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Kinetics of dissolution of calcium oxalate monohydrate in the presence of Hydrothiazide and Furosemide

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Abstract:
Dissolution rates of calcium oxalate monohydrate (COM) were studied in the presence of Furosemide (Fm) and Hydrothiazide (Hz). Experiments were carried out at pH=6.5, t= 37 ºC, ionic strength =0.15 mol.dm^{-1} and degree of under-saturation (σ) = 0.09. The results revealed that the inhibition followed surface controlled mechanism. The retardation effect followed the sequence Fm> Hz.

Keywords: Human stones, COM, Hydrothiazide, Furosemide, Kinetics

1. Introduction

The nucleation, growth and dissolution of crystals are of particular importance in biological systems, specially, calcium containing salts which are the major mineral components [1-4].

The formation of stones in urinary tract is one of the oldest diseases suffered by humans. Calcium oxalate mono-hydrate, calcium oxalate dehydrate are the major constituents of urinary stones since urine is usually supersaturated with respect to them. Calcium oxalate is the major inorganic component of kidney stones kidney stone disease is a common chronic disorder in humans with the majority of stones being primarily composed of calcium oxalate monohydrate (COM) Crystals, which is the most thermodynamic stable from of calcium oxalate.$CaO_x.4H_2O$ (COM) used as water proofing material for concrete constructions [1,2].

The study of urinary chemistry with respect to stone forming minerals provides a wealth of information on the risk of renal Calculi formation. Super-saturation of calcium oxalate in the urine is responsible for the formation of calcium oxalate stones. The major part of urinary oxalate is derived from endogenous synthesis, while adsorption of dietary oxalate accounts for only a minor part of the urinary excretion. The increase in urinary excretion may be attributed to oxalate synthesis from orally administered ethylene glycol by the oxalate synthesizing enzymes in liver and kidney. In normal urine, the ratio of calcium to oxalate is usually equal molar or greater than 5 : 1 (Calcium and oxalate). Since the stiochimetric relationship between calcium and oxalate in various crystal habits of calcium oxalate is 1 : 1, increase in urinary excretion of oxalate have a greater effect on crystalline mass than the increase in excretion of calcium. Hence, any therapeutic agent that can decrease the urinary excretion of oxalate retards inhibits the formation of calcium oxalate stones within the urinary tract [1,2].

Furesemide (FM); 5. (aminosulphonyl) – 4 – chloro 2 – [(2 – fumyl – methyl) amino] benzoic acid, which drug is a loop diuretic that is used or ally in the treatment of edematous states associated with cardiac, renal and hepatic failure and the treatment of hypertension [5]. Hydrochloro thiazide (HZ) is a diuretic drug of thiazide class that acts by inhibiting. Hz is calcium – sparing diuretic, meaning it can help the body get rid of excess water while still keeping calcium. It is also used for treatment of congestive heart failure, symptomatic edema, and diabetes in sipidus, renal tubular acidosis and the prevention of kidney stones [6]. Thiazides increase the re-absorption of calcium by reducing (Na) re-absorption in kidney. Hydrochlorothiazide may be used to mask use of performance – enhancing drugs and is classed by "world Anti Doping Agency as a specified substance".

In the present study, the effect of hydrochlorothiazide (Hz) and Furosemide (FM) on the mechanism of dissolution of COM crystals using constant composition method were studied at pH=6.5, t= 37 ºC, ionic strength =0.15 mol.dm^{-1} and degree of under-saturation (σ) = 0.09 .

2. Experimental

2.1. Materials

Calcium chloride, sodium oxalate, sodium chloride, were made from analytical grade reagents (Fisher scientific company). A definite weighed of the salts were dissolved in a volume of deionized distilled water equal to 40 % of the final volume. The solutions were then filtered through pre-washed Millipore filter pads (0.22 ml, Millipore filters), quantatively transferred to grade volumetric flasks and diluted to the volume using de-ionized distilled water. The prepared solutions analyzed through cation exchange resin (Dowex – 50).

Hydrochlorothiazide (10^{-3}M) was prepared by dissolving suitable weight in hot water. Furosemide solution prepared by dissolving the calculated weight in small amount of ethanol till complete dissolving then the suitable volume completed using distilled water.

