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PREGNANCY BLUES - TREATING ANEMIA WITH FOLIC ACID LOZENGES REVIEW

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ABSTRACT

Folic acid also known as folate is an essential vitamin. It is converted to folate in our body. Folate is the natural form of the vitamin, found in whole foods. Methylfolate is the most bioavailable form of vitamin B9. Folic acid helps in producing new cells and keeps them healthy. Folic acid when formulated as lozenges is very convenient for administration and its used to prevent neural tube defects which develops in early pregnancy, sufficient intake of this vitamin even before pregnancy have protective benefits and reduces the risks. It can prevent the pregnancy blues like miscarriage, preterm delivery and maternal anemia. Its recommended to take folate for three months prior to pregnancy, continue through pregnancy and also post partum. A growing baby absorbs folic acid from its mother. Folate deficiency anemia is tested by complete blood count (CBC) to measure the number and appearance of RBC. Lack of folate makes RBC to look large and immature. Each type of anemia is caused by something different, each ranges from mild to severe. RBC plays a central role in this condition, with all forms of anemia tiredness or fatigue is the most common symptom because of low RBC. Shortness of breath, dizziness, headache, coldness in hands and feet, pale or yellowish skin are the signs along with irregular heartbeat. Low RBC causes heart to work harder to move oxygen rich blood through the body. So treating this condition with folic acid lozenges is the most easy, economical and safe to the patient

INTRODUCTION

Anemia is a medical condition where the RBC count is less than the normal, the blood do not have sufficient healthy red blood cells. It results from lack of red blood cells or dysfunction RBC in the body leading to reduced flow of oxygen to the organs in the body or tissues. The RBC in the body is low and it is measured according to the amount of hemoglobin, the protein present in RBC carries the oxygen from the lungs to the body's tissue. In women suffering from anemia the hemoglobin is less than12.0g/100 ml. According to National heart, lung & blood institute anemia is the most common blood disorder in women and children.The different types of Anemias include:

1. Anemia due to vitamin B12 deficiency
2. Anemia due to folate (Folic acid deficiency)
3. Anemia due to iron deficiency
4. Anemia of chronic disease
5. Hemolytic Anemia
6. Idiopathic aplastic Anemia
7. Megaloblastic Anemia
8. Pernicious Anemia
9. Sickle cell Anemia
10. Thalassemia
11. Aplastic or Hypoplastic Anemia
12. Sideroblastic Anemia-Acquired and Hereditary
13. Myelodysplastic syndrome
14. Autoimmune Hemolytic Anemia
15. Congenital dyserythropoietic Anemia (CDA)

16. Diamond blackfan Anemia
17. Fanconi Anemia

STATISTICS: As per WHO Anemia is a serious global health problem that particularly affects young children and pregnant women. WHO estimates 42% of children less than 5 years of age and 40% of pregnant women worldwide are anemic. Anemia is widespread in India, 58.6% of children, 53.2% non pregnant women and 50.4% pregnant women are suffering as per 2016 NFHS (National family health survey). Anemia can cause a loss of upto 4% of gross domestic product, which means a loss of $113 billions or Rs. 7.8 lakh crore, which is five times India's budget for health, education and social protection in 2018-2019. The worldwide market for folic acid is expected to grow at a CAGR (Compound annual growth rate) of roughly 4.8% over the next 5 years, it will reach 170 million USD in 2024, from 130 million USD in 2019.

FOLIC ACID: Folic acid is the synthetic form of folate which is naturally occuring vitamin B, Folate (B-9). It is a form of water-soluble B vitamin. Folic acid prevents major birth defects of baby's brain (Anencephaly) and spine (Spinabifida). Pregnant women are prescribed 400 micrograms(mcg) of folate every day. Folic acid deficiency causes neural tube defects (NTD) it is used by the body to manufacture DNA, RNA and metabolize amino acids necessary for cell division. It is an essential vitamin having bioavailability of 50 to 100%, metabolism is by liver and excretion through urine. Its molar mass is 441.40 gmol-1. Solubility in water is 1.6 mg/l (at 25 C).

