

Review Article

## Enteric Coated Iron Folic Acid Tablets: Compromised Efficacy at Cost of Safety

Babar Iqbal<sup>1</sup>, Azim Akhtar<sup>2</sup>, Nafees Ahmad<sup>2</sup>, Sanjula Baboota<sup>1</sup>, Kanchan Kohli<sup>1</sup>, Amin-ul aziz<sup>2</sup> and Kashish Aziz<sup>1\*</sup>

<sup>1</sup>Department of Pharmaceutics, Jamia Hamdard, New Delhi, India

<sup>2</sup>Unicare India Ltd. Noida, India

### Abstract

Iron is essential for the synthesis of hemoglobin in erythrocytes and its deficiency can cause Anemia. An estimated 1.62 billion people are suffering from Anemia worldwide with its highest prevalence in developing countries specially India. Therefore, Government of India has started a strategic nutritional and weekly iron folic acid supplementation (WIFS) program to reduce its prevalence and severity among Indian women and adolescent girls. WIFS supplementation mainly includes either sugar coated ferrous sulfate (red tablet) or enteric coated ferrous sulfate tablets (blue tablets) as a prime dosage form to serve the people. Comparing these two dosage forms, conventional oral preparation of Ferrous Sulfate (sugar coated tablets) can cause dose related gastrointestinal side effects such as nausea, constipation, anorexia, heart burn, vomiting, diarrhea and approximately 25% of patients experiencing these side effects, whereas, there is some evidence that enteric-coated or delayed release Ferrous Sulfate preparations may reduce these gastrointestinal discomforts and could be more effective considering absorption of iron along the entire intestine, primarily in the duodenum and the jejunum, but, several reported case studies have been published so far which dictated that dissolution of iron formulation in acidic media such as gastric juice helps in its absorption and indicating better treatment outcomes with sugar coated tablets. Moreover, by passing the dissolution of iron tablets in gastric juice via enteric coating may result in its poor absorption. Hence, efficacy of iron supplement is being compromised at cost of safety (to avoid side effects) by formulating into enteric coated tablets. This review will focus on information on burden of Anemia in India and various reported case studies which showed that sugar coated ferrous sulfate tablets might not be interchangeable with enteric coated ferrous sulfate tablets with compromised efficacy.

**Keywords:** IFA-WIFS; Iron Absorption; Anemia; NNAPP.

### Introduction

Iron is a vital component for every cell in the body and it is essential for the synthesis of hemoglobin in erythrocytes and deficiency of it can cause Anemia [1]. Anemia is a condition in which hemoglobin concentration falls below the standard value [2]. An estimated 1.62 billion people (24.8%) of the population including half billion women of reproductive age are suffering from Anemia worldwide [2, 17]. The highest prevalence is reported in preschool age children (47.4%) and lowest prevalence in men

(12.7%) [3], which corresponds to 25% of the population globally [4]. Anemia may be caused by low dietary intake of iron, poor iron (less than 20 mg/day) and folic acid intake (less than 70 mg/day), poor bio-availability of iron (3-4% only) in phytate fibre rich Indian diet and chronic blood loss due to infection like malaria and hookworm infestations [5]. Moreover iron deficiency is highly prevalent in developing countries specially India. Government of India and state governments with technical support by UNICEF and partners have an Anemia Control Program for over a decade. The main objective of the program is to reduce the prevalence and severity of anemia in girls [6].

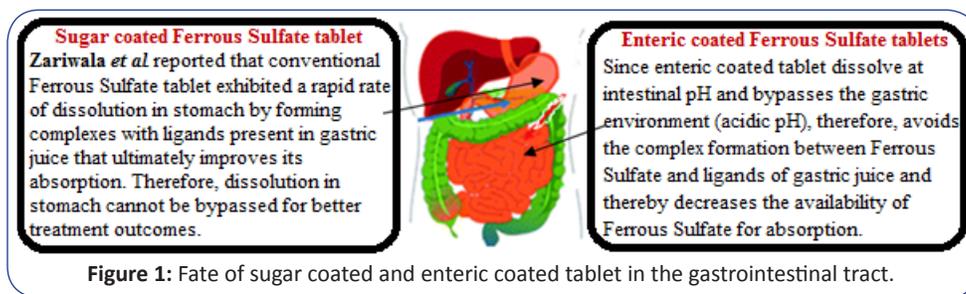
The program strategy is weekly iron and folic acid supplementation (WIFS) with solid or liquid preparations. Oral preparation of ferrous sulfate can cause dose related gastrointestinal side effects such as nausea, constipation, anorexia, heart burn, vomiting, diarrhea with approximately 25% of patients experiencing these side effects. Gastrointestinal discomfort may be minimized by initiating ferrous sulfate therapy at smaller doses and gradually titrating upwards until the desired dose is achieved. Concurrent administration of ferrous sulfate with food may also minimize gastrointestinal discomfort but it can lead to decrease in the amount of iron absorbed [7]. There is some evidence that enteric-coated or delayed release ferrous sulfate preparations may cause less nausea, reduced gastrointestinal side effects but several reported case studies have been published so far which indicate that dissolution of iron formulation in gastric juice helps in its absorption and better treatment outcomes could be possible. Furthermore, bypassing the dissolution of iron tablets in gastric juice may result in its poor absorption [8, 9]. The fate of sugar coated and enteric coated tablet in the gastrointestinal tract is shown in fig 1.

