Journal of Pharmaceutical Sciences xxx (2018) 1-11

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Development and Characterization of Gastroretentive High-Density Pellets Lodged With Zero Valent Iron Nanoparticles

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ARTICLE INFO

Article history:
Received 26 January 2018
Revised 30 May 2018
Accepted 12 June 2018

Keywords:
absorption
gastroretentive drug delivery system
bioavailability
pharmacokinetics
toxicology

ABSTRACT

The objective of the present study is to improve iron bioavailability using high-density gastroretentive pellets of zero valent iron nanoparticles (ZVINPs). ZVINPs were prepared by the chemical reduction method and were characterized for surface morphology, surface charge, and thermal properties. High-density gastroretentive pellets of iron nanoparticles were prepared using spheronization technique. Pellets were characterized for its micromeritic properties, *in vitro* drug release, and *ex vivo* permeability. The pharmacokinetic parameters, organ distribution, and toxicity of the optimized pellets were investigated in Wistar rats. *In vivo* results revealed more than 2-fold increases in oral bioavailability of iron by pellets compared to plane ferrous sulfate. Toxicological studies of the carriers indicated no evidence of liver damage in acute treatment; however, few complications were observed in chronic treatment groups. These results indicated that ZVINPs pellets successfully improve the oral iron bioavailability but need to obtain more information on repeated dose toxicity to initiate the clinical evaluation of investigational products.

Introduction

Iron is an essential component of body, which makes 70% of both hemoglobin and myoglobin. Hemoglobin is a part of RBCs, which helps to carry oxygen from lungs to tissues. Iron deficiency is the second most common cause of anemia in the elderly.[1] Further iron requirements increase during pregnancy, mensuration, lactation, and high growth periods. Apart from the dietary deficiency, iron deficiency anemia is typically associated with low iron absorption. The most frequent causes of low iron bioavailability are attributed to physical state of iron, narrow absorption window and involvement of common divalent metal transporter.[2] Further orally administered iron display low systemic availability that requires multiple iron therapy leading to a greater potential for toxicity particularly in major organs like liver and pancreas.[3] Moreover long term and frequent iron administration cause therapeutic noncompliance from the patient's perspective. Currently, nanoparticles have been investigated to improve the oral bioavailability of poorly soluble drugs. Nanoparticles owing to their unique surface properties employ more than one physiological mechanism to enhance drug absorption. In view of this context, Desai et al.[4] investigated the effect of particle size on gastrointestinal tissue uptake. Results suggested that the cell uptake efficacy of 100 nm size particles by the intestinal tissue was 15- to 250-fold higher compared to larger size microparticles. Similarly Reineke et al.[5] examined the effect of microparticles size on intestinal absorption with and without pharmacologic inhibitors. Results suggested that more than 1 mechanism involved in the cellular absorption of nanoparticles including both phagocytic and nonphagocytic process. Moreover, iron formulations possess instability, incompatibility, and toxicity because of premature oxidation of iron. Nanotechnology plays an important role to overcome these limitations.[6] Considering the usefulness of nanocarriers, the aim of the present research work is to develop zero valent iron nanoparticles (ZVINPs) with a view to improve the oral bioavailability of iron. Furthermore, poor oral iron bioavailability is because of incomplete absorption, narrow absorption window, and short gastric retention time.[7] Controlled release gastroretentive drug delivery systems could help in overcoming poor bioavailability of narrow absorption window drugs.[8] Sankar and Jain[9] investigated the role of gastroretentive sustained-release formulation on the oral bioavailability of acyclovir. Results indicated that gastroretentive formulation consisting of carbomer, polyethylene oxide, and sodium alginate was found to maintain sustained plasma concentrations than the immediate release tablet with 261% higher relative bioavailability compared to immediate-release formulations. Taking the advantages of gastroretentive drug delivery systems, the objective is further extended to prepare high-density controlled release gastroretentive (GRHD) pellets of ZVINPs using barium sulfate, carbomer, and microcrystalline

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https://doi.org/10.1016/j.xphs.2018.06.014
0022-3549/

Table 1
Compositions of Pellets With ZVINPs

S.No.	Formulation Code	Batch Quantity (g)	Coated ZVINPs (mg)	Barium Sulfate (mg)	Carbopol (mg)	DCP (g)	MCC (g)
1	F1	20	200	250	400	9.57	9.57
2	F2	20	200	200	400	9.60	9.60
3	F3	20	200	150	400	9.62	9.62
4	F4	20	200	100	400	9.65	9.65

cellulose (MCC) to improve oral iron bioavailability. Barium sulfate, being a heavy inert material used to prolong gastric retention time, was selected to increase the density of dosage form, encourage gastric retention and enable prolonged and continuous input of entrapped drug to the upper part of the gastrointestinal tract (GIT), resulting in an improvement in pharmacokinetics parameters. Barium sulfate is used as an X-ray contrast medium, which is often helpful to outline the particular structure under investigation. Carbomer is a biocompatible pH-dependent anionic polymer, remains collapsed in the acidic pH of the stomach preventing an undesirable drug release in the stomach, and decreases premature oxidation of iron, epigastric discomfort, nausea, and vomiting. In order to overcome pharmacokinetics limitations associated with conventional iron formulations, the present study involved controlled release high-density gastroretentive formulation of ZVINPs to improve the oral bioavailability of iron. Prepared controlled release gastroretentive formulation provides a sustained release of ZVINPs into the specific area thereby facilitating the iron absorption through a narrow absorption window. The complete pharmacokinetics study was performed in Wistar rats to compare the bioavailability of plain iron suspension and marketed suspension to establish the quality, safety, and efficacy of developed products.

