

Physicochemical Development Department¹, R & D, Krka, d.d., Novo mesto, University of Ljubljana, Faculty of Chemistry and Chemical Technology², Ljubljana, New Formulations Research Department³, R & D, Krka, d.d., Novo mesto, Slovenia

Development and optimization of the drug release determination of iron from iron prolonged release tablets

M. KINCL¹, R. BIBIČ¹, M. VEBER², F. VREČER³

Received September 16, 2002, accepted October 28, 2002

Maja Kincl, Krka, d.d., Novo mesto, Physicochemical Development Department, R & D, Šmarješka cesta 6, SL-8501 Novo mesto, Slovenia
maja.kincl@krka.si

Pharmazie 58: 257–259 (2003)

The aim of this research was to develop and optimize the drug release determination of iron from iron prolonged release tablets. First, solubility characteristics of ferrous sulfate in different aqueous media with a pH in the range of 1 to 8 were studied. According to the results obtained different physicochemical conditions that influence drug release of iron from iron prolonged release tablets were checked. Various aqueous media with a pH in the range of 1 to 7.4, different volumes of dissolution media, various rotation speeds of stirring elements, different dissolution apparatus (apparatus 1/basket apparatus and apparatus 2/paddle apparatus according to USP/Ph. Eur.) were verified. For evaluation of dissolved iron two different methods were checked: atomic absorption spectrometry and redox titration. Redox titration was proved to be a reproducible, discriminatory, selective and cost effective method for evaluation of dissolved iron from iron prolonged release tablets and can be applied in the quality control of solid dosage forms containing iron compounds.

1. Introduction

Iron prolonged release tablets produced by Krka contain ferrous sulfate in a special net structure polymer, which enables slower and sustained release of ferrous ions in the gastrointestinal tract. Prolonged release ferrous sulfate tablets are reported to be better tolerated than ordinary immediate release ferrous sulfate tablets. Continuous and controlled release of ferrous ions in the stomach and intestine prevents the accumulation of high concentrations of ferrous ions in the particular area of the gastrointestinal tract and reduces the side-effects to a minimum.

For evaluation of dissolved iron from ferrous sulfate immediate release tablets, USP 25 specifies atomic absorption spectrometry, which is a very precise technique for determination of metal ions in complex samples [1]. But there has been no official dissolution method for prolonged release tablets containing ferrous sulfate [1–3].

Hence, this study was undertaken to develop and optimize a method for drug release determination of iron from prolonged release tablets and a method for evaluation of dissolved iron, which will be as discriminatory, selective and effective as atomic absorption spectrometry, but superior and also cost effective to be applied in quality control laboratories.

2. Investigations and results

Solubility of ferrous sulfate in different aqueous media with a pH in the range of 1 to 8 at ambient temperature was determined by the shaking-flask method [4].

In the solubility studies 0.1 M hydrochloric acid, 0.01 M

hydrochloric acid, purified water for chromatography and different buffer solutions i.e. acid phthalate buffer solution pH 3.0, acid phthalate buffer solution pH 4.0, acetate buffer solution pH 4.5, acetate buffer solution pH 5.5, phosphate buffer solution pH 6.0, phosphate buffer solution pH 6.8, phosphate buffer solution pH 7.4 and phosphate buffer solution pH 8.0 were used [5–6]. The solubility of ferrous sulfate after 72 hours of shaking was determined by atomic absorption spectrometry method (AAS). Solubility values of ferrous sulfate in mg/ml at ambient temperature are shown in the Table. The influence of various aqueous media with different pH on iron release is shown in Fig. 1. The influence of the volume of the dissolution medium on drug release of iron is shown in Fig. 2.