**\*Corresponding author:** Kashish Aziz, Department of Pharmaceutics, Jamia Hamdard New Delhi, India, Tel: 09818337912; E-mail: drkashish27@gmail.com

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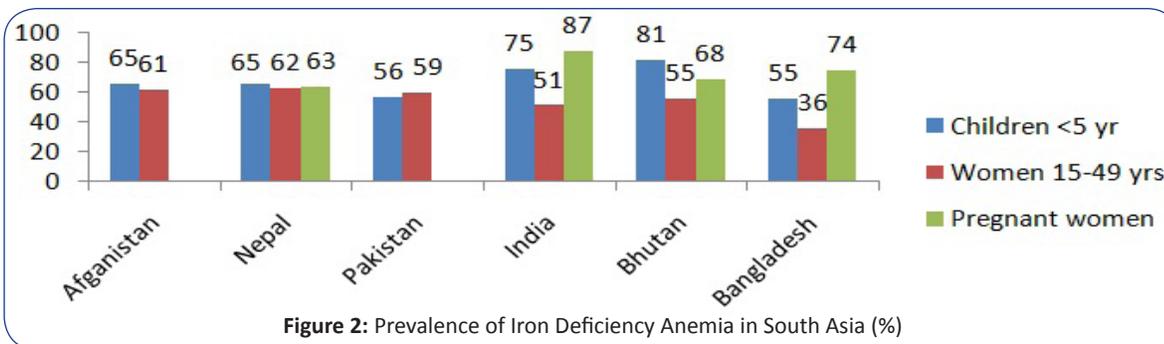
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### Burden of Anemia in India

WHO has estimated that prevalence of Anemia in developed and developing countries among pregnant women is 14 % and 51% respectively while the prevalence in India is estimated to be 65-75 % [3, 18]. Moreover, Figure 2 depicts of Anemia across south Asian countries with India having the highest prevalence (87%) among pregnant women [5]. An Indian study on 4,456 hospital women showed that 17.9% (798) of them were Anemic, out of this 2.15%(96) were found to be severely Anemic and 6 died due to severe Anemia [10].

Anemia after 1 year of implementation. In the state of Gujarat alone, prevalence of Anemia was reduced from 74.2% to 53.5% within one year, with estimated compliance of over 90%. Since cost of the program was low (approximately US\$ 0.58 per adolescent per year), the project was expanded by government to 11 states. Now weekly iron and folic acid supplementation is given to approximately 120 million adolescent girls under the national implementation of weekly iron & folic acid supplementation since 2013 [12].



In another survey of NFHS, half of women in India (55%) have Anemia, including 39 % with mild Anemia, 15 % with moderate Anemia and 2 % with severe Anemia. In addition to this, survey also revealed that the state of Assam is the worst affected with 72% of married women being Anemic, followed by the state of Haryana (69.7%) and Jharkhand respectively (68.4%) [3].

### Major Challenge Faced with WIFS

Gastrointestinal discomfort and cost are major challenges associated with conventional sugar coated tablets of ferrous sulfate and folic acid. This challenge can be avoided with enteric coated or modified release tablet and hence demand of these dosage form increased in last few years. However, several case studies described below have been published so far indicating that dissolution of iron in gastric juice helps in its absorption and hence better treatment outcomes. Lack of awareness in patient about absorption of iron from enteric coated tablets and gastrointestinal discomfort with sugar coated tablets are still challenges faced by WIFS.

