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Research paper

Iron(II) sulfate release from drop-formed lipophilic matrices developed by special hot-melt technology

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Abstract

Iron(II) sulfate-containing lipophilic matrices were developed by a special hot-melt technology (melt solidification in drops), using stearin, white wax and their mixture as conventional bed materials. The special technology resulted in spherical particles which can be filled directly into capsules; these store iron as a depot and ensure a slow and uniform release, whereby the irritation of the gastric mucosa by the iron can be decreased. The rates of dissolution of the iron(II) sulfate from the various lipophilic matrices were different, but fundamentally low. Kinetic calculations demonstrated that the rate of dissolution of the iron(II) sulfate was of approximately zero kinetic order. The results of in vivo experiments on rabbits correlated well with the in vitro data. The plasma curves for the animals treated with the iron(II) sulfate preparations varied with the excipients in the depot products. The properties and ratio of the bed materials influenced the release of the iron(II) sulfate. In all probability, the release of the active agent can be regulated through the use of a melt of stearin and white wax in different ratios. The development products functioned as a sustained-release system and ensured elimination of the irritation of the gastric mucosa. At the same time, the results justified the applicability of the special hot-melt technology in the development of the solid dosage form.

Keywords: Hot-melt technology; Lipophilic matrix; Gastric mucosa irritation; Iron(II) sulfate; Sustained release, in vitro dissolution, in vivo experiment

1. Introduction

Iron compounds are most often administered for the treatment of anaemia [1]. Eighty percent of all anaemia cases involve anaemia sideropenica, a disease due to an iron deficiency. Iron therapy is indicated only after the correct diagnosis of an iron deficiency, and oral therapy is the first choice [2]. Iron(II) salts are administered orally because of their very well absorption. Iron of either dietary or medicinal sources is absorbed mainly from the upper part of the small intestine by active and passive transport processes [3].

The present-day technologies are time-consuming and expensive (e.g. wet granulation, tablet pressing and coating) and the iron compounds accelerate the attrition and corrosion of the machines. Another problem may be the oxidation of iron ($Fe^{2+} \Rightarrow Fe^{3+}$) [4].

Iron therapy demands preparations from which Fe^{2+} is well absorbed, which have adequate bioavailability, which carry no risk of an iron overdose and which do not irritate the stomach. Difficulties arise in the manufacturing and there are disadvantages (such as gastric irritation) of oral therapy [5].

Most of the medicines in the present daily therapy of anaemias are administered as tablets. The advantage of the tablet form over the effervescent tablet, drop or syrup is that it does not adversely affect the condition of the teeth and it undergoes less oxidation. In cases of anaemia, tablets are generally used twice or thrice a day (for a period of months). The advantage of sustained-release tablets is that they make one daily dose possible, which improves the compliance of the patients and decreases the risk of gastric irritation, which is especially important with iron compounds [5]. The embedding of a drug into a lipophilic matrix is often applied to ensure sustained or slow release [6,7]. The mechanism of release of the embedded drug differs from that for other formulations. The erosion and/or decomposition of the bed material by enzymes or body fluids, and the dissolution of

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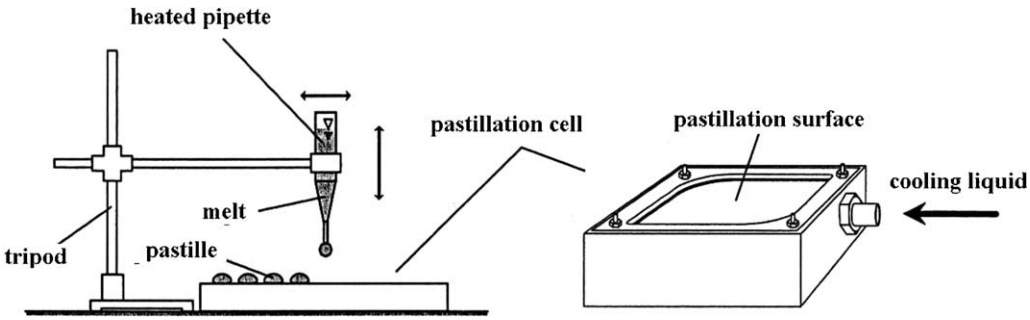

Fig. 1. Melt solidification with the special laboratory equipment.

the active agent play the major role [8]. Melt technologies might be the appropriate ways of producing sustained-release particles [9,10]. Polyethylene glycols [11], waxes [12], stearic acid [13], fats, fatty acids, fatty alcohols and glycerides [9,10] are typical examples of meltable binders, or bed materials.

