

The preparation and characterization of ferrous sulphate hydrates

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Ferrous sulphate BP, $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, dehydrates to form $\text{FeSO}_4 \cdot 4\text{H}_2\text{O}$ when the relative humidity (RH) is less than 65%, or on heating at 40 °C. The tetrahydrate was also prepared by recrystallization at 60 °C from aqueous solutions of the sulphate. Commercial dried ferrous sulphate BP is $\text{FeSO}_4 \cdot \text{H}_2\text{O}$ but the method of preparation given in the BP produces $\text{FeSO}_4 \cdot 4\text{H}_2\text{O}$ which is the stable form at RH < 65% (25 °C). A crystalline monohydrate was prepared either by heating the tetrahydrate on a boiling water bath to constant weight or heating the heptahydrate under vacuum at 60 °C in the presence of water vapour evolved from the water of crystallization. An X-ray amorphous form of $\text{FeSO}_4 \cdot \text{H}_2\text{O}$ was made by heating the heptahydrate at 100 °C under vacuum with the removal of water vapour. Crystalline $\text{FeSO}_4 \cdot \text{H}_2\text{O}$ rehydrates to the heptahydrate when RH > 65% but the amorphous form recrystallizes as the stable tetrahydrate at RH > 0 and < 65%. The various hydrates were characterized by DSC and X-ray diffraction. A simple procedure is described for obtaining data to construct a RH-composition phase diagram. The method combines measurement of any weight changes of each hydrate after storage at various controlled humidities together with a direct measurement of RH over the hydrate pairs. The thermal dehydration pathways are reported together with the RH-composition phase diagrams.

In a joint recommendation of the American Pharmaceutical Association and the APhA Academy of Pharmaceutical Sciences to the US Department of Health, Education and Welfare (1974), ferrous sulphate was classified in a category of drugs 'whose solid oral dosage forms it is not possible at this time to state categorically there is, or is not, a potential for bioequivalence and/or quality assurance problems that would not have serious implications for therapy'. Large differences had been reported between the dissolution rates of twelve commercial tablet formulations of ferrous sulphate (Blezek et al 1970). The differences were attributed to chemical reactions occurring between ferrous sulphate and other ingredients of the tablets, to surface adsorption of ferrous sulphate and to other formulation variables. The particular hydrate in each formulation was not stated and no reference was made to the possibility that the differences in dissolution rate may be due to rehydration during storage and/or dissolution.

Two salts of ferrous sulphate are official in the BP, ferrous sulphate, $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ and dried ferrous sulphate. According to the Pharmaceutical Codex (1979) and Martindale (1982) $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ loses 6 molecules of water of crystallization at 38 °C and the BP monograph describes dried ferrous sulphate as ferrous sulphate deprived of part of its water of crystallization by drying at 40 °C. The BP specifies 80 to 90% of FeSO_4 which corresponds to material

consisting mainly of $\text{FeSO}_4 \cdot \text{H}_2\text{O}$ plus variable amounts of higher hydrates. However, Sutherland & Mitchell (1982) showed that heating $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ at 40 °C gives the tetrahydrate and not material which consists essentially of the monohydrate as required in the BP monograph. Since various commercial samples of dried ferrous sulphate were found to be the monohydrate it is evident that the commercial material is not prepared by heating $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ at 40 °C.

Tablets and capsules containing ferrous sulphate are most often prepared using dried ferrous sulphate. This is understandable since uncoated tablets of the heptahydrate would crumble in dry air due to efflorescence and if coated the water vapour released may attack the coat. However, according to Stephenson (1965), tablets prepared using dried ferrous sulphate dissolve slowly due to rehydration of the salt with the formation of a hard cement on the surface of the tablet. In addition, rehydration produces an increase in mass of 64% and Sutherland & Mitchell (1982) showed that with uncoated tablets, made using Avicel pH 102 as a direct compression agent, the increase in mass was accompanied by an increase in volume which affected the tablet structure. Since tablets with acceptable hardness, disintegration time and dissolution time could be prepared using either the mono or tetrahydrate salts, it was suggested that the tetrahydrate may be a suitable

alternative to dried ferrous sulphate since the increase in mass on rehydration is only 24% and the volume change did not seriously affect the tablet structure.

Work on the preparation, thermal behaviour and relative humidity-composition phase diagrams of ferrous sulphate hydrates is now reported.