### Prevention and Control of Anemia in India

India was the first developing country to start National Nutritional Anemia Prophylaxis Program (NNAPP) for controlling Anemia in Indian women and adolescent girls. However output of the program has been disappointing because majority of pregnant women did not receive IFA tablets. Among those who received IFA tablets less than 10% took more than 90 tablets of IFA during pregnancy. Data represented in figure 3 clearly indicate the need for screening of all pregnant women for Anemia and provide appropriate dose of IFA to non Anemic and mildly anemic women [11].

### Reported Case Study

Seshadri, et al. 1989 examined the impact of iron supplementation in the form of sugar coated tablets on school going children of different ages and sex. The sugar coated tablets containing 20 mg Fe and 0.1 mg folic acid were given daily for a period of 60 days to a group of children. The dose of Fe and folic acid were selected and conform with NNAPP recommendation [13]. The results indicated significant rise in hemoglobin level (Figure4).

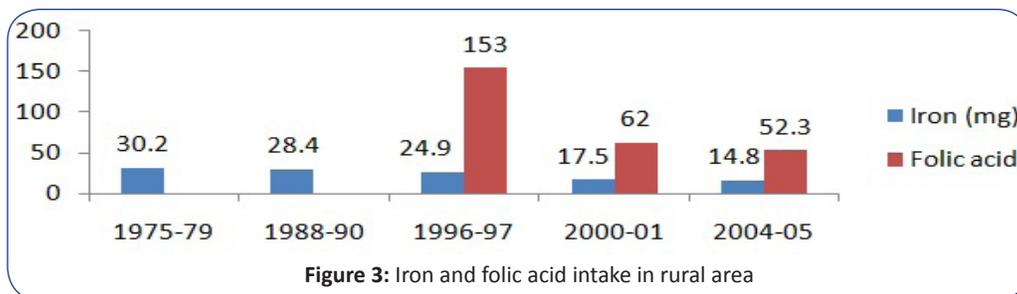


Figure 3: Iron and folic acid intake in rural area

Rudinskas.L et al 1989 studied the clinical response of anemic patient to enteric coated tablets. They have reported that enteric-coated ferrous sulfate tablets failed to alleviate iron deficiency anemia. The results of their case study indicated that enteric coated tablets are poorly absorbed because they likely reaches a point

and variably (Figure 5 & 6). Iron absorption from ferrous sulfate conventional-release tablets was significantly higher than any of the preparations evaluated ( $P < 0.05$ ), and equivalent to 41% of the  $FeSO_4$  standard [16].

Kaltwasser et al.1991 compared the bioavailability of Tardyferon\*

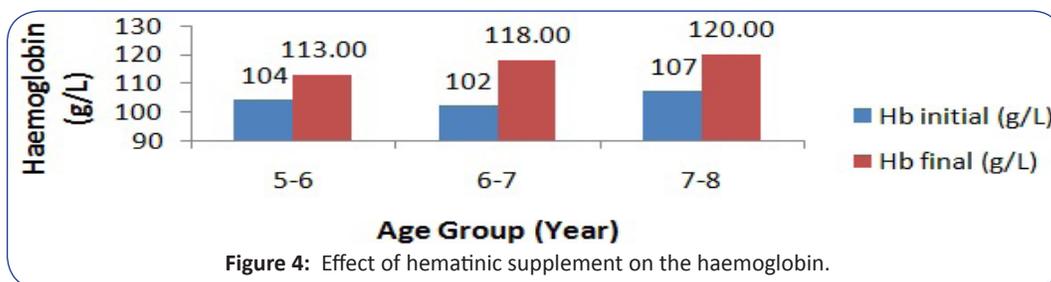


Figure 4: Effect of hematinic supplement on the haemoglobin.

in the intestine, past the duodenum and upper jejunum, where absorption is less efficient [14].

Rhodes. J et al 1968 observed a steep change in iron absorption from two doses placed simultaneously at different sites in the gastrointestinal tract. The absorption of iron in duodenum was relatively poor than in gastric and upper jejunum. However absorption of iron in stomach and upper jejunum is lower. The poor absorption of iron in duodenum may be due to pH or concentration of pancreatic enzyme [15].

Zariwala .M.G et al. 2013 carried out comparative *in vitro* drug release profile studies of various salts of iron in different dosage forms (table 1). This study inferred that, at pH 1.2, the conventional release tablets exhibited a rapid rate of dissolution while the modified release tablets and capsules dissolved gradually

(brand name of prolonged-release coated tablets of Iron as Ferrous Sulfate) with a quick-release ferrous ascorbate preparation in 18 healthy phlebotomized volunteers, using a stable 54 Fe iron isotope. The study did not find any difference in iron intestinal absorption measured on day 21 between the two preparations. Moreover, after two months of treatment, hemoglobin levels increased to approximately baseline values in both treatment groups [19].

