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Prediction of surface tension of phenolic compounds (Anti-Leukemia agents) using regression

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***Abstract**:*
The chemical activity, adsorption, dissolution, and bioavailability of a drug may depend on the surface of the molecule. To develop new and better molecules with improved qualities of drugs, knowledge of surface tension is of most importance. In this study different molecular models have been used to describes surface tension of phenols derivatives as anti-leukaemia agents. To developing the models for surface tension of phenol derivatives we used descriptors like Mor04m, Mor23m, FDI, RDF045m, MATS5p, R3e, eHOMO, eLUMO RDF045m, MATS5p, R3e and the best model proposed for surface tension. for this we used several statistical parameters like R, PRESS, R2cv, SSY, SPRESS, PSE, LSE, PE etc. to validate the model.

Keywords: *QSAR, Surface Tension, Molecular descriptors, 3D MoRSE descriptors, FDI descriptors, RDF descriptors, Moreau autocorrelation descriptors, correlation coefficient.*

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I. Introduction

Surface tension is a contractive tendency of the surface of a liquid that allows it to resist an external force. Surface tension is an important property that markedly influences the ecosystem. Surface chemistry has a large influence in many industries. In the life sciences, surface area is gaining importance in the characterization of materials during their development, formulation and manufacturing. Surface chemistry has a large influence in many industries. The application of the knowledge of surface tension is of utmost importance to yield new and better performing products. Surface tension can influence the development, production and performance of pharmaceutical, food, biomaterial and other products.[1]

The rate and extent of drug absorption in the gastrointestinal (GI) tract are determined by factors such as dissolution, disintegration and the aqueous solubility of the drug. These factors should be considered because they have a significant impact on properties of drugs, such as uptake, distribution, transport, and eventually bioavailability[2,3] By applying special surface treatments such as contact angle and surface tension measurements to pharmaceutical compounds, drug distribution, dissolution behavior and release pattern in various body fluids can be improved. In vitro conditions designed to simulate the physiological environments of the GI tract should be controlled for drug dissolution experiments which mimic the in vivo conditions[4].

The range of surface tensions for oral formulations were 36.6–64.7 dynes/cm. Nasal formulations had surface tensions below that of the normal mucosal lining fluid with a range of 30.3–44.9 dynes/cm. Ophthalmic OTC formulations had the largest range of surface tensions at the surface-to-air interface of 34.3–70.9 dynes/cm; however, all formulations indicated for treatment of dry eye had surface tensions higher than that of normal tears, while those for treatment of red eye had surface tensions below. Therefore, surface tension at the surface-to-air interface of liquid formulations is dependent on the route of administration, environment at site of introduction, and for ophthalmics, what the formulation is indicated for[5].

There are two primary mechanisms in play. One is an inward force on the surface molecules causing the liquid to contract[6,7] Second is a tangental force parallel to the surface of the liquid.[7] This tangential force (per unit length) is generally referred to as the surface tension.

Surface tension is exposed, for example, any time an object or insect (e.g. water striders) that is denser than water is able to float or run along the water surface. At liquid-air interfaces, surface tension results from the greater attraction of water molecules to each other (due to cohesion) than to air (due to adhesion). The net effect is an inward force at its surface that causes water to behave as if its surface were covered with a stretched elastic membrane. Because of the relatively high attraction of water molecules for each other, water has a high surface tension (72.8 millinewtons per meter at 20°C) compared to that of most other liquids. Surface tension is an important factor in the phenomenon of capillarity.

Surface tension has the dimension of force per unit length or of energy per unit area. The two are equivalent but when referring to energy per unit of area, people use the term surface energy which is a more general term in the sense that it applies also to solids and not just liquids. In materials science, surface tension is used for either surface stress or surface free energy. Surface tension values of phenol derivatives which used in the study are given in Table (i).

Using computational method, we suggest model having best prediction power for Surface tension. Computational chemistry is applications of computer and computer enable calculations in chemistry for various purposes. One most important scope of computational Chemistry is QSAR and QSPR followed by Drug Designing. QSAR i.e. Quantitative Structure Activity Relationship provides a way to correlate the effect of structure over activity in terms of mathematical descriptors viz. Topological Indices. Quantitative structure-activity relationships (QSAR) represent an attempt to correlate structural or property descriptors of compounds with activities. These physicochemical descriptors, which include parameters to account for hydrophobicity, topology, electronic properties, and steric effects, are determined empirically or, more recently, by computational methods. Activities used in QSAR include chemical measurements and biological assays. QSAR currently are being applied in many disciplines, with many pertaining to drug design and environmental risk assessment.