MATERIALS AND METHODS

Materials

Ferrous sulphate heptahydrate and dried ferrous sulphate were obtained from various commercial sources. The heptahydrate salt usually contained traces of tetrahydrate, due to efflorescence but this was readily converted back to the heptahydrate by storage at a relative humidity of 79% for 24 h. The dried ferrous sulphate was the monohydrate. Ferrous sulphate tetrahydrate was crystallized as well-formed pale green crystals from an aqueous solution of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ at 60 °C but was more conveniently prepared by heating the heptahydrate at 40 °C when the crystals lost three molecules of water of crystallization to give aggregates of microcrystalline tetrahydrate.

Thermal analysis

Thermal analyses were performed using a Perkin Elmer DSC 1B differential scanning calorimeter. Crystals were ground in an agate mortar and 1–5 mg samples were weighed on a Cahn Gram electro-balance directly into aluminium sample pans. Scans were made at between 5 to 20 °C min^{-1} using Perkin Elmer standard pans, hermetically sealed pans or sealed pans with a 0.1–0.2 mm pinhole.

A hydrate will lose water at any temperature provided the vapour pressure of water surrounding the solid is less than the equilibrium vapour pressure at that temperature. The rate of loss depends on the leakiness of the pan and other experimental conditions such as sample size, packing, and heating rate. In sealed pans, water vapour cannot escape without rupturing the pan and hence dehydration but not vaporization reactions can take place. In sealed pans with a pinhole, the pinhole permits the escape of water vapour but the rate of vapour loss becomes appreciable only when the vapour pressure within the pan is equal to the outside pressure. Vapour loss occurs over a much narrower temperature range than in an open pan and the thermogram shows a sharper endothermic peak. Hence in sealed pans with a pinhole both dehydration and vaporization reactions can take place although these do not necessarily occur simultaneously (see Results). Vap-

orization of the water of crystallization from the pans with a pinhole was estimated quantitatively by weighing the pans after each endothermic peak.

Relative humidity-composition diagram

The different hydrates were stored in desiccators over various saturated salt solutions at 25 °C to give relative humidities (RH) of 12, 33, 43, 54, 65, 68, 75, 84, and 92% (National Physical Laboratory 1958). Weight changes were measured until a constant weight was established and the hydrate present at each RH was deduced from the hydration state of the starting material and any gain or loss in weight.

The RH above mixtures of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ with various proportions of the monohydrate, or the tetrahydrate or water (saturated solutions) was determined with a Rotronic Hygroskop BT and a WA measuring station at 25 °C. The measuring station is a temperature-controlled sealed chamber fitted with a combined humidity-temperature probe. The instrument was calibrated using non-saturated lithium fluoride solutions of known RH.

After measuring the RH above each hydrate pair the composition of the mixture was checked using a Du Pont 900 thermal analyzer with a TGA module.

X-ray diffraction

X-ray diffraction patterns were determined using a Phillips wide-angle X-ray diffractometer and either Ni filtered $\text{CuK}\alpha$ or $\text{FeK}\alpha$ radiation. The location and intensity of the peaks at different values of 2θ were compared with standard values for FeSO_4 hydrates (Powder diffraction file 1981).

RESULTS AND DISCUSSION

Dehydration reactions are known to depend on water vapour pressure (Wheeler & Frost 1955; Dell & Wheeler 1965; Boldyrev et al 1979). Friesen et al (1980) and Burt & Mitchell (1980), using a Perkin Elmer DSC 1B, showed the effect of varying the experimental conditions on the thermal behaviour of nickel sulphate. In the present work on the hydrates of ferrous sulphate, a combination of standard pans, sealed pans and sealed pans with a pinhole, under both atmospheric pressure and a vacuum of –70 kPa, was used to determine DSC thermograms in the presence and absence of water vapour. Scheme 1 shows the sequence of dehydration reactions. The temperature maxima of the transition peaks are included in Scheme 1 to indicate the range obtained for a number of scans and different experimental conditions but the sequence of the peaks is of more significance than the temperatures

at which they occur. Although the peak maximum is close to the temperature where a higher hydrate is completely converted, this can occur at any temperature within the stability range of the higher hydrate.

The first transition occurred around 60 °C and was apparent as a minor endothermic peak or as a shoulder on the second peak. Peak 1 was most obvious in sealed pans and was missing from thermograms obtained under vacuum which suggests that the presence of water is necessary for the reaction. Dehydration to either the hexahydrate or the pentahydrate is the most likely reaction and although not reported in previous studies of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (Wheeler & Frost 1955; Chihara & Seki 1953; Safiullin et al 1968; Pribylov 1969) both hydrates occur naturally (Powder diffraction file 1981).

Peak 2, which occurred under all experimental conditions, is due to the formation of the tetrahydrate, either from $\text{FeSO}_4 \cdot 6\text{H}_2\text{O}/\text{FeSO}_4 \cdot 5\text{H}_2\text{O}$ or directly from the heptahydrate without the formation of an intermediate hydrate (no peak 1).

