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Aspects of the Influence of Magnesium Ions on the Formation of Calcium Oxalate

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Summary. The influence of magnesium ions on the solubility and formation of calcium oxalate was studied. Both calcium oxalate mineral constituents of urinary calculi (whewellite and weddellite) were prepared in the presence of Mg^{2+}-ions. For preparation, a gel growth technique and precipitation in aqueous solutions were used. The metastable weddellite formed only when Mg^{2+} concentration, reaction, temperature and precipitation velocity (see text) were combined in the proper way. It is concluded that Mg^{2+}ions may induce an increase of solubility of calcium oxalate but in contrast also broaden the Ostwald-Miers range, thus favouring the formation of larger crystals.

Key words: Urinary calculi, Magnesium influence, Calcium oxalate, Solubility.

INTRODUCTION

The existence of calcium oxalate as one of the main constituents of urinary calculi (10, 13) explains the great interest in factors influencing the formation of this compound.

Since Hammersten (5) described the effect of magnesium salts on the solubility of calcium oxalate, different opinions have been expressed on the role of magnesium in the crystallisation process. An increase of solubility (1, 4, 5, 7, 11), a decrease of crystal growth rate (2) and an effect on the formation of different calcium oxalate modifications (whewellite and weddellite) (8) have all been reported.

The present study deals with the interpretation and consideration of the effects of Mg^{2+} ions on the solubility and formation of calcium oxalate.

MATERIAL AND METHODS

The following materials were used: $CaCl_2$ dihydrate, $MgCl_2$ hexahydrate, ammonium oxalate monohydrate $(NH_4)_2C_2O_4 \cdot H_2O$ oxalic acid dihydrate $H_2C_2O_4 \cdot 2\,H_2O$, (all of analytical grade) and bromoscresol green indicator (pH 3.6-5.4). All the above chemicals were supplied by Merck AG, Darmstadt (West-Germany) and natural gypsum ($CaSO_4$ dihydrate) was obtained from the collection of minerals of the mineralogical institute of the Free University of Berlin. Sodium meta silicate pentahydrate ($Na_2SiO_3 \cdot 5\,H_2O$) (chemical grade) was supplied by Carl Roth OHG, Karlsruhe (West Germany). The H^+ form of the ion exchange resin: Dowex 50W x 16 (50 - 100 mesh), and the oxalate form of the resin: Dower 1 x 16 (200 - 400 mesh) were supplied by Fluka AG, Buchs (Switzerland).

Since urinary calculi form in supersaturated solution, methods depending on this principle were used. Both a precipitation method and a crystal growth in a gel system were used because of their separate advantages.

The diffusion controlled method of crystal growth in gels, because of gel properties (i.e. pore size, communication of pores, inactivation of heterogeneous nuclei (dust particles) by incorporating them into the gel structure) results in fewer, more perfect and larger crystals than those obtained by the precipitation method (6).

The main disadvantages of the crystal growth method in gels are the relatively long times necessary to produce products and the difficulty in control of parameters such as pH and additives during the reaction. For example pH is only easily controlled as long as gel formation has not taken place. These disadvantages suggest a preference for the precipitation method despite the smaller and less perfect crystals.

In addition it was necessary to vary the time in which supersaturation was reached (precipitation velocity) in order to produce weddellite and this is easily achieved with the precipitation method.

Since temperature is a main factor in crystal production, temperature control was carried out by means of either a water bath or an electric drying oven.

Straight glass tubes 2.5 cm in diameter and 20 cm in height were used for the growth in gels. The tubes were filled to 10 cm with "sodium-free" silica gel. This gel was prepared with the aid of an ion exchange resin. 8.5 g $Na_2SiO_3.5\,H_2O$ was dissolved in 50 ml of distilled water and treated with a sufficient quantity of kationic exchange resin (e.g. 50 g of Dowex 50 W x 16) until a pH of approximately 4 was achieved. Before gelling, calcium or oxalate supplying compounds (see Table 1) were added to the solution or in the case of gypsum crystals and ion exchange resin supplying $C_2O_4^{2-}$ ions (Dowex 1 x 16) the solution was carefully poured on top of them so that they remained on the bottom of the glass tubes. After gelling, either calcium or oxalate ions (see Table 1) were allowed to diffuse from a supernatant solution into the gel. "Sodium free" silica gel was used to study the influence of Mg^{2+} ions without disturbance by other uncontrollable additives.

