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Research paper

Development of spherical iron(II) sulfate heptahydrate-containing solid particles with sustained drug release

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Abstract

The aim of this work was to develop a simple, economic procedure for the manufacturing of coated iron(II) sulfate particles by using a crystallization technique for the development of round particles, followed by coating with a lipophilic material. Several batches of iron(II) sulfate heptahydrate were produced by a cooling crystallization, with variation of the crystallization parameters. The spherical crystals were coated with stearin. The products were characterized for particle size, roundness, bulk density and *in vitro* drug dissolution. Crystallization was performed from deionized water with no addition of seed crystals and by cooling by applying a linear cooling rate. The developed iron(II) sulfate crystals were round with average diameter of 729 ± 165 μm. The best form for the sustained release of iron(II) sulfate was the sample HTP-2 which contained 11% of stearin relative to the iron(II) sulfate. The spherical crystallization of iron(II) sulfate is simple and fast, and does not require a dangerous, expensive solvent. The round particles can coat directly with lipophilic material which results in slow release of iron(II) sulfate and protects the iron(II) from oxidation and inhibits the loss of crystal water. The coated crystals can be filled into capsules to yield the final dosage form.

Keywords: Spherical crystallization; Iron(II) sulfate; Stearin; Sustained release; Roundness

1. Introduction

From a point of view of pharmaceutical technology, there is an increasing demand for drug substances which can be processed directly, i.e. which can be pressed into tablets or filled into capsules without preliminary granulation. Spherical crystallization is an especially suitable procedure to comply with this demand. By using of spherical crystallization, an active ingredient formed as nearly round particles can be manufactured. These particles have good flow properties and a high bulk density and can be coated and/or pressed appropriately [1]. The term of spherical crystallization is due to the Japanese researcher Kawashima, who described the formation of round particles of salicylic acid in Science in 1982 [2]. He applied three solvents and since then this technique has been called *typical spherical crystallization*. In fact, spherical crystallization or agglomeration includes all the crystallization methods which result in round particles with a certain size. With adequate parameters (e.g. the cooling rate, the rotation speed of the mixer, the nature of the solvent, the presence or not of seed crystals, etc.), it is possible to change the morphological properties and the crystal habit during the crystallization process, e.g. from solution, whereby spherical single crystals or crystal agglomerates can also be produced [3–8]. Löffler et al. [9,10] described a process for the manufacturing of spherical crystals of iron(II) sulfate heptahydrate. To reach of round particles and yield optimization, same and foreign ions as well as polymeric materials were used.

Iron salts for the current daily therapy of anemia are administered in coated tablet form: this allows sustained

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release, which improves the comfort of the patients (the daily dose is just one tablet) [11–13] and decreases the risk of gastric irritation (slow dissolution). Several iron salts are suitable for iron replacement (e.g. iron(II) succinate, iron(II) lactate, iron(II) fumerate, iron(II) glycine sulfate, iron(II) glutamate, iron(II) gluconate, iron(II) citrate, iron(III) hydroxide, etc.). The absorption of iron compounds is compared with that of iron(II) sulfate, as standard; its absorption is regarded as the 100% level [14]. At present, a number of medicines available on the market contain iron(II) sulfate as active agent. The methods for the preparation of iron(II) sulfate-containing medicines (e.g. wet granulation, tablet pressing and coating) are time-consuming and expensive, and the iron compounds accelerate the attrition and corrosion of the machines.

The aim of this work was to develop a simple, economic procedure for the manufacturing of coated iron(II) sulfate particles by using a cooling crystallization technique without seeding and polymeric materials for the development of round particles, followed by coating with a lipophilic material. The crystals produced are required to have a particle size mainly in the range 500–1000 μm and the coating process to ensure the sustained release of iron(II) sulfate from the lipophilic matrices. The particle size range was important because of the coating process and the dissolution rate of the iron(II) sulfate heptahydrate.