II. Material And Methods

The QSAR equation is linear model which relates variations in biological activity to variations in the values of computed (or measured) properties for a series of molecules[8]. For the method to work efficiently, the compounds selected to describe the "chemical space" of the experiments (the training set) should be diverse[9]. A Quantitative Structure/Activity Relationship (QSAR) is the study of the dependence of the chemical structure on an observable experimental property or 'activity' over a collection of chemical compounds. Modelling this relationship allows predictions to be made about properties of previously unseen chemical compounds.

We found mostly in many QSAR models single descriptor is not sufficient to express completely of property or activity of given set of compounds. So we use more than one descriptor to achieved goal And this type of analysis known as multiple linear regression analysis 'MLR'. In order to build linear relationship and test model, the 49 compound data sets was used as training to build model. Finally with the selected eight different descriptors, we will build several linear models using the training data sets and following equations were obtained. Among the generated QSAR models; two models were selected on the basis of various statistical parameters such as squared correlation co-efficient (r2) which is relative measure of quality of fit.

To developing the first model for Surface Tension of phenol derivatives in we used eight descriptors Mor04m, Mor23m, FDI, RDF045m, MATS5p, R3e, eHOMO, eLUMO. There are 49 observations (molecules) are used to built this model for Surface Tension. By regression Statistics we get correlation coefficient is 0.9903, r^2 is 0.9806, Adjusted R Square *is* 0.9529, and Standard Error is 7.059 for model-I which described by equation (1).

Predicted Surface Tension = (0.483087 x Mor04m**) + (**-0.73664 x Mor23m**) + (**56.61545 x FDI**) + (**0.115954 x RDF045m**) + (**0.596032 x MATS5p**) + (**-11.1539 x R3e**) + (**0.483197 x eHOMO**)+ (**-6.3629 x eLUMO**)**

…..(1)

Table no 1: Analysis of variance of Model –I for Surface Tension

	df	*SS*	*MS*	*F*	*Significance F*
Regression	8	103440	12930	259.49	5.70E-32
Residual	41	2043	49.829		
Total	49	105483			

To developing the second model for Surface Tension of phenol derivatives in we used eight descriptors Mor29p, Mor20e, Mor04m, Mor23m, FDI, RDF045m, MATS5p, R3e. There are 49 observations (molecules) are used to built this model for Surface Tension. By regression Statistics we get correlation coefficient is 0.557233, r^2 is 0.310509, Adjusted R Square *is* 0.172611, and Standard Error is 8.106761 for model-II which described by equation (2).

Predicted Surface Tension = (12.46901 x Mor29p) + (-8.4828 x Mor20e) + (-0.163 x Mor04m) + (-23.1893 x Mor23m) + (246.1167 x FDI) + (0.160262 x RDF045m) + (-0.00673 x MATS5p) + (-4.4777 x R3e) -191.407

…..(2)

Table no 2: Analysis of variance of Model –II for Surface Tension

	df	*SS*	*MS*	*F*	*Significance F*
Regression	8	1183.86	147.9825	2.251726	0.04337362
Residual	40	2628.783	65.71957		
Total	49	3812.642			

Modelling of Surface Tension of Phenol derivatives we used 3D MoRSE descriptors (3D Molecule Representation of Structures based on Electron diffraction), Folding Degree Index (Φ) FDI, radial distribution function (RDF), Moreau–Broto Autocorrelation Descriptors, GETAWAY Descriptors (R3e (autocorrelation of lag3/weighted by atomic Sanderson electro negativity) Descriptors), Quantum-Chemical Descriptors (eHOMO, eLUMO) Descriptors.