2.2. Preparation of seed:

COM seed crystals prepared as pervious [3] and the seed prepared was examined using XRD, FTIR, SEM, TGA and SSA.

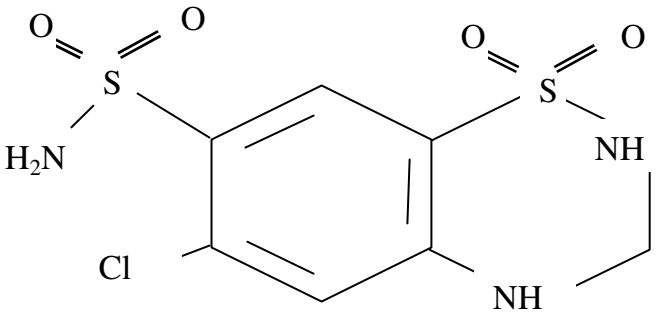
2.3. Techniques:

Dissolution experiments were carried out in double walled glass vessel thermo-stated at 37° ± 0.05 °C. The vessel contents were stirred in presence of N_2 gas bubbling to exclude atmospheric CO_2.

3. Results and discussion:

The effect of FM and Hz on the mechanism of dissolution of COM crystals are studied at 37°C, I = 0.15 mol.dm^{-3}, pH = 6.5 using seeded method and for comparison, the effect of lasix (solution) drug on the mechanism of dissolution of COM crystals was studied.

Table (1) shows the effect of different concentrations of (Hz) on the rates of dissolution of COM crystals at the experimental conditions and T_{Ca}^{2+} : T_{Ox}^{-2} = 1 : 1. The results revealed that: (i) Increasing the concentration of (Hz) led to decreasing the rate of dissolution of COM crystals. (ii) The concentration as low as 10^{-6} mol.dm^{-3} reduced the dissolution rate of COM crystals by at least 35.7 % compared to that in the absence of Hz at the same relative under-saturation (σ = 0.09)



(Hz)

Table (2) and Fig. (1) illustrated the effect of different ionic strength (I = 0.01 – 0.3) on the rates of dissolution of COM crystals at the same experimental conditions.

Table (1): Effect of FM on the dissolution of COM crystals at σ0.09, t=37°C, I=0.15 mol dm^{-3}, pH=6.5 using using pH-state method

$R/10^{-7}$	$1/C / 10^{6}$	R_0/R_0-R_1	$R_1/10^{-9}$	%
2	5	1.975	8.885	50.63
2.5	4	1.779	7.881	56.21
3	3.3	1.64	7.0236	60.97
4	2.5	1.485	5.878	67.34
5	2	1.370	4.8608	72.99
6.7	1.5	1.285	3.9918	77.82
10	1	1.119	1.914	89.37
20	0.5	1.08	1.3332	92.59
100	0.1	1.01	0.1782	99.001

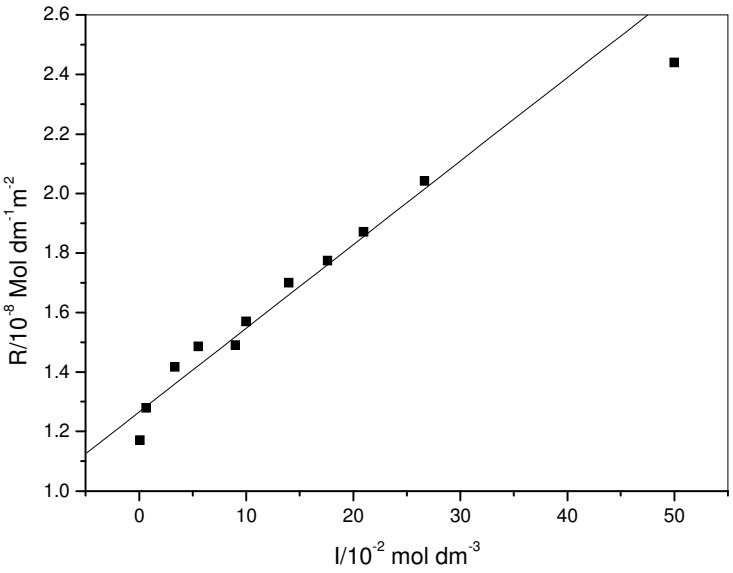


Fig.1: Effect of change of ionic strength on the rate of dissolution of COM in the presence of 10^{-6} M Hz at 37ºC