2. Materials and methods

2.1. Materials

The basic material used in the spherical crystallization was commercial iron(II) sulfate heptahydrate (Ferrosi sulfas heptahydricus, Ph. Eur. 4, Hungaropharma, Budapest, Hungary) with particle sizes of 10 μm–2 mm. Stearin (Stearinum, Ph. Hg. VII, Hungaropharma, Budapest, Hungary) was used as the coating material during the coating process.

2.2. Methods

2.2.1. Crystallization experiment

The laboratory experiment relating to the crystallization process was carried out in water by cooling in a mechanically stirred tank. A Schmizo duplicate reactor crystallizer with a volume of 0.5 L was used, equipped with a mixer, the mixing speed of which could be regulated. The crystallization process can be carried out according to different cooling programs with a Julabo thermostat connected to the set (Julabo Labortechnik, Seelbach, Germany). The saturated solution of iron(II) sulfate heptahydrate at 58 °C was used in the experiments (135 g $FeSO_4 \cdot 7H_2O$/100 g water) and the end temperature of the mother solution was 25 °C. Several batches were produced, with variation of the following crystallization parameters: agitation speed, cooling method and rate, and seeding. From an economic point of view, the crystals produced were required to have a round form and a particle diameter of 500–1000 μm (Table 1). A fivefold scaled-up experiment was executed by applying the parameters found best in laboratory experiments.

2.2.2. Coating of spherical crystals

The laboratory sample whose parameters were found to be optimal in the preliminary study was subjected to a scale-up process. One hundred grams of the iron(II) sulfate heptahydrate crystals with a diameter of 500–1000 μm was coated in a rotating steel pan, with stearin as coating material. The carrier liquid of the melted stearin was 95% alcohol. An air spray technique was used for the atomization of the liquid. The process parameters were as follows: nozzle diameter: 0.8 mm, atomization air pressure 0.1 bar, flow rate of coating liquid: 5 ml/min, coating liquid temperature: 60 °C, drying air temperature: 20 ± 2 °C and pan rotation speed: 25 rpm.

2.2.3. Determination of particle size and roundness

To determine the size and the roundness of the particles produced with the crystallization and coating processes, an image analyzer (Laborlux light microscope, Quantiment 500MC image analyzer – Leica Cambridge Ltd., Anglia) was used. Its software makes it possible to measure the diameter of the particles and also to calculate the roundness according to the following relationship:

$$\text{roundness} = \text{perimeter}^2/4\pi \cdot \text{surface area} \cdot 1.064$$

Table 1
Crystallization parameters of iron(II) sulfate samples in laboratory experiments

Sample	T_s (°C)	V_C (°C/min)	Cooling method	n (min^{-1})	Solvent
Fe/2[c]	54	0.35	Lin.	600	Tap water
Fe/3	54	1.3	Lin.	600	Tap water
Fe/4	58	1.3[a] 0.35[b]	Exp.	600	Tap water
Fe/5	58	1.3[a] 0.35[b]	Exp.	600	Distilled water
Fe/6	58	0.35	Lin.	800	Distilled water
Fe/7	58	0.35	Lin.	800	Deionized water
Fe/8	58	0.55[a] 0.2[b]	Lin.	800	Deionized water
Fe/10	58	0.28	Lin.	800	Deionized water
Fe/11[d]	58	0.17	Lin.	800	Deionized water

T_s = starting temperature, V_C = cooling rate, n = agitation speed.
[a] Between 0 and 60 min.
[b] Between 60 and 135 min.
[c] Use of seed crystal (6.0 g).
[d] +1 h mixing after the end of crystallization (15 °C).

The value 1.064 is the correction factor of the perimeter. If the roundness value is about 1, the shape of the investigated particles is approximately round. Five hundred particles were measured.

In certain cases, sieve analysis was used to determine the particle size distribution (DIN ISO 3310, Retsch GmbH and Co., Haan, Germany).

