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Review Article

Methylcobalamine (Vitamin B12): Water Soluble Vitamin with Various Pharmacological Aspect

Roopesh Kumar Yadav, Sudhanshu Mishra*, Deepti Jain

School of Pharmaceutical Science, Rajiv Gandhi Prodyogiki Viswavidyalaya, Bhopal, India

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*Address for Correspondence:
Sudhanshu Mishra, Assistant Professor, Dr M C Saxena College of Pharmacy, IIM Road Lucknow, India

Abstract

Vitamin B12 is a water-soluble vitamin that plays a key role in the brain's proper functioning and nervous system, in blood flow, and in reducing weakness and tiredness. In their food, most people get adequate vitamin B12, but in some health conditions (e.g. inadequate sleep, stomach/intestinal disorders, inflammation, cancer), there could be a shortage. If left unchecked, severe Vitamin B12 deficiency results in anemia and nerve damage. Vitamin B12 deficiency is typically treated using parenteral and oral dosage formulations, but absorption and compliance problems are involved with these routes of administration. Most significantly, the function of this missing intrinsic factor has been shown to assist in vitamin B12 absorption and a deficiency known as pernicious anaemia. Vitamin B12 is only partially absorbed when delivered by mouth to patients with pernicious anemia, but hematologically re-absorbed in patients with pernicious anemia. Parenteral administration of the extrinsic element will treat pernicious anaemia satisfactorily. There are several roles and advantages of vitamin B 12 in the human body with therapeutic effects also.

Keywords: Water Soluble Vitamins, Methylcobalamine, Vitamin B12, Pernicious Anaemia.

INTRODUCTION-

Although they serve many roles in the body, vitamins and minerals are fundamental supplements. There is a barely recognizable distinction between getting enough (which is solid) of these supplements and getting too much (which create overdose). The only way to get sufficient proportions of the vitamins and minerals required by our body remains to eat a solid regimen.[1] Vitamins and minerals are seen as important nutrients because they have diverse functions in many ways, such as assisting in bone metabolism, wound healing, and building up our body structure, and even converting nourishment into vitality and restoring cell damage.[2]

Types of Vitamins

Fat-soluble vitamin- The adipose tissues of the body and the liver store fat-soluble vitamins. The A, D, E, and K vitamins are fat-soluble.[3] These are less demanding to store than water-soluble vitamins, and they will remain in storage form in the body for a long amount of time, and a few months in some cases. In the digestive tract, fat-soluble vitamins are absorbed with the aid of fats or lipids.

Water-soluble vitamin-Vitamins that are water-soluble do not survive in the body for a long time. They can't be processed by the body and they get released from urination. Water-dissolvable vitamins are expelled more often along these lines than fat-solvent ones. Water solvents are vitamin C and B vitamins.[4]

Vitamin B12 is a water-soluble vitamin that plays a crucial role in the proper functioning of the brain and nervous system, blood production, and stress and fatigue control. [5,6]

- Types of vitamin B12
  - Methylcobalamin (A most active form of vitamin B12)
  - Hydroxycobalamin
  - Adenosylcobalamin
  - Cyanocobalamin

Healthy diet sources of vitamin B-12 include: milk products such as milk, cheese and yogurt, beef, fish, chicken, eggs, certain nutritional yeast products and mushrooms, certain kinds of soy milk, and breakfast cereals are enriched with vitamin B-12. Before active therapy is needed, it is often best to sustain a balanced diet and consume healthy quantities of nutrients. For a balanced diet, the signs of malnutrition are easily eroded.[7,8]

Benefits of Vitamin-B12

- For the proper function of the brain and the nervous system, vitamin B-12 is essential. It is also active in red blood cell development and helps to produce and control DNA.