Experimental Details

Materials

Ferric chloride, ferrous sulfate, sodium borohydride, and carbopol were purchased from Hi-Media Laboratories (Mumbai, India). Sodium citrate was purchased from Loba chemie Pvt. Ltd. (Mumbai, India). Soya lecithin and sodium lauryl sulfate (SLS) were purchased from Sigma Aldrich Pvt. Ltd. MCC, dicalcium phosphate (DCP), and ethanol were purchased from SD Fine Chemicals Ltd. (Mumbai, India). All other chemicals used were of analytical grade.

Preparation of ZVINPs

ZVINPs were synthesized by following sodium borohydride reduction method.[10] The synthesis process involved reduction of ferric chloride with sodium borohydride in the presence of sodium citrate. Resultant nanoparticles were prevented from agglomeration by adding stabilizer-like SLS. Briefly, 0.05 M ferric chloride solution was prepared in ethanol and water (1:2). Solution of sodium citrate (10%) and SLS (0.5%) preheated to 50°C were added very slowly to the solution of ferric chloride to work out the actual molar concentration that is, 0.05 M ferric chloride. Sodium borohydride solution was freshly prepared by dissolving 0.4-g sodium borohydride in 100-mL deionized water in a separate beaker. Sodium borohydride is then added drop wise into the ferric chloride solution (1:1) and were mixed continuously in the dark with continuous nitrogen bubbling. Finally, green color nanoparticles were prepared; mixture was centrifuged for 20 min at 5000 rpm. Pellets were washed twice with absolute alcohol to remove water. The prepared ZVINPs were used immediately for the preparation of high-density gastroretentive pellets.

Preparation of Gastroretentive High-Density Pellets

Before pelletization, ZVINPs were coated with lecithin to prevent iron nanoparticles from premature oxidation by utilizing the ionic affinity between positive charge of iron and the negative charge of lecithin. Gastroretentive high-density pellets lodged with coated ZVINPs were prepared by simple extrusion and spheronization process by using barium sulfate as high-density material, carbopol as sustain release polymer, and DCP and MCC as diluents. Pellets were produced with 20 g of powder blend containing 1% of coated ZVINPs, 1.25% of barium sulfate, 2% of carbomer 934P, 45% of MCC, 45% of tricalcium phosphate, and 5% of magnesium stearate. Pellets were prepared by mixing the components with demineralized water and made into suitable dough mass for pelletizing process. Four different formulations F1, F2, F3, and F4 were prepared with varying concentration of diluents and barium sulfate to achieve the required residence time. The formulation conditions were listed in Table 1.

Characterization of Prepared Formulation

Particle Size and Distribution

Particle size, size distribution, and zeta potential of prepared ZVINPs were determined at 25°C in a low-volume quartz cuvette by

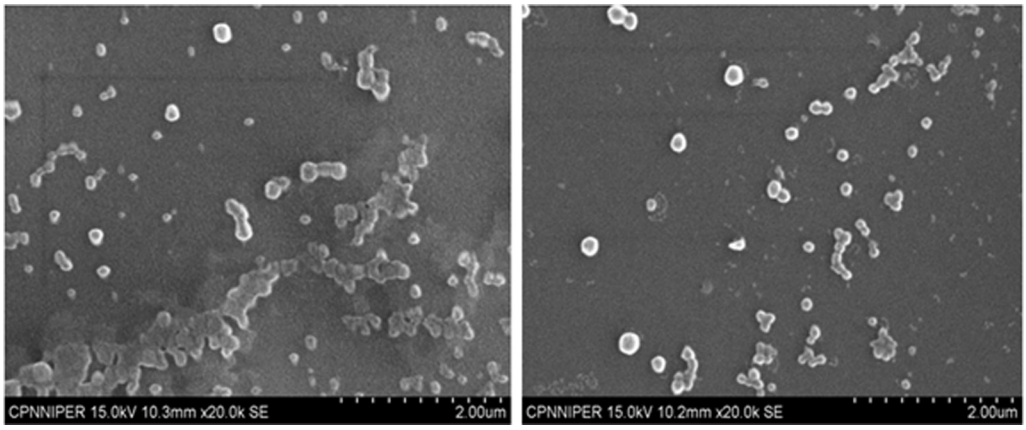

Figure 1. SEM images of coated ZVINPS (left) uncoated ZVINPS (right).