2.2.4. Stereomicroscopic study

The habits of the particles were studied with a Zeiss stereomicroscope (Zeiss KL 1500 LCD, Jena, Germany).

2.2.5. Measurement of flow time and bulk density

A volume of 100 ml from each sample was investigated to determine the flow time and bulk density (g/100 ml) with the ASTM-D (USA-standard) apparatus. Six parallel measurements were performed for each sample.

2.2.6. Thermoanalytical tests

In order to observe the physical and chemical changes occurring in response to heating, thermoanalytical investigations (TG and DTG) were performed with a MOM apparatus (MOM, Budapest, Hungary). The test parameters were as follows: mean sample mass: 50 mg, and heating rate: 5 °C/min. The studies were performed in air atmosphere.

2.2.7. In vitro drug dissolution study

Dissolution studies were performed with a Pharma Test PTW 2 apparatus (Pharma Test GmbH, Hainburg, Germany), using the paddle method, under sink conditions. The medium was 900 ml of artificial gastric fluid (pH 1.2 ± 0.1) with a temperature of 37 ± 0.5 °C. The rotation speed was 100 rpm. Samples of 5 ml were extracted at regular time intervals: 0.5, 1, 2, 3, and 4 h, and analyzed 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.

3. Results and discussion

3.1. Crystallization experiments

Cooling crystallization can be used for iron(II) sulfate because it has a large solubility variation with temperature in water and its supersaturation is generated on the decrease of temperature. Iron(II) sulfate exists in crystal forms with 1–7 molecules of water. The water solubilities of the various hydrate forms differ, and also vary with temperature [15]. Iron(II) sulfate crystals dissolved in water crystallize as the heptahydrate under appropriate circumstances. For the preparation of the heptahydrate, the cooling crystallization was also used. Different process parameters related to the cooling method, the cooling rate, the agitation speed, the type of water, and the use of a seed crystal influence the crystal nucleation, the crystal growth and the habit of the crystals (see Table 1).

Samples with different process parameters were examined in parallel for critical parameters such as the particle size and roundness value (Table 2). Our researches were started at an initial temperature of 54 °C (below the temperature of maximal saturation of the solution), with different cooling rates (0.35 and 1.3 °C/min), and with low agitation speed (Fe/2 and Fe/3). A seed crystal was also used in the case of sample Fe/2, to facilitate nucleation. The crystals produced were approximately round (Fig. 1), but the particle size distribution did not meet the requirement (500–1000 μm) (Table 2). At a higher cooling rate (Fe/3), the phases of nucleation and of crystal growth were not separated, and therefore the simultaneous appearance of more crystals was observed. In the further investigations, we used a saturated solution (referred to Fe(II)-$SO_4 \cdot 7H_2O$) (58 °C) and the other process parameters such as the cooling method and the use of distilled water or tap water were varied (Fe/4 and Fe/5). The results were disappointing. We obtained crystal agglomerates with small particle size (Fe/5) (Fig. 1).

In the following tests we returned to the process parameters used for sample Fe/2, but the initial temperature of 58 °C was retained. A 0.33 °C/min linear cooling rate was applied, the agitation speed was increased (Fe/6), and for the production of sample Fe/7 deionized water was used instead of distilled water. The change was marked. The particle diameter for sample Fe/6 was nearly 500 μm, and sample Fe/7 displayed the best roundness. Although the particle size for sample Fe/7 was on average 300 μm, the process with deionized water resulted in beautiful transparent crystals (Fig. 2) (Table 2).