- Each cell in the body's metabolism relies on vitamin B-12 since it plays a role in the fatty acid synthesis and the production of energy. By helping the human body digest folic acid, vitamin B-12 helps the release of energy.[9]
- Millions of red blood cells are generated by the human body every minute. Without vitamin B-12, these cells do not replicate properly. Red blood cell production is decreased if the levels of vitamin B-12 are too low. Anemia may occur if the count of red blood cells decreases.[10]

Absorption of Vitamin B12- It is protein-bound as humans take vitamin B12 orally. There is also some preliminary evidence that unbound B12 can be actively absorbed in higher rates through the membranes under the tongue than through passive diffusion in the digestive tract, especially when combined with an absorption enhancer.[11] When the protein-B12 complex reaches the intestine, the stomach secretes acids and enzymes that separate B12 from the protein. Another protein that takes up and brings B12 through the small intestine and the stomach is R-protein (aka cobalophilin, haptocorrin, and transcobalamin I). The stomach cells also produce a protein called intrinsic factor (IF) that passes to the small intestine (R-protein is found in saliva and stomach). The cobalamins then take the final part of the small intestine, the ileum, to the intrinsic portion. [12] Through passive diffusion, certain inactive B12 analogs are most likely absorbed. About 60 percent of the overall volume of B12 in the body is contained in the liver and 30 percent is stored in the muscles. People typically secrete 1.4 µg/day of B12 through their bile through their small intestines. It binds to transcobalamin II-II after B12 is absorbed into the intestinal cells (TC2). Transcobalamin II captures B12 and passes it to other body tissues via the blood and cerebrospinal fluid. While B12 is transferred to cells by transcobalamin II, haptocorrin is present in around 3/4 of B12 in the blood (aka transcobalamin I and cobalophilin). B12 is released from TC2 in the form of hydroxocobalamin until the B12-TC2 complex enters the cell where it is required.[13] It is then converted into methylcobalamin or adenosylcobalamin and used by its respective enzymes. Transcobalamin II also transports B12 to the liver for transcobalamin III storage. Excess B12 is excreted in the urine. This usually occurs only after injection of B12.[14]

STRUCTURAL CHARACTERISTICS AND CHEMISTRY OF VITAMIN B12-

Vitamin B12 is a class of cobalt and corrin ring molecules that possess vitamin activity. The sixth coordination site of the corrin ring is either a cyano group (-CN), a hydroxyl group (-OH), a methyl group (-CH-) or a 5'-deoxyadenosine group, creating four forms of vitamin B, including, cyanocobalamin, hydroxocobalamin, methylcobalamin, and adenosylcobalamin.[15,16]

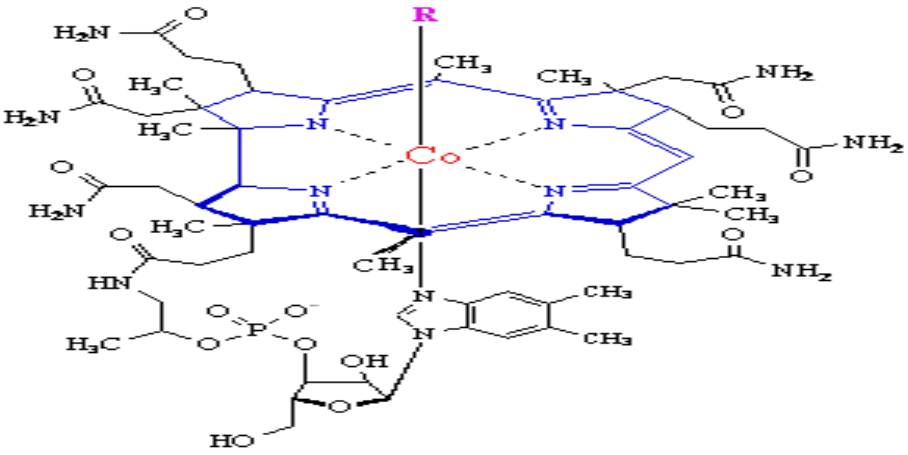

Figure 1: Structure of Vitamin B12

Solubility: Solubilized in organic solvents that are expelled with inert gas, such as ethanol and DMSO.[17] The solubility of vitamin B12 is approximately 10 and 75 mg/ml, respectively, in these solvents. In water, vitamin B12 is also soluble at a concentration of 50 mg/ml.[18]

Stability/Shelf Life: Light-sensitive, Hygroscopic; when exposed to air, may absorb about 12 % water.[19]

Pharmacokinetics-

Absorption: Readily absorbed in ileum and sublingual routes by passive diffusion. Dietary vitamin B12 is present in conjunction with food proteins and must be released inside the gastric lumen at low pH exposure to promote absorption in the small intestine. Individuals intake roughly 2.4 µg of vitamin B12 every day, of which about 50-60% is absorbed.[20,21]

Protein binding- Very high.

