



Dissolution behaviour of ferric pyrophosphate and its mixtures with soluble pyrophosphates: Potential strategy for increasing iron bioavailability



Tian Tian^a, Elena Blanco^a, Stoyan K. Smoukov^b, Orlin D. Velev^a, Krassimir P. Velikov^{c,d,*}

^a Department of Chemical and Biomolecular Engineering, North Carolina State University, Raleigh, NC 27695-7905, USA

^b Department of Materials Science and Metallurgy, University of Cambridge, Cambridge CB3 0FS, UK

^c Unilever R&D Vlaardingen, Olivier van Noortlaan 120, 3133 AT Vlaardingen, The Netherlands

^d Soft Condensed Matter, Debye Institute for Nanomaterials Science, Utrecht University, Princetonplein 5, 3584 CC Utrecht, The Netherlands

ARTICLE INFO

Article history:

Received 14 October 2015

Received in revised form 3 March 2016

Accepted 22 March 2016

Available online 23 March 2016

Keywords:

Iron pyrophosphate
Food fortification
Iron supplementation
Iron bioavailability

ABSTRACT

Ferric pyrophosphate (FePP) is a widely used iron source in food fortification and in nutritional supplements, due to its white colour, that is very uncommon for insoluble Fe salts. Although its dissolution is an important determinant of Fe adsorption in human body, the solubility characteristics of FePP are complex and not well understood. This report is a study on the solubility of FePP as a function of pH and excess of pyrophosphate ions. FePP powder is sparingly soluble in the pH range of 3–6 but slightly soluble at pH < 2 and pH > 8. In the presence of pyrophosphate ions the solubility of FePP strongly increases at pH 5–8.5 due to formation a soluble complex between Fe(III) and pyrophosphate ions, which leads to an 8–10-fold increase in the total ionic iron concentration. This finding is beneficial for enhancing iron bioavailability, which important for the design of fortified food, beverages, and nutraceutical products.

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1. Introduction

Iron deficiency is currently known as one of the major global nutritional disorders, especially in women, infants and children. Fortification of foods with iron is considered as an effective way to solve this problem (Lynch, 2011; Zimmermann & Hurrell, 2007). However, design of stable products containing highly bioavailable iron sources remains a challenging goal (Moretti et al., 2006). On one hand, water-soluble mineral salts or complexes with high bioavailability may cause physico-chemical instabilities and sensorial problems with the products. On the other hand, the slow dissolution of mostly insoluble mineral compounds in the form of large particles becomes the rate limiting step and leads to low bioavailability. One approach to solve this dilemma is to use high surface area colloidal particles to enhance the dissolution of iron compounds such as ferric pyrophosphate ($\text{Fe}_4(\text{P}_2\text{O}_7)_3$, FePP) as a delivery system (Velikov & Pelan, 2008). FePP is a food additive that is white in colour, a rarity among insoluble iron compounds. However, colloidal FePP dispersions are not characterized well, with their physical properties relevant for product stability

and appearance not being well established (Rossi, Velikov, & Philipse, 2014; van Leeuwen, Velikov, & Kegel, 2012a, 2012b, 2012c; van Leeuwen, Velikov, & Kegel, 2014).

FePP has been shown to have good formulation properties, with generally acceptable, but not ideal, bioavailability, and FAO/WHO recommends doubling the current dose of FePP to meet the fortificant requirements (Fidler, Walczyk, et al., 2004; Sakaguchi, Rao, Nakata, Nanbu, & Juneja, 2004; Tsuchita et al., 1991). The importance of the pH dependent solubility of iron has been discussed by many authors. Zhu et al. studied the effect of pH on the bioavailability of iron in soluble ferric pyrophosphate (a soluble complex of ferric pyrophosphate and citric acid) and other iron fortificants, using a Caco-2 cell culture model with, or without, the combination of *in vitro* digestion (Zhu, Glahn, Nelson, & Miller, 2009). They found that exposure to pH 2, followed by adjustment to pH 7, markedly decreased FeSO_4 bioavailability, most likely due to a combination of oxidation and formation of less soluble Fe(III) salts. Chelating of iron ions was shown to minimize the effects of pH on iron bioavailability (also shown as good alternative to administration of colloidal iron dextran in maintenance hemodialysis (Gupta et al., 1999)).

