations are ti be preserved at pH 4.5 – 5.0 while such preparations containing Ascorbic acid, it is preserved at pH 6 and 7. Cyanocobalamin is not stable in the presence of both Nicotinamide and Thiamin. However either of these vitamins alone does not decompose Cyanocobalamin.

In injections, Cyanocobalamin is unstable in the presence of Nicotinamide and Thiamine. About 30 % Cyanocobalamin potency is lost at room temperature in 1 year in the presence of 20 mg of Nicotinamide and Thiamine per ml. Cyanocobalamin is completely destroyed when the amount of Nicotinamide and Thiamine is increased to 50 mg / ml.

The darkening of B Complex Vitamin solutions containing Cyanocobalamin in high concentrations is avoided by increasing the air in the ampoules.

The effect of sugars on the stability of Cyanocobalamin indicates that at the end of 6 months shelf life, Glucose and fructose cause 23 % loss, sorbose 11 % , lactose 18 % and both maltose & sucrose 3 %

In presence of Cysteine, complete destruction of Cyanocobalamine occurs at elevated temperatures., while other amino acids cause 10 – 13 % only. Cyanocobalamin show a loss of potency in the presence of reducing agents and are stable in Basal medium containing Ascorbic acid.

G. Ascorbic Acid

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The stability of Ascorbic acid is improved in aqueous solutions by addition of Sodium Chloride. The improvement is due to lower concentration of dissolved oxygen.

Ascorbic acid solution may be sterilized by heating at 98 – 100 deg. Cent with a bactericide provided The pH of the solution is less than 6.4 and an antioxidant such as Thiourea (0.012 %) is present, Chlorocresol (0.2 %) is used as Bactericide.

Ascorbic acid solutions slightly deepen in colour when exposed gamma irradiation. When Ascorbic acid is mixed with equal volume of Nicotinamide solution, a canary yellow addition compound which Differs in melting point from either of the components is obtained, but the resulting mixture maintains full potency of both the ingredients.

In syrups, above pH 4.0, Ascorbic acid is decomposed very rapidly, the addition of sugars, alcohol, and Polyhydric Alcohol has a stabilizing aeffect. A 20 % excess of Ascorbic acid is used in preparing Syrups. The stability of Syrup is increased by the presence of other B group vitamins. The efficacy of a mixture of Sodium Bisulphite, Sorbitol, Propylene Glycol and Tetra Sodium Salt of Edetic acid as stabilizers for Ascorbic Acid Syrups.

After prolonged storage, Ascorbic acid tablets developed decolouration due to the presence of moisture. for this reason, dry granulation should be used for the manufacture of tablets. Ascorbic acid is stable for a longer period in tablets prepared by using non aqueous granulating agent such as Methylene Chloride in Chloroform and Alcohol Mixture. Stability is further increased if the tablets are stored in moisture free amber coloured containers.

Glycerol gives maximum protection to Ascorbic acid. Magnesium Chloride and Ferrous Gluconate have a slight protective action towards Ascorbic acid.

Glycerol gives maximum protection to Ascorbic acid than Sorbitol.

The colour stability of Ascorbic acid tablets as studied by light reflectance is found to be closely related to chemical stability. Lubricant low in metallic Ion contents such as Stearic acid and hydrogenated Vegetable Oil gives maximum stability , while the alkaline lubricants such as Magnesium and Calcium Stearate and minerals such as Talc and Sodium Silico Aluminate cause excess colour reversion.

Ferrous Ions has no deterious effects on Ascorbic acid, but Ferric Ions either in inorganic or organic form accelerates deterioration.

Ascorbic acid can be used as stabilizer for a Vitamin B Complex solution. The presence of Ascorbic acid in solutions containing Thiamine, Riboflavine, Pyridoxine and Nicotinamide completely displaces oxidation – reduction equilibrium which exists among the B Group Vitamins, avoiding Thiochrome precipitations and promoting formation of Chloroflavin.

The stability of Ascorbic acid in 95 % cane sugar syrup in the presence of Citric acid, Sodium Citrate, Sodium dihydrogen phosphate, Sodium dihydrogen citrate, Ferric Citrate, Ferric Ammonium Citrate, or Sodium Glycerophosphate at 37 deg. Cent shows a deleterious effect. In presence of these salts even E.D.T.A. and Cysteine do not give protection to the vitamin.

Sodium Chloride has no deleterious effect on the stability of Ascorbic acid.

H. Vitamin " D " (Cholecalceferol / Ergocalceferol)

In preparations containing 25 % or more of minerals, Vitamin D deteriorates due to increased exposure to air resulting from the larger surface area.

Vitamin D syrup containing 0.15 % Tween 80 as solubilizer is prepared in which the following compounds are used as stabilizing agents. 0.01 % Ethyl Gallate, 0.01 % Butylated Hydroxy Toluene.

