Global Advanced Research Journal of Microbiology (ISSN: 2315-5116) Vol. 3(8) pp. 133-143, October, 2014
Available online http://garj.org/garjm/index.htm

Full Length Research Paper

Synthesis, spectroscopic, Thermal kinetic and computational studies on Charge-Transfer Complexes: (Panto & Ome)-prazole drug as donor and DDQ, CHLC & Iodine as acceptor

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Accepted 10 October, 2014

Charge transfer (CT) complexes were carried out using the most widely selling and effective pharmaceutical drugs as Pantoprazole (PANT) and Omeprazole (OMER) as electron donors; solid interaction with different benzoquinone derivatives as acceptors and Iodine were isolated and characterized by IR and ^{1}H-NMR (Nuclear magnetic resonance) .Thermo gravimetric analysis with different heating rates (TGA) were studied on solid state complexes using computational integral methods for Coats Redfern and Ozawa using various solid state kinetic reaction models and established activation energy, energy band gape and thermodynamic parameters . The Differential Scanning Calorimetric (DSC) technique was used to study the nature decomposition of charge transfer complexes. The morphological structure were discussed and examined via Scanning Electron Microscopy (SEM).The molecular structures of Pentaprazole, DDQ, CHLC and I_2& charge transfer complexes in the ground state were made by using Gaussian 03 program package.

Keyword: thermal kinetic studies, pharmaceutical drugs, benzoquinone derivatives, Computational chemistry.

INTRODUCTION

Mulliken was the first who introduced the charge transfer phenomena (Mulliken 1952). The organic charge transfer complexes were intensively investigated due their application in many biological fields, solar energy storage, surface chemistry and their uses in quantitative estimation of drugs[2].In this study Omeprazole (OMER) {5-Methoxy-2[[4- methoxy-3, 5-dimethyl-2-pyridinyl]sulfinyl] - 1H-benzimidazole} and Pantoprazle (PANT). {5-(Difluoronylmethoxy)-2-[[3,4-dimethoxy-2 pyridnyl)methyl]sulfinyl]-1H-benzimidazole}, in the form of {pantoprazole sodium sesquihydrate}, are two irreversible proton pump inhibitors (PPIs) are used as donors with benzoquinone derivatives as acceptors and Iodine. The formed charge transfer complexes are synthesized and characterized by mid infrared spectroscopy, elemental analysis, and proton magnetic resonance ^{1}HNM.Thermal studies were characterized by using thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC).

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Table 1. Abbreviations of CT complexes in solid state

CT complex	Symbol used
1:1(PANT: I_2)	I
1:1 (PANT: DDQ)	II
1:1 (OMER: DDQ)	III
1:1 (PANT: CHL)	IV
1:1 (OMER: CHLC)	V
2:1(PANT: CHLC)	VI
2:1(OMER: CHLC)	VII
1:1(OMER: I_2)	VIII
2:1 (PANT:I_2)	VIIII
2:1 (OMER:I_2)	IX
1:1 (PANT:CLC)	X
1:1 (OMER:CLC)	XI

2. Experimental

2.1. Synthesis of solid complexes

Reagent grade Pantoprazole, Omeprazole, Iodine (I_2), Chloranilic acid (CHLC) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone(DDQ) were used without purification.
The charge transfer complexes were prepared as described in ref (Obaid et al., 2012).

3. RESULTS AND DISCUSSION

3.1. Comparative Study of IR Spectraand ^{1}H-NMR spectra of CT complexes

The IR absorption spectra of the reactants and CT complexes were recorded in the frequency range 4000-650 cm^{-1} using Perkin Elmer spectrometer. The observation of the main infrared bands of the donors and acceptors (iodine I_2, chloranilic acid CHAC and DDQ) in the respective complex spectra strongly support the formation of CT- complexes to distinguish between weak CT complexes and the products of electron transfer for Proton transfer interaction (Foster 1969). The IR spectra of the complexes showed differences compared with those of OMER and PANT drugs. Assignments of the characteristic infrared spectral bands of the free donor as well as formed CT-complexes are reported in Table 1.The shifts which have been seen were used as evidence for the formation of the new CT complexes. The lone pair on the nitrogen atom of the aromatic ring may cause the donation process of electrons to acceptor as most studied cases suggested.(IR spectra's are provided in supplementary materials).

