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Formulation and Evaluation of Cyproheptadine and Multivitamin Suspension

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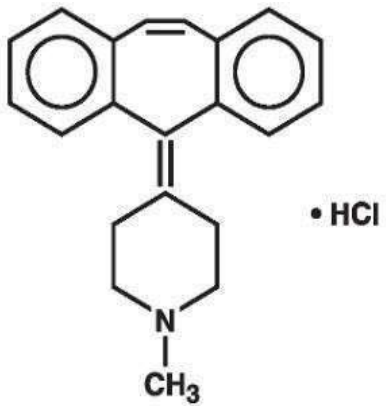
Abstract:-

Cyproheptadine is an antihistamine that has been used as an appetite stimulant in nursing home residents. This medication has a number of anticholinergic effects that may cause symptoms such as blurred vision, dry mouth, urinary retention constipation, tachycardia and delirium in older patients. These effects generally limit its utility in long term care. Although cyproheptadine been used in this setting, no studies have been undertaken to date using cyproheptadine as an Orexigenic in this population. Much of the data regarding its benefit as such comes from studies involving the pediatric population. Cyproheptadine has also been studied in the treatment of weight loss in both cancer and anorexia nervosa

Weight loss and malnutrition present a significant challenge to providers in the long term care arena who frequently must evaluate and treat residents for these issues. Reasons for the incidence of unintentional weight loss includes multiple comorbid conditions, polypharmacy, depression and the cachexia of aging. The purpose of this review was to identify current research related to the use of appetite stimulants in long term care.

INTRODUCTION: -

CYPROHEPTADINE HCL



- **IUPAC Name:-** 4-(5H-Dibenzo[a,d]cycloheptene-5-ylidene)-1-methylpiperidine
- **Empirical formula:-** C21H21N
- **Molecular weight:-** 287.4
- **Solubility:-** Which is soluble in water, freely soluble in methanol, sparingly soluble in ethanol, soluble in chloroform, and practically insoluble in ether.
- **History :-**

Cyproheptadine sold under the brand name Periactin among others, is a first-generation antihistamine with additional anticholinergic, antiserotonergic, and local anesthetic properties. It was patented in 1959 and came into medical use in 1961.

- **Pharmacokinetics:**
- **Absorption**

A single study examining the difference in absorption of orally administered versus sublingually administered cyproheptadine in five healthy males demonstrated a mean Cmax of 30.0 mcg/L and 4.0 mcg/L, respectively, and a mean AUC of 209 mcg.h/L and 25 mcg.h/L, respectively. The Tmax of orally and sublingually administered cyproheptadine was 4 hours and 9.6 hours, respectively. Protein binding not Available

- **Metabolism**

The principle metabolite found in human urine has been identified as a quaternary ammonium glucuronide conjugate of cyproheptadine.

- **Route of elimination**

Approximately 2-20% of the radioactivity from an orally administered radio-labeled dose of cyproheptadine is excreted in the feces.

- **Mechanism of action:**

Cyproheptadine appears to exert its antihistamine and antiserotonin effects by competing with free histamine and serotonin for binding at their respective receptors. Antagonism of serotonin on the appetite center of the hypothalamus may account for cyproheptadine's ability to stimulate the appetite.

- **Uses**

Cyproheptadine is an antihistamine used to relieve allergy symptoms such as watery eyes, runny nose, itching eyes/nose, sneezing, hives, and itching. It works by blocking a certain natural substance (histamine) that your body makes during an allergic reaction. This medication also blocks another natural substance in your body (serotonin). This medication should not be used in newborn or premature infants.

- **Side Effects: -**
  - Drowsiness,
  - Tired feeling,
  - Insomnia,
  - Dizziness,
  - Blurred vision,
  - Loss of coordination,
  - Upset stomach

VITAMINS:-

A vitamin is an organic molecule that is an essential micronutrients which an organism needs for the proper functioning of body. Essential nutrients cannot be synthesized in the body, either at all or not in sufficient quantities, and therefore must be obtained through the diet. The term vitamin does not include the three other groups of essential nutrients: minerals, essential fatty acids, and essential amino acids. Vitamins are not single molecules, but groups of related molecules called vitamers.