It has been previously shown that when rate of dissolution is rapid enough, assured by decreasing the particle size, the bioaccessibility and bioavailability of FePP can be increased to the level of

* Corresponding author at: Unilever R&D Vlaardingen, Olivier van Noortlaan 120, 3133 AT Vlaardingen, The Netherlands.

E-mail address: krassimir.velikov@unilever.com (K.P. Velikov).

FeSO₄ (Fidler, Davidsson, et al., 2004; Hilty et al., 2010; Kandori, Kuwae, & Ishikawa, 2006; Rohner et al., 2007; Wegmuller et al., 2004; Zimmermann & Hilty, 2011). Rohner et al., for example, demonstrated that amorphous FePO₄ nanoscale particles synthesized by flame spray pyrolysis have solubility and relative bioavailability values not significantly different from FeSO₄ (Zhu, Glahn, Nelson, & Miller, 2009). Although this approach is known to give good bioavailability, comparable to that of soluble iron sources, the high cost of the colloidal particle synthesis process limits its application in developing countries (Fidler, Davidsson, et al., 2004; Wegmuller et al., 2004). In this study a simple and inexpensive strategy to increase FePP powders solubility in water without reducing the particle sizes is reported.

Even for water-soluble iron sources, it is still possible to have low absolute bioavailability. For example, the iron ions can form various insoluble salts (e.g. iron hydroxides or oxides) in the small intestine at pH around 5–7.5 (Dressman et al., 1990). In addition, the soluble iron mineral source may form insoluble complexes in the gastrointestinal (GI) tract with other species like polyphenols – abundant in teas and plants in general, which is known to significantly inhibit iron adsorption in the human body (Petry, 2013). On the other hand, the addition of complexing agents like EDTA has demonstrated the potential to improve the absolute bioavailability of insoluble iron sources by increasing the iron concentration in soluble form and minimizing the side reaction between iron ions and the adsorption inhibitors (Cho, Mejia, Morel, & Samuel-Fernando, 2002). Iron phosphate would not only have a high stability, but also help preserve the organoleptic properties of the product. The combination of iron phosphate and NaEDTA would form *in situ* an FeEDTA complex with better bioavailability when compared to other iron sources, like FeSO₄, due to improved solubility at pH in the small intestine. Although this approach is mostly suitable for dry products, it provides an opportunity to design various products with assured stability and bioaccessibility. This approach, however, was not efficient in elemental iron supplementation in corn Masa flour (Walter, Pizarro, & Olivares, 2003).

Despite the broad studies of iron bioaccessibility and absorption to develop food supplements and fortificants, there is not enough information regarding the quantitative solubility of FePP as a function of pH and also in the presence of other ions that can influence the protolytic equilibrium. The solubility of iron is determined by the solubility product, which is pH dependent, as the solubility of both Fe³⁺ and P₂O₇⁴⁻ are strongly dependent on pH (Rashchi & Finch, 2000; Stumm & Morgan, 1995). The factors, including solubility and binding constants of formed iron complexes, play a major role in iron bioavailability, since they influence the degree to which iron is absorbed (Hunt, 2005). Most iron absorption is thought to occur in the duodenum (pH 6–6.5) and upper jejunum (pH between 7 and 9) after reduction of Fe³⁺ to Fe²⁺ by an enzyme (ferro-reductase) located in the gut wall (Benito & Miller, 1998; De Domenico, Vey Ward, & Kaplan, 2008). Thus, high solubility of iron in media at pH > 5 would lead to good bioavailability, if only considering pH. Therefore it is important to know the equilibrium solubility FePP under different pH conditions relevant to the human gastro-intestinal tract (Dressman et al., 1990). Such measurements are not readily available for FePP, despite its wide use as an iron supplement (Jiang, Parekh, Leonard, & Wang, 1999).

