Kinetics of Dissolution of COM Crystals in the Presence of some Organic Solvents

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Abstract: Dissolution rates of calcium oxalate monohydrate crystals were studied in absence and presence of propionic acid (PA), acetone, dimethyl-sulfoxide (DMSO), iso propanol (IPA) and dimethyl-formamide (DMF). It was found at the experimental conditions of PH : 6.5, t = 37^0C, I= 0.15 mol dm^{-3} and σ = 0.09, the dissolution followed surface controlled mechanism. The order of inhibition of additives on the rates of dissolution of COM crystals at experimental conditions was: PA > acetone > DMSO > IPA > DMF. The effects of change of I, pH, σ and Temperature on the rates of dissolution of COM crystals in the presence of, 10^{-7} mol dm^{-3} were studied.

1. Introduction:

Stone formation in renal systems is one of the oldest and the most common form of crystal deposition disease. Analytical results show calcium oxalate (CaC_2O_4) to be one of the major inorganic components of renal stones and is found to be present in almost all kidney and bladder stones. About 39.4% of the total composition of the calculi is found to contain purely calcium oxalate and also it occurs along with calcium phosphates and apatites [1].

Calcium oxalate is one of the main constituents of deposits in urinary tract. Crystallization of calcium oxalate is of particular interest not only from the theoretical point of view but also because of its biological importance. The exact mechanism of the initiation of the calcium oxalate stone formation is not completely understood. Factors leading to the nucleation, crystal growth and aggregation of various hydrates of calcium oxalate depend not only on the excess of calcium and oxalate concentration but also on the presence of various foreign substances [2].

One of the challenges for applied crystal science in the last decade has been the development of processing methodologies which secure the production of good quality crystals that are free from impurities. The fact that solvents may be active in modifying the growth form or phase of a crystal has been recognized and accommodated in production. Equally successful has been the development of additives capable of tailoring the specific growth form of crystal to optimize function through control of habit and morphology [3].

Stone formation is related to the balance between supersaturation and inhibitors existing in urine. An important part of the study of urinary stone formation is to develop an understanding of interactions between the stone crystals and the components of organic matrix. The effect of pH, foreign ions, organic solvents and the degree of supersaturation in aqueous systems have been extensively studied. Few investigations have been made to the study of the effect of solvent.

In the present study the effects of PA, acetone, DMSO, IPA and DMF on the dissolution mechanism of dissolution COM crystals at conditions similar to that of human body were studied.

2. Experimental:
Preparation of solutions:

Pyrex glass ware and analytical grade chemicals were used throughout, water was purified by deionization followed by triple distillation. It was stored in a pyrex vessel under nitrogen. Solutions of calcium chloride, sodium oxalate were made from analytical grade reagents (EL.Nasr pharmaceutical chemicals company fisher scientific company and baker chemical company) weighed amounts of the salts were dissolved in a volume of deionized distilled water. Those solutions were then filtered through prewashed millipore filter pads (0.22m, Millipore filters), quantatively transferred to grade volumetric flasks and diluted to the required volume with deionized distilled water. Those solutions were analyzed by passing aliquots through a cation exchange resin (Dewix-50) in the hydrogen form and titrating the eluted acids with standardized sodium hydroxide solutions of suitable concentration using phenolphthalein as indicator.

Preparation of seed:

Calcium oxalate seed was prepared by adding one liter of (0.1 M) calcium chloride solutions to one liter of sodium oxalate solution (0.1M) at 298°K at a rate of 250 ml per half an hour. The calcium oxalate solution was constantly stirred for one day and was then filtered and the seed crystals were washed with deionized distilled water to remove surface contamination due to chloride and oxalate ions. The seed crystals were aged for one month, then were refiltered and washed further with deionized distilled water and this process was repeated several times. The seed was then filtered and dried. The seed material was then subject to x-ray powder diffraction studies, scanning electron microscope and the determination of specific surface area (SSA), IR and TGA analysis.

Measurements of surface area:

The surface area was calculated adopting the value of A° for cross-section of krypton SSA value was $3.73 \ m^2g^{-1}$.

Preparation of Inhibitors:

Solutions of Dimethyl formamide (DMF), Dimethyl sulfoxide (DMSO), Acetone, Isopropyl alcohol (IPA), Propionic acid (PA) were prepared by taking suitable volume of the liquids then completed by deionized distilled water to suitable volume. The desired concentrations were prepared by dilution the solution of: DMF (Adwic Company), Acetone (Adwic Company), DMSO (Fluka AG, chem...Fabrik CH-9470 Buchs), Isopropyi alcohol (Adwic company), Proponic acid (Laboratory Rasayan).