Vaporization of the water of crystallization liberated in the first two dehydration reactions gives rise to the third endothermic peak. A weight loss corresponding to 3 moles of water per mole of hydrate was confirmed by weighing the pans with a pinhole before and after peak 3. Peak 3 was absent from thermograms made using sealed pans and there was no weight loss because water vapour cannot escape. Peak 3 was also missing in scans made under vacuum using sealed pans with a pinhole since the water liberated on dehydration evaporates simultaneously and the heat of vaporization contributes to the peak 2 endotherm.

Peak 4 represents the dehydration of the tetrahydrate to the monohydrate together with the simultaneous evaporation of water of crystallization, except in sealed pans where the water vapour cannot escape and the endotherm is due to dehydration only. In sealed pans with a pinhole, a weight loss corresponding to 3 moles of water per mole of hydrate was confirmed gravimetrically by weighing the pans before and after peak 4.

Between the dehydration reaction, peak 4, and the final dehydration of the monohydrate, peak 6, there was a pronounced endothermic reaction. This was found only with the heptahydrate and tetrahydrate when using sealed pans from which the liberated water of crystallization cannot escape as vapour. Because of the high pressure, some of the water will exist in the liquid state and hence peak 5 is attributed to the heat of solution arising from partial dissolution of some of the monohydrate in the liberated water. Under the conditions represented by peak 5, three phases are present, namely, FeSO_4 , $\text{H}_2\text{O}(\text{s})$, $\text{FeSO}_4(\text{solution})$ and $\text{H}_2\text{O}(\text{g})$. Scheme 1 gives the overall dehydration pathway for $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$; $\text{FeSO}_4 \cdot 4\text{H}_2\text{O}$ undergoes reactions 4, 5 and 6 only while $\text{FeSO}_4 \cdot \text{H}_2\text{O}$ undergoes reaction 6 only.

Fig. 1 shows the RH% versus composition phase diagram for the hydrates of ferrous sulphate at 25 °C. The vertical lines were obtained from weight changes of the various hydrates under conditions of controlled humidity and the horizontal lines were obtained using the Rotronic Hygroskop to determine the RH above various mixtures of each hydrate pair and above saturated solutions of ferrous sulphate. This combination of weighing and measurement of RH provides a simple method for constructing a

Scheme 1. Dehydration of ferrous sulphate.

Peak	Range of peak maxima °C	Experimental conditions	Reaction
1	52–65	A ^a , B, C ^a	$\text{FeSO}_4 \cdot 7\text{H}_2\text{O}(\text{s}) \rightarrow \text{either } \text{FeSO}_4 \cdot 6\text{H}_2\text{O}(\text{s}) + \text{H}_2\text{O}(\text{l})$ $\rightarrow \text{or } \text{FeSO}_4 \cdot 5\text{H}_2\text{O}(\text{s}) + 2\text{H}_2\text{O}(\text{l})$
2	53–69	A, B, C, D	$\text{FeSO}_4 \cdot 6\text{H}_2\text{O}(\text{s}) \rightarrow \text{FeSO}_4 \cdot 4\text{H}_2\text{O}(\text{s}) + 2\text{H}_2\text{O}(\text{l})$ or $\text{FeSO}_4 \cdot 5\text{H}_2\text{O}(\text{s}) \rightarrow \text{FeSO}_4 \cdot 4\text{H}_2\text{O}(\text{s}) + \text{H}_2\text{O}(\text{l})$
3	80–106	A, C	$3\text{H}_2\text{O}(\text{l}) \rightarrow 3\text{H}_2\text{O}(\text{g})$
4	106–120	A, B ^b , C, D	$\text{FeSO}_4 \cdot 4\text{H}_2\text{O}(\text{s}) \rightarrow \text{FeSO}_4 \cdot \text{H}_2\text{O}(\text{s}) + 3\text{H}_2\text{O}(\text{g})$
5	150–167	B	see text
6	305–345	B ^b , C	$\text{FeSO}_4 \cdot \text{H}_2\text{O}(\text{s}) \rightarrow \text{FeSO}_4(\text{s}) + \text{H}_2\text{O}(\text{g})$

A Standard pan.

B Sealed pan.

C Sealed pan with small pinhole.

D As C but under a vacuum of -70 kPa.

^a Not always present; may occur as a shoulder on the second peak.

^b Liberated water not released from pan.