The aim of this study was to prepare iron(II) sulfate-containing solid spherical particles by means of a special hot-melt technology (melt solidification in drops) on a laboratory scale. This technology is new in the field of iron processing. We used natural, conventional bed materials for the production, such as stearin and white wax. The advantages of the technology applied are that it is a solvent-free process, and is therefore environment-friendly, and it is a time- and cost-saving process, because the particles are produced in one step and can be filled into capsules directly and applied in oral therapy. A further aim was to attain the sustained release of the active agent from the particles and to perform the in vitro and in vivo evaluation of the samples.

2. Materials and methods

2.1. Materials

Iron(II) sulfate monohydrate (particle size 44–104 μm, relative density 3.08, Ph. Eur. Merck Eurolab GmbH, Darmstadt, Germany) was used as the active agent. The bed materials were white wax (Cera alba, density approximately 0.95, melting point 62–66 °C, Ph. Hg. VII, Hungaropharma, Budapest, Hungary), and stearin (Stearinum, relative density 0.85, melting point 54–67 °C, Ph. Hg. VII, Hungaropharma, Budapest, Hungary) and their mixture.

2.2. Methods

2.2.1. Preparation of the experimental product

Iron(II) sulfate-containing spherical particles were prepared by melt solidification with a special hot-melt technology. This method for the production of drop-formed particles was developed by Bülau and Ulrich [14,15]. The essence of this method is the drop forming of the melted material with laboratory equipment (Fig. 1), so as to obtain solid spherical particles (Fig. 2). The iron(II) sulfate was suspended in the molten bed materials (stearin and white wax). The preheated melt (suspension) was dropped onto a cooled surface by means of a heated pipette. The parameters that could be varied were the temperature of the melt, the temperature and the material of the cooled surface, the size of the drops and the distance between the pipette and the cooled surface. The effects of the process parameters on the geometrical properties of the particles were determined in preformulation studies.

In this way the cooling plate was first chosen with regard to its surface free energy. The choice fell on steel, because this has a moderate surface energy (30.17 mN/m). Higher (e.g. enamel, 51.12 mN/m) and lower (e.g. teflon, 18.75 mN/m) surface energies did not result in spherical particles. Enamel deformed the drops before solidification (the drop 'jumped' on the surface) and teflon caused fast solidification of the melt before drop formation [16]. The shape and structure of the resulting particles depended strongly on the temperature of the melt during drop

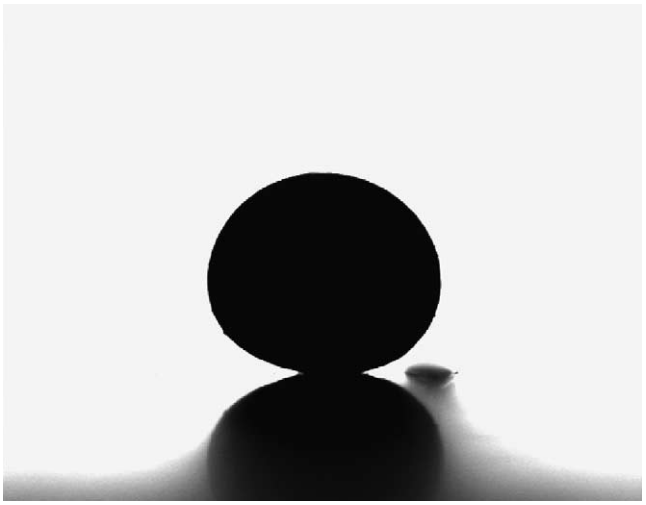

Fig. 2. Round particle of formulation 2 during solidification. Particle size, 2.0 mm.

formation and on the temperature of the solidification surface. The melt temperature of the bed materials for dropping was determined by the contact angle of the melt on the steel. The temperatures of the cooling plate (10.6 °C) and the melt (T_{melt}) and the parameters of the drop forming were characterized in preformulation studies [16].