Potentiometric measurements:

pH measurements were made with a combined pH glass electrode (model 9100 metrohm AG company) Emf measurements were made by calcium ion selective electrode (U4-9101 Herisau), in conjugation with a Calomel reference electrode (model 90.02 orion Research incorporated laboratory products group). The electrodes were checked before and after each dissolution experiment using the buffer solutions recommended, by Bates. pH glass electrode and using calcium chloride solutions with definite concentrations in case of calcium selective electrode. If combined pH glass electrode measurements differed from the required, the electrode was reconditioned in warm HCL solution in case of calcium ion selective electrode, if the measurements were differed from the required, the electrode was put in solution of $10^{-2}M$ $CaCL_2$ for few days.

In dissolution experiments-using potentiostate, the studies were made at constant Emf. Metrohm combititrator: consisted of dosimate model 665. Impulsomate model 614, pH-mater model-632 stirrer model E649, was used to control the addition of titrant solution consisting of 0.15 M sodium, chloride, into the reaction vessel since the impulsomate provides proportional system was able to respond to a change of Emf of < 0.002 mv on the addition of reagents.

Dissolution Experiments:

The crystal dissolution experiments were carried out in water thermostated double-walled pyrex glass vessels. The cells were maintained at the required temperature (37°C) by circulating thermostated water through the outer jackets. The cell contents were stirred with a magnetic stirrer (and pre-saturated nitrogen gas bubbled through the solutions during the experiments to exclude carbon dioxide).

In dissolution experiments, a measured volume of de-ionized distilled water was transferred to the cell and a known volume of sodium chloride was added, then definite volume of calcium chloride solution was added followed by slow addition of known volume of sodium oxalate solution over a period of five minutes. The total volume was usually 300 ml and the pH was adjusted to the required value (6±0.05) using standard sodium hydroxide solution or/and standard hydrochloric acid solution. Satisfactory stability of the undersaturated solution was verified by constant pH reading for at least 30 minutes in experiments using pH-state, and by stability of Emf reading also at 30 minutes in potentiostate experiments. Following the addition of dry seed crystals, dissolution began immediately and combined pH glass electrode was used to controlling the addition of titrant solution consisting of 0.15 M sodium chloride in experiments using pH-state, while calcium ion selective electrode in conjugation with calomel reference electrode were used in experiments using potentiostate.

In addition, samples were periodically withdrown and filtered at the reaction temperature through Millipore filters (0.22 M), perior to solution and solid-phase analysis.

3. Result and Discussion:

The kinetics of growth and dissolution of the hydrates and transformations between them allow industrial processes to be modeled. On the other hand, CaOx is the major constituent of kidney stones in the western hemisphere. Thermodynamic (supersaturation) and kinetic (nucleation, growth and aggregation) factors play a role in the pathogenesis of this disease. While CaOx dihydrate (COD) crystals occur in urine, the monohydrate (COM) is much more common in stones[4].

In the present work, dissolution rates of calcium oxalate monohydrate(COM) crystals were

studied in the absence and the presence of some organic solvents.

In the present work, the rates of dissolution of COM (K_{so}= 9.899 x 10^{-8}) have been investigated at 37°C in absence and presence of trace amounts of natural products from medicinal plants in undersaturated solution. For many sparingly soluble sates M_aA_b, the rate of dissolution normalized for seed surface area, can be expressed by the equation :

$$R = d[M_aA_b]/dt = KS\sigma^n \qquad (1)$$

Where:

K = is the dissolution rate constant

S = is proportional to the number of dissolution sites available on the seed crystals.

n = is the effective order of reaction

σ = is the relative degree of under saturation.

The degree of relative under saturation, σ, may be expressed by the equation.

$$\sigma = \left[\pi_0^{\frac{1}{2}} - \pi^{\frac{1}{2}} \right] / \pi_0^{\frac{1}{2}} \qquad (2)$$

where:

π : is the motor concentration product of calcium oxalate in the solution.

π_0 : is the solubility value at the same ionic strength (0.15 mol dm^{-3} in the present work).

The relative under saturation σ, for a solution containing equal calcium and oxalate ions (present work) can be defined :

$$\sigma = \left([Ca^{2+}]_t - [Ca^{2+}]_{eq} \right) / [Ca^{2+}]_{eq} \qquad (3)$$

The subscripts "t" and "eq" are values at time "t" and at equilibrium respectively.