Table: Solubility of ferrous sulfate and ionic strengths of the media at ambient temperature

Medium	Solubility (mg/ml)	Ionic strength (mol/l)
Hydrochloric acid 0.1 M	6.8	0.1
Hydrochloric acid 0.01 M	6.0	0.01
Acid phthalate buffer pH 3.0	5.8	0.05
Acid phthalate buffer pH 4.0	5.5	0.05
Acetate buffer solution pH 4.5	5.8	0.05
Acetate buffer solution pH 5.5	3.1	0.05
Purified water	4.1	0
Phosphate buffer solution pH 6.0	0.63	0.06
Phosphate buffer solution pH 6.8	0.0030	0.08
Phosphate buffer solution pH 7.4	0.019	0.1
Phosphate buffer solution pH 8.0	0.082	0.1

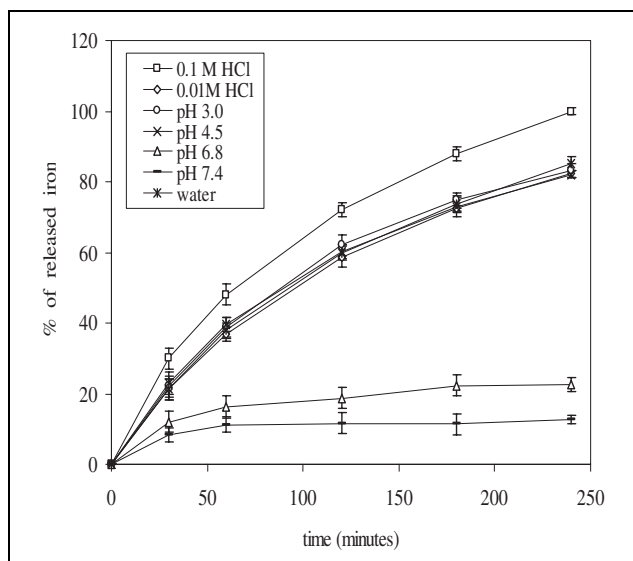


Fig. 1: Influence of various aqueous media with different pH and ionic strengths on drug release of iron (Apparatus: 1 (baskets). Medium: specified in 4.4. Volume: 900 ml. Rotation speed: 100 rpm. Temperature: 37 ± 0.5 °C. AAS determination of dissolved iron.)

The influence of the stirring elements on drug release of iron is shown in Fig. 3.

The influence of the different rotation speeds of the stirring elements on drug release of iron is shown in Fig. 4. For evaluation of dissolved iron two different methods were used: atomic absorption spectrometry, which is specified in USP 25 (for ferrous sulfate immediate release tablets) and redox titration by 0.001 M ceric ammonium sulfate. Comparison of the two methods for evaluation of dissolved iron from prolonged release tablets shows no significant differences.

3. Discussion

Referring to the data in the Table the solubility of ferrous sulfate depends on pH and ionic strength of the aqueous medium and the anion of the buffer solution used. Solubility experiments show that ferrous sulfate is highly soluble in acidic media and very slightly soluble in media with higher pH. Solubility in hydrochloric acid solutions decreases with lower ionic strength and higher pH, whereas in buffer solutions solubility decreases with higher ionic strength and higher pH and especially depends on the anion of the buffer solution used.

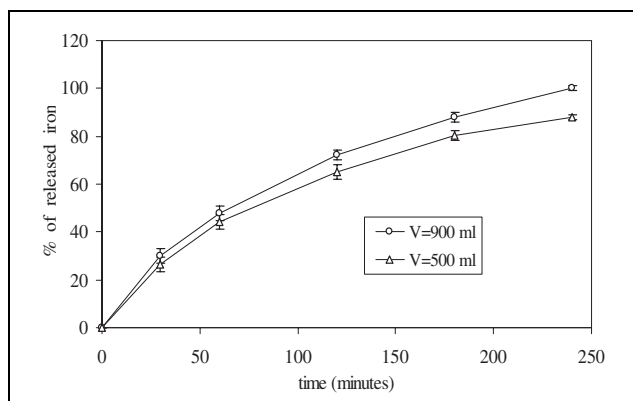


Fig. 2: Influence of the volume of the dissolution medium on drug release of iron (Medium: 0.1 M hydrochloric acid. Volume: 500 ml and 900 ml. Other conditions see: Fig. 1.)