The developed samples were as follows:

formulation 1: 50% Fe(II)SO_4 + 50% stearin, T_{melt} = 57.9 °C
formulation 2: 50% Fe(II)SO_4 + 50% white wax, T_{melt} = 66.8 °C
formulation 3: 50% Fe(II)SO_4 + 25% stearin + 25% white wax, T_{melt} = 66.8 °C

2.2.2. Morphological study

The properties of the formulations (surface and cross-section) were observed by scanning electron microscopy (Hitachi 2400S Hitachi Scientific Instrument Ltd, Tokyo, Japan). A Polaron sputter coating apparatus (Polaron Equipment Ltd, Greenhill, UK) was applied to induce electric conductivity on the surface of the sample. The air pressure was 1.3–13 mPa.

2.2.3. In vitro drug dissolution study

The dissolution of iron(II) sulfate was studied with a Pharma Test PTW 2 apparatus (Pharma Test GmbH, Hainburg, Germany) paddle method, under sink conditions, for 6 h. The medium was 900 ml of distilled water (pH 5.7 ± 0.1), artificial gastric fluid (pH 1.2 ± 0.1) or phosphate buffer (pH 7.5 ± 0.1). The medium temperature was 37 ± 0.5 °C. The rotation speed was 100 rev./min. Samples of 5 ml were extracted at regular time intervals (0.5, 1, 2, 3, 4, 5 and 6 h), and were analysed with a Perkin Elmer 4100 atomic absorption spectrometer (Bodenseewerk Perkin Elmer GmbH, Überlingen, Germany) under the following conditions: flame-atomizing, wavelength 248.3 nm, slit width 0.7 nm, air–acetylene gas mixture (air, 0.8 l/min; acetylene, 3.5 l/min), and read time 5 s. The results were evaluated with Excel at the 95% confidence level.

2.2.4. In vivo study

New-Zealand white rabbits (mean body weight 2632 ± 155 g), six animals in each group, were treated orally with the particles (dosage 20 mg iron(II) sulfate/kg). The particles were introduced directly into the stomach via a catheter and were washed in with 30 ml of water. The control animals were treated with an equivalent dose of iron(II) sulfate in aqueous solution (0.5% w/v). Blood samples were collected from the marginal ear veins 12 or 14 times, at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8 and 10 h, with two additional samples at 0.25 and 0.75 h for the aqueous solution. Heparin was used as anticoagulant. Samples were stored at 5 °C until analysis.

Afterwards, the animals were anaesthetized with i.v. pentobarbital, the mucous membranes of the stomach and ileum were examined and the macroscopic changes were evaluated.

Animal investigations were carried out with the approval of the Ethical Committee for Animal Research, University of Szeged (registration number I-74-7/2002).

2.2.4.1. Evaluation of the active agent. Iron(II) concentrations in plasma samples were measured with the aid of a Ferrozin kit (Diagnostikum Rt, Budapest, Hungary). At pH 4.8, Fe^{3+} dissociates from transferrin and is reduced to Fe^{2+} by the ascorbic acid incorporated in the kit. This Fe^{2+} forms a red complex with ferrozin. Its absorbance at 560 nm is directly proportional to the Fe^{2+} concentration. The test is linear up to an Fe^{2+} concentration of 179 μmol/l.

For the analysis, 200 μl of plasma or standard solution was used. The plasma Fe^{2+} concentrations were measured against a reagent blank. The physiological Fe^{2+} concentration was determined on blood samples taken at 0 h, just before the treatment. This value was subtracted from the Fe^{2+} concentrations measured after the treatment.

2.2.4.2. Pharmacokinetic evaluation. Computerized data processing was carried out with MEDUSA 1.8. Curves were fitted to the concentration values within each group and pharmacokinetic analysis was performed in accordance with the one-compartment open pharmacokinetic model.