- **History of vitamins: -**

All vitamins were discovered (identified) between 1913 and 1948. Historically, when intake of vitamins from diet was lacking, the results were vitamin deficiency diseases. Then, starting in 1935, commercially produced tablets of yeast-extract vitamin B complex and semi-synthetic vitamin C became available.

This was followed in the 1950s by the mass production and marketing of vitamin supplements, including multivitamins, to prevent vitamin deficiencies in the general population. Governments have mandated the addition of some vitamins to staple foods such as flour or milk, referred to as food fortification, to prevent deficiencies. Recommendations for folic acid supplementation during pregnancy reduced risk of infant neural tube defects.

- **Classification of Vitamins: -**

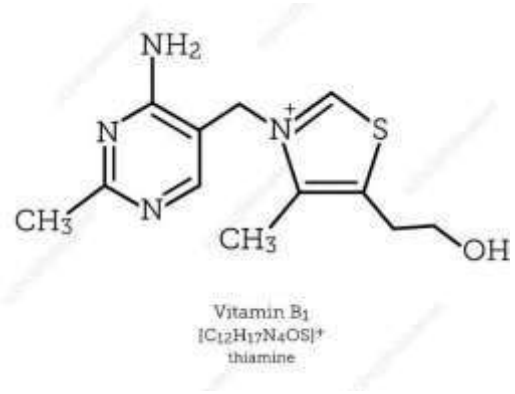
Vitamins are classified as either water-soluble or fat-soluble. In humans there are 13

vitamins:

4 fat-soluble (A, D, E, and K)

9 water-soluble (8 B vitamins and vitamin C).

VITAMIN B1 (THIAMINE):-



- **IUPAC Name:-** 2-[3-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-methyl-1,3-thiazol-3-ium- 5yl]ethanol
- **Molecular weight:-** 300.81
- **Empirical formula: –** C11H17CIN4OS
- **Solubility:-**

Vitamin B1 is the soluble in

1. Water
2. Glycerol
3. Methanol

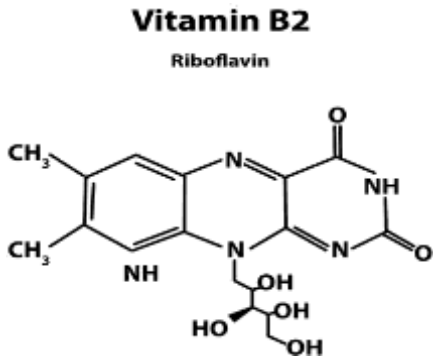
- ***Uses: - It is used***

1. To treat beri beri.
2. Numbness in feet and hands.

- ***Deficiency Symptoms: -***

1. Loss of appetite
2. Fatigue

VITAMIN B2 (RIBOFLAVIN): -

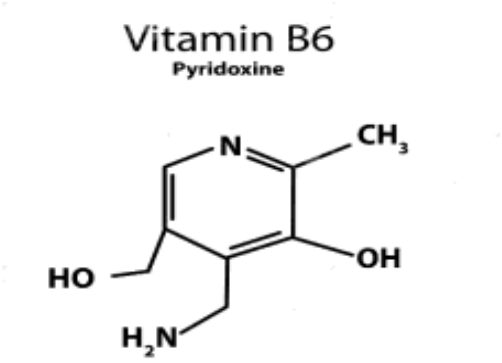


- **IUPAC Name:-** 7,8-Dimethyl-10-[(2S,3S,4R)-2,3,4,5-tetrahydroxypentyl]benzo[g]pteridine 2,4- dione
- **Empirical formula:–** C17H20N4O6
- **Molecular weight:–** 376.4
- **Solubility:-** Riboflavin is soluble in water 0.12g per 100ml, in ethanol at . 0045g per 100ml, and it is insoluble in acetone, benzene, hexane, and chloroform.

It helps to breakdown fat, protein and carbohydrate.