Examination of Fig. 1showed that the order approximately equals two. This order suggested that the reaction followed surface controlled mechanism. Anions of the additive molecule slow down the rate of dissolution of COM crystals by adsorption on mineral surface in competition with oxalate ions reducing thus the number of empty sites to receive dissolving lattice oxalate anions. The same case occurs in case of cationic part of the additive which will adsorb at Ca^{2+} active sites in competition, with calcium ions. In this case of inhibition, it might be expected to be highly sensitive to the nature (morphology) of the exposed crystal surface which decreased the rate constant

Table (2):Effect of change of ionic strength on the rates of dissolution of COM crystals in the presence of 10^{-6}M(Hz) at 37^{o}C.

R/10^{-8} Mol dm^{-1}m^{-2}	I/10^{-2} mol dm^{-3}
1.17	0.1
1.19	1
1.31	5
1.38	7
1.49	9
1.57	10
1.7	14
1.88	16
1.99	20
2.22	25
2.44	50

Tables 3 and 4 illustrated the effect of change of pH of the medium on dissolution of COM crystals at experimental conditions in the absence and the presence of Hz. Examination of Tables 3 and 4 revealed that: (i) Hydrochloro- thiazide (Hz) was good inhibitor for dissolution of COM crystals in basic medium). This might be due to adsorbion of Hz on Ca^{2+} active sites blocking them which leading to decrease the dissolution rates of COM crystals. The concentrations of Hz that could inhibit the dissolution process indicate that this inhibitor is effective and that of low surface coverage. We can notice that when the concentration of Hz increased the rates of dissolution decreased due to blocking the active sites on the crystal surfaces by the Hz.

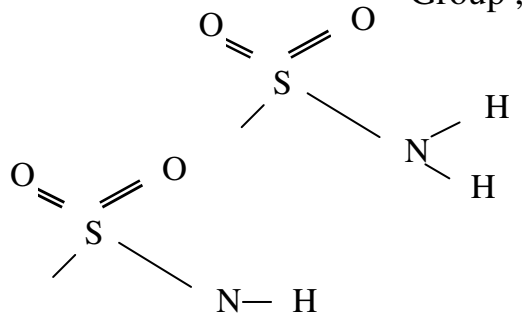
Table (3): Effect of change pf pH on dissolution, rates of COM crystals at σ = 0.09, 37°C, I = 0.15 : mol.dm^{-3}, T_{ca}^{2+} : T_{ox}^{2-} = 1:1 using pH-state method.

pH	R/10^{-8} mol min^{-1}m^{2}
2.5	4.690
3	3.778
3.5	3.450
4	3.138
4.5	2.880
5.5	2.347
6.0	2.073
6.5	1.800
7	1.569
7.5	1.353
8	1.137
8.5	0.951
9	0.763
9.5	0.577
10	0.416
10.5	0.284
11	0.187
12	0.058

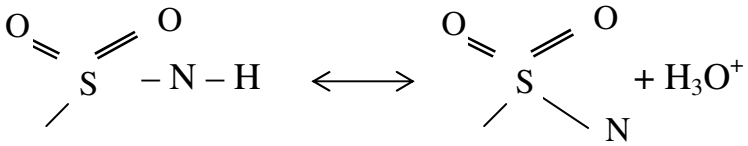
Table (4): Effect of change of pH on dissolution rates of COM crystals in the presence of 10^{-6} mol.dm^{-3} Hz at σ=0.09 , t=37^{o}C, I=0.15 mol.dm^{-3} using pH-state method.

pH	R/10^{-8} mol min^{-1}m^{2}
4.5	0.928
5	1.040
6	1.125
6.5	1.157
7.5	3.010
8	6.086
9	2.272
9.5	1.802
10	1.545
10.5	1.493
11	1.390
12	1.099

Group ,



increasing of inhibition of Hz with basisty of mediun in this study ruled out the role of last groups in inhibition process.