The plasma concentration curve was plotted and the main pharmacokinetic parameters were determined: the absorption half-life ($t_{1/2abs}$), the elimination half-life ($t_{1/2elim}$), the mean residence time (MRT), the time to peak (t_{max}) and the peak concentration (C_{max}). The area under the curve (AUC_∞) needed for the estimation of the bioavailability was also calculated [17].

The statistical evaluation of the kinetic parameters was performed by SPSS ANOVA one-way statistical analysis.

3. Results and discussion

3.1. Pharmaceutical technological evaluation

For development of the iron(II) sulfate-containing lipophilic matrices, we used a special hot-melt technology (melt solidification in drops) which provides solid spherical particles. The pharmaceutical technological parameters of the samples, such as the mass, size and the iron(II) sulfate content of the particles were homogeneous and suitable for capsule filling (Table 1). The uniformity in particle size, mass and Fe^{2+} content confirm the reproducibility of the special hot-melt technology and its applicability in the iron processing.

3.2. In vitro drug release studies

The in vitro release of iron (II) sulfate from the produced formulations was studied in different fluids,

Table 1
Parameters of iron(II) sulfate-containing formulations

	Formulation 1	Formulation 2	Formulation 3
Mass (g)	0.0106 (±0.001)	0.0105 (±0.002)	0.0109 (±0.002)
Size (mm)	1.792 (±0.051)	1.998 (±0.189)	1.776 (±0.078)
Fe(II)SO_4 content (mg)	6.41 (±0.183)	6.97 (±0.483)	6.15 (±0.074)
Fe^{3+} content[a] (%)	0.42 (±0.01)	0.43 (±0.01)	0.43 (±0.02)

[a] Starting Fe^{3+} content, 0.40%.

Table 2
Kinetic parameters of formulations

	Zero-order model		First-order model	
	Rate constant (k)	Correlation coefficient (R)	Rate constant (k)	Correlation coefficient (R)
Formulation 1	−8.3007	0.9768	−0.0839	0.9978
Formulation 2	−3.4952	0.9843	−0.0220	0.9907
Formulation 3	−4.9306	0.9905	−0.0435	0.9983

such as distilled water, artificial gastric fluid and phosphate buffer. The highest drug release was detected in the artificial gastric fluid, with an acid character. Drug materials such as iron(II) sulfate give rise to irritation if the concentration is high in the stomach. The produced samples store iron in the solid state, incorporated in the lipophilic matrix. The iron(II) sulfate released from the matrices must be in the dissolved form in the stomach for effective absorption in the proximal intestine. Since most of the solid iron(II) sulfate incorporated in the lipophilic matrices was released in the stomach, so the in vitro release results for the artificial gastric fluid are shown in the article. The rates of dissolution of the iron(II) sulfate from the various lipophilic matrices were basically low. However, considerable differences were observed in the amount of active agent liberated. The greatest quantity of iron(II) sulfate was dissolved from formulation 1, i.e. 70% of the total iron content. This was followed by formulation 3, with 45% release, and then formulation 2, from which 26% of the total drug content was liberated during the study (Fig. 3). In the in vitro tests, no significant differences in drug release were detected between formulations 2 and 3, whereas there were significant differences between formulations 1 and 2, and between formulations 1 and 3. The results of the significance calculation were also prognosticated by the rate constants. The kinetic calculations demonstrated that the rate of dissolution of the iron(II) sulfate was of approximately zero kinetic order, which means that the product stores iron as a depot and ensures its slow and uniform release (Table 2). This is a very important requirement with a view to the prevention of gastric irritation.

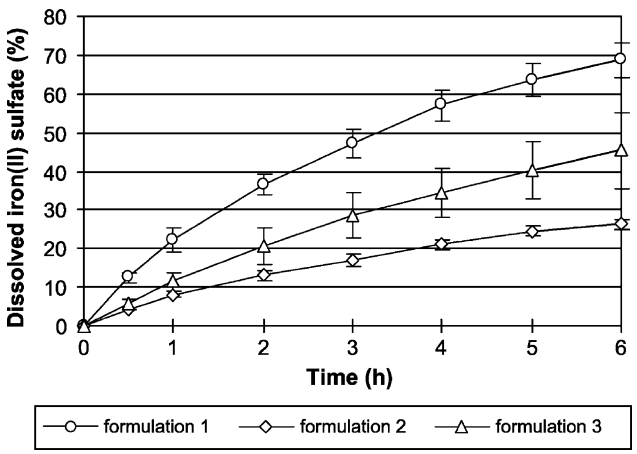

Fig. 3. In vitro dissolution of iron(II) sulfate in artificial gastric fluid at 37 °C, from formulations 1 (○), 2 (◇) and 3 (△).

