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Article

COMPUTATIONAL STUDY ABOUT CYTOTOXICITY OF METAL OXIDE NANOPARTICLES INVOKING NANO-QSAR TECHNIQUE

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ABSTRACT

Nano compounds are highly ranked in the research domain due to their remarkable structural aspects and other physical properties. Now a days, metallic oxides nanoparticles are being used in renewable energy, water treatment, food & agriculture, textiles, medical, electronics, photo-physical, cosmetics, pharmaceutical, automobiles and many other fields. Apart from their huge beneficial aspects, cytotoxic effects of these nano-sized compounds are widely reported. In the present analysis, a group of 17 metal oxides nanoparticles have been studied invoking conceptual Density Functional Theory (DFT) based descriptors. Experimental cytotoxicity is explained qualitatively in terms of our computed data. Nano- QSAR modelling has been performed using multi linear regression analysis between experimental toxicity and evaluated theoretical descriptors. A high value of regression coefficient explains efficacy of our predicted model.

Keywords: DFT, Cytotoxicity, multi linear regression, nano metal-oxide

1. INTRODUCTION

Nano compounds (of size 1-100nm) have captivated the researchers' attention due to their novel properties and advantages over macro and micro counterparts of a chemical compound. From the literature, it is known that the size of a chemical compound plays a major role in the bio-activity. Nanoparticles were reported with greater pharmacological activity even with reduced drug dose owing to their surface properties [1, 2]. Formulation

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of nano drugs or chemicals is a simple task when compared to assessing their biological activity. Determination of biological activity of a chemical compound is necessary when a new chemical is discovered from nature. Estimation of biological activity, determining effective dose range and safety consumes a lot of time involving animal models and human volunteers' clinical trials. Long-term toxic effects of a chemical are difficult to trace out even in the clinical trials as the probable reactions in the body may not be observed immediately after a compound enters the biological system. Significantly, quantitative structure activity relationship (QSAR) is helpful in reducing the time and cost spent for the studies. These nanoparticles are used in vast number of products now-a-days to improve the performance of manufactured goods. Unfortunately, these incorporated nanoparticles are causing toxic effects in a variety of biotic components either by dermal contact or inhalation or by ingestion [3-5]. Recently it was reported that silver nanoparticles used in various manufactured goods are the reason for toxic effects in some aquatic organisms [6] due to their gradual leaching from goods to the environment. Autopsy was reported in a person on heavy exposure to titanium dioxide nanoparticles for prolonged period of time. Similarly particles from various manufactured products have been causing toxic effects in biotic components of the environment. Experimental results from the previous researches are helpful in correlating the activity with the predicted values in in-silico drug design. In-silico drug design is a tool of bio-chemoinformatics where the physico-chemical properties of chemical compounds are determined computationally invoking descriptors. QSAR/QSPR approach plays important role in the determination of activity of a chemical compound. Owing to the size, nanoparticles are more potent and a maximum concentration of the dose is absorbed and distributed in the biological system. Biological systems exposed for prolonged period with nanoparticles are proved toxic. Metal oxide nanoparticles are used in various manufactured products intended for the biological use. Prolonged exposure of these particles causes various toxic effects including cancers [7, 8]. Determining toxic effects of the chemicals at a target site of biological system is not transparent and the effects may not be completely screened. Computational techniques are paramount in screening various effects of the chemical substance in the biological systems, which reduces the experimental costs and consumes time. QSAR/QSPR approach can be utilised to forecast the physicochemical behaviour of the nano compounds which are not yet synthesised. Descriptors play a major role in this approach; mathematically relates the structure and activity/property of a compound. Validation of QSAR/QSPR approach is important for the results to be acceptable. In the present study, metal oxides are optimised invoking Density functional theory (DFT) and Hartree-Fock (HF) method.

2. COMPUTATIONAL METHODOLOGY

17 metal oxide nanoparticles used in various marketed products were optimised in the present research work are listed in Table 1. Metal-oxide nanoparticles were optimised invoking DFT methodology using B3LYP functional, MPW1PW91 functional and LanL2MB basis set, 6-311G basis set. Descriptors were derived by ab-initio Hartree-fock method using LanL2DZ basis set and 6-311G basis set. The molecules are optimised to obtain the lowest energy state possible. The Eigen values obtained after optimisation were used to determine the Global properties i.e., Hardness (η), Softness (s), Electronegativity (χ), Electrophilicity index (ω) of the molecules. Derived global descriptors are correlated with the experimental activity to describe the level of correlation.

Despite the beneficial aspects of nanoparticles like improved bioavailability, increased surface area of particles is reported with cytotoxic effects [9] on prolonged exposure to the biological components. Cytotoxicity is an important property of the nano size metal-oxide rather than their macro and micro counterparts. Experimental in-vitro toxicity of nano sized metal oxides has been reported by Jerzy Leszczynski (Nature 2011). In-vitro studies of cytotoxicity were expressed in terms of logarithmic value of molar $1/EC_{50}$, given in Table 2 are expressed in mol l^{-1}.