Our previous work [3, 8-10] indicated that the presence of basic groups in additive molecules increased inhibitory effect of it in crystallization and dissolution of COM additives. Also, small molecular weigh, flexible, hydrophilic and containing polar functional groups are good inhibitor [3, 11]. Negatively charged macromolecules as THP inhibit growth and aggregation of calcium oxalate ions occur through calcium ions [12.13].

Fig. 2 showed linearity with intercept equal to unity which suggested that the adsorption of Hz on the COM crystal surface follows Langmuir isotherm with relatively high affinity, but the number of adsorption sites

is small. COM surface has centers of positively and negatively charged ions there fore the solute molecules might be accommodated on the surface of the seed crystals. It was appeared that Hz molecules adsorb onto specific sites of the surface.

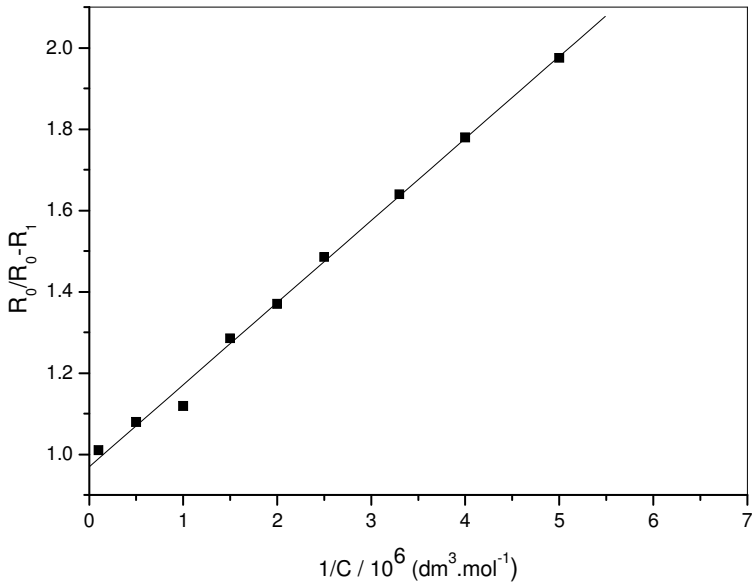


Fig. 2: Plots of R_0/R_0-R_1 against $[Hz]^{-1}$ of dissolution of COM

The validity of application of Langmuir isotherm proved surface controlled mechanism and rule out the adsorption of (Hz) molecules at Ca^{2+} active sites, blocking them decreasing their numbers i.e decreasing the dissolution rates of COM crystals [14].

Table (6) showed the effect of Furosemide (FM) on the dissolution rates of COM crystals at $\sigma = 0.09$, t = 37°C, I = 0.15 mol.dm^{-3} using seeded method. From the results, it can be found that concentrations as low as 10^{-6} mol dm^{-3}. The percentage of inhibition was 89.3%. The effectiveness of low concentration of FM ruled out the adsorption of FM molecule on the surface active sites, blocking them reducing the dissolution rates of COM crystals.

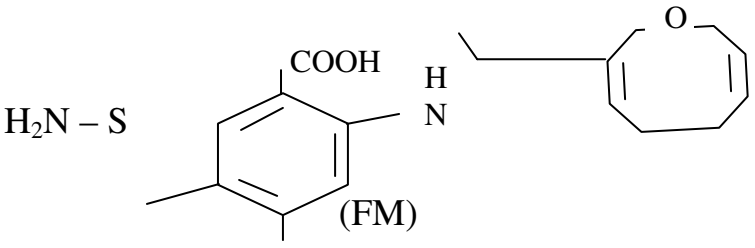
Table (5): values of $R_0/ (R_0 – R_1)$ and $[additive]^{-1}$ for dissolution of COM crystals at 37°C, σ=0.09, I=0.15 mol dm^{-3} and pH = 6.5 in the presence of Hz

$C/10^{-7}$ mol.dm^{-3}	$1/C/10^6$	R_0/R_0-R_1	$R_1/10^{-8}$ mol dm^{-1} m^{-2}
1	10	16.99	1.69387
2	5	10	1.61982
2.5	4	8.3	1.58296
4	2.5	5.5	1.47256
5	2	4.7	1.41686
6.5	1.5	3.7	1.31337
10	1	2.8	1.157014
20	0.5	1.92	0.8624
100	0.1	1.2	0.29997