In non-stiochiometric concentration of calcium and oxalate ion :

$$\sigma_t = [Ca^{2+}]_t [C_2O_4^{2-}]_t^{\frac{1}{2}} [[C_a^{2+}]_{eq}[C_2O_4^{2-}]_{eq}]^{\frac{1}{2}} [[C_a^{2+}]_{eq}[C_2O_4^{2-}]_{eq}]^{\frac{1}{2}} (4)$$

the theormodynamic solubility product :

$$K_{sp} = [Ca^{2+}][C_2O^{2-};_4]f^2;_z \qquad (5)$$

Where :

f_z : is the activity coefficient of divalent ion

The activity coefficients of divalent cation and anion were assumed to be equal and were obtained using the extended Debye Huckel equation proposed by Davis[5].

$$-\log f_z = AZ^2 \left[\sqrt{\frac{I}{1+I}} - 0.31 \right] \qquad (6)$$

Where:

Z : is the charge on the ion (valence).

I : Is the molar ionic strength and

A : is contant

In order to be able to analyse the kinetis of dissolution reactions in terms of concentrations of free ionic species, it is necessary to take into account ion- pair and complex formation, also some computations were made, as described previously. [5-6]

Nucleus in dissolution process is a microscopic hole in the crystal surface whereas, in growth process a nucleus is small hill of material stacked on the crystal surface.

COM crystals are prepared, X-ray, IR, Scanning electron microscope, TGA and S.S.A analysis confirm the COM crystal structure. The effect of change temperature, concentrations, weights of seed crystal used to intiat the dissolution process, rate of stirring and ionic strengthes on the rate of dissolution of COM were studied.

The effect of degree of under-saturation (σ = 0.04 – 0.15) on the rate of dissolution of COM crystals were studied table (1), Fig (1)

Table (1): Dissolution of calcium oxalate crystals T_{ca+2} : T_{ax-2} = 1:1 at t= 37° C and ionic strength 0.15 mal dm^{-3} (NaCl) using E.M.F.

ExpNo.	$TCa^{+2}/10^{-4}$	$10^2\,\sigma$	Seed/mg	Rate/10^{-9} mal min^{-1} m^2
10	1.914	4	10	2.250469831
11	1.894	5	10	3.310876924
12	1.854	7	10	5.903879458
13	1.814	9	10	8.740460458
14	1.794	10	10	10.68246937
15	1.774	11	10	12.314689480
16	1.735	13	10	16.51267932
17	1.695	15	10	20.20896798
18	1.814	9	50	8.750143820
19	1.814	9	90	8.735216841
20	1.814	9	300	8.7209632
21	1.814	9	500	8.71502463
22	1.814	9	700	8.71094632
23	1.814^a	9	10	8.740460458
24	1.814^b	9	10	8.75143215

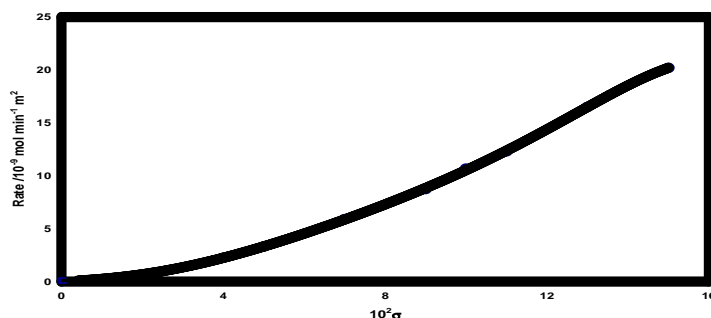a) String rate (200) r.p.m   b) String rate (500) r.p.m

Fig. (1): Plots of rate of dissolution against degree of undersaturation, using EMF.