In the ^{1}H NMR spectra of the complexes, generally, the protons of the donors are shifted to a lower field. The ^{1}H NMR spectra of the complexes of PANT and OMER with different acceptors were recorded in DMSO solvent using tetra methylisilane (TMS) as internal standard.The chemical shifts (δ) of the different types of protons are listed in tables (3-2), and compared with the spectrum of the free drug (Saleh et al., 2003). For PANT and OMER complexes it was observed the downfield shifted of both drugs after complexation.
The ^{1}H NMR spectra of OMER drug alone, The 4-methyl, 2-methoxy and methylene groups were appeared in 2.16 ,3.785 and 4.2. After complexation with DDQ it shifted δ_{OCH3}= 3.57, δ_{CH3}=3.8 and δ_{CH2}= 4.2 and it shifted to δ_{OCH3}= 3.7, δ_{CH3}=2.55 and δ_{CH2}= 4.75 in the complexation with CHLC.
The ^{1}H NMR spectra of PANT drug alone, the assignment of methoxy and methylene groups, it appeared at 3.65 and 4.4. After complexation with iodine it shifted δ_{OCH3}= 3.94 and δ_{CH2}= 4.08 and it shifted to δ_{OCH3}= 3.7 and δ_{CH2}= 4.679 in the complexation with CHLC. From previous values,It was new complex in downfield shifting than drugs alone.(^{1}H NMR spectra's are provided in supplementary materials)

3.3 Thermogravimetric analysis (TGA) and DTG

The well-established thermo gravimetric analysis (TGA) and differential scanning calorimetry (DSC) techniques have been reliably widely used over many decades in studying the thermal behavior and properties of various types of materials and evaluating the thermal parameters for their degradation processes[5].These methods have allowed determination of the chemical steps of the

Table 2. Main bands (cm-1) in infrared spectra of PANT and OMER donors with I2, CHLand DDQ acceptors:

	Compound	$\dot{u}_{C-O}$ cm^{-1}	$\dot{u}_{S=O}$ cm^{-1}	$\dot{u}_{C=C}$ cm^{-1}	$\dot{u}_{C=N}$ cm^{-1}	$\dot{u}_{C-H}$ cm^{-1}	$\dot{u}_{N-H}$ cm^{-1}	$\dot{u}\dot{u}_{O-H}$ cm^{-1}	$\dot{u}_{CN}$ cm^{-1}	$\dot{u}_{C=O}$ cm^{-1}
	Pantoprazole drug	1042	1072	1464	1589	3157	--------	-------	-------	--------
	Omeprazole drug	1000	1203	1406.98	1585.9	2970	2970	--------	--------	--------
I	1:1(I_2:Pantoprazole)	1015	1110	1492	1619	3426.19	-------	-------	--------	---------
II	1:1 (DDQ:Pantoprazole)	1017	1153	1435.06	1563.37	2940.70			2300	1632.41
III	1:1 (DDQ:Omeprazole)	1199.75	1270.62	1432.62	1559.93	2940.39	2940.39	-------	2225.88	1616
IV	1:1 (CHL:Pantoprazole)	1026	1108.8	1498	1616	2200	-------	2260	--------	1720
V	1:1 (CHL:Omeprazole)	1153.55	1266.29	1371.16	1526.58			2936.40	--------	1624.41

Table 3- ^{1}H NMR assignement of PANT and OMER charge transfer complexes

Compound	δ_{OCH3}	δ_{CH3}	δ_{CH2}	C_1, C_2, C_9, C_{11}, C_{12} (Aromatic C-H)	O-H	N-H
PANT	3.65	-----	4.4	6.7, 7,7.07, 7.28,7.49	-----	-----
I	3.94	-----	4.08	6.5, 7, 7.2,8 and 8.2		-----
II	2.5	-----	3.6	6.9,7.2,7.7,8and 8.4	-----	
IV	3.7	-----	4.679	6.34,7.4,7.8, 8.4 and 9.2	10.8	-----
OMER	3.785	2.16	4.73	7, 7.2, 7.5and 8.1	-----	13.457
III	3.57	3.8	4.2	7.2, 7.6,7.962 and 8.347	-----	10.5
V	3.7	2.588	3.8	7.4,7.7,8 and 8.4	9.2	
VIII	3.85	2.55	4.75	6.08, 6.4,7.55,8.4	-----	10.5

Table 4. Activation energy and Frequency factor for CT complexes

Compound	Ea	A	Cs
I	-6004.75	3.73E-03	0.2931
II	-6904.111	3.12E-03	2.42857
III	-7205.55	4.32E-03	3.9
IV	-7258.31	2.87E-03	2.38462
V	-7184.34	2.78E-03	2.26667
VI	-6779.48	1.26E-03	1.26316
VII	-7264.24	2.18E-03	0.36111

Table 5. Activation parameters of the thermal decomposition of III (OMER-DDQ) complex calculated according to E_1 model:

Methods of analysis		First decomposition step		Second decomposition step	
		E_a x10^{-4} (KJ/mol)	A (S^{-1})	E_a x10^{-4} (KJ/mol)	A (S^{-1})
Coats-Redfern Method	β = 5	3.623282	2.182698 x10^{-4}	9.12751	54
	β = 10	3.198156	3.853183 x10^{-4}	8.40541	101
	β = 15	3.169604	5.72819 x10^{-4}	7.836528	141
	Av.	3.330347	3.921357 x10^{-4}	8.45648	99
Ozawa Method	α = 0.1	22.68824	2.3 x10^{-10}	20.5092	69
	α = 0.2	28.27125		23.97859	
	α = 0.3	----------		29.74878	
	α = 0.4	57.27854		----------	
	α = 0.5	----------		20.7818	
	α = 0.6	27.4825		----------	
	α = 0.7	----------		23.11896	
	α = 0.8	----------		----------	
	α = 0.9	31.78426		----------	