The aim of other preliminary studies was to increase the particle size. The process parameters for sample Fe/7 were taken as basis and the influence of the cooling rate on the particle size was studied (Fe/8–Fe/11). Particle size distributions measured by sieve analysis and the bulk densities of the crystallized products are listed in Table 3. There were no significant differences in the samples with respect to their bulk density and roundness. Their flowability was

Table 2
Particle diameter and roundness value of iron(II) sulfate samples in laboratory experiments

Sample	Average diameter (μm) (±SD)	Roundness (±SD)
Fe/2	359 (±86)	1.45 (±0.21)
Fe/3	252 (±116)	1.50 (±0.29)
Fe/4	214 (±109)	1.46 (±0.20)
Fe/5	275 (±133)	1.49 (±0.18)
Fe/6	490 (±166)	1.32 (±0.08)
Fe/7	295 (±170)	1.20 (±0.05)
Fe/8	432 (±105)	1.46 (±0.26)
Fe/10	638 (±96)	1.32 (±0.13)
Fe/11	734 (±183)	1.21 (±0.09)

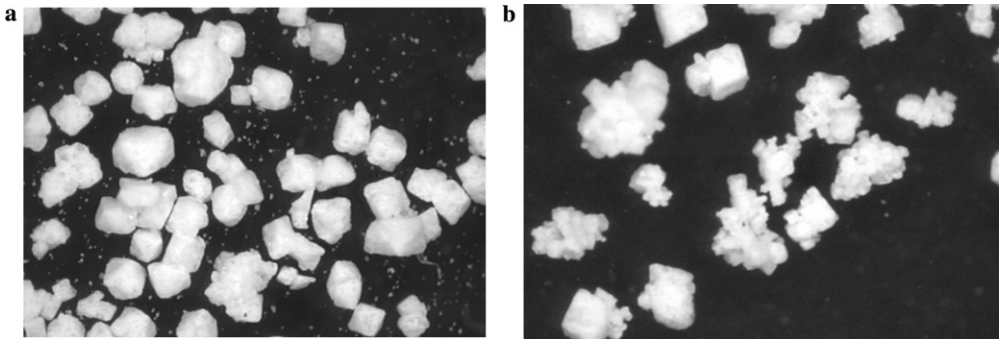

Fig. 1. Stereomicroscopic pictures of iron(II) sulfate heptahydrate samples (magnification: 1.6×). (a) Fe/2, average diameter: 359 (SD ± 86). (b) Fe/5, average diameter: 275 (SD ± 133).

indicated by the time of flow to be appropriate. Sample Fe/10 was the best as concerns the particle size distribution, but the best values for roundness, standard deviation of roundness and bulk density were given by sample Fe/11, produced with the lowest cooling rate. The results show that the low cooling rate is important parameter in the process of the crystal growth. The faster cooling resulted in a lot crystal nucleus (Fe/8) and the system had low energy for crystal growth, as follows the particle size of the crystals is smaller than that of lower cooling rate (Fe/11).

The crystal water contents of the samples produced were tested in thermoanalytical examinations and were calculated from the decreases in sample mass on heating. The water contents were determined to be: Fe/8: 6.57 mol, Fe/10: 6.88 mol, and Fe/11: 6.90 mol H_2O.

A fivefold scaled-up experiment was executed by applying the parameters found best in laboratory experiments (Fe/11). The crystallization of Fe/12 was performed in deionized water with no addition of seed crystals, and by cooling in a linear manner, at a cooling rate of 0.2 °C/min. The agitation rate was adapted to the larger scale in order to yield similar mixing to that in the laboratory experiment: it was decreased from 800 to 400 min^{-1}. The composition of the solution was 1.81 kg $FeSO_4 \cdot 7H_2O$ + 1.35 kg deionized water. The particle size distributions of the crystals produced in the best laboratory experiment (Fe/11) and in the scaled-up crystallization (Fe/12) are compared in Fig. 3. The data in Fig. 3 show that the scale-up led to an improvement in the particle size distribution. The proportion of particles in the range 500–1000 μm increased: more than 60% of Fe/12 lay in this range. Thus, the scale-up process was highly favorable with respect to the particle size. The other characteristics (mean diameter, time of flow, bulk density and roundness) of Fe/12 in comparison with Fe/11 are shown in Table 4. The flowability of sample Fe/12 did not change greatly, the bulk density decreased slightly and the roundness became slightly worse, but it was still satisfactory. However, these changes were not significant, and sample Fe/12 was given a good classification.