Metabolism: Occurred in the liver.

Biological half-life: 6 days.

Elimination: Urine/Bile

TYPES OF FORMULATIONS USED FOR VITAMIN B12 DELIVERY-

There is a various formulation used to reduce the risk from the deficiency of vitamin B12 like Mucoadhesive buccal tablets, Microencapsules, Lozenges, Liposomes, Buccal films, Nasal Spray, Intranasal drop, Topical microemulsion, Oral Spray, gelatin compositions (for parenteral), pen (inhaler), buccal mucoadhesive hydrogel films and toothpaste, etc. The following table no 1.0 include the different approaches of vitamin B12 in detail-[22-28]

Table 1: Comparative Table of Various Approaches of Vitamin B12

Formulations	***Method of preparation***	***Formulation Ingredients***	***Characterization method***	***Advantages***	***Disadvantages***	***Bioavailability***
Mucoadhesive buccal tablets	Direct compression	hydroxypropyl methyl cellulose (HPMC), carbopol 971p (CP971p), and chitosan (Cs)	Thickness, weight, drug content, hardness, friability, surface pH, *In vitro* drug release, and mucoadhesion	Rapid onset of action, elevated patient acceptability, administration, and dose removal is easy.	Low effectiveness in terms of flavor, irritation, low permeability, and patient acceptability. Less surface area also.	up to 2.7-folds that of Neurotone I.M.injection
Microencapsulation	Spray-drying technique	Modified chitosan, Vitamin B-12, Deionised water	Scanning Electron Microscopy, particle size,UV spectrophotometric method , release and its stability	Improving the stability of nutrition, preventing ingredient reactions and decay. The coating matrix essentially separates particles and prevents them from contacting one another.	High material loss, Sustained-release preparations. Time-consuming. , Suitable to larger particles.	
Microencapsulation	Emulsion technique	Vitamin B-12, PEG - 6000, Shellac , Liquid Paraffin, Acetone, Cyclohexane, Mannitol, Tween 80	Strength, Percentage Yield, Dissolution Rate, Accelerated stability testing	Higher stability, prevent their deterioration, preventing ingredient interactions		
Hard gelatin capsules		10 mg vitamin B12,10g vitamin B1,10 g riboflavin, 50g niacinamide,5 g calcium pantothenate, 4.5 grains desiccated whole liver, 1980 g of iron	Weight variation, content Uniformity Disintegration time, Dissolution time	tasteless, odorless, easy to administrate, Attractive to appearance, Easy to handle and carry.	absorb water	
Lozenges 1000 mcg		Folate 42%, Vitamin B-12(as Cyanocobalamin) 41,667%, Fructose, Microcrystalline Cellulose, Sorbitol, Natural Flavors, Stearic Acid (vegetable source), Magnesium Stearate (vegetable source) and Silicon Dioxide.	Particle size distribution, moisture content, flow, blend uniformity, hardness, tablet weight, thickness	Increase the retention time of the dosage form, increases bioavailability reduces gastric irritation and bypasses the first-pass metabolism.	No drinking or eating before or during use. Should not be swallowed	
Liposomes		Phosphatidylcholines, glycerin, natural orange flavor, stevia, potassium	Size-around 450nm positive surface charge, loading efficiency	Increase absorption and bioavailability Improve their transit across the	high production cost., may undergo oxidation and	