Table no 3: Observed and Predicted value of Surface Tension using Eq. (1)

S. No.	Substituents	Surface Tension ± 3.0dyne/cm	*Predicted Surface Tension ± 3.0dyne/cm*	*Residuals*	*Standard Residuals*
1	**4-OCH3**	38.6	50.597	-12	-1.858
2	**4-OC2H5**	38	47.67	-9.67	-1.498
3	**4-OC3H7**	37.5	38.756	-1.256	-0.195
4	**4-OC4H9**	37.1	36.089	1.0113	0.1566
5	**4-OC6H13**	36.5	37.305	-0.805	-0.125
6	**H**	40.9	46.413	-5.513	-0.854
7	**4-NO2**	60.2	57.699	2.5013	0.3874
8	**4-Cl**	44.7	46.648	-1.948	-0.302
9	**4-I**	53.9	52.418	1.482	0.2295
10	**4-CHO**	52	53.893	-1.893	-0.293
11	**4-F**	38.5	48.541	-10.04	-1.555
12	**4-NH2**	57.4	47.284	10.116	1.5667
13	**4-OH**	57.1	48.406	8.6944	1.3465
14	**4-CH3**	38.8	44.665	-5.865	-0.908
15	**4-C2H5**	37.6	39.449	-1.849	-0.286
16	**4-NHCOCH3**	52.8	42.643	10.157	1.573
17	**4-CN**	57.8	53.074	4.7257	0.7319
18	**4-OC6H5**	46.3	42.217	4.0827	0.6323
19	**Bisphenol-A**	46	39.797	6.203	0.9606
20	**4-Br**	47.2	48.672	-1.472	-0.228
21	**4-C (CH3)3**	32.9	39.867	-6.967	-1.079
22	**3-NO2**	60.2	57.437	2.763	0.4279
23	**3-NHCOCH3**	52.8	43.584	9.216	1.4273
24	**3-Cl**	44.7	48.647	-3.947	-0.611
25	**3-C(CH3)3**	32.9	40.119	-7.219	-1.118
26	**3-CH3**	38.8	46.163	-7.363	-1.14
27	**3-OCH3**	38.6	46.346	-7.746	-1.2
28	**3-N (CH3)2**	44	43.886	0.1145	0.0177
29	**3-C2H5**	37.6	40.259	-2.659	-0.412
30	**3-Br**	47.2	40.852	6.3478	0.9831
31	**3-CN**	57.8	56.782	1.0182	0.1577
32	**3-F**	38.5	45.592	-7.092	-1.098

33	**3-OH**	57.1	45.143	11.957	1.8517
34	**3-NH2**	57.4	45.074	12.326	1.909
35	**2-CH3**	38.8	45.858	-7.058	-1.093
36	**2-Cl**	44.7	48.523	-3.823	-0.592
37	**2-F**	38.5	45.679	-7.179	-1.112
38	**2-OCH3**	38.6	40.774	-2.174	-0.337
39	**2-C2H5**	37.6	39.408	-1.808	-0.28
40	**2-OH**	57.1	45.445	11.655	1.805
41	**2-OH, 4CH3**	51.6	43.597	8.0034	1.2395
42	**2-NH2**	57.4	45.317	12.083	1.8713
43	**2-CN**	57.8	56.038	1.7619	0.2729
44	**2-NO2**	60.2	59.143	1.0566	0.1636
45	**2-Br**	47.2	50.981	-3.781	-0.586
46	**2-C (CH3)3**	32.9	40.031	-7.131	-1.104
47	**4-C3H7**	37.1	37.459	-0.359	-0.056
48	**4-C4H9**	36.7	36.344	0.3562	0.0552
49	**4-C5H11**	36.4	35.625	0.7749	0.12

III. Result And Discussion

In case of modeling Surface Tension to build linear relationship and test model, the 49 compound data sets was used as training to build models. With the selected eight to ten different descriptors, we will build linear models using the training data sets and equations (1) and (2) were obtained. QSAR & QSPR attempts to find consistent relationship between physiochemical properties and molecular structure, so that these "Relationship Rules" can be used to evaluate the activity and properties of new compounds.

In order to confirm most powerful predictable Model for surface tension we have apply some statistical parameter[10]. These statistical parameters are support Model-I for surface tension due to low value of LSE and PE is much greater than R for model-I (Eq.1); is the better model compares to other. The cross-validated PRESS and SSY as recorded in Table (i) indicates model-I (Eq.1) for surface tension is a better model and will give excellent result. And according to SPRESS and PSE values model-I (Eq.1) is a better model and will also give excellent result.

Table no 4 Statistical parameters for Model I and Model II

S. No.	Statistical parameters	Model I	Model II
1	N	49	49
2	no of Descriptors	8	8
3	R	0.990	0.557
4	R2	0.981	0.311
5	SE or Sd	7.059	8.107
6	PRESS	2042.988	2628.783
7	SSY	1750.838	1183.860
8	R^2cv	-0.143	-0.550
9	SPRESS	7.147	8.107
10	PSE	6.457	7.325
11	R^2A	0.953	0.173
12	LSE	2042.988	2628.783
13	PE	0.573	0.637
14	Q=r/sd	0.140	0.069
15	PRESS/SSY	1.167	2.221

IV. Conclusion

By the study of surface tension of phenols derivatives as anti-leukaemia agents, models discussed earlier Model I shows excellent result in prediction of surface tension. Statistical approach PRESS, SSY, SPRESS, PSE values supported this model. Higher Q and Lower LSE.