Table 6. Activation energy of CT-complexes of Pantoprazole and Omeprazole donors with different acceptors

Compounds	α	Ozawa methods	Coats-Redfern-Sestak methods	Ozawa-chen methods	T_g K	T_m K	T_p K
		n	E_c(J/mol)	Ec(J/mol)			
I	5	1.454767	0.01715	0.083	314	320	324
	10			0.11952	316	319	321.2
	15			0.13944	318	321	323.6
II	5	1.410633	0.01051	0.083	318	321	323
	10			0.11869	317.5	321	323.2
	15			0.13944	318	321.5	323.5
III	5	1.697633	0.00664	0.083	318	321.5	323
	10			0.11952	316.5	319	321.5
	15			0.13944	318.8	321.2	323.5
IV	5	1.3829	0.00858	0.08383	315.5	318.2	321.5
	10			0.11952	316.8	319.5	321.5
	15			0.13944	317.5	321.5	323.3

investigated degradation and the evaluation, by some methods of the kinetic parameters of each step.The evaluation of the kinetic parameters has been often performed by using thermogravimeric curves (TG curves) recorded at different heating rates.The aim of the kinetic study of thermal analysis data is to find out the most probable kinetic model which best describes the process and allows the calculationof reliable values for the parameters like the order of reaction (n), activation energy (Ea) , enthalpy of reaction (ΔH^0), entropy of reaction(ΔS^0) , Gibb's free energy changes(ΔG^0) and the frequency factor(A).Many methods exist to characterize the degradation kinetics of various materials.In this section, the results from the thermal analysis experiments on the CT-compounds formed were examined in details.Thermal analysis comprises a group of techniques in which a physical property of a substance is measured as a function of temperature, while the substance is subjected to a controlled temperature programs.Thermal analysis (TGA and DTG) plays an important role in the determination and identification of materials, change in phase,thermal dehydration,decomposition reaction,solid state formation as well as to study the physicochemical behaviors and the stability of the CT-complexes under investigation,TG and DTG analysis were carried out under N_2 flow.

3.3.1 Kinetics methods

The rate of reaction dα/dt (min^{-1}) can be expressed as a combination of the rate constant k(T) and the reaction model f(α**)** (Sestak and Satava 1973):

dα/dt= k(T) f(α)

wheret is time, T is the temperature and α is the fraction decomposed at time. Replaced the rate constk (T) by the Arrhenius equation, then gives

dα/dt=A exp[-E/RT] f(α)

Where the pre-exponential factor A and the activation energy E are the Arrhenius parameters and R is the universal gas constant .In thermal analysis the data may be analyzed in two ways. The first and the most direct treatment is to record the compositional change in the properties recorded with the change of temperature .The second treatment is to perform a kinetic analysis in order to obtain the reaction mechanism and the kinetic parameters. In the second approach, the uses of non-isothermal procedures are becoming more widely accepted because they are more convenient then the classical isothermal.Non isothermal conditions, the rate constant k is independent of the reaction time and can be eliminated through the trivial transformation:

β dα/dt=A exp[-E/RT] f(α)

Where β= dT/dt is the heating rate (K/sec), and dα/dT is the rate of reaction (K^{-1}).

Rearanged and integration of this equation gives the integral conversion function g(α):

$$g(\alpha)=\int_0^{\alpha}\frac{d\alpha}{f(\beta)}=\frac{A}{\beta}\int_0^{T}\frac{-E}{RT}\,dT$$

g(α)=kT

A plot of g(α) versus T should give straight line if the corrected form of g(α) versus T is reached. The correct form of g(α) were analyzed according to the kinetic equations (Sharp et al., 1966). The temperature effect on the rate of non-isothermal solid reaction is a function of temperature may be written as:

$\ln\frac{d\alpha/dT}{g(\alpha)}$ β= ln A –E/RT

Where dT/dt, A is the frequency factor and E is the activation energy of the reaction.Due to the difficulty in obtaining accurate differential data from Strip charts so often use the integral form:

$g(\alpha)= A/\beta\, e^{-E/RT}$

Several approaches have been used to calculate the kinetic parameters from the experimental data using integral methods, Coats and Redfern methods (Coats and Redfern 1964) and Ozawa-Ozawa (Ozawa 1970), method were used in this study.The derivations of the methods are outlined in the original papers.The red and green electron density that we see in a benzene ring and groups associated with any administration that the electrons are then

Here the uses of the final operative equations are investigated and given below.