Table 1: Computed DFT based Global Descriptors

No.	Compound	Energy gap	Hardness (η)	Softness (S)	Electro-negativity (χ)	Electrophilicity index (ω)
1	Al_2O_3	0.1288	0.0644	7.7627	0.1561	0.1892
2	Bi_2O_3	0.0869	0.0434	11.5114	0.1345	0.2084
3	CoO	0.0639	0.0319	15.6494	0.161	0.4056
4	Cr_2O_3	0.1239	0.062	8.0684	0.1541	0.1916
5	CuO	0.1454	0.0727	6.8766	0.1563	0.1681
6	Fe_2O_3	0.0464	0.0232	21.5424	0.1892	0.7711
7	In_2O_3	0.1372	0.0686	7.2896	0.1982	0.2865
8	La_2O_3	0.0666	0.0333	15.0060	0.1172	0.2063
9	NiO	0.0474	0.0237	21.0837	0.1777	0.6656
10	Sb_2O_3	0.1643	0.0822	6.0853	0.1216	0.0901
11	SiO_2	0.2182	0.1091	4.5837	0.2472	0.280
12	SnO_2	0.1552	0.0776	6.4432	0.1324	0.1129
13	TiO_2	0.0638	0.0319	15.6739	0.1683	0.4441
14	V_2O_3	0.0683	0.0341	14.650	0.1399	0.2864
15	Y_2O_3	0.0986	0.0493	10.140	0.1227	0.1526
16	ZnO	0.0865	0.0432	11.5674	0.1571	0.2855
17	ZrO	0.0496	0.0248	20.1653	0.1552	0.4856

All the molecules were optimised using Gaussian 03 package. Invoking Koopman's theorem, ionisation energy and electron affinity were calculated using the formulae,

$I.E = -\varepsilon_{HOMO}$ (1)

$E.A = -\varepsilon_{LUMO}$ (2)

Hence, ionisation energy and electron affinity are utilised to compute various global properties like hardness (η), softness (S), electronegativity (χ), electrophilicity index (ω) and chemical potential (μ):

$$\eta = (IE - EA)/2 \quad (3)$$

$$S = 1/2\eta \quad (4)$$

$$\chi = -\mu = (IE + EA)/2 \quad (5)$$

$$\omega = \chi^2/2\eta \quad (6)$$

The observed activity parameters; the global properties were given in Table 1 and Table 2. All the parameters are expressed in electron volts (eV).

Table 2: Computed descriptors invoking HF method

S. No	Compound	Energy gap	Hardness (η)	Softness (S)	Electro-negativity (χ)	Electro-philicity index (ω)	Exper-imental activity (mol L^{-1})
1	Al_2O_3	0.4066	0.2033	2.459	0.2212	0.1203	2.49
2	Bi_2O_3	0.2117	0.1058	4.7216	0.1025	0.0496	2.82
3	CoO	0.3227	0.1613	3.0990	0.1622	0.0815	3.51
4	Cr_2O_3	0.2731	0.1365	3.6613	0.1704	0.1063	2.51
5	CuO	0.3265	0.1632	3.0625	0.1259	0.0485	3.20
6	Fe_2O_3	0.0848	0.0424	11.7896	0.1743	0.3580	2.29
7	In_2O_3	0.4095	0.2047	2.4421	0.2029	0.1005	2.81
8	La_2O_3	0.2331	0.1165	4.2894	0.1102	0.0521	2.87
9	NiO	0.3054	0.1527	3.274	0.1704	0.0950	3.54
10	Sb_2O_3	0.4044	0.2022	2.4723	0.1179	0.0344	2.64
11	SiO_2	0.4998	0.2496	2.0025	0.2507	0.1259	2.20
12	SnO_2	0.4411	0.2205	2.2673	0.1815	0.0747	2.01
13	TiO_2	0.3639	0.1819	2.748	0.1933	0.1027	1.74
14	V_2O_3	0.3585	0.1792	2.790	0.1837	0.0942	3.14
15	Y_2O_3	0.3148	0.1574	3.1761	0.1803	0.1032	2.87
16	ZnO	0.3153	0.1576	3.1715	0.1752	0.0973	3.45
17	ZrO	0.3224	0.1611	3.1018	0.1811	0.1017	2.15

Multi linear regression analysis (MLR)

Global descriptors computed invoking DFT and HF-method were correlated with the experimental activity of the compounds (log $1/EC_{50}$) using minitab 16 statistical software. Testing of regression analysis revealed that the methods were approximate.

3. APPLICATION/RESULTS AND DISCUSSION

3.1. Results

17 metal-oxide compounds were optimised invoking Density functional theory and Hartree-Fock method. Optimisation of a chemical compound yields Eigen values which were used to compute energies of HOMO (highest occupied molecular orbital) and LUMO (lowest occupied molecular orbital) and inturn global properties like Hardness (η), Softness (s), Electronegativity (χ), Electrophilicity index (ω). Invoking Koopmans theorem, Eq. 1 and 2 are used to compute ionisation energy (I.E) and electron affinity (E.A) of the compounds. Further, the energies obtained from Eq. 1 and 2 are used to

derive various global properties. All the computed global properties invoking DFT and HF method are listed in Tables 1 and 2.