Before adding a supernatant solution, gels were stored for 48 h to allow gelling. During gelling pH alteration was studied by means of an indicator (bromocresol green included in the gel). When gelation was complete the pH was between 5 and 6 which is comparable to normal urine pH.

The formation of acids (either H_2SO_4 or HCl as co-products of the calcium oxalate formation was inevitable. In spite of this, the gel-incorporated indicator showed only a slight pH alteration during reaction period (i.e. in the reaction area the pH was between 4 and 5).

During the reaction the glass tubes were stored in an electric drying oven at 37 ± 1°C.

Table 1 indicates the reactants for the calcium oxalate formation in "sodium free" silica gel. The reactants were incorporated in the gel or dissolved in a supernatant solution.

Crystals were seen after 1 1/2 to 2 days in the gel. They were allowed to grow for approximately 5 weeks and then harvested, washed with distilled water and dried in an electric drying oven at 37°C. The products were identified by X-ray diffraction as $CaC_2O_4.H_2O$ (whewellite) in all cases. Studies by electron microscopy (EM) showed that an increase of concentration of the reactants favoured twinning and an increase of the concentration of Mg^{2+}ions had the same effect.

Precipitation was carried out at 100°C by adopting the method described by Treadwell (12) because at ambient temperature $CaC_2O_4.3\,H_2O$ will form. 0.1 molar $(NH_4)_2C_2O_4$ solution was added dropwise to a $CaCl_2$-solution (1 g $CaCl_2$. 2 H_2O in approximately 150 ml H_2O plus a spatula tip of NH_4Cl). The Mg^{2+} ions were added to the $CaCl_2$ solution as $MgCl_2.6\,H_2O$. The conditions and results for the precipitation at 100°C are shown in Table 2.

The approximate size of the crystals was investigated by EM. The two extremes are shown in Figs. 1 and 2. By X-ray diffraction identification it became evident that only whewellite had formed.

Another series of precipitation experiments was carried out to obtain weddellite. Precipitation conditions were varied in two ways: firstly the velocity of adding the $(NH_4)_2C_2O_4$ solution (precipitation velocity, see above) and secondly temperature. Table 3 gives the conditions and results of these experiments. Fig. 3 shows weddellite obtained by precipitation. In these experiments temperature was controlled by means of a water bath.

Table 1. Reactants for the formation of calcium oxalate in gels. (Specification is given in material section). The resulting product was identified as whewellite

Calcium supply	Oxalate supply
$CaSO_4.2H_2O$ (Gypsum)	$H_2C_2O_4$, ion exchange resin ($C_2O_4^{2-}$ form)
Ion exchange resin (H^+ form)	Ion exchange resin ($C_2O_4^{2-}$ form)
Ca Cl_2	$H_2C_2O_4$, $(NH_4)_2C_2O_4$.
$CaCl_2$ + $MgCl_2$ molar ratio 10:1	$(NH_4)_2C_2O_4$
$CaCl_2$ + $MgCl_2$ molar ratio 3.3:1	$(NH_4)_2C_2O_4$
$CaCl_2$ + $MgCl_2$ molar ratio 1:1	$(NH_4)_2C_2O_4$

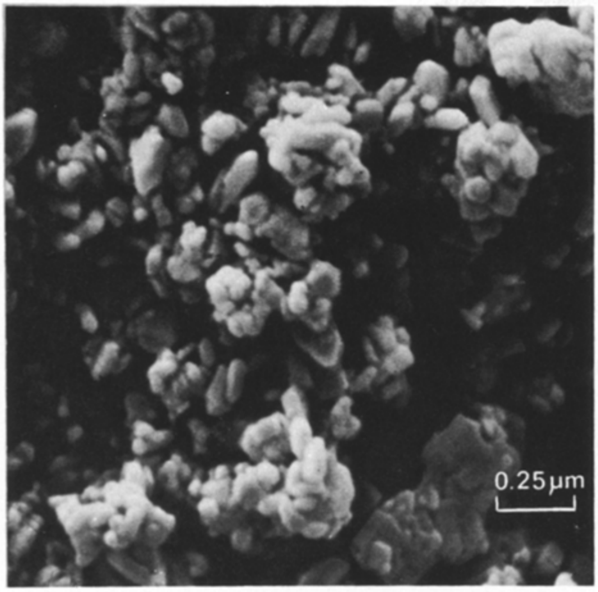

Fig. 1. Precipitate at a Ca^{2+}: Mg^{2+} molar ratio of 1:0 (EM)