LOZENGES: The word Lozenge is derived from french word 'Losenge' which means a diamond shaped geometry having four equal sides. They can deliver drug multi directionally into the oral cavity or to the mucosal surface. Lozenges often referred to as a diamond – a form of rhombus. They are small flavored tablets made from sugar or syrup often medicated typically medicated tablet intended to be dissolved slowly in the mouth to temporarily stop coughs, lubricate, and soothe irritated tissues of the throat (usually due to a sore throat), possibly from the common cold or influenza. Today lozenges are used for drugs like analgesics, anesthetics, antimicrobials, antiseptics, antitussives, aromatics, astringents, corticosteroids, decongestants and demulcents as they are easy to handle. Though the lozenge dissolution time is about 30 minutes it depends on the patient as patient controls the rate of dissolution and absorption by sucking until it dissolves.

CLASSIFICATION OF LOZENGES:

1. **According to site of action:** Local effects are antiseptics, decongestants while vitamins and nicotine are examples of systemic effect.
2. **According to texture and composition:**

(a) Chewy or caramel based medicated lozenges

(b) Compressed tablet lozenges

(c) Soft lozenges

(d) Medicated & Non - medicated lozenges

(e) Hard lozenges

(f) Center filled hard lozenges

EXAMPLES OF MEDICATED LOZENGES:

1. Nicotine lozenges
2. Linctagon lozenges
3. Fungilin lozenges
4. Flurbiprofen lozenges
5. Low dose- natural human interferon alpha lozenges
6. Actiq lozenges
7. Zinc gluconate lozenges
8. Zinc acetate lozenges
9. Amyl metacresol& 2,4 – dichlorobenzyl alcohol lozenges
10. Salbutamol sulphate lozenges
11. Ketoconazole lozenges
12. Paracetmol lozenges
13. Clotrimazole lozenges
14. Artesunate oral retentive lozenges
15. Montelukast sodium lozenges
16. Marshallow root extract lozenges
17. Ginger & garlic lozenges
18. Itraconazole topical delivery lozenges
19. Ondansetron hydrochloride lozenges
20. Fluconazole tablet lozenges
21. Hexylresorcinol lozenges
22. Fluoride lozenges

23. Fentanyl lozenges

23. Clotrimazole lozenges

ADVANTAGES:

1. Easy to administer to both pediatrics and geriatrics.
2. Extends the time of release, drug remains in the oral cavity to elicit local activity.
3. Systematic absorption of drugs is possible through buccal cavity.
4. Do not require water intake for administration.
5. Masks the taste of drugs.
6. Less production time and cost.
7. Better patient compliance.
8. Avoids first pass metabolism.

LOZENGES – FORMULATIONS: Lozenges can be formulated into a stable dosage form and to provide a better mode of administration of many drugs.

Criteria for the formulations:

1. Selecting the suitable drug molecules.
2. Selecting appropriate drug carrier excipients.
3. Selecting appropriate type of lozenge formulation.

METHOD OF PREPARATION: Medicated lozenges are prepared by heating and congealing technique.

Step 1: Combine sugar, corn syrup and water by heating.

Step 2: Adding drug to the candy matrix.

Step 3: Addition of polymer, colouring agents, flavoring agents etc.

Step 4: It is poured into moulds of desired shape and size to form a candy.

Step 5: Seal and wrap the candy in polyethylene wrapping.

MARKETED LOZENGES:

Cepacol lozenges, Chloraseptic lozenges, Clotrimazole lozenges, Koflet- h lozenges, Lockets, Nicorette, Strepsils, Sualin, Sucrets, Therazine, Vicks, Vigroids, TusQ, KuffQ lozenges.

EVALUATION PARAMETERS:

***1.* In Process Quality Control of Candy Base Manufacturing:** As the candy base manufacture is commenced, a check on following parameters is performed: corn syrup and sugar delivery gears, temperature, steam pressure and cooking speed of pre cookers and temperature, steam pressure, cooking speed and vaccum of candy base cookers.

2. Moisture Analysis: Gravimetric, Karl Fisher titration and Azeotropic distillation methods are used to determine the moisture content of lozenges. In gravimetric method, sample (1g) is weighed and placed in vaccum oven at 60-70℃ for 12-16hrs. Final weight is subtracted from initial and the difference in moisture content is calculated. Karl Fischer titration involves calculating a sample to contain 10-250mg water in titration flask and titrated with Karl Fischer reagent. In azeotropic distillation method, 10-12g candy is pulverized and placed in 500ml flask to which 150-200ml toluene is added. Flask is connected to a reflux condenser and is refluxed for 1-2hrs. Water collected gives the amount of water present in the sample.