3.2. Discussion

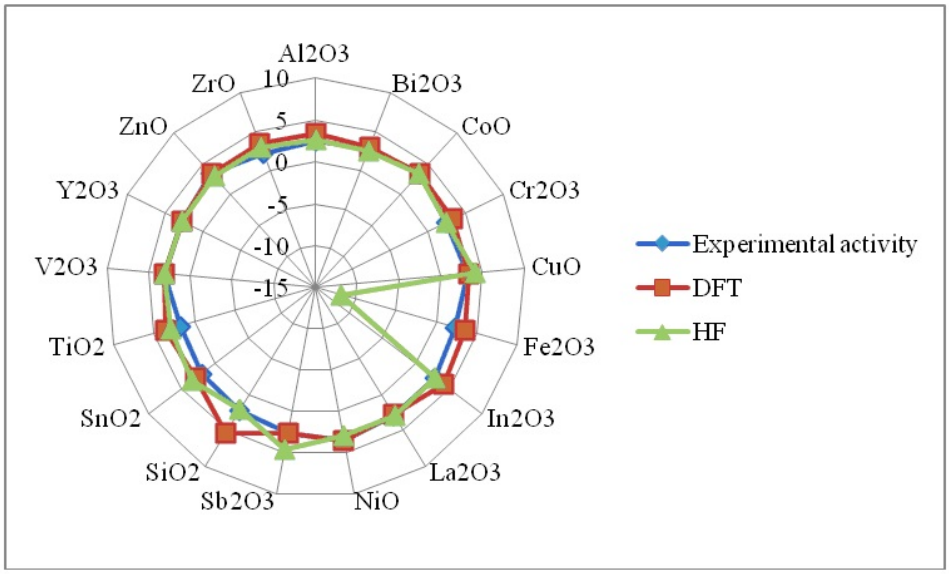
From DFT approach, Fe_2O_3, NiO and ZrO are observed with high softness values 21.5424eV, 21.0837eV and 20.1654eV. From HF-method, Fe_2O_3 nano-particles were observed with greater softness, 11.7896eV. High value of softness indicates greater reactivity of the nano compounds. Greater is the reactivity, greater is the potency as well as the cytotoxic effects of the material. Experimental activity of nano metal-oxides is found to be greater in case of NiO, CoO and ZnO with 3.54mol l^{-1}, 3.51mol l^{-1} and 3.45mol l^{-1} respectively.

Table 3: Comparison of regression equation testing with the experimental activity

Compound	Experimental activity	DFT	HF
Al_2O_3	2.49	3.3698	2.573
Bi_2O_3	2.82	3.0152	2.5075
CoO	3.51	3.4504	3.3147
Cr_2O_3	2.51	3.3309	2.4932
CuO	3.20	3.377	4.0917
Fe_2O_3	2.29	3.5828	-11.764
In_2O_3	2.81	4.1653	2.9694
La_2O_3	2.87	2.8283	2.9574
NiO	3.54	3.5512	2.9568
Sb_2O_3	2.64	2.638	4.6510
SiO_2	2.20	5.3102	2.0592
SnO_2	2.01	2.8772	3.4711
TiO_2	1.74	3.5334	2.972
V_2O_3	3.14	3.1632	3.142
Y_2O_3	2.87	2.7635	2.8486
ZnO	3.45	3.3892	2.9639
ZrO	2.15	3.4116	2.9094

To determine the accuracy of the theoretical analysis, multi linear regression is used. In MLR studies, all the theoretical descriptors were correlated with the experimental activity of the metal oxide yielding a regression equation and regression coefficient (R^2). Regression analysis for DFT has exhibited regression coefficient (R^2) of 0.933 and by HF method the R^2 was 0.918. A high value of regression coefficient validates our effort in correlating the theoretical data with their experimental counterparts. Testing of the regression equation was done by substituting the descriptors values in the equation for every metal oxide compound. The results obtained were approximately similar to the experimental values with some exceptional compounds like Fe_2O_3 and TiO_2 with much variance from the experimental value. The data is presented in Table 3. From testing, it has been observed that the values obtained by both DFT and HF method are approximately similar except in case of Fe_2O_3 by HF method. Fig 1 represents the graph which compares theoretical activity against the experimental activity.

Figure 1: Comparison of Experimental activity with theoretical activity invoking DFT and HF method.



Here we have described as theoretical activity because, it is the activity obtained by substituting the descriptors in the regression equation. From the graph it is observed that the experimental activity of all the metal oxide compounds is merely correlating with the theoretical activity except in case of Fe_2O_3 Sb_2O_3 and SnO_2 using HF method.

4. CONCLUSION

In the present research, we have studied the toxicity of various nano metal oxide compounds used in various manufactured products. These manufactured products containing nano compounds may directly or indirectly come in contact with the biotic components and on prolonged exposure to these compounds yields toxic effects. So here, we have determined the activity in terms of the theoretical descriptors and correlated with the experimental activity and a nice correlation was observed. The values obtained invoking DFT and HF methods are almost similar and were approximately correlated with the experimental activity.

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