- **Sources:-** Yoghurt, Cheese, Eggs, Pumpkin, Sweet potatoes, Fish
- **Uses:-**
    1. Promotes good eye sight
    2. Maintaining the body energy supply
    3. Protects against anaemia
- **Deficiency Symptoms**:-
    1. Redness of tongue
    2. Blurred vision
    3. Swollen throat

VITAMIN B6 (PYRIDOXINE):-



- **IUPAC Name:–** 4,5-Bis(hydroxymethyl)-2-methylpyridine-3-ol
- **Empirical formula:–** C8H12CINO3
- **Molecular Weight:-** 205.64
- **Solubility:–** Vitamin B6 is a water-soluble vitamin. Water-soluble vitamins dissolve in water so the body cannot store them.
- **Sources:-** Chicken, Fish, Peanut, Soya bean,Oats
- **Uses:-**

1. Necessary for proper function of sugar,fats & proteins
2. Development of brain, nerves

- **Deficiency symptoms:-**
    1. Skin rashes
    2. Tiredness & low energy
    3. Anaemia

SUSPENSION:

It may be defined as a coarse dispersion of finely subdivided insoluble solid drug suspended in a suitable liquid (usually aqueous) medium.

It is a heterogeneous system consisting of a solid disperses in a solid, liquid or gas. It is a biphasic preparations particle of one or more solids basically it may be flocculated or deflocculated.

- ***ORAL SUSPENSION:***

It contains one or more active ingredients suspended in a suitable vehicle. Suspended solids may slowly separate on keeping but are easily re-dispersed. It should be packed in wide mouth bottles.

A Pharmaceutical suspension is a coarse dispersion in which internal phase is dispersed uniformly throughout the external phase. The internal phase consisting of insoluble solid particles having a specific range of size which is maintained uniformly throughout the suspending vehicle with aid of single or combination of suspending agent. The external phase is generally aqueous in some instance, may be an organic or oily liquid for non-oral use.

ADVANTAGES OF ORAL SUSPENSIONS:

It is a better means of administration than of solid dosage forms such as tablet, capsules especially when swallowing is difficult.

1. It is an ideal dosage form for infants and old patients because of easy administration.
2. It contains sub-divided solid particles, surface area is large and this is taken advantage of drugs which are adsorptive.
3. Suspensions are chemically more stable than solutions.

DESIRABLE PROPERTIES OF SUSPENSIONS:

1. It should not be rapid settling of suspended particles.
2. The particles do settle they must not form a hard cake at the bottom of the container.
3. It should be re-dispersible into uniform mixture when shaken.
4. A suspension should be easily pourable.
5. The color and odor should be acceptable and pleasing for oral and external uses.
6. Appropriate preservatives should be incorporated in order to minimize the microbial contamination.
7. It should be physically & chemically stable.
8. Parenteral/Ophthalmic suspension should be sterilizable.

APPLICATION:-

- Suspension is usually applicable for drug which is insoluble or poorly soluble.

E.g. Prednisolone suspension.

- To prevent degradation of drug or to improve stability of drug.

E.g. Oxytetracycline suspension.

- To mask the taste of bitter of unpleasant drug.

E.g. Chloramphenicol palmitate suspension.

- Suspension of drug can be formulated for topical application

E.g. Calamine lotion.

The reasons for the formulation of a pharmaceutical suspension:

- ✓ When the drug is insoluble in the delivery vehicle.
- ✓ To mask the bitter taste of the drug.
- ✓ To increase drug stability.
- ✓ If patient has a difficulty of swallowing solid dosage form.
- ✓ Faster rate of dissolution and oral absorption than solid dosage form.