Table (6): Effect of FM on the dissolution of COM crystals at σ=0.09, t=37°C, I=0.15 mol dm^{-3}, pH=6.5 using using pH-state method

$R/10^{-7}$	$1/C / 10^{6}$	R_0/R_0-R_1	$R_1/10^{-9}$	%
2	5	1.975	8.885	50.63
2.5	4	1.779	7.881	56.21
3	3.3	1.64	7.0236	60.97
4	2.5	1.485	5.878	67.34
5	2	1.370	4.8608	72.99
6.7	1.5	1.285	3.9918	77.82
10	1	1.119	1.914	89.37
20	0.5	1.08	1.3332	92.59
100	0.1	1.01	0.1782	99.001

Furosemide is an organic anion transport which is responsible for secreting acidic substance [15].



From the molecular structure, we can suggest that FM molecule will be adsorbed on Ca^{2+} active sites through electrostatic attraction. So, we can suggest that the inhibition of dissolution of COM in presence of FM was more pronounced than that in presence of Hz. This might be due to molecular weight, flexibility, basisty and hydrophilicty. As increasing the molecular size of the additive may laying on the crystal surface preventing adsorption of another molecules so decrease inhibitory effect of the additive [3]. Also there are some another factors which affect an the inhibition action of the additives: (i) Ratio of its charge to the mass; when the charge is greater than the mass, it will be good inhibitor. (ii) Iso-electric point; when it is small, the inhibition increase.

$$\frac{R_0}{(R_0 - R_1)} = \frac{1}{1 - b} + \frac{K_{ads}}{K_{des}\,(1-b)} \cdot \frac{1}{C} \longrightarrow (1)$$

Where R_0 and R_1 are the rate of dissolution in the absence and the presence of additive, respectively. The value of constant "b" is such that $0 < b < 1$

while the ratio $\frac{K_{ads}}{k_{des}} = K_L$ is called affinity constant of the inhibitor

As indicating from eq. (1) plotting against $\frac{1}{C}$ $\frac{R_0}{(R_0 - R_1)}$ for the substrate and [additive]$^{-1}$ should be linear plots and the value of "K_L" for the additives tested may obtained (The inverse of the slope of line) = 5.263×10^6 $dm^3.mol^{-1}$ only as phenomenological measure of the affinity of adsorbents for the substrate. Plot of $R_0/(R_0 - R_1)$ for FM illustrated in Fig. 2 From the results, linear relationship and intercept of one, indicated the adsorption of FM molecules on the Ca^{2+} active sites in competition wit OX^{2-} anions at crystal surface. Adsorption of FM molecules reduced the number of Ca^{2+} active sites on COM surface, loading to decrease of dissolution of COM crystals in the presence of FM comparing K_2 value of FM = 5.263×10^6 and for Hz = 5.6×10^5 dm^3 mol^{-1}, support the order of inhibition FM > Hz.

In the present study, FM was used as a raw material. In comparison, the drug lasix (solution) was used at σ = 0.09 and at the same experiment conditions. It was found that the percent of Inhibition of 10^{-6} $mol.dm^{-3}$ decreased the dissolution rate of COM crystals by 35%. The percent of inhibition by 10^{-6} mol. dm^{-3} of Furosemide was 89%. So the order of inhibition of FM and Lasix was:

FM > Lasix

4. Conclusion

The following are the main conclusions that may be drawn from the results obtained:

1. Dissolution of COM crystals in the presence of hydrochloric thiazide and Furosemide.
2. Thiazide and Furosemide are good inhibitor for dissolution of COM crystals.
3. The order of dissolution process in the presence of Hz was ≈ 2 which suggest. Surface controlled mechanism at experimental conditions.
4. Inhibition of Hz decrease by increasing ionic strength of the medium.
5. Increasing of pH of the medium till pH = 8 decreasing the degree of inhibition of Hz and after pH = 8 the inhibition of dissolution rates of COM increase.
6. FM inhibits the dissolution of COM crystals at the experimental conditions.
7. Affinity constants (K_L) was found 5.263×10^6 and 5.6×10^5 dm^3 mol^{-1} in case of FM and Hz, respectively.

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