The effective order of dissolution process of COM crystals was found   2 which suggest surface controlled mechanism. The effect of change of temperature on the rates of dissolution of COM were studied Fig(2).
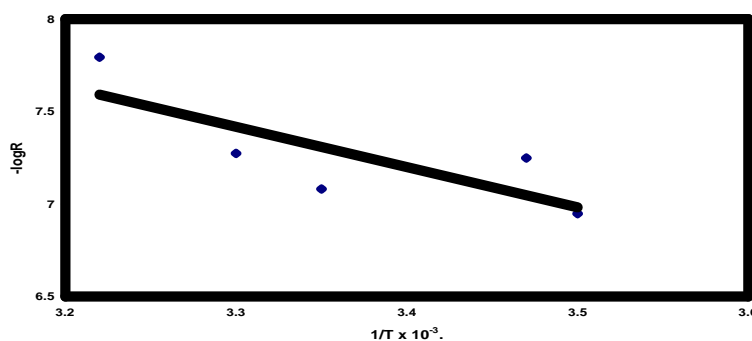

Fig. (2): Plots of -logR against 1/T for dissolution of calcium oxalate monohydrate crystals σ = 0.09, using EMF.

The activation energy was found equal to   5 K. cal which support surface– controlled mechanism. Also the stirring dynamics didn't affect on the dissolution rates of COM crystals. The effect of change of pH of medium on the rats of dissolution was studied. From the study, increasing the pH of medium lead to decrease the dissolution rates of COM crystals.

The effect of change of ionic strength on the rate of dissolution of COM crystals was studied. From the study increasing ionic strength of medium leading to increase the dissolution rates of COM crystals at experimental conditions.

Additives of both an organic and inorganic nature play an important role in crystallization processes . It is important to know how the additives influence the crystallization process . The type of polar functional groups contained in additives , the number of polar functional groups contained per molecule , hydrophobic and hydrophilic regions , the molecular weight and concentration of additives and a close match between the spacing of acid groups and the spacing of cations of the crystal surface are considered factors that influence crystallization it is proposed that the additives have two functions :

a. They could inhibit crystal growth by binding to the growth sites of the crystals.
b. They could act as a heterogeneous nucleator.

The dissolution of COM crystals in the presence of dimethyl formamide, DMF, dimethyl sulfoxide (DMSO), acetone, isopropanol (IPA) and propionic acid (PA). the order of inhibition of dissolution rates of COM crystals was found:
PA > acetone > DMSO > IPA > DMF

It was found that concentrations as low as 10^{-6} mol dm^{-3}, markedly reduced, the dissolution rates by factors at least 98, 95, 89, 86 and 55 times compared to that in the absence of additives at the same relative under-saturation ($\sigma = 0.09$) which suggest the order of inhibition of the additives:
PA > acetone > DMSO > IPA > DMF

The low concentrations of inhibitors that could inhibit the dissolution or crystallization processes indicates that these inhibitors are effective and that low surface coverage indicates the rate determining step. When the concentration of additives molecules increase, the rates of dissolution decrease due to blocking of the active sites on the crystal surfaces by the additives:

When the concentrations of the additive molecules increase, the rates of dissolution decrease due to blocking of the active sites on the crystal surfaces by the additives . Cations may be adsorbed at anionic sites and inhibit the dissolution when present at very low levels and vice versa[7].

Adsorption growth factor depends strongly on the nature of the substrate, adsorption sites. The amount of bound growth factor increased almost linearly with its concentration in the solution. It is generally assumed that, the proteins are mainly adsorbed through electrostatic attraction between hydroxyl apatite (HA) surface and anionic groups. The adsorption studies indicated that compounds with the same structure may react quite differently, depending on the surface characterisitics. In some extent, the difference of adsorption capabilities of the additives are very effective factors.[8]

Natural materials contain impurities which are released by dissolution disintegration of the mineral. There are two possibilities existing

  a. The impurities are released into the solution, from which they are adsorbed reversibly to the surface of the mineral, acting there as inhibitors.
  b. They are adsorbed irreversibly at the surface either directly from the disintegrating mineral, or they are the first released solution from which they are adsorbed to the surface.

In case (a) , the surface concentration is related to the impurity concentration in the solution by an adsorption isotherm. But in case(b) it was assumed , complete irreversible binding of released impurities to the mineral surface so the impurity concentration become zero . If reversible adsorption of inhibitors is operative, then surface adsorbed inhibitors should be released to the solution and their surface concentration should be reduced significantly. If re- adsorption of the impurities would occur, the surface concentration of adsorbed inhibitors should be higher in the mineral than that of the solution Studies indicated:

a. Adsorption of the inhibitors to the mineral surface is irreversible.
b. Inhibition are not captured from the solution.

The surface controlled dissolution kinetics of natural calcium oxalate minerals depend on the experimental conditions employed to obtain them. The surface concentration of the inhibitors depends on the thickness of the oxalate layer removed by dissolution and on their concentration in the bulk solid . Therefore, the inhibition raises strongly with the thickness of the removed layer (d), until sufficiently large (d), remains constant. Inhibitors are not adsorbed from solution [9].