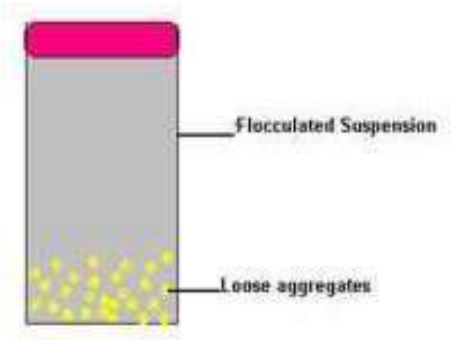


Fig.1.2: Flocculated Suspension

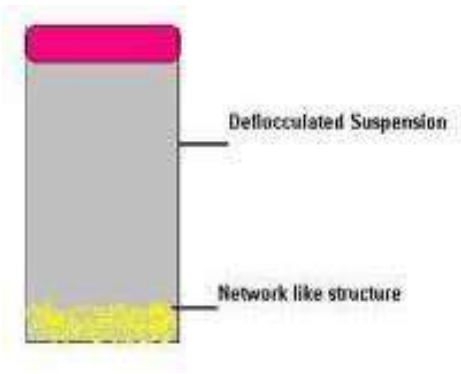


Fig. 1.3: Deflocculated Suspension

The Sedimentation Behavior of Flocculated and Deflocculated Suspensions:

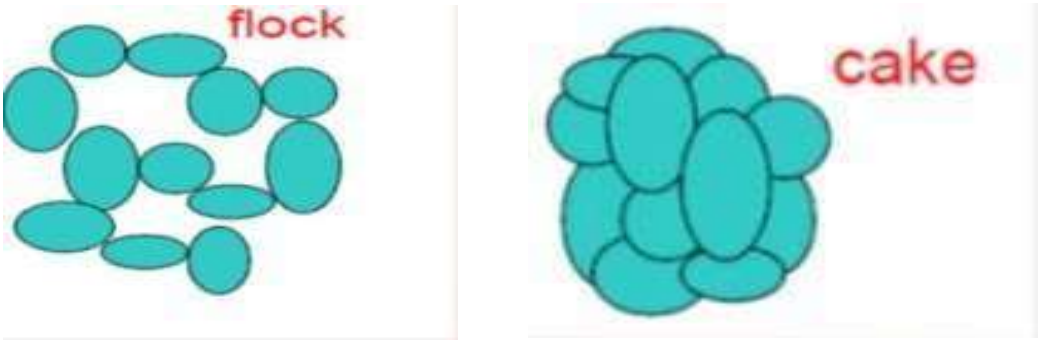


Fig.1.4: Schematic representations of cake and flock formed in flocculated and deflocculated suspension respectively

Flocculation & Deflocculation:-

Table 1.1: Difference between flocculated and non-flocculated suspension

Flocculated Suspension	**Non-flocculated Suspension**
Particles forms loose aggregates and form a network like structure	Particles exist as separate entities
Weakly bonded to form fluffy conglomerates	Repulsion energy is high
Rate of sedimentation is high	Rate of sedimentation is slow
Sediment is rapidly formed	Sediment is slowly formed
Sediment is loosely packed and doesn't form a hard cake	Sediment is very closely packed and a hard cake is formed
Sediment is easy to redisperse	Sediment is difficult to redisperse
Suspension is not pleasing in appearance	Suspension is pleasing in appearance
The floccules stick to the sides of the bottle	They don't stick to the sides of the bottle

Flocculated Suspensions:-

In flocculated suspension, formed flocks (loose aggregates) will cause increase in sedimentation rate due to increase in size of sedimenting particles. Hence, flocculated suspensions sediment more rapidly. The volume of final sediment is thus relatively large and is easily re-dispersed by agitation.

Important Characteristics of Flocculated Suspensions:-

- Particles in the suspension are in form of loose agglomerates.
- The sediment is formed rapidly.

- The sediment is loosely packed.
- The sediment is easily re-dispersed by small amount of agitation.

Deflocculated suspensions:-

In deflocculated suspension, individual particles are settling, so rate of sedimentation is slow which prevents entrapping of liquid medium which makes it difficult to re-disperse by agitation. This phenomenon also called 'cracking' or 'claying'.

Important Characteristics of Deflocculated Suspensions:-

- In this suspension particles exhibit as separate entities
- Particle size is less as compared to flocculated partice
- This type of suspension has a pleasing appearance.