		sorbate, vitamin B12, purified water		barriers of the gastrointestinal tract. Improve the therapeutic efficacy of dietary supplements	hydrolysis, Shorter half-life. Lower solubility.	
Buccal films	By positron annihilation lifetime spectroscopy	vitamin B12, sodium alginate, and Carbopol 71G	Dissolution test, weight, thickness, surface pH, swelling index, drug content uniformity, in vitro residence time, folding endurance in vitro release, and permeation studies.	Preferable over tablets in terms of flexibility and thinness thus being less obtrusive and more acceptable to the patient	Eating and drinking may become restricted, the possibility of the patient swallowing the dosage form.	
Nasal Spray Once weekly		Sodium citrate, citric acid, and glycerin and benzalkonium chloride in purified water	pH between 4.5 and 5.5. spray pattern, Accelerated Stability at a higher temperature	Flexible and patient compliance	Irritation of nasal mucosa and can be interrupted by respiratory disorders	6.1%.
Intranasal		Cyanocobalamin 0.5% , citric acid 0.12%, sodium citrate 0.32%, glycerin 2.23%, benzalkonium chloride 0.02% and 96.79% water.	viscosity (less than 1000 cps), spray pattern, Accelerated Stability at a higher temperature	Lower viscosity avoids the GI tract and hepatic metabolism, bypasses the BBB enhancing drug bioavailability and allowing a lower therapeutic drug dose and fewer systemic side effects free of mercury compounds	Low volume of drug that can be administered	7%
Nasal Spray	Methylcobalamin 500 (mcg) Benzalkonium chloride 0.02 (mcg) Glycerin 223(mcg) Glycofurol 100(mcg) Sodium citrate dehydrate 0.38(mcg) Citric acid anhydrous Water 10 (ml)	pH, Osmolarity, drug content, appearance, a transmission rate	Hepatic first-pass metabolism is absent, Rapid drug absorption and quick onset of action can be achieved, the bioavailability of larger drug molecules can be improved	Suitable for potent medicines since it is easy to spray only a small amount into the nasal cavity. There could be fewer medications with constant and regular administration.		
Topical micro-emulsion	Titration method	Stearylamine,tween80,span20,labrafil ,propylene glycol ,oleic acid	(DSC), X-ray diffraction, particle size, conductivity,	Facilitate in preparing, perfect stability, increasing speed	A large concentration of surfactant and co-	

		and Cyanocobalamin (Vitamin B12)	surface tension, and viscosity	and stability drug solubility, controlling drug delivery rate, Improvement of hydrophilic and lipophilic drug bioavailability	surfactant is necessary for stabilizing the droplets of the microemulsion. Limited solubilizing capacity for high-melting substances	
Oral Spray		Oral Spray Methylcobalamin ,d-alpha-tocopherol , potassium sorbate,citric acid,peppermint oil, water	specific gravity 1.035 g/mL ,pH of 3.95,dencity,viscocity	Faster onset and longer duration of action. ease of administration, elimination of the first-pass metabolism	Taste masking is a major problem not applicable to drugs that require high large doses, not suitable for sustained-delivery systems as it interferes with eating, drinking, and talking.	
Gelatin compositions (for parenteral)		Distilled water, 6 g of vitamin B12, 1000 g Type A gelatin, 10 % aqueous sodium carbonate, 45 g. of benzyl alcohol	Sterility tests pH of 4.5. Leaker Tests. Particulate matter testing. Sterility tests	Act immediately and allow the administrator to control drug delivery. , improve medication adherence.	painful, need a specialist for administration and source of infection	
Pen (inhaler) 20-30 puffs		Vegetable Glycerin USP, Deionized Water, Organic Fruit Flavor Extract (Water, Organic Ethyl Alcohol, and Natural Flavors), Vitamin B12	Dosage control torque tests for metered inhalers,auto-injectors,	No Harmful Or Addictive Ingredients, recycle	Dehydration, headache, Nausea, Stomachache	
Buccal mucoadhesive hydrogel films.	Solvent casting technique	Chitosan, B12, Polyvinyl alcohol, polyethylene glycol 400, propylene glycol, maleic anhydride. Agar powder and mucin	Thickness, weight variation, drug content, percentage moisture uptake and moisture content, surface pH, mechanical properties, in vitro release and mucoadhesion, percentages of moisture content, percentage drug released, FTIR, drug/polymer interaction	Low enzymatic activity, longer retention time at the absorption site		
Toothpaste (With two brushes a day 3.6 µg)		10% glycerin, 10% hydrated silica,30% purified water,10% sorbitol ,30%	pH, Spreadability, abrasiveness, foaming ability, cleaning ability, fineness, moisture and volatile	Increases the risk of scratches even when you brush gently. If the enamel gets scratched, more		