Recently, it was reported that the mechanism of the interaction of calcium oxalate with an organic molecule depend on the size , ionic charge and structure of additive molecules.[10 - 11] Small molecules with high charge density preferentially interact electrostatically with charged lateral faces and high energy tips of growing crystals.

So in the present work the additive molecules are adsorbed on the active Ca^{2+} ion sites. This can be interpreted in terms of Langmuir – type isotherm between $R_o / R_o - R_I$ against $[additive]^{-1}$ must be linear. Values of $(R_O - R_I / R_O)$ and $[additive]^{-1}$ of dissolution of COM crystals at relative undersaturation, $\sigma = 0.09$, are listed in table (2). Fig.(3) Confirms the applicability of this simple adsorption isotherm at the same relative undersaturation, $\sigma = 0.09$, which reflects the adsorption of these additives at the active Ca^{2+} ion sites. Most of these solvents in the present work are ionized so they are adsorbed electrostatically (since the dissolution rates depends on the ionic strength of the medium) to the surface of COM. The value of affinity constants, K_L, (given by inverse slopes of the lines in fig.(3) are 6.34, 3.42, 1.16, 1.07 and 0.33 $x10^7$ dm^3 mol^{-1} for PA, acetone. DMSO , IPA and DMF respectively. These values of K_L reflect the high adsorption affinity at the same relative undersaturation $\sigma = 0.1$ which runs in the order: PA> Acetone > DMSO > IPA > DMF.

Table (2): Effect of $R_o/(R_o-R_I)$ against $[Additive]^{-1}$ of dissolution of COM in presence of proponic acid, acetone, DMSO, isopropanol and DMF.

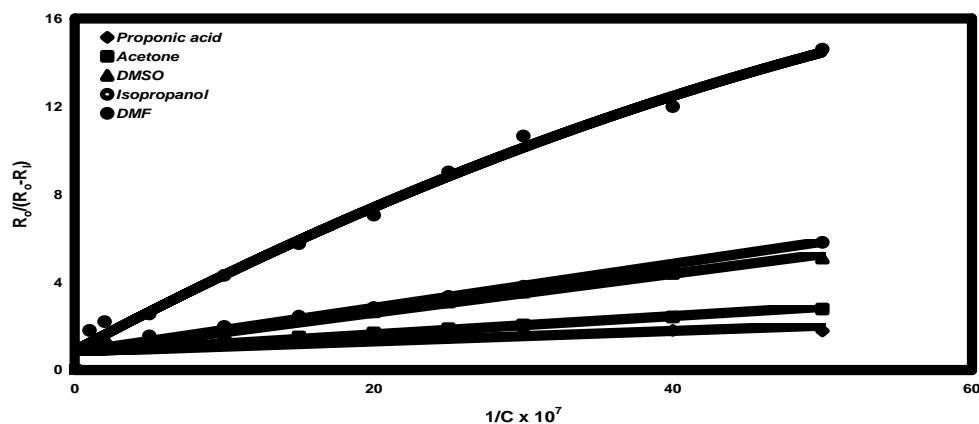| 10^6 [Additive]$^{-1*}$	$(R_o – R_I) / R_O$				
	Proponic acid	Acetone	DMSO	Isopropanol	DMF
1	1.020	1.045	1.120	1.15	1.801
2	1.050	1.121	1.210	1.24	2.203
5	1.099	1.150	1.501	1.55	2.550
10	1.215	1.343	1.845	1.98	4.305
15	1.301	1.501	2.250	2.45	5.750
20	1.396	1.690	2.650	2.84	7.050
25	1.504	1.880	3.100	3.35	9.010
30	1.605	2.05	3.549	3.81	10.65
40	1.804	2.410	4.400	4.75	11.99
50	1.780	2.775	5.101	5.81	14.599

Fig. (3): Plot of $R_o/(R_o-R_I)$ against [Additive]$^{-1}$ of dissolution of COM in presence of proponic acid, acetone, DMSO, isopropanol and DMF.

The effects of changing pH, temperature, σ and I of the medium on the inhibitory effect of DMSO on the rate of dissolution of COM were studied.

Based on the assumption that the degree of inhibition may be affected by the degree of relative undersaturation , the dissolution of COM crystals in the presence of 10^{-7} mol dm^{-3} DMSO has been investigated at different σ values (σ = 0.09 – 0.25).