The drug release result in artificial gastric fluid is in accordance with the physico-chemical properties, and more particularly with the solubility properties of the iron(II) sulfate and the auxiliary materials too. White wax and stearin are both insoluble in water and in acid medium, but stearin has an acid character and contains some water-soluble acid. Accordingly the highest drug release was observed from formulation 1, which contained stearin as bed material. The drug release was lower from formulation 3, containing stearin and white wax, and least from formulation 2, which contained only white wax as bed material.

The drug release profiles are in accordance with the surface of the samples too.

On the basis of the results of the in vitro experiments, stearin, white wax and their mixtures, in the quantities used and with the mentioned technology, appear suitable for the production of iron(II) sulfate-containing solid preparations with the desired biological effect, without stomach irritation.

3.3. In vivo experiments

A summary of the in vivo studies in rabbits is shown in Fig. 4. The curves demonstrate the increase in the plasma iron(II) concentration in comparison with the basic level measured before treatment. The points are the mean plasma iron(II) concentrations with the standard deviation in each group of six animals. As concerns the basic plasma iron level, no significant differences could be observed between the different groups.

The curves in Fig. 4 reveal that the absorption was fastest from the iron(II) sulfate solution administered as a control. The peak plasma iron(II) concentration (C_{max}) (9.77 ± 3.84 μmol/l) was reached within 1 h. For the three

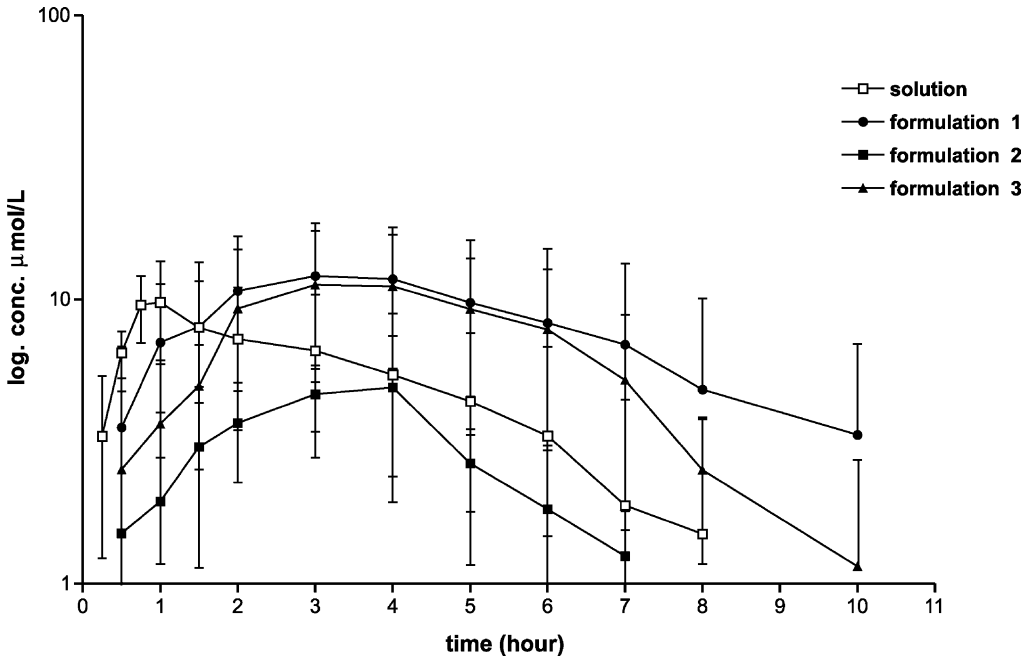

Fig. 4. Plasma iron levels in rabbits after oral administration of iron(II) sulfate-containing formulations.

formulations studied, the absorption was considerably slower: the C_{max} values were measured 3 and 4 h after administration. The plasma level was 12.11 ± 6.43 and 11.28 ± 6.16 μmol/l for formulations 1 and 3, respectively. For the animals treated with formulation 2, C_{max} was only 4.90 ± 2.52 μmol/l. As regards the three preparations, the lowest plasma iron concentrations were measured for formulation 2, and these values fell to the normal level by 8 h.