Table 3
Particle size distribution, bulk density and roundness of the crystallized products

No.	Particle size distribution (%)			Bulk density (g/cm^3)	Roundness (±SD)
	>1000 μm	500–1000 μm	<500 μm		
Fe/8	0.1	37.7	62.2	0.943	1.46 (±0.26)
Fe/10	1.3	64.8	33.9	0.971	1.32 (±0.13)
Fe/11	38.3	51.6	10.1	1.010	1.21 (±0.09)

The images of the commercially available iron(II) sulfate heptahydrate and that developed by means of cooling crystallization are demonstrated by stereomicroscopic pictures.

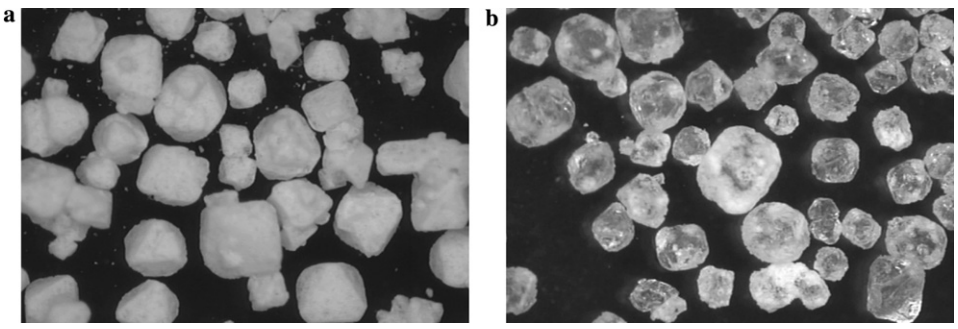

Fig. 2. Stereomicroscopic pictures of iron(II) sulfate heptahydrate samples (magnification: 1.6×). (a) Fe/6, average diameter: 490 (SD ± 166). (b) Fe/7, average diameter: 295 (SD ± 170).

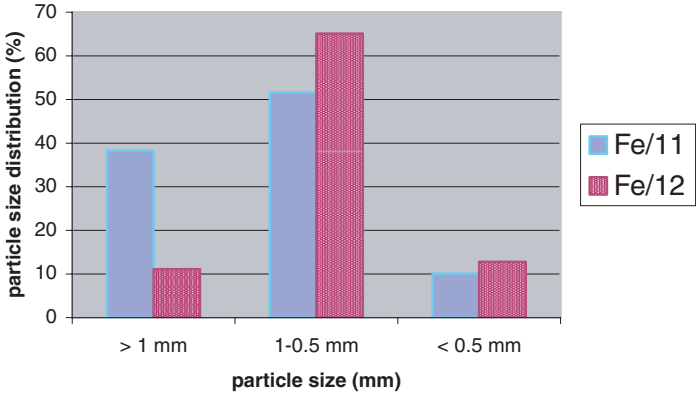

Fig. 3. Particle size distributions of samples Fe/11 and Fe/12.

Table 4
Comparison of the pharmaceutical technological parameters of samples Fe/11 and Fe/12

Sample	Mean diameter (μm)	Time of flow (s/100 cm^3)	Bulk density (g/cm^3)	Roundness
Fe/11	734 ± 183	10	1.010	1.21 ± 0.09
Fe/12	729 ± 165	8	0.994	1.32 ± 0.11

The iron(II) sulfate available on the market is very heterogeneous, and the crystal shape is diverse (Fig. 4), consequently it is unsuitable for coating process. As concerns the crystal habit, the crystals are mainly monoclinic, but orthorhombic crystals can also be found, which is in agreement with the data in the literature [16]. The crystal surfaces are white and matt, which leads to the conclusion that crystal crumbling occurs due to the effect of the atmosphere. The crystals of sample Fe/12 developed by cooling crystallization from solution are like glass, semitransparent with a sea-green colour, and approximately round. The conventional body-centered cubic structure of the crystals is transformed into a rounded, spherical form owing to the parameters of the crystallization process. Iron(II) sulfate prepared in the scaled-up experiment was used for coating experiments.