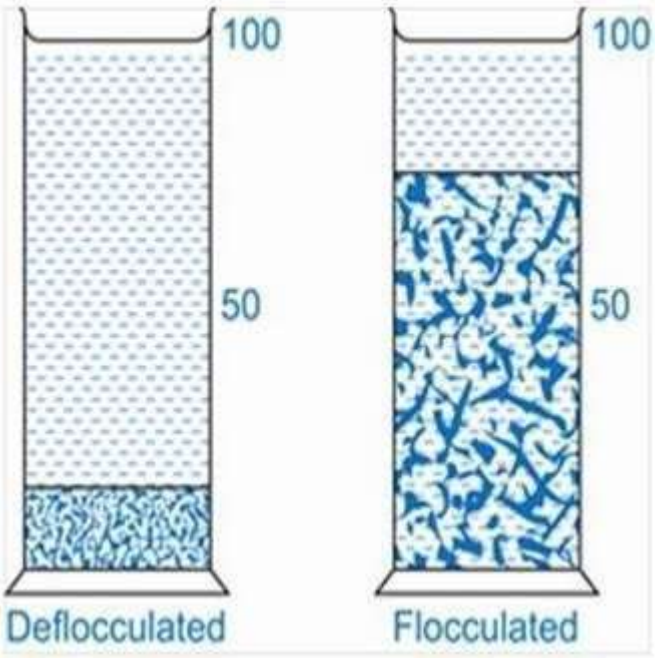


Fig. 1.5 : Schematic representation of deflocculated and flocculated suspension

Formulation Additives:-

In addition to vehicle, coloring, sweetening and flavoring agents, which are common in liquid dosage forms, the following additives are required to prepare suspensions which include:

1. Suspending and Thickening agents
2. Wetting Agents
3. Buffers
4. Preservatives
5. Flavoring and Coloring Agents
6. Sweetening Agents
7. Humectants
8. Antioxidants
9. Osmotic Agents

1. Suspending and Thickening agents:-

They are added with the objective to increase apparent viscosity of the continuous phase thus preventing rapid sedimentation of the dispersed particles. Suspending agent are also known as hydrophilic colloids which form colloidal dispersion with Water and increase the viscosity of the continuous phase. Suspending agent form film around particle and decrease inter particle attraction.

2. Wetting Agents:-

Hydrophilic materials are easily wetted by water while hydrophobic materials are not. However hydrophobic materials are easily wetted by non-polar liquids. If the material is more hydrophilic less difficulty in wetting by water. the hydrophobic drug particles must be wetted properly for the uniform dispersion in the continuous medium. If the drug particles are not wetted properly, the suspension may exhibit poor physical stability and poor dissolution properties.

3. Buffers:-

Buffers are the materials which when dissolved in a solvent will resist any change in pH when an acid or base is added. Buffers used should be compatible with other additives. Most commonly used buffers are salts of week acids such as carbonates, citrates, gluconates, phosphate and tartrates.

Buffers have four main applications in suspension systems that are mentioned below:-

- Prevent decomposition of API by change in pH
- Physiological stability is maintained
- Maintain physical stability

4. Preservatives:-

The naturally occurring suspending agents such as tragacanth, acacia, xanthan

gum are susceptible to microbial contamination. If suspension is not preserved properly then the increase in microbial activity may cause stability problem such as

- loss in suspending activity of suspending agents,
- loss of color, flavor and odor,
- change in elegance

5. Flavoring and Coloring Agents:-

They are added to increase patient acceptance. There are many flavoring and coloring agents are available in market. Only sweetening agent are not capable of complete taste masking of unpleasant drugs therefore, a flavoring agents are incorporated. Flavoring and perfuming agents can be obtained from either natural or synthetic sources. Natural products include fruit juices, synthetic products like aromatic oils such as peppermint oil and lemon oil, herbs, spices and distilled fractions

Coloring agents:-

Colors are obtained from natural or synthetic sources. Color aids in identification of the product. The color used should be acceptable by the particular country.