3. Determination of Sugar and Corn Syrup Ratios:
This is performed by "Dextrose equivalent method and Lane Eynon Titration method".

4. Determination of Percentage of Reducing Sugars:
Standard anhydrous dextrose (3g) is dissolved in 500ml water. The solution is boiled for 2 min and 2 drops of methylene blue is added and titrated against 25 mL of alkaline cupric tartrate solution (Fehling's solution) to a yellowish red end point.

(3g) x (Volume of standard dextrose solution consumed by Fehling’s solution)/500=

Reducing sugar factor for 3g dextrose.

Sample (10g) of candy base is dissolved in 250ml of water and titrated with 25 ml of Fehling's solution in the same manner as the standard.

Reducing sugar factor x 100/ Sample weight/250 x volume of sample solution by Fehling’s solution = Percent reducing sugar

Table 1: Formulation of folic acid lozenges:

S. No	Excipients	Examples
1.	a) Sugar b) Sugar free vehicles c) Fillers	Dextrose, sucrose, maltose, lactose Mannitol, sorbitol, polyethylene glycol 600 & 800. Di calcium phosphate, calcium sulfate, calcium carbonate, lactose, microcrystalline cellulose.
2.	Lubricants	Magnesium stearate, calcium stearate, stearic acid, PEG, vegetable oils and fats.
3.	Binders	Acacia, corn syrup, sugar syrup, gelatin, polyvinyl pyrrolidone, tragacanth, methylcellulose.
4.	Coloring agents	Water soluble and lake dyes, FD & C colors, orange color, red color etc.
5.	Flavoring agents	Methanol, eucalyptus oil, spearmint, cherry flavor, Raspberry, orange, lemon, peppermint, vanilla, mint, grape, maple, chocolate, coffee etc.
6.	Whipping agents	Milk protein, egg albumin, gelatin, xanthum gum, starch, pectin, algin and carrageenan.
7.	Humectants	Glycerin, propylene glycol and sorbitol.

The solid content of salvage solution is determined using a refractometer, forming checks involves a check on candy rope diameter. Visual inspection (cooling checks) is performed in order to analyze any stress cracking due to rapid cooling, air bubble formation, surface cracking and black specks.

5. Physical and Chemical Testing for Lozenges: Hardness of lozenges is determined by Pfizer or Monsanto hardness tester, while diameter and thickness are determined by vernier caliper. The Fourier transform Infrared Spectroscopy (FTIR) determines the drug excipient interaction studies while friability is determined by Roche Friabilator operated at 25rpm for 4min. In weight variation determination, 20 lozenges are weighed and average weight determined; individual weight is compared to the average weight. *In-vitro* drug release is carried out in USP II paddle type dissolution apparatus. In drug content determination, appropriate number of lozenges are crushed and dissolved in an appropriate solvent and the absorbance of the solution is measured spectrophotometrically.

6. Microbial Check on Lozenges: In this microbial check, the presence of any bacterial, mold or spore contamination is checked in raw materials, finished products, machinery, cooling tunnels, environmental conditions and storage drums. Laboratory microbial testing should include the following counts: total plate, total coliform, yeast and mold, *E. coli*, *Staphyllococcus*, *Salmonella.*

7. Stability Testing for Lozenges: Lozenges are subjected to stability testing under following conditions: 2 months at 60°C, 3-6months at 45°C, 9-12 months at 37°C, 36-60 months at 25°C. Lozenges in their final packs are subjected to the following conditions for stability testing: 25°C at 80% relative humidity (RH) for 6-12 months, 37°C at 80% RH for 3 months, 25°C at 70% RH for 6-12 months.

CONCLUSION:

The development of lozenges as oral drug delivery system helps in improved efficacy, achievement of therapeutic serum concentration of the drug is more rapid. It’s a good oral confectionary product. Oral dosage forms have ease of ingestion and their toxicity is delayed due to onset of action which permits to recover than in case of other dosage form.

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