3.2. Coating experiments

One aim was to prove that the prepared spherical crystals can be coated rapidly and easily, and additionally that the coat on the particles can control the release of iron(II) sulfate. The starting material was 100 g from the 0.5 to 1 mm fraction of sample Fe/12. In one of our earlier publications, favorable results were obtained by using stearin to protect the active substance and to prolong the dissolution [17]. In this case too, therefore, stearin was chosen as coating material. The coating experiments were performed in all three cases in a steel pan with the spraying method in such a way that a constant amount of iron(II) sulfate was treated with various amounts of stearin (HPT1–HPT3).

Table 5
Properties of coated particles and uncoated iron(II) sulfate heptahydrate

	Uncoated $FeSO_4 \cdot 7H_2O$	HTP-1	HTP-2	HTP-3
Amount of stearin (%)	0	4.5	11	28
Roundness (±SD)	1.32 (±0.11)	1.27 (±0.11)	1.32 (±0.08)	1.19 (±0.05)
Average diameter (μm) (±SD)	729 (±165)	768 (±173)	782 (±172)	894 (±152)

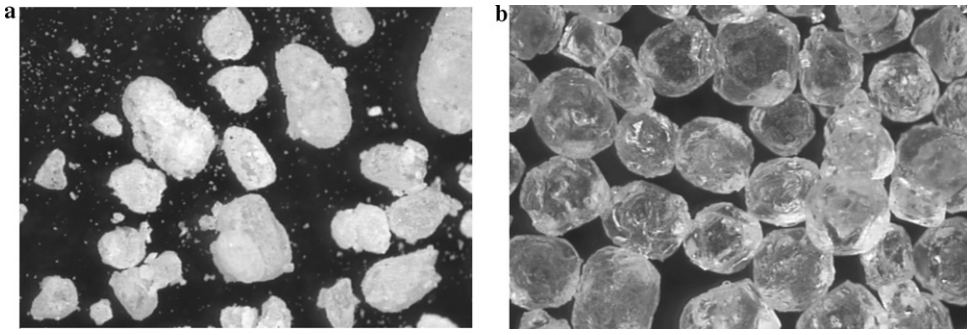

Fig. 4. Stereomicroscopic pictures of commercially available and developed iron(II) sulfate heptahydrate crystals (magnification: 1.6×). (a) Commercial product, size range: 10–2000 μm. (b) Fe/12, average diameter: 729 ± 165 μm.

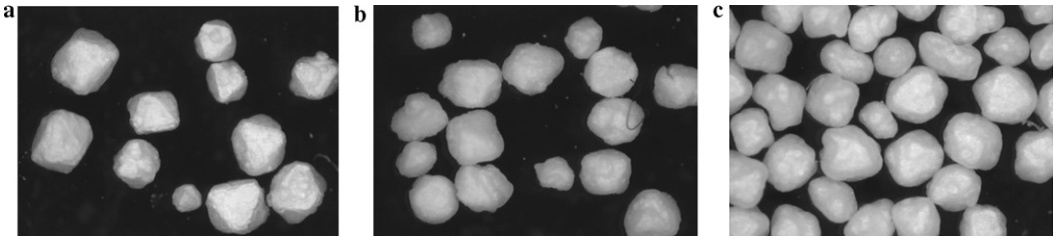

Fig. 5. Stereomicroscopic pictures of iron(II) sulfate heptahydrate crystals coated with stearin (magnification: 1.0×). (a) HPT-1, mean diameter: 768 μm. (b) HPT-2, mean diameter: 782 μm. (c) HPT-3, mean diameter: 894 μm.