3.3.1-a Coast and Red fern Equation

The equations are given below:

$$-\ln\left[\frac{g(\alpha)}{T2}\right]=-ln\frac{AR}{\beta E}(1-2RT)]+\frac{E}{RT}$$

The quantity $\ln\left[\frac{AR}{\beta E}(1-2RT)\right]+\frac{E}{RT}]$ is reasonably constant for most values of E and the temperature range over which most reactions occur.However both E and A could vary with experimental heating rate.By plotting the appropriate left-hand side of the above equation versus 1/T ,The slope equals E/R. The correction form of g(α) must be used in the equation in order to allow the calculation of the activation energy.

3.3.1-b The Ozawa-Ozawa Method

-log β= 0.4567(E/RT)+constant

In this method, Plots -log β versus 1/T gives parallel lines for each value of α. The slope of these lines give the activation energy (slope=-0.4567(E/R)).The frequency factor is calculated from the equation:

$g(\alpha) =A/\beta\, e^{-E/RT}$

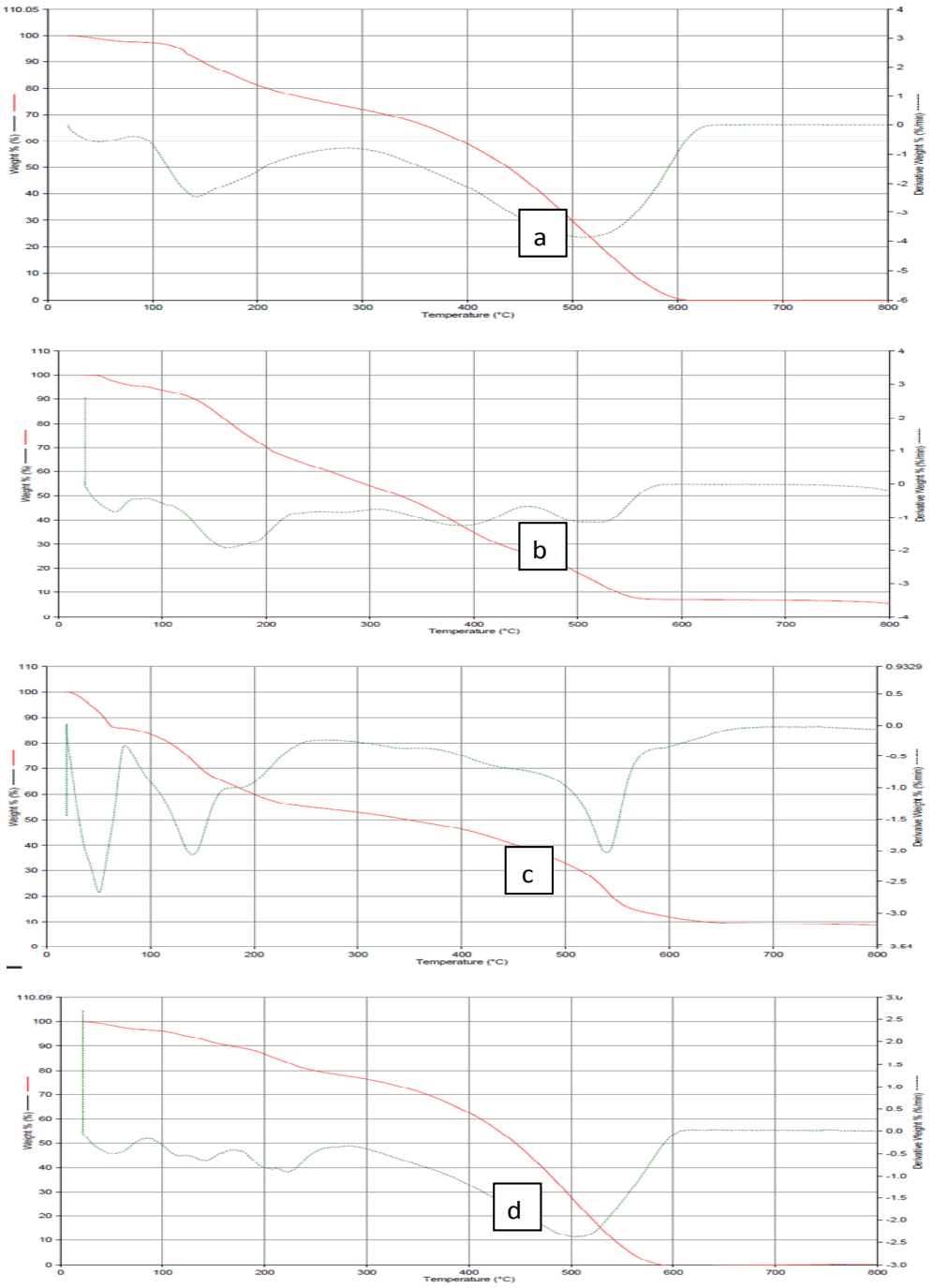

Figure 1. TGA-DTG curves for (a) OMER-CHLC (b) PANT-CHLC (c) PANT-I2 (c) PANT-DDQ at 50C/min.