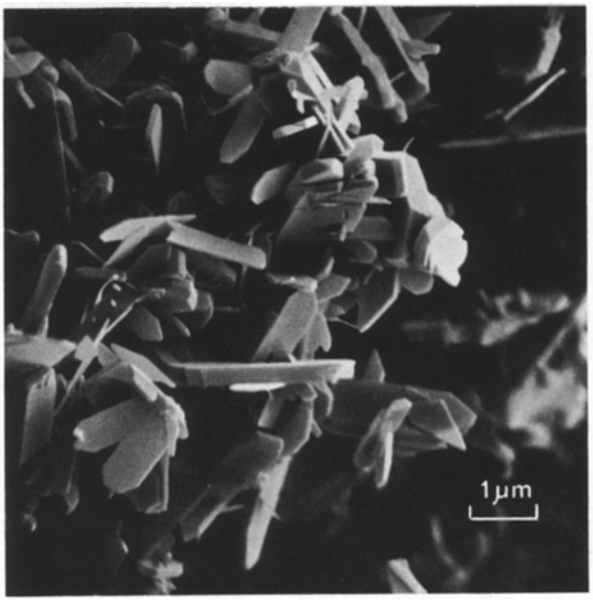

Fig. 2. Precipitate at a Ca^{2+}: Mg^{2+} molar ratio of 1:10 (EM)

Table 2. Conditions and results for the calcium oxalate precipitation at 100°C. The $(NH_4)_2C_2O_4$ solution was added dropwise. The resulting product was identified as whewellite

Ca^{2+}: Mg^{2+} molar ratio	Turbidity following addition of increasing ml $(NH_4)_2C_2O_4$ solution	Approximate particle size
1:0	immediately	ca. 0.3 μm
10:1	immediately	ca. 0.3 μm
7.5:1	ca. 5 ml	ca. 0.4 μm
5:1	ca. 5 ml	ca. 0.4 μm
2.5:1	ca. 10 ml	ca. 0.5 μm
1:1	ca. 20 ml	ca. 0.8 μm
1:2.5	ca. 30 ml	ca. 1.5 μm
1:5	ca. 40 ml	ca. 2.0 μm
1:7.5	ca. 40 ml	ca. 2.5 μm
1:10	ca. 50 ml	ca. 2.5-3 μm

Table 3. Conditions and results for the calcium oxalate precipitation following varying of temperature, precipitation velocity and Ca^{2+}: Mg^{2+} molar ratio. ("Fast" means direct mixing of the reactant solutions)

Ca^{2+} : Mg^{2+} molar ratio	Precipitation velocity	Temperature	Product
1:0	fast	30°C	whewellite
1:1	dropwise	30°C	whewellite
1:2.5	dropwise	30°C	whewellite
1:2.5	fast	30°C	whewellite & weddellite
1:2.5	fast	100°C	whewellite

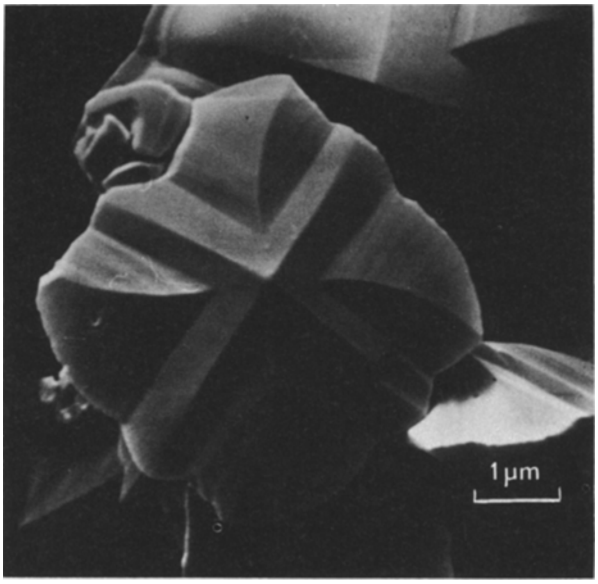

Fig. 3. Weddellite obtained by precipitation (EM)