Observed value of Surface Tension was plotted against and Predicted values Using **Eq. (1)** shown in Figure below. The figure clearly indicates there is a significant co-relation between Observed and Predicted values of Surface Tension. Only 2HOPH, 2APH, 3HOPH, 3APH, 4APH, 4HOPHA [benzene-1,2-diol, 2-aminophenol, benzene-1,3-diol, 3-aminophenol, 4-aminophenol, N-(4-hydroxyphenyl)acetamide respectively]shows deviation. Other molecule shows excellent co-relation for Surface Tension. (Correlation coefficient is 0.9903, r^2 is 0.9806).

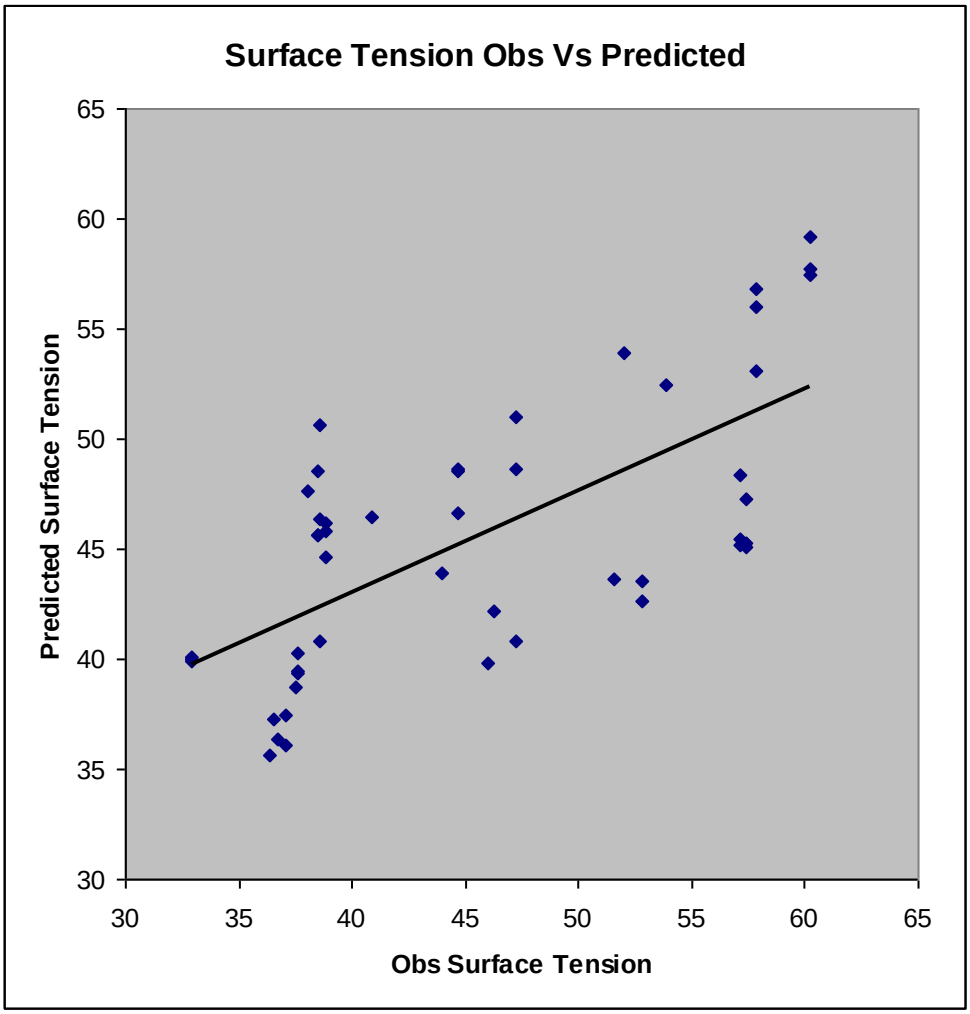

Figure 4.10 Correlation of Observed and Predicted value of Surface Tension Using Eq. (1)

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