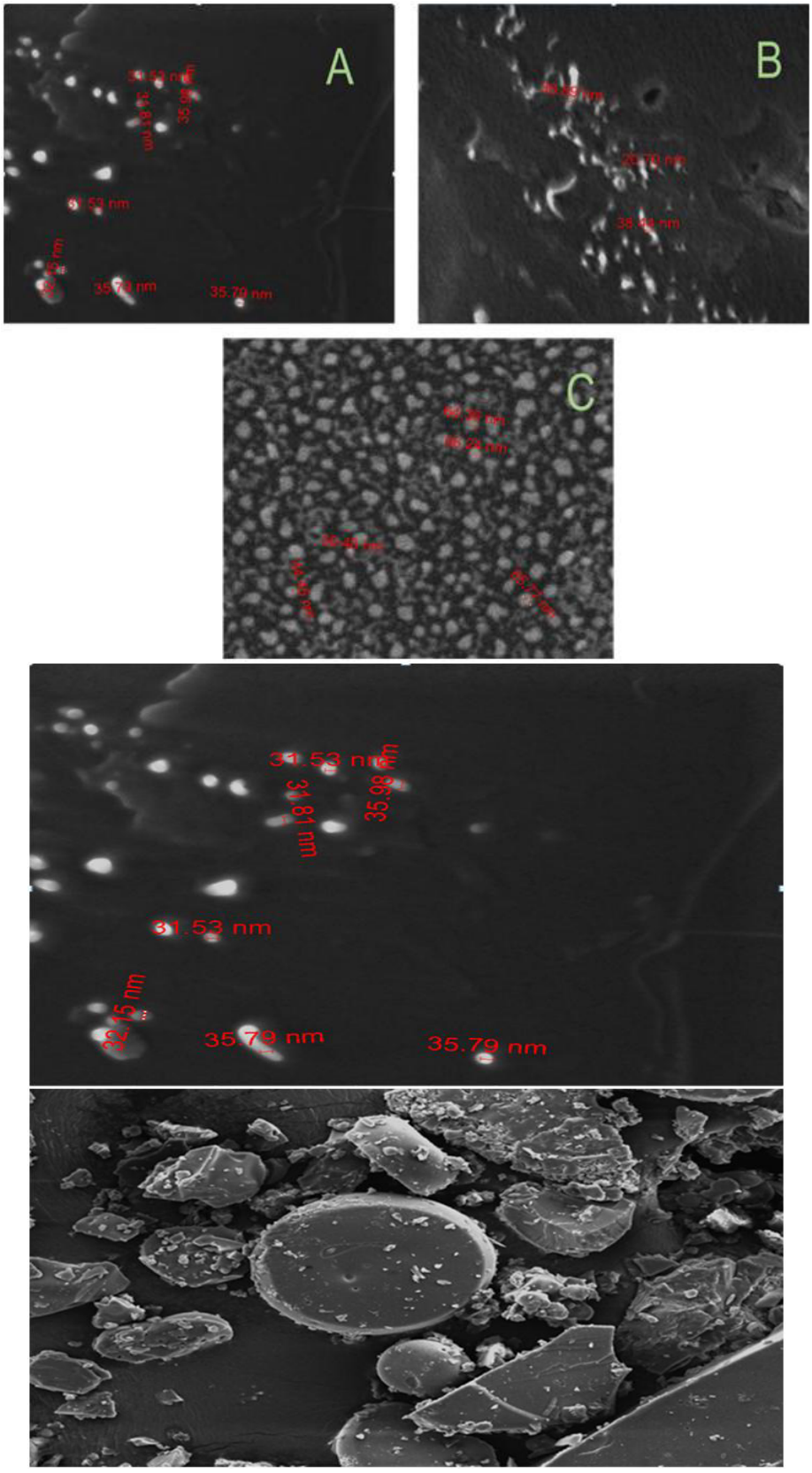

Figure 2. SEM image of CT-compound of PANT:DDQ

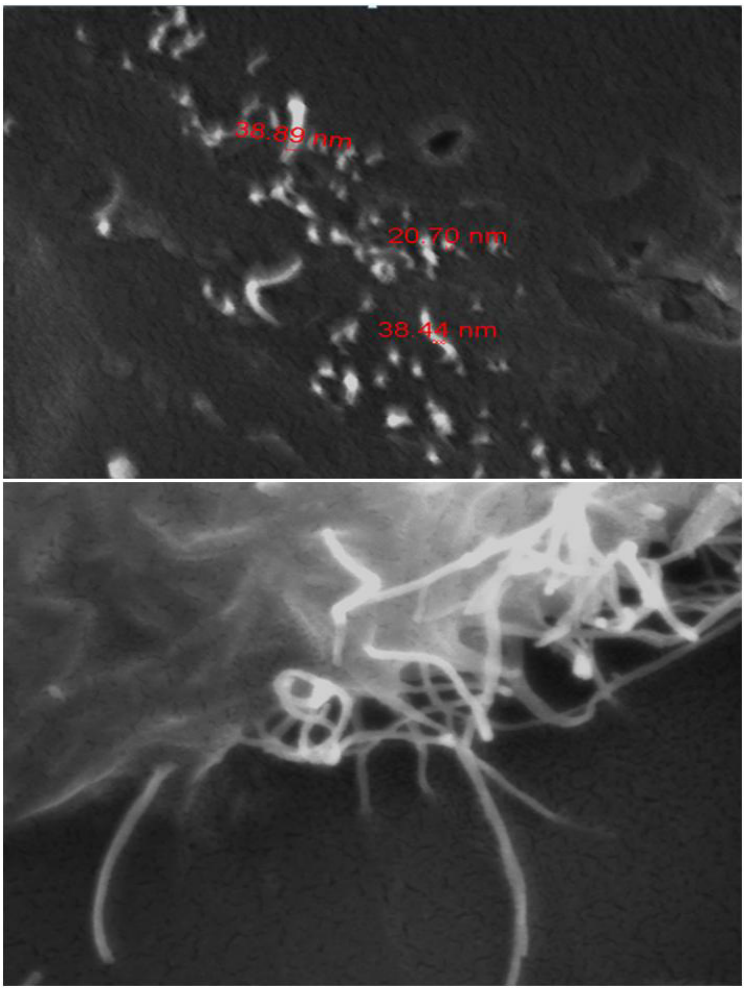

Figure 3. SEM image of CT-compound of OMER:DDQ

3.3.1-c Determination of reaction order of decomposition

The reaction order of decomposition can be determined from equation: (Horowitz and Metzger 1963).

$Cs=(n)^{1/1-n}$

Where Cs is the weight fraction of substance present at the DTG peak temperature T_s and given by:

$$Cs=\frac{Ws-Wf}{W0-Wf}$$

Where W_s stands for the weight remaining at a given temperature T_s, The DTG peak temperature, W_0 and W_f are the initial and final weight of the substance respectively.

For the first order process the Coats-Redfern equation may be modified and written in the form: (Nath and Arora 1993).

$$\log\left[\frac{\ln\left[\frac{Wf}{Wf-W}\right]}{T2}\right]=\log\left[\frac{AR}{BE*}\left(1-\frac{2RT}{E*}\right)\right]-\frac{E*}{2.303RT}$$

Where W_f is the weight loss at the completion of the reaction.W is the weight loss up to temperature T, R is the gas constant, E^* is the activation energy in J/mol and β is the heating rate, Since $1-\frac{2RT}{E*}\cong 1$.A plot of the left hand side against 1/T gives straight line with slope equal $E^*/2.303R$ and from intercept we find A (Arhenius constant).The activation energy and the arhenius constant were calculated by linear regression.The entropy ΔS^*, the enthalpy $\Delta H^*$and the free energy of activation ΔG^*will calculate using the following thermodynamically equations:

$$\Delta S^*= 2.303\left(\log\left(\frac{Ah}{kt}\right)\right) R$$

$$\Delta H^*=E^*-RT$$

$$\Delta G^*=\Delta H^*-T\Delta S^*$$

Where k and h are the Boltzmann and Plank constants respectively. The thermal analysis curve of CT complex of pantoprazole was studied from ambient temperature to 800 ^{0}C in nitrogen atmosphere, at different heating rates (5,10 and 15^{0}C/m). All of these complexes figure. (3-1)have one essential maxima peak mass loss, this result proves that