After storage at 17 – 37 deg. Cent , the stability of the syrups proved stable during 6 months. Ethyl Gallate inhibits and Ascorbic acid accelerates the inversion of Saccharose in Vitamin d Syrups.

Vitamin D in both aqueous and oily Injection solutions is thermolabile. The degradation of Vitamin D in aqueous injections is less than in oil ones. The Vitamin D injections can be sterilized by filtering through Batericides.

I. Vitamin " K"

Vitamin K is unstable in In-Organic Carriers, but is stable in Organic Carriers. The percentageretention of Vitamin K in each powder was follows:

Aluminium Silicate Synthetic : 26 % ; Silica Gel 23 % ; Magnesium Carbonate 21 % ; Magnesium Silicate 19 % and Magnesium Oxide 11 %.

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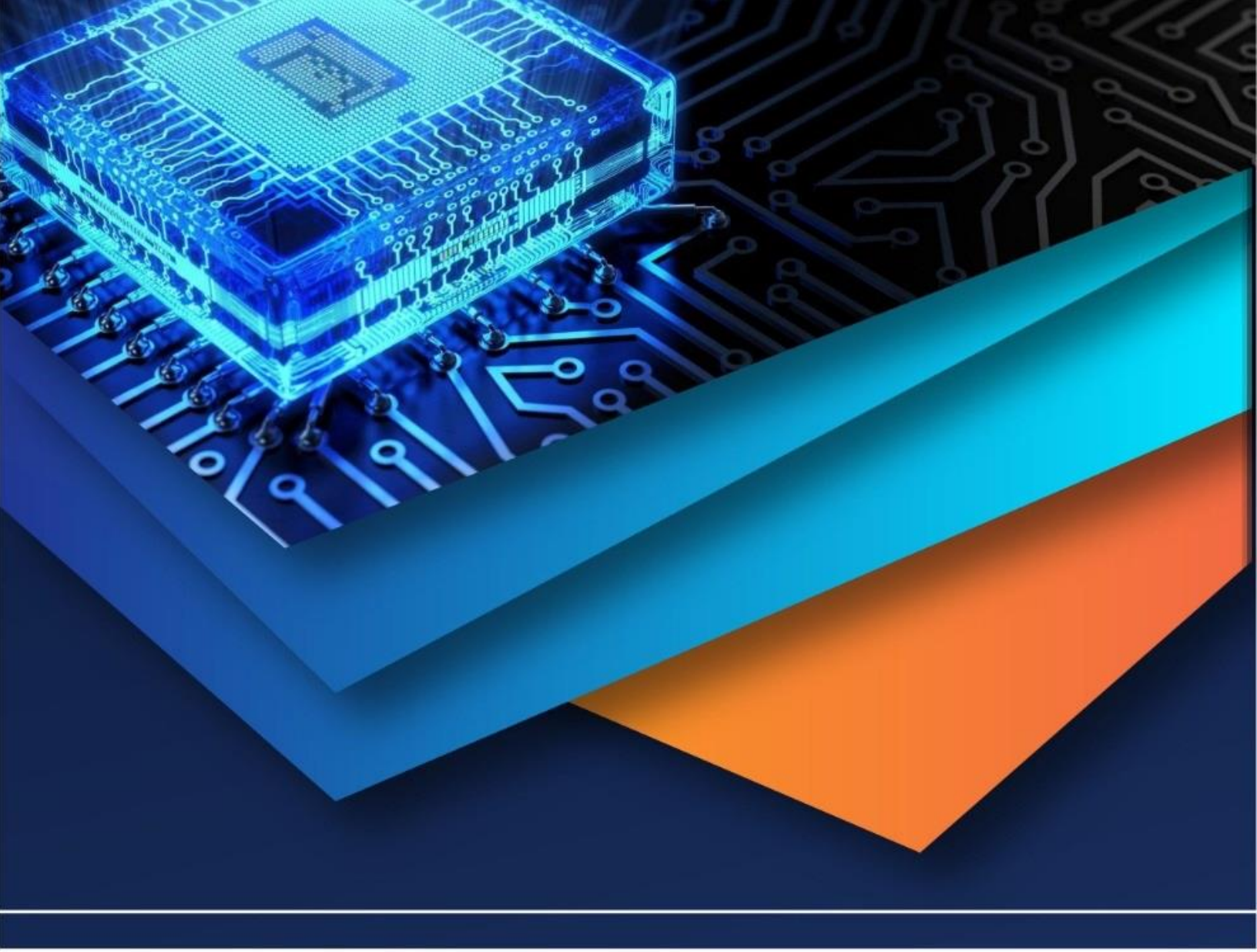

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