It was found that the change in pH of the medium in the presence of 10^{-7} mol dm^{-3} didn't affect the rates of dissolution of COM crystals at experimental conditions of (σ = 0.09, t = 37^{0}C, pH = 6.5).

The effect of change of ionic strength on the rates of dissolution of COM crystals in the presence of 10^{-7} mol dm^{-3} at the same experimental conditions was studied. It was found that increasing ionic strength of the medium leads to increasing the rate of dissolution of COM crystals i.e decrease the degree of inhibition of DMSO. The changing of rates of dissolution of COM in crystals with changing ionic strength of the medium indicates that the inhibition is electrically in its nature.

The effect of change of σ on the rates of dissolution of COM the presence of 10^{-7} mol dm^{-3} was studied. The order of dissolution of COM crystals in the presence of 10^{-7} mol dm^{-3} was found = 2 which indicates surface controlled mechanism fig. (4)

The effects of change of temperature on the rate of dissolution of COM crystals in the presence of 10^{-7} mol dm^{-3} were studied. Fig(5).

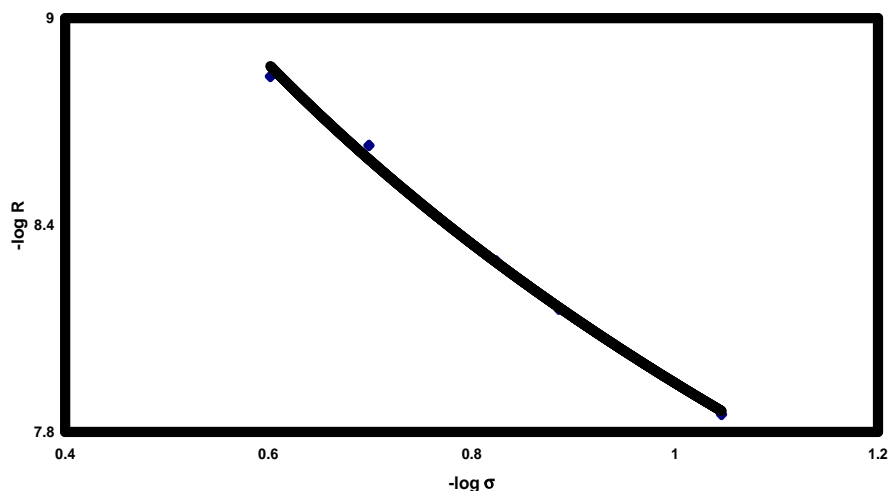The activation energy was found equal to 2.5 k. cal rule out the surface controlled mechanism.

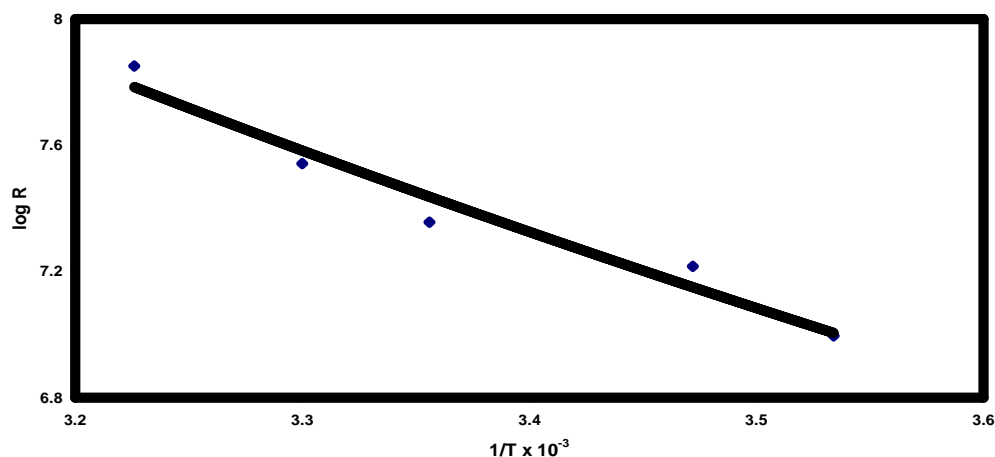**Fig. (4): Effect of change σ in the presence of 10^{-7} M (DMSO) at 37 ^{o}C.**

Fig. (5): Effect of temperature on the rate of dissolution COM in the presence of 10^{-7} M DMSO, σ = 0.09 at EMF

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