The pharmacokinetic parameters determined from the curves are indicated in Table 3. The absorption half-life ($t_{1/2abs}$) for the iron(II) sulfate solution was 0.26 h, whereas it was 1.66 h for formulation 1, 1.07 h for formulation 2 and 1.40 h for formulation 3. The difference was significant for each formulation. Significant differences in elimination half-life ($t_{1/2elim}$) were observed in relation to formulations 2 and 3. However, no significant differences were found in MRT between the solution (3.92 h) and the formulations (5.19, 4.05 and 5.06 h, for formulations 1–3, respectively). The time to peak plasma concentration (t_{max}) was 1.07 h for the solution, in contrast with 3.06 h for formulation 1, 2.58 h for formulation 2 and 3.03 h for formulation 3. The differences were significant.

The highest C_{max} were measured for formulations 1 and 3 (13.88 and 12.41 μmol/l, respectively), followed by the aqueous solution (9.65 μmol/l) and formulation 2 (5.58 μmol/l). The AUC values extrapolated to infinity were higher for formulations 1 and 3 (95.6 and 68.7 μmol/l h) than for the solution (46.4 μmol/l h), but the difference was significant only in the case of formulation 1. The bioavailability relative to the iron(II) sulfate solution was 205.9, 147.9 and 47.5% for formulations 1, 3 and 2, respectively.

The results of the in vivo experiments indicate that all three formulations belong to the sustained-release category. The absorption half-lives of the products were significantly increased relative to that of the iron(II) sulfate solution, and the active agent reached the C_{max} statistically later for all three preparations. The highest C_{max} and AUC values were measured for the product produced with stearin (formulation 1) and that containing stearin (formulation 3).

Table 3
Pharmacokinetic parameters calculated from plasma curves of rabbits after oral administration of iron(II) sulfate-containing formulations

Treatment	Absorption half-life (h)	Elimination half-life (h)	MRT (h)	t_{max} (h)	C_{max} (μmol/l)	AUC_∞ (μmol/l h)	Bioavailability[a] (%)
Solution ($n = 6$)	0.26 (±0.10)	2.38 (±0.46)	3.92 (±1.25)	1.07 (±0.22)	9.65 (±3.60)	46.4 (±34.4)	100.0
Formulation 1 ($n = 6$)	1.66* (±0.77)	1.84 (±0.85)	5.19 (±2.21)	3.06* (±1.27)	13.88 (±6.09)	95.6* (±57.7)	205.9 (±113.5)
Formulation 2 ($n = 6$)	1.07* (±0.52)	1.42* (±0.46)	4.05 (±0.62)	2.58* (±0.84)	5.58 (±2.33)	22.1 (±6.41)	47.5 (±12.6)
Formulation 3 ($n = 6$)	1.40* (±0.34)	1.60* (±0.23)	5.06 (±0.97)	3.03* (±0.31)	12.41 (±8.18)	68.7 (±34.5)	147.9 (±67.9)

Mean difference related to solution is significant (*$P < 0.05$).
[a] Bioavailability relative to solution (100%).