		xylitol,3% carrageenan,3% sodium lauryl Sulfate,3% titanium dioxide,0.30%-1% oil of wintergreen,Methylcobalamin (Vitamin B12),	content, tube inertness,Test for F-, Pb, As, and stability studies.	stains may appear, and the risk of decay increases, allergic reaction to this drug is rare.		

COMMON POINTS

For the treatment of pernicious anemia, we administered oral methylcobalamin 3 times per day, which provides a total of 1000 µg of methylcobalamin daily, oral sprays of vitamin B12 delivers (0.3 mL). Common ingredients of vitamin B12 formulations are (Vitamin B12), potassium sorbate, Deionised water. The pH of all the formulations are found to be 4.5 to 6.5[29]

STORAGE CONDITIONS

Methylcobalamin is a substance that is susceptible to light and can thus be shielded from light. In cartons, keep the formulation sealed until it is fit for use. Hold upright at a controlled room temperature of 59 °F to 86 °F (15 °C to 30 °C). Protect from the freezing of the formulation.[30]

COMPARISON BETWEEN VARIOUS FORMULATIONS OF VITAMIN B12

Cost: Suggested retail prices indicate that the cost of oral Vitamin B12 therapy at a dose of one Also high compared to buccal and parenteral dosage form buccal patches are cheap compared to the other two formulations.1000 µg tablet daily is approximately equivalent to the cost of taking 500 mg of calcium and 1000 IU of Vitamin D [24]. As the dose of the drug given by oral is high, the cost is also high compared to the other two formulations. [31]

Safety: Vitamin B12 injections can be dangerous in anti-coagulated patients Hypo-kalmia and cardiac arrest has been reported when megaloblastic anemia is treated intensively. Pain full and require assistance. Oral administration is safe compared to intramuscular injection but requires 1000µg-2000 µg per day. buccal patches are convenient, safe, and easy to insert and the low drug is required prolonged effect can be obtained. [32,33]

Various Functions of Vitamin B12 in Human Body-

The significant reactions involved in vitamin B12 metabolism describe its critical role in several physiological processes. Vitamin B12's main purposes are summed up as follows:[34]