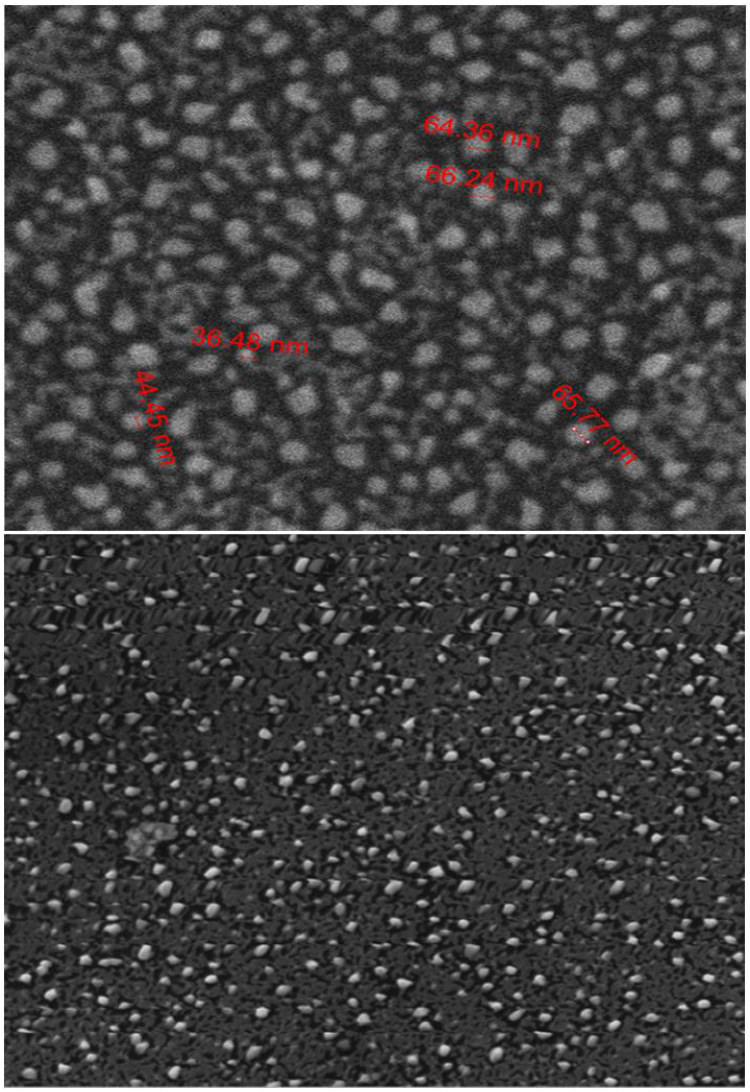

Figure 4. SEM image of CT-compound of PANT:CHLC

the formed compounds are new organic compounds that have their own chemical and physical behavior on the other hand the complete degradation of these compound indicates that these compounds are pure organic compounds.The thermal analysis curves gave a pattern of maximum stages of decomposition. For OMER-CHLC figure (3-1a), decomposed in two main steps, the first one from 61^{0}C-210^{0}C and the second step from 220 ^{0}C to 600 ^{0}C. PANT-CHLC complexes figure. (3-1b), decomposed in three main steps, the first one from 73^{0}C-277^{0}C, the second step from 290 ^{0}C to 477^{0}C, and the final one from 490 ^{0}C to 615^{0}C

For PANT-I_2 complex(I) (3-1c), it gives two stages of decomposition.The first step in the decomposition is from 77^{0}C to 210 ^{0}C .The second step was the decomposition of the complexfrom 220^{0}C to 705 ^{0}C. For, PANT-DDQ (3-1d), decomposed in three steps, the first one from 65^{0}C-150^{0}C,the second step from 170 ^{0}C to 251^{0}C, and the final one from 269 ^{0}C to 600^{0}C.For OMER complexes, all these curves were studied kinetically by Ozawa and Coat Redfern methods for the determination of activation energy and frequency factor.

3.4 Scanning electron microscope

A scanning electron microscope (SEM) is a type of electron microscope that images a sample by scanning it with a high-energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals that contain information about the sample's surface topography, composition, and other properties such as electrical conductivity.Magnification in a SEM can be controlled over a range of up to 6 orders of magnitude from about 10 to 500,000 times (Kiernan 2000). SEM