In this study the equilibrium solubility profile of FePP in the product- and physiologically-relevant pH range of 1.0–8.5 is reported, as well as the effects of excess pyrophosphate ions on solubility at different pH values. The increase in solubility, due to complexation at a pH close to that in the intestinal condition, is proposed as a new concept for increasing iron bioaccessibility.

2. Materials and methods

2.1. Materials

Ferric pyrophosphate powder (FePP) (average size 2.5 μm according to supplier specification) was obtained from Dr. Paul Lohmann GmbH. Tetrasodium pyrophosphate (NaPP), iron (III) chloride, acetic acid, sodium acetate, ammonium acetate and Ferene S were purchased from Sigma-Aldrich. Deionised (DI) water was produced by RiOs16 and Synergy Ultrapure Water Systems from Millipore.

2.2. Experimental procedure

After mixing 0.1 g FePP (13.42 mM) with 10 ml DI water, differing amounts of tetrasodium pyrophosphate NaPP (0.1 g, 0.05 g, 0.025 g, 0.01 g) were added to the mixture, respectively. Under the external stirring with a magnetic stirrer, 0.1 M HCl or 0.1 M NaOH was added to FePP or FePP-NaPP dispersion dropwise until a certain pH was reached. Samples were kept at room temperature under shearing at 1200 rpm. After 1 week, the pH of each sample was measured again to verify the accuracy. One ml of every sample was added to a 1.5 ml centrifuge tube and the supernatant was collected to measure the dissolved iron concentration after 6000 rpm centrifuge (3500g) for 10 min. The Fe concentration in supernatants was determined by ICP-IES and UV-vis measurements. The dissolved FePP concentration (mM) was calculated by dividing the Fe concentration (mM) by the number of iron atoms, $n_{Fe} = 4$. The concentration of soluble iron in mg/L can be obtained by multiplying the FePP concentration in mM, as displayed in the figures, by $n_{Fe} \times Mw = 4 \times 55.845$.

2.3. Characterization

2.3.1. ICP-AES

Inductively coupled plasma atomic emission spectroscopy (ICP-AES) was used for independent verification of the Fe concentration from UV-vis spectroscopy. The ICP used was Optima 2000 DV from Perkin Elmer Corp. The relative error of ~2% assumed for values >20 ppm (<http://www.personal.psu.edu/hxg3/MCL/reproducibility.htm>).

2.3.2. UV-vis

Ultraviolet-visible spectroscopy (UV-vis) was used for the quantification of dissolved iron in ionic form, by absorbance measured at 594 nm, using a UV-vis spectrophotometer (V550, Jasco Corp., Japan). Ferrene S was chosen as the colorimetric agent for this experiment primarily because of its high extinction coefficient (35,500 M⁻¹ cm⁻¹) (Artiss, Strandbergh, & Zak, 1983; Artiss, Vinogradov, & Zak, 1981). The Ferrene is only strongly coloured when complexing with the Fe²⁺ ion, so part of the procedure involves the reduction of any Fe³⁺ ions dissolved in solution to Fe²⁺. Ascorbic acid was used for the reduction, with the solution being kept acidic to speed the reduction and prevent oxidation back to the Fe³⁺ form. For a 1 cm path length cuvette, and 28.2 mM Fe solution, absorbance of A = 1 is expected. The reduction time needed to convert Fe³⁺ to Fe²⁺, measured by UV-vis, is reported in Supplementary Fig. 1S. The errors for UV-vis measurements were calculated from the standard deviation of at least three measurements. After adding NaPP, the concern about the Ferene S method was that NaPP would modify the peak position or the extinction efficient of the spectrum. Supplementary Fig. 2S shows that the peak remains in the same range. Assuming the value of the extinction coefficient still to be 35,500 M⁻¹ cm⁻¹, the calculated

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