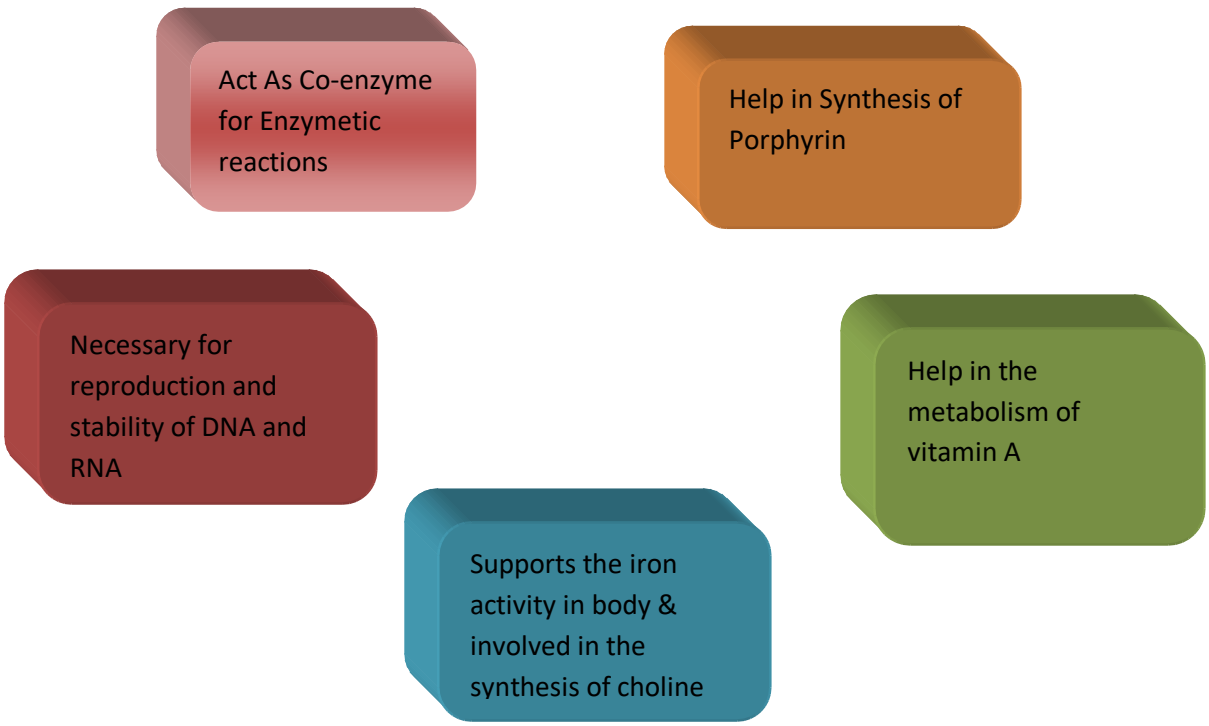

Figure 2: Functions of Vitamin B12 in Human Body

Deficiency and abundance of vitamin B12-

A common diagnosis, especially in older adults, is vitamin B12 deficiency. The deficiency is also attributed to gene mutations that encode essential proteins in the metabolism of cobalamin, diet (vegetarian, vegan diet) and decreased production of stomach acids needed for vitamin B12 to be absorbed. Other common causes are pernicious anemia (malabsorption of vitamin B12); atrophic gastritis; gastrectomy; Zollinger-Ellison syndrome; intestinal diseases, especially of the ileum (celiac disease, Crohn's disease, ileitis); pancreatic insufficiency; parasitism; bacterial overgrowth; medicament use (antiepileptic agents, proton pump inhibitors, histamine receptor antagonists, metformin, antibiotics); diabetes mellitus; renal insufficiency; smoking; and alcohol abuse. Although vitamin B12 deficiency has been intensively studied, in the literature the reverse condition, abnormally high levels, is scarcely discussed. In both circumstances, elevated plasma levels (when not associated with external supply) lead to an improvement in vitamin B12 metabolism, either increased synthesis or reduced B12-binding protein clearance.[35]

Safety and Precautions-

- For pregnant or breast-feeding mothers, vitamin B12 is Possibly Healthy when taken by mouth in the quantities prescribed. 2.6 mcg a day is the optimal level for pregnant women. No more than 2.8 mcg a day can be taken by breastfeeding females
- Post-operative stent placement: Avoid using a vitamin B12, folate, and vitamin B6 mixture when having a coronary stent. This combination can increase the risk of narrowing of the blood vessels.
- Should not use vitamin B12cIn Allergy or sensitivity to cobalt or cobalamine conditions.
- Do not take Vit B12 Inherited eye disease, Leber's disease It will severely affect the optic nerve, which may lead to blindness.[36]

CONCLUSION

The intramuscular approach is uncomfortable and requires medical dosing assistance and is very expensive since it absorbs faster, the retention time is short (fast reaction). Since the GI tract is a lipid-based membrane, oral ingestion of B12 requires a significant volume of drug, and being more hydrophobic in nature is less desirable for the absorption of vitamin B12 hydrophilic drug. From the above details, the oral route is more reliable in the treatment of pernicious anemia, improves the bioavailability of vitamin B12, and there are particular advantages to this route of drug delivery, including bypassing the first-pass effect and preventing pre-systemic removal inside the GIT.

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