RESULTS AND DISCUSSION

Whewellite was obtained by crystal growth in gels and by precipitation. Weddellite did not occur in the presence of Mg^{2+} ions but did so when temperature and precipitation velocity were varied (Tables 2 and 3). So the presence of Mg^{2+} ions could not be the main factor governing the formation of weddellite (1) and there must be other factors. As temperature variation can obviously have no influence on the formation of urinary calculi in vivo the variation of renal excretion of the critical ions (Ca^{2+}, $C_2O_4^{2-}$) and of water (i. e. the time to supersaturation) may have an influence on the formation of the two calcium oxalate minerals contained in urinary calculi.

The other point concerns the increase in solubility of calcium oxalate induced by Mg^{2+} ions. Table 2 gives two kinds of information on the formation of calcium oxalate in the presence of Mg^{2+} ions: With increasing Mg^{2+} concentration there is an increase of $(NH_4)_2C_2O_4$ solution required before crystallites form. But in addition the crystal size of the product increases (EM investigation, Figs. 1 and 2).

Results from both experimental models are consistent with the concept of crystal growth in disperse media where the number of nuclei is governed by nucleation energy. This varies for homogeneous and heterogeneous nucleation respectively. In other words nucleation rate and growth rate depend on supersaturation but are affected by additives (such as Mg^{2+} ions) so that the Ostwald-Miers (metastable) range is affected.[1]

Formed nuclei may have difficulties in growing to macroscopic crystals because of surface adsorption of the additives. They may even dissolve again more easily because of induced surface defects so that the number of formed crystals decreases but their ultimate size increases because of the unaltered amount of supersaturation. This increase of ultimate crystal size is obvious from Table 2 and Figs. 1 and 2.

Desmars and Tawashi (3) have undertaken growth rate studies of calcium oxalate in physiologically normal saline (0. 9% NaCl) which was buffered to the desired pH and under the influence of Mg^{2+} ions and pH. They found that "the presence of magnesium and acidic pH significantly prolonged the lag time between bringing the 2 reactants together and the appearance of crystallites in the growth medium. They suggested that this happened because of surface adsorption of Mg^{2+} ions in the surface monolayer of calcium oxalate.

What happens to seed crystals present in the growth medium during the lag time? If there is an increase of solubility of calcium oxalate dependent on Mg^{2+} concentration the seed crystal should dissolve or at least stop growing.

Meyer and Smith (9) reported that Mg^{2+}ions in normal urine concentration (molar ratio Ca^{2+}: $Mg^{2+} \sim 1:3$) did not inhibit the growth of seed crystals in buffer solutions but in normal urine growth was inhibited.

The results of the growth studies reported (Table 2) are consistent with the above results. The increase of $(NH_4)_2C_2O_4$ solution consumption necessary to produce calcium oxalate crystals under the influence of Mg^{2+}ions might be explained by surface adsorption of Mg^{2+} on calcium oxalate surfaces, thus decreasing growth rate by inactivating surfaces and decreasing the number of formed crystals by inactivating formed nuclei. Nevertheless the rate of supersaturation remains unaffected so that seed crystals or other particles acting as crystallisation bases may increase in volume.

It is concluded that Mg^{2+} ions do not increase the solubility of calcium oxalate but instead broaden the Ostwald-Miers range. In this light the administration of magnesium salts seems to be inadequate prophylaxis against calcium oxalate urinary calculus formation.

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[1] Ostwald-Miers (metastable) range is the space between the saturation curve and the spontaneous nucleation curve in a saturation-temperature diagram. Within this range nucleation does not take place but seed crystals can grow because of supersaturation. The breadth of the Ostwald-Miers range depends mainly on nucleation energy. This may be varied by chemical additives or by impurities (e. g. dust particles which may serve as heterogenous nuclei)

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