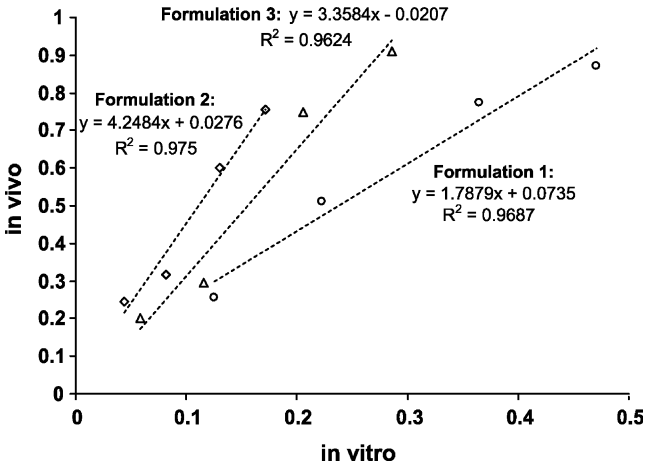

Fig. 5. In vitro/in vivo correlation based on pooled data of formulations 1 (○), 2 (◇), and 3 (△).

The kinetic parameters revealed that the best sustained-release preparation was the product which contained stearin as bed material.

The sustained release of the active agent led us to expect that the effect would be achieved without accompanying gastric irritation. To check on this, the gastric mucosa of the rabbits was examined after the in vivo study. After treatment with the iron(II) sulfate solution, considerable gastric irritation was observed as a result of the iron reaching the stomach suddenly in a high concentration. However, no gastric irritation was noticed after the in vivo treatment the three formulations.

3.4. In vitro/in vivo correlation

The in vitro/in vivo correlations for the three formulations were explored by comparing the in vivo drug release obtained from deconvolution with the in vitro release data [18,19]. The results in Fig. 5 indicate approximately linear correlations between the in vivo and the in vitro fractional release for the matrix systems. The slopes and the intercepts obtained from the pooled data for the three formulations suggested that the overall in vitro release is faster than the in vivo release.

3.5. Macromorphological analysis

These investigations related in part to the properties of the particles (before and after administration) and in part to the potential irritation of the gastric mucosa of the rabbits.

The electron microscopic pictures showed that each particle has a spherical form with a more or less even and continuous surface. The quality of the surface was crucially determined by the bed materials.

Formulation 1, prepared with stearin (Fig. 6), has an uneven surface with cracks in it (Fig. 6a). The iron

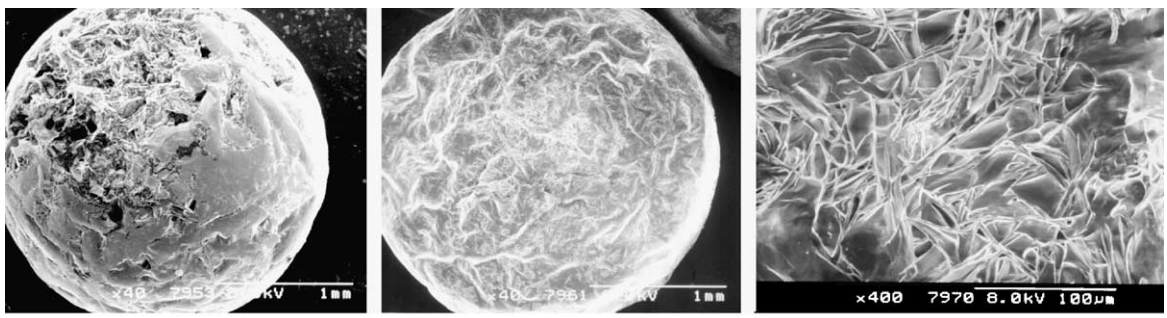

Fig. 6. Electron microscopic pictures of formulation 1 (bed material, stearin): surface of the intact particle (a), surface of the particles after the in vivo study (b,c).