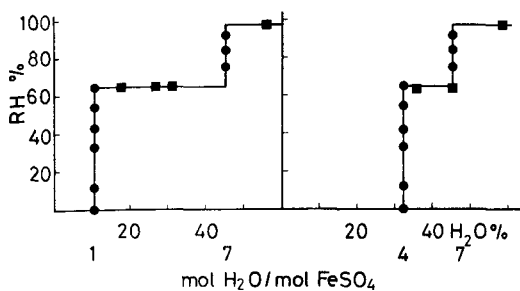
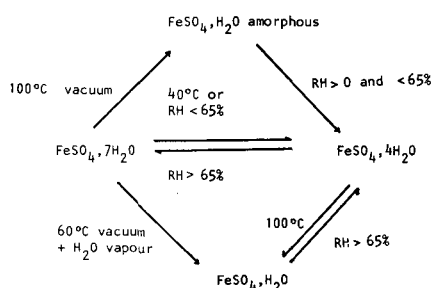


FIG. 1. Relative humidity-composition phase diagram of ferrous sulphate at 25 °C. ● mol H₂O/mol FeSO₄ determined from weight change; RH controlled by saturated salt solution. ■ RH measured using Rotronic Hygroskop; % water in hydrate pair by TGA. (Determination of the % water in the hydrate pair is not essential; the locus of the horizontal line is given directly by the Rotronic Hygroskop.)

RH-composition phase diagram of hydrated drugs.

The heptahydrate is stable above RH 65% and dehydrates reversibly to the tetrahydrate at RH less than 65%. The tetrahydrate is stable up to RH 65% and, at 25 °C, does not dehydrate to the monohydrate even in a desiccator over calcium chloride or under vacuum. Dried ferrous sulphate remains as the monohydrate up to RH 65% and then rehydrates to the heptahydrate through the intermediate formation of the tetrahydrate as confirmed by X-ray diffraction. At no RH is the monohydrate in equilibrium with the tetrahydrate and therefore, at 25 °C, the monohydrate is a metastable form.

Scheme 2. Ferrous sulphate phase changes.



Although the method given in the current BP for making dried ferrous sulphate from ferrous sulphate is incorrect, correct procedures were given in the 1898 BP and in the 1926 USP. The USP method involves heating the heptahydrate at 40 °C, which gives the tetrahydrate, and then heating on a boiling

water bath to constant weight. X-ray diffraction analysis confirmed that the reaction product was the crystalline monohydrate. A crystalline monohydrate was also made by heating the heptahydrate under vacuum at 60 °C in the presence of water vapour liberated by the dehydration reaction. However, heating under vacuum at 100 °C with the removal of water vapour gave a product showing no X-ray diffraction lines using CuK α radiation. All other hydrates of ferrous sulphate, both commercial and prepared in the laboratory gave intense diffraction lines using a Cu target but CuK α radiation is less than ideal for ferrous salts since the X-rays have a wavelength of 1.54 λ which is just below the absorption edge of Fe (1.74 λ) and results in a high background intensity. Hence the X-ray analyses of the monohydrate were repeated using FeK α radiation which confirmed that the material obtained by dehydration at 100 °C under vacuum in the absence of water vapour is X-ray amorphous. The importance of checking the X-ray results using a FeK α target was illustrated by the observation that FeSO₄·H₂O prepared by heating FeSO₄·7H₂O at 60 °C under vacuum with the removal of water vapour appeared amorphous to CuK α radiation but on repeating the analysis using FeK α radiation was found to contain some crystalline FeSO₄·H₂O plus traces of FeSO₄·4H₂O. The DSC thermogram of the amorphous material was identical to that of the crystalline monohydrate (i.e., showing peak 6 only) and the weight loss corresponded to the loss of one mole of water per mole of hydrate. Brief exposure of the amorphous material to atmospheric moisture (e.g. RH 43% for 10 min) led to the appearance of two marked exothermic reactions in the thermograms at between 96–146 and 146–165 °C. These presumably represent transitions from the amorphous monohydrate to the crystalline monohydrate and to the crystalline tetrahydrate. The amorphous FeSO₄·H₂O was stable at room temperature in the absence of water vapour but the characteristic tetrahydrate diffraction lines appeared within 20 h on storage at RH 43%. This is in marked contrast with the behaviour of crystalline FeSO₄·H₂O which does not rehydrate until RH exceeds 65%. Conditions for the various dehydration and rehydration reactions are summarized in Scheme 2. Amorphous FeSO₄·H₂O was more sensitive to atmospheric oxidation than the crystalline monohydrate. A colour change from brown to yellow was obvious within minutes at RH 68% and basic ferrous sulphate hydrate, H₂OFe₃(SO₄)₂(OH)₅·H₂O was detected by X-ray analysis after storage at RH 68% for one day.

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