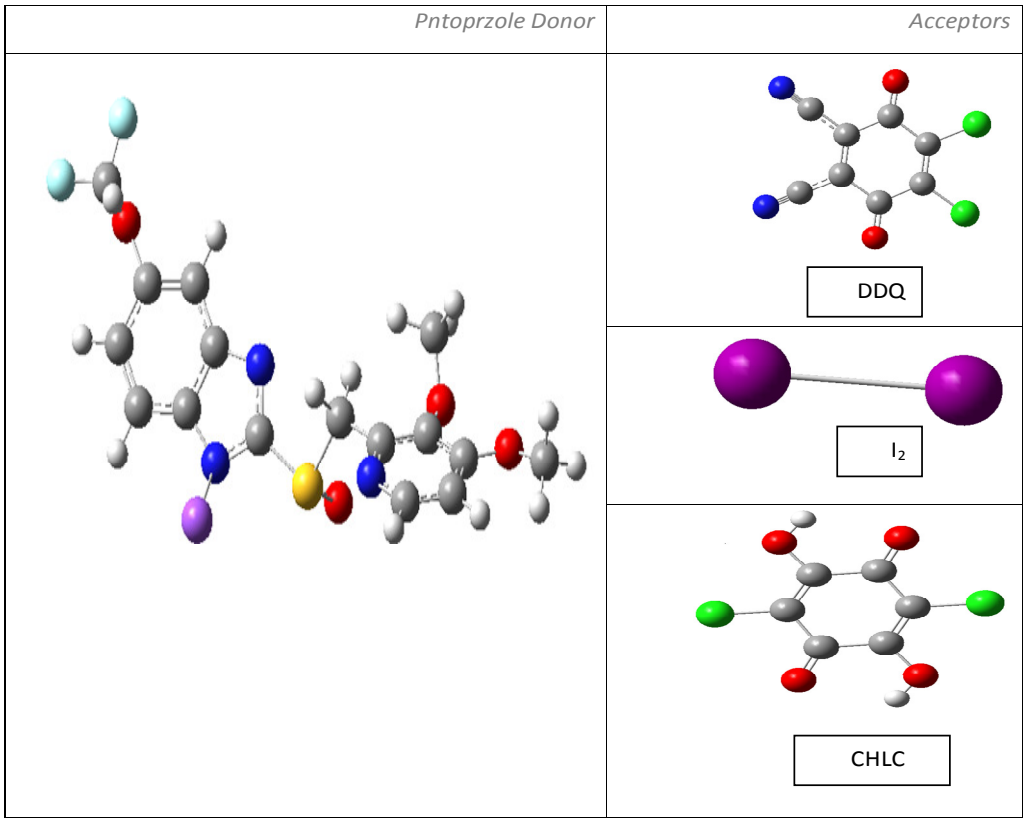

Figure 5. The structures of donor and acceptors by using Gaussian computational chemistry.

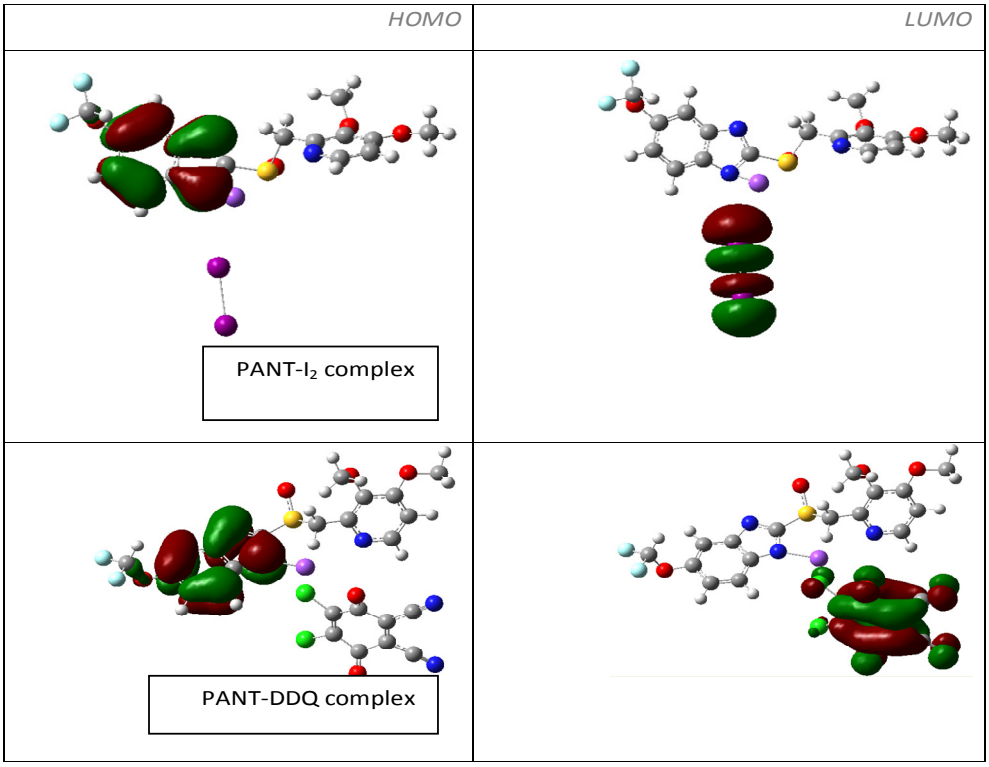

Figure 6. HOMO and LUMO Molecular orbitals in the formation of CT complexes between PANT and different acceptors.

images of PANT-DDQ Figure. (3-2) indicate that structure is spherical in the sample with 20.7-38.89 nm particle size while for OMER-DDQ Figure.(3-3) indicate that structure as belt (rod) in the sample with 36.48-66.24 nm particle size. SEM images of 1:1 PANT-CHLC, indicate that structure is capsules complicated together in the sample.

3.5 Computational chemistry as theoretical study on charge transfer complexes of Pantoprzole donor

The molecular structures of Pentaprazole, DDQ , CHLC and I_2&charge transfer complexes in the ground state were optimized by PM3 , HF method and Becke 3-Lee-Yang-Parr (B3LYP) functional and supplemented with the standard 6-31G* basis set (referred to as HF calculations) and 6-31G** basis set (referred to as DFT calculations). Using GAUSSVIEW program (Frisch et al., 2000), the HF and DFT theoretical calculations were made by using Gaussian 03 program package (Gaussian 03 program 2004).

The most important orbitals in a molecules are the frontier molecular orbitals, called highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). These orbitals determine the way the molecule interacts with other species.

We have successfully calculated the geometries of the various Pentaprazol, DDQ, CHLC and I_2 figure.(3-5) and the complexes between them figure.(3-6), which support the idea that the Pantoprazole and Omeprazole drugs act as donors due to high electron density while I_2 , DDQ and CHLC act as acceptors.

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