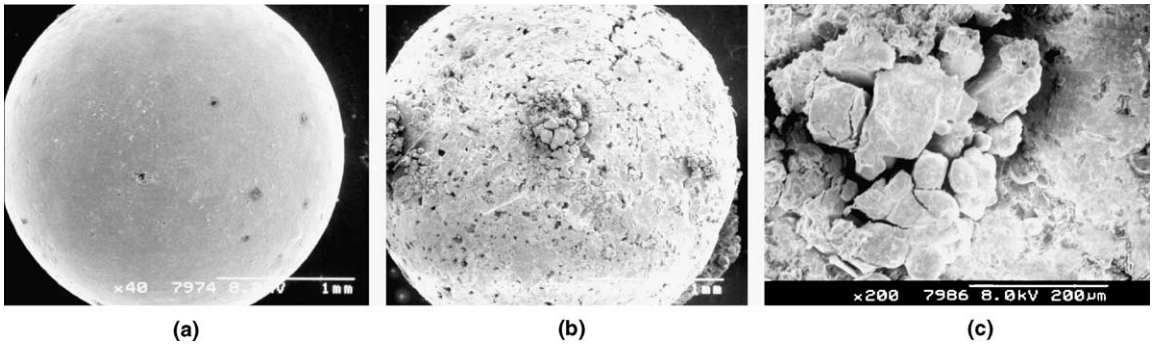

Fig. 7. Electron microscopic pictures of formulation 2 (bed material, white wax): surface of the intact particle (a), surface of the particles after the in vivo study (b,c).

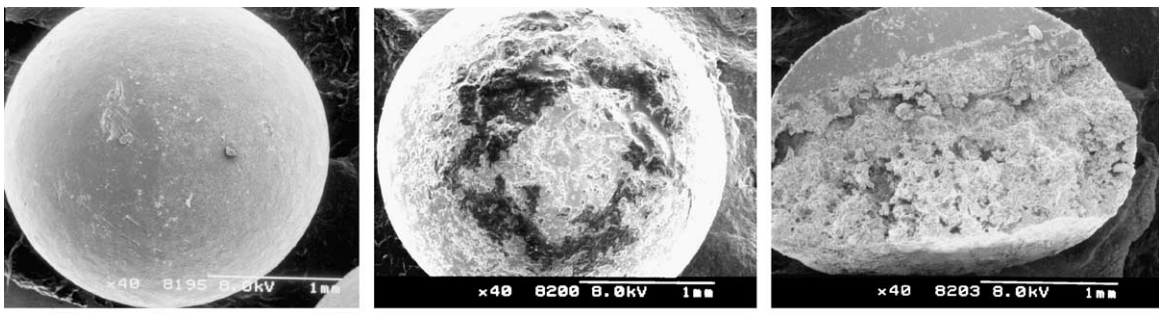

Fig. 8. Electron microscopic pictures of formulation 3 (bed material, stearin and white wax): surface of the intact particle (a), surface of the particle after the in vivo study (b), cross-section of the particle after the in vivo study (c).

liberation is presumed to be accelerated by dissolution through these cracks. After the animal tests, the particles in the stomach of the animals were found to be unbroken, i.e. the particles did not disintegrate in vivo. The auxiliary agent remained as a framework keeping the spherical shape, but superficial changes were noted. The surface became even, the cracks disappeared (Fig. 6b) and recrystallization of the stearin could be observed (Fig. 6c).

For formulation 2, prepared with white wax (Fig. 7), the particle surface was completely smooth, and no cracks were noted (Fig. 7a). Formulation 2 had a more compact structure than that of formulation 1. The particles remained unbroken after the in vivo study, but traces of superficial erosion (Fig. 7b) and iron(II) sulfate aggregation on the surface (Fig. 7c) could be observed.

Formulation 3, which contained both the bed materials, also had a smooth, even surface (Fig. 8). The explanation of this even surface is that a mixture of stearin and white wax in a ratio of 1:1 was used and the white wax corrected the roughness of the surface (Fig. 8a). After the animal tests, the particles found in the stomach of the animals had a spherical shape, but the surface had become uneven as a result of the dissolution of iron(II) sulfate (Fig. 8b). After the in vivo study, the particles exhibited a spongy structure (Fig. 8c).

4. Conclusions

The results revealed the suitability of the special hot-melt technology for the production of drop-formed particles with the slow release of iron(II) sulfate. The slow release of the active agent with zero kinetic order can be ensured by means of lipophilic bed materials (stearin and white wax) with low melting point. The results of in vivo experiments on rabbits correlated well with the in vitro data. Consequently, the liberation of the active agent can be regulated through the use of a melt of stearin and white wax in different ratios. Since the properties of the lipophilic skeleton building materials determine the liberation of the active agent, the system probably functions similarly with other water-insoluble drug materials.

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