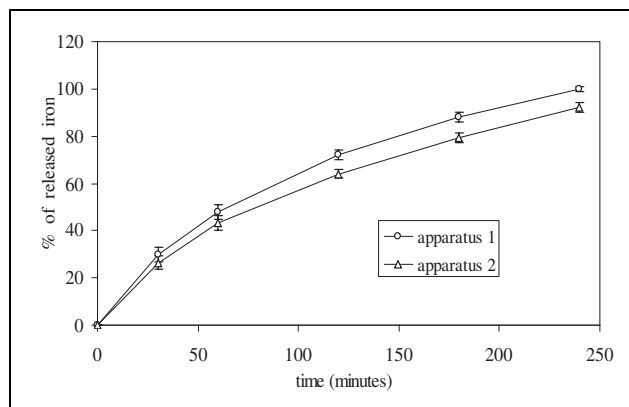


Fig. 3: Influence of the stirring elements on drug release of iron (Apparatus: 1 (baskets) and 2 (paddles). Medium: 0.1 M hydrochloric acid. Other conditions see: Fig. 1.)

The optimized drug release conditions are: use of apparatus 1/basket apparatus at 100 rpm in 0.1 M hydrochloric acid as dissolution medium, a volume of the medium 900 ml at 37 ± 0.5 °C, sampling times 30, 60, 120, 180 and 240 min and iron determination by redox titration with 0.001 M ceric ammonium sulfate.

According to the solubility data of ferrous sulfate sink conditions in selected dissolution media are obtained.

The method for evaluation of iron released from prolonged release tablets was validated. Repeatability of the method (system precision), linearity of the method, specificity/selectivity of the method and robustness of the method (influence of filters) were validated. All the parameters met the validation requirements.

Redox titration is as discriminatory, reproducible unpretentious and selective method for the evaluation of dissolved iron like atomic absorption spectrometry, but much faster and more cost effective than atomic absorption spectrometry.

Therefore, for the determination of iron dissolved from prolonged release tablets for routine work in quality control laboratories we propose redox titration.

4. Experimental

4.1. Materials

Concentrated hydrochloric acid (analytical grade) was obtained from Riedel de Haën (Munich, Germany), sodium hydroxide and concentrated sulfuric acid, both analytical grade, were from J. T. Baker (Phillipsburg, NJ, USA), potassium dihydrogen phosphate, ferroin redox indicator (1,10-phenantroline hydrochloride), ferrous sulfate, ceric ammonium sulfate were all

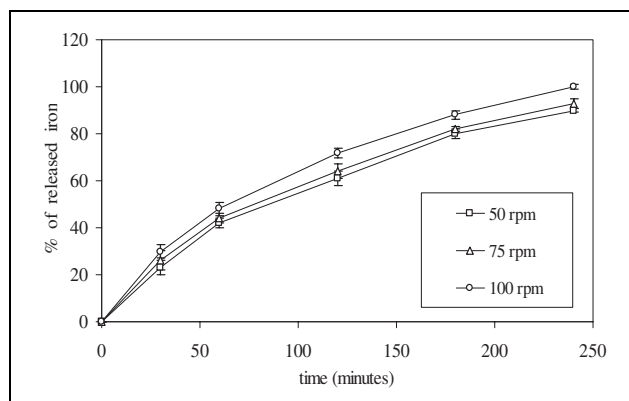


Fig. 4: Influence of different rotation speeds of the stirring elements on drug release of iron (Medium: 0.1 M hydrochloric acid. Rotation speeds: 50 rpm, 75 rpm and 100 rpm. Other conditions see: Fig. 1.)

analytical grade and from Fluka (Munich, Germany). Reference standard solution of iron (1000 µg/ml), analytical grade, was obtained from Alfa Aesar Johnson Matthew (Karlsruhe, Germany) and purified water for chromatography was from a Milli-Q purification unit (Millipore, Milford, MA, USA). Membrane filters (0.45 µm and 0.8 µm) were from Millipore (Milford, MA, USA). Injection syringes (10 ml and 20 ml) were from Sartorius GmbH (Goettingen, Germany), bent cannulas for dissolution sampling were from VanKel (USA) and pipettes from Hirshman (Germany). Ferrous sulfate used for solubility experiments was obtained from Merck (Darmstadt, Germany). Iron prolonged release tablets containing 40 mg of iron in the form of ferrous sulfate were produced by Krka, d.d., Novo mesto, Slovenia.