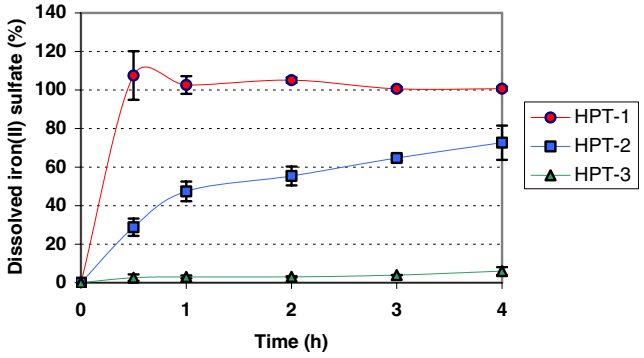

Fig. 6. In vitro drug release of coated samples into artificial gastric juice.

Table 6
Kinetic parameters of coated iron(II) sulfate heptahydrate samples

	Zero-order model	
	Rate constant (k)	Correlation coefficient (R)
HPT-1	–	–
HPT-2	−15.717	0.9685
HPT-3	−1.161	0.9524

Spraying was carried out with a solution of stearin in 95% ethanol at 60 °C. The amount of stearin, and the roundness and diameter values of the starting and the coated particles are presented in Table 5 and Fig. 5 depicts stereomicroscopic pictures of the coated samples. The rate of dissolution of the active substance from coated products in artificial gastric juice is illustrated in Fig. 6. The data on each sample are evaluated separately.

Sample HPT-1: This has a favorable roundness as compared with the roundness of the uncoated crystals. Stearin, used in an amount of only 4.5%, levels off the unevenness of particles by sticking to the surface holes but this amount is not sufficient to form an even, appropriately thick layer on the surface of the crystals. As a consequence, the release of the active substance from the sample is too fast.

Sample HPT-2: The roundness here is equal to the roundness of the uncoated crystals. For this sample, stearin applied in 11% relative to the iron(II) sulfate covers the entire surface of the particles with an evenly thick layer and does not change the shape or roundness of the crystals. The rate of dissolution of the active substance measured *in vitro* reveals the slow, properly sustained release of iron(II) sulfate.

Sample HPT-3: The roundness of the crystals has been improved (even better than the roundness for sample HPT-1), which can be attributed to the 28% of stearin used. The thick layer not only smooths the surface of the crystals, but also retards the release of iron(II) sulfate exaggeratedly under *in vitro* circumstances.

Kinetic calculations were performed on the basis of the results of the *in vitro* dissolution test (Table 6). Sample HPT-1 cannot be described as following either zero- or first-order kinetics because of the fast drug liberation. The correlation coefficients of HPT-2 and HPT-3 calculated according to the two kinetic models are similar. In view of this, sample HPT-2 can be expected to have the best form, with the sustained release of iron(II) sulfate.

4. Conclusions

The following statements can be made in connection with the spherical crystallization of iron(II) sulfate heptahydrate and the coating of the developed crystals.

Through the use of crystallization in laboratory experiments, spherical $FeSO_4 \cdot 7H_2O$ crystals were developed with a mean diameter of 500–1000 μm. The procedure is simple and rapid, and does not require a dangerous, expensive solvent. In a fivefold scaled-up experiment, particles with the desired requirements were achieved. The size and surface of the spherical crystals were suitable for coating. The coating procedure was developed for coating the surface of particles prepared with stearin. The coat produced from stearin ensures the slow release which is important because of the decrease of the gastric irritation and it protects the iron(II) from oxidation and inhibits the loss of crystal water. The rate of iron(II) sulfate release was influenced by the thickness of the stearin layer. As a result of this work, the filling of coated crystals into capsules to form the final dosage form can be proposed.

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