6. **Sweetening Agents**:-

They are used for taste masking of bitter drug particles. A bulk sweeteners is used at concentration of 15-70% w/w of the total weight of the suspension.

7. Humectants:-

Humectants absorb moisture and prevent degradation of API by moisture. Total quantity of humectants should be between 0-10 % w/w. Humectants are added to retard the evaporation of aqueous vehicle from dosage forms during storage and use.

8. Osmotic Agents:-

They are added to produce osmotic pressure comparable to biological fluids when suspension is to be intended for ophthalmic or injectable preparation.

9. Antioxidants:-

Antioxidants are required in certain pharmaceutical suspensions to enhance the chemical stability of the therapeutic agent, where this may be compromised by oxidation.

Stability of Suspensions:- A- Physical Stability:

- Appearance, color, odor and taste
- pH

- Sedimentation rate
- Sedimentation volume
- Compatibility with container

B-Chemical Stability:

- Degradation of active ingredient
- Viscosity change
- Antimicrobial activity

MATERIAL AND METHOD:-

Ingredients used in the Formulation:-

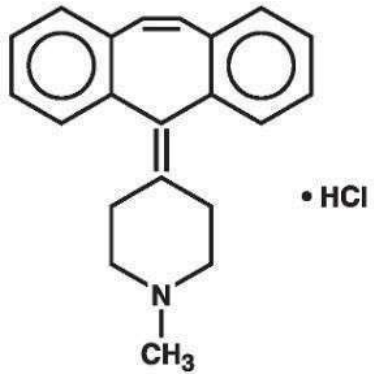
Sr. No.	Name of Ingredient
1	Cyproheptadine
2	Vitamin B1
3	Vitamin B2
4	Vitamin B6
5	Vitamin C
6	Glycerin
7	Sorbitol
8	Tragacanth
9	Methyl Paraben
10	Propyl Paraben
11	Caramel
12	Lemon Oil

Equipments used in Formulation:-

Sr. No.	Equipments
1	Electronic Balance
2	Magnetic Stirrer

DRUG PROFILE-

CYPROHEPTADINE HCL:-



- **Synonyms: -** Periactin, Eiproheptadine, Periactinol
- **Chemical Name:-** 4-(5H-Dibenzo[a,d]cycloheptene-5-ylidene)-1-methylpiperidine
- **Empirical formula:-** C21H21N

- **Molecular weight:-** 287.4
- **Dose:-** 2mg/5ml
- **Typical properties:-**
- **Solubility:-** Which is soluble in water, freely soluble in methanol, sparingly soluble in ethanol, soluble in chloroform, and practically insoluble in ether.
- **Description:-** White to slightly yellowish crystalline solid.
- **Applications:–**
  - Cyproheptadine is an antihistamine medicine. It is used to stimulate the appetite and promote weight gain.
  - Cyproheptadine relieves red, irritated, itchy, watery eyes; sneezing; and runny nose caused by allergies, irritants in the air, and hay fever.

EXPERIMENTAL WORK

PROCEDURE FOR PREPARATION OF SUSPENSION:-

The powder of Cyproheptadine, Vitamin B_1 , Vitamin B_2 , Vitamin B_6 , Vitamin C are taken.

- These powders are mixed together and passed from sieve no 80.
- Then prepare a sugar syrup using water.
- Then add methyl paraben and propyl paraben as preservative in prepared sugar syrup.
- Then take Glycerin, sorbitol and Tragacanth and mix together and then add it to sugar syrup.
- Then stir it vigorously for 15min. Till suspension becomes thick.
- Then add the powder mixture to the sugar syrup.
- Again add tragacanth to maintain its consistency.
- Colouring agent Caramel Brown is added and lemon oil is added as flavouring agent.
- Prepared suspension is filtered using clean cotton cloth .
- Pack the prepared suspension in amber colour bottle.
- Label the prepared suspension neatly

Table 5.1: Formula for the preparation of Cyproheptadine and Multivitamin Suspension

Sr. No.	Ingredients
1	Cyproheptadine
2	Vitamin B1
3	Vitamin B2
4	Vitamin B6
5	Vitamin C
6	Glycerin
7	Sorbitol
8	Tragacanth
9	Methyl Paraben
10	Propyl Paraben
11	Caramel
12	Lemon Oil
13	Sugar Syrup
14	Water

PREFORMULATION STUDIES:-.