### Conclusion

Several new oral iron preparations claimed to have less adverse effects and good efficacy are available in market today. However, our literature finding concludes many controversial reports that doubt the significant efficacy of these new iron preparations over conventional formulation. Moreover, above mentioned case studies inferred that conventional sugar coated tablets might not

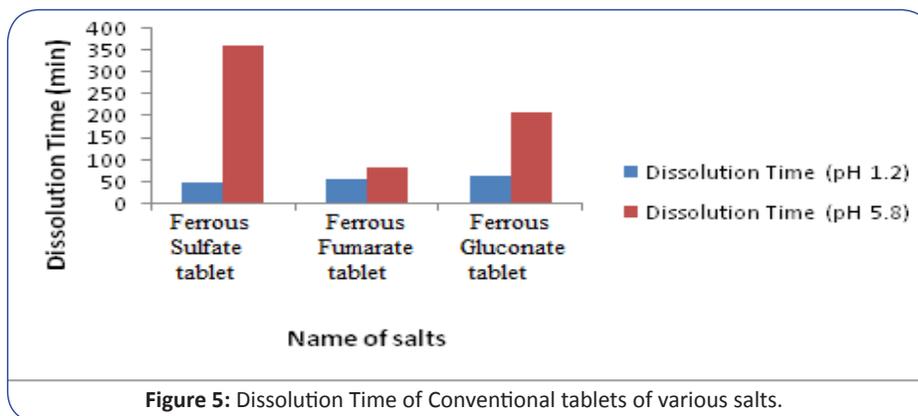


Figure 5: Dissolution Time of Conventional tablets of various salts.

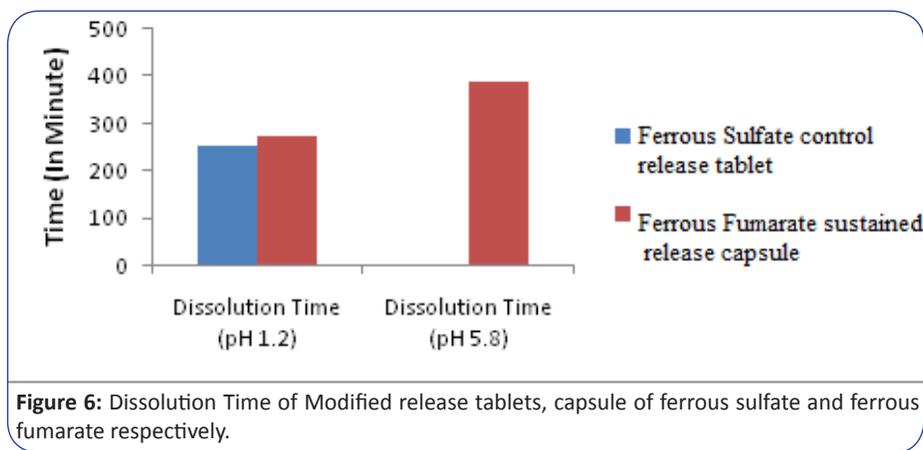


Figure 6: Dissolution Time of Modified release tablets, capsule of ferrous sulfate and ferrous fumarate respectively.

Table 1: Comparative iron absorption from different iron salt formulations.

Iron Preparation	Iron Absorption (%)
Ferrous Sulfate Tablets	41
Ferrous Gluconate Tablets	30.5
Ferrous Fumarate Tablets	31.5
Ferrous Sulfate plus ascorbic acid Tablets	29.5
Ferrous Fumarate plus minerals and vitamin capsule	33.5
Ferrous Gluconate plus folic acid syrup	33.5
Ferrous Gluconate plus ascorbic acid syrup	32

interchange with enteric coated tablets considering enhanced availability of iron at desired absorption site due to its highly solubilized form in conventional tablets and thereby increase in the bioavailability. This can be explained by fact that on exposure to low pH of gastric environment, ferrous or ferric ions forms complex with ligands present in the gastric secretion and favors its solubility. Furthermore, cost analysis of conventional and newer oral iron preparations revealed that newer oral iron preparations are 4-5 times costlier than conventional oral iron preparations [20].

Therefore it can be unfortunately concluded that the effect of iron supplement is being compromised to avoid the side effects by formulating into enteric coated tablets. However, “enteric coated tablets are still being marketed and most physicians and pharmacists may not know that many ferrous sulfate preparations are enteric-coated and that response may be inhibited.

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