4.2. Instrumentation

For solubility experiments a Vibromix 402 EVT shaker (Slovenia) and a pH meter (Radiometer Analytical S.A.; Copenhagen, Denmark) were used. For drug release of iron an Erweka DT 6 RE dissolution tester (Germany) was used. For AAS evaluation of dissolved iron Perkin Elmer, model 2100 (Wellesley, MA, USA) atomic absorption spectrophotometer was used. For evaluation of dissolved iron by redox titration a multidosimat 655-Methrom (Switzerland) was used. Also water bath GFL, ultrasonic bath (Donau-lab-sonic, DLS 700-T; Zurich, Switzerland) and analytical balance (Mettler-Toledo AT261 DeltaRange; Greifensee, Switzerland) were used.

4.3. Solubility experiments

Solubility of ferrous sulfate at ambient temperature in different aqueous media with a pH in the range of 1 to 8 and different ionic strengths was determined by the shaking-flask method. The solubility of ferrous sulfate after 72 h of shaking was determined by atomic absorption spectrometry method (AAS).

All the aqueous media used for solubility experiments i.e. 0.1 M hydrochloric acid, 0.01 M hydrochloric acid, acid phthalate buffer solution pH 3.0, acid phthalate buffer solution pH 4.0, acetate buffer solution pH 4.5, acetate buffer solution pH 5.5, phosphate buffer solution pH 6.0, phosphate buffer solution pH 6.8, phosphate buffer solution pH 7.4 and phosphate buffer solution pH 8.0 were prepared according to the prescriptions in the USP 25.

Ionic strengths of the media used in the solubility experiments are shown in the Table.

4.4. Drug release

Parameters included in the study of drug release of iron: — type of apparatus, — medium, — volume of the medium, — rotation speed, — temperature: constant ($37 \pm 0.5^\circ\text{C}$), — sampling times: after 30, 60, 120, 180 and 240 min, — method for evaluation of dissolved iron.

Various aqueous media with a pH in the range of 1 to 7.4 were verified. In the drug release experiments the same aqueous media as in solubility experiments were prepared. Two different volumes of dissolution medium (500 ml and 900 ml), various dissolution apparatus (apparatus 1/basket apparatus and apparatus 2/paddle apparatus according to USP/Ph. Eur.) and different rotation speeds of the stirring elements (50 rpm, 75 rpm and 100 rpm) were used. For evaluation of dissolved iron two different methods were applied: atomic absorption spectrometry and redox titration with 0.001 M ceric ammonium sulfate.

For AAS evaluation of dissolved iron 10 ml of sample solution were withdrawn from each dissolution vessel by a syringe equipped with a bent cannula and filtered through a 0.45 µm membrane filter Millipore type HA.

For determination of dissolved iron by redox titration 15.0 ml of sample solution were withdrawn from each dissolution vessel by a pipette.

All the parameters included in the study were tested at six tablets.

4.5. Atomic absorption spectrometry (AAS)

By atomic absorption spectrometry % of dissolved ferrous and ferric ions in total were determined. Method: linear standard curve (1.0 µg Fe/ml, 2.0 µg Fe/ml, 3.0 µg Fe/ml, 4.0 µg Fe/ml, 5.0 µg Fe/ml). Procedure: 5.0 ml of filtered sample solution/50 ml of 0.1 M hydrochloric acid → AAS evaluation of dissolved iron. Resonance line: 248.3 with background. Slit width: 0.2 nm. Lamp: Fe (Hollow cathode lamp). Lamp current: 30 mA. Gas mixture: acetylene/air. Sensitivity check: 5.0 µg/ml 0.20 A-s.

4.6. Redox titrations

By redox titration % of dissolved ferrous ions was determined. Instrument: Multidosimat 655-Methrom. Titrant: 0.001 M ceric ammonium sulfate. Indicator: ferroin indicator (1,10-phenantroline hydrochloride). Equivalent: each ml of 0.001 M ceric ammonium sulfate is equivalent to 0.0558 mg of Fe(II). Change of color at the equivalence point: from reddish orange to grey-blue.

References

- 1 USP 25, NF-20, p. 734, United States Pharmacopeial Convention, Inc., Rockville 2002
- 2 European Pharmacopoeia Supplement 4.2 to the Fourth Edition, Council of Europe, Strasbourg 2002
- 3 British Pharmacopoeia 2001, London, United Kingdom 2001
- 4 Avdeef, A.; Berger, C. M.; Brownell, C.: *Pharm. Res.* **17**, 85 (2000)
- 5 <http://www.eudra.org/emea.html>
- 6 <http://www.fda.gov/cder/guidance/index.htm>