Pre-formulation is the stage of development during which the physicochemical properties of the drug substance are characterized and established.

To ensure that the various formulations are optimized for their intended use, pre- formulation studies should be conducted not only to evaluate the characteristics of candidate drugs but also potential formulation excipients, and their interactions with drug substances, in order to select appropriate formulation ingredients.

Physical Characterization of main ingredient:-

Physical Characterization of main ingredient that is Cyproheptadine HCL is shown in table:

Table 5.2: Pre-formulation study for Cyproheptadine HCL

Parameter	**Result**
Nature	Crystalline solid
Color	Pale Yellow
Taste	Slightly Bitter
Solubility	Soluble in: Water, Chloroform Freely soluble: Methanol Insoluble: Ether

Physical Characterization of other ingredients in Formulation:-

Physical Characterization of other ingredients is shown in table

1. **VITAMIN B1:-**

Color:- White Powder **Taste:-** Slightly Bitter **Odor:-** Sulfuric smell

2. **VITAMIN B2:-**

Color:- Yellow to Orange-yellow

Taste:- Bitter

Odor:- Unpleasant

3. **VITAMIN B6:-**

Color:-White **Taste:-** Bitter **Odor:-** Odorless

4. **METHYL PARABEN:-**

Nature:- Crystalline Powder

Color:- Colorless

Odor:- Faint

5. **PROPYL PARABEN:-**

Color:- Colorless

Odor:- Odorless od Faint Aromatic

6. **SORBITOL:-**

Color:- White Crystalline Powder **Odor:-** Caramel Like Odor **Taste:-** Sweet

7. **TRAGACANTH:-**

Color:- Greenish

Odor:- Odorless

Taste:- Tasteless

EVALUATION PARAMETERS FOR CYPROHEPTADINE SUSPENTION:-

1. **pH:-** pH quantitative measure of the acidity or basicity of aqueous or other liquid solution. The pH scale usually ranges from 0 to 14. A solution with pH less than 7 is considered acidic; a solution with a pH greater than 7 is basic; or alkaline. pH of formulated suspension was determined by using pH paper.

2. **Sedimentation volume:-** A most important parameter in the evaluation stability of the suspension. Sedimentation volume is a ratio of the ultimate volume of sediment (Vu) to the original volume of sediment (VO) before settling. Settling of solid particles or floccules under gravitation force in liquid at bottom of the container.
3. **Redispersibility:-** If a pharmaceutical suspension produces sediment upon storage, it is essential that it should be readily dispersible so that uniformity of dose is assured.
4. **Drug excipient compatibility**

Excipients are added along with the active pharmaceutical ingredient in formulations. Most excipients possess biological activity but having role in administration, mediating the release of the active component, and providing stability against degradation.

Packaging, storage and direction for use:-

- **Packaging:-** Dispense in a tight, light-resistant container (amber color container) as defined in the USP. To avoid direct contact from sunlight.
- **Storage:-** Store at 20-25°C (68-77°F)
- **Direction:-**
  - Shake well before use.
  - Cyproheptadine comes in a tablet and a solution (liquid) form to take via mouth.
  - It is usually taken two or three times in a day.
  - Take cyproheptadine at around the same time(s) every day.

RESULT AND DISCUSSION:-

Evaluation tests:-

- **pH :-**

pH of the suspension is measured using pH paper. pH was found in the range of **4.5-5.5**

- **Colour :-**

The colour of the cyproheptadine suspension was observed as **Brown**.

- **Sedimentation Volume:-**

Sedimentation volume for formulated suspension was found to be **0.8**

Conclusion :-

- This Study demonstrates that cyproheptadine is a safe and effective way to promote weight gain in children.
- Cyproheptadine treatment was well tolerated and resulted in significant weight gain in malnourishment.

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