AN INSIGHT INTO MEDICINAL ACTIVITY THROUGH PHYSICAL TECHNIQUES

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Abstract: The efficiency of a drug in curing a particular ailment or disease depends on how fast in drug is assimilated in the blood and the subsequent drug-DNA interactions that follows macroscopic study of drug activity is being attempted by some clinical methods. Understanding of the same through molecular interactions is being done using physical techniques. Imaging, Tomography and Ultrasonic scanning are a few techniques developed and used extensively. However understanding of the drug activity through physical methods like refractivity, diamagnetic susceptibility and electron ionization cross-section had been undertaken by Murthy and his group since 1994. A brief review of the work undertaken by Murthy and his group is presented in this work. The latest work on refining the algebraic relation between molecular electron ionization cross-section (Q) and the medicinal parameters protein Binding(PB), Bioavailability(BA), Log P and Half-life(HL) and dosage(D) is presented along with application to a few medicinal systems.

Curing an ailment or disease depends upon how efficiently the drug molecule interacts with the DNA molecule. The macroscopic study of drug DNA interaction **effectively** and the drug activity shows how fast a disease is cured. This is understood from MRI, CTS, ultra sound scanning, Mammography, Tomography etc., techniques.

The author attempted to estimate dosage of few medicinal compounds through physical techniques like bond polarizabilities, refractivity method, diamagnetic susceptibility method and electron ionization cross section through an empirical relation which relates the drug dosage to the electron ionization cross section Q, to plasma protein binding, half-life period and dosage D.

The present investigation is found to pave way for a new direction of study of drug activity without recourse to technique involving expensive instrumentation.

Keywords: Molecular Electron Ionization Cross-Section Refractivity, Susceptibility, Half-Life of A Drug, Dosage and Toxic Effects.

Introduction: The constant pursuit in pharmacology and pharmaco-chemistry is to study how efficiently a drug interacts with DNA and hence be used to treat a particular disease. The study

of Drug-DNA interactions and the effective monitoring of a drug for a disease have acquired a lot of importance in recent days owing to the necessity to treat dreadful diseases like AIDS, Alzheimer's disease, cancer etc,. The Drug-DNA interactions and the effective dosage of a drug have been studied by many physico-chemical, quantum mechanical and spectroscopic techniques. However the effective use of refractive index(r), diamagnetic susceptibility (χ_M) and molecular electron ionization cross-section (Q) for these studies remained very limited until Murthy along with his collaborators attempted in this direction.

This paper gives a brief review of the method of evaluation of molecular electron ionization cross-section (Q) from molecular polarizability (α_M), diamagnetic susceptibility (χ_M) and its relevance in discussing dosage (D) in relation to Protein binding (PB), Bioavailability (BA), Log P and Half-life (L). An algebraic relation relating all these medicinal parameters (Murthy, Raghuram and Murthy[1,2]) is developed and is applied to evaluate dosages.
The refinement to the algebraic relation is proposed in this paper and this method is applied to evaluate dosages of few NSAID and Anti histamine. The results are discussed very critically.

The studies on polarizability, diamagnetic susceptibility and molecular electron ionization cross-section of few systems of medical importance have been studied by Murthy and co-workers since 1994. Srinivasulu[3] studied certain flavonoids and flavinones and correlated molecular electron ionization cross-section with their medical properties in his doctoral thesis[3]. While Suresh Babu[4] studied diamagnetic susceptibilities and related properties of a few plant drug molecules[4], Phaniraja Rao[5] correlated Q with interesting properties of drugs like curing night blindness and hereditary diseases. Ramesh Babu[6] discussed physical properties and medical activity of a few antibiotics. Nagalakshmi[7] used optical studies using lasers for diabetic diagnosis and Kavitha[8] extended application of refractivity studies to diabetic diagnosis. Raghuram[9] studied polarizability, diamagnetic susceptibility and molecular electron ionization cross-section of few antimalarial, antihistamine, antidepressant, anti-inflammatory and antibiotic and correlated Q with dosages.

Methodology: The method of evaluation of molecular polarizability, diamagnetic susceptibility and molecular electron ionization cross-section has been outlined in references 1and 2.

For data on molecular electron ionization cross-section in conjunction with medical parameters, Plasma Protein Binding, Bioavailability, Log P, half-life and dosage have been found to fit into an algebraic expression.

$$\left(\frac{QLD}{Log\ P}\right)^{\frac{\sqrt{(PB)(BA)}\ L^{7/4}}{5}} = \text{Constant } K \qquad (1)$$

Where Q is the molecular electron ionization cross-section in 10^{-16} cm^2, L is half-life period of the drug expressed per day, D the dosage in m.gm/day and log P is a parameter characteristic of the molecular activity PB and BA refer to protein binding and biological activity.

The molecular electron ionization cross-section Q is evaluated for Nonsteroidal Anti-inflammatory drugs and Antihistamine. The necessary data on the polarizability and the diamagnetic susceptibility for these systems are obtained through the methods suggested in ref.1and 2. The values of half-life, Dosage, Log P, PB, BA are obtained from Wikipedia.

The data on Q, PB, BA, Log P, L and D is presented in Table-I

Table I: Anti - Inflammatory (NSAID)

SNo	Compound	Qx10^{-16} cm^2	PB	BA	Log P	L(days)	K	Dosage (mg/day)
1	Indometacin	12.081	1	0.99	3.655	0.1875	1.472	200
2	Sulindac	13.2990	1	0.90	2.699	0.3250	1.199	400
3	Diclofenac	13.7148	1	0.99	4.218	0.1667	1.044	150
4	Flurbiprofen	10.522	0.99	0.25	4.078	0.2375	1.058	200
5	Diflunisal	6.7074	0.99	0.85	3.876	0.4167	0.738	1500
6	Rofecoxib	18.562	0.93	0.87	3.89	0.7083	1.419	25

Table II: Antihistamines

SNo	Compound	Qx10^{-16} cm2	PB	BA	Log P	L(days)	K	Dosage (mg/day)
1	Diphenhydramine	16.7780	0.99	0.86	2.979	0.625	1.416	100
2	Chlorpheniramine Maleate	21.9760	0.72	0.50	3.563	1.0	1.312	24
3	Hydroxizine	12.0650	0.93	0.25	3.036	1.042	1.084	95.49
4	Cyclizine	20.936	0.50	0.258	3.338	0.833	1.041	39.72
5	Ketotifen	24.523	0.75	0.60	3.003	1.667	1.719	3.508
6	Astimizole	12.747	0.96	0.25	5.572	1.00	1.103	13.50

From eqn.(1) it follows that

$$\left(\frac{QLD}{Log\ P}\right)^m = k = \text{constant where } m = \frac{L^{7/4}\sqrt{(PB)(BA)}}{5}$$

So $$D = \left[\frac{K^{1/4} log P}{QL}\right] \quad \text{---------- (2)}$$

The average value of K for NSAID is found to be 1.155 and for antihistamines 1.129.
Using these values of K, the dosage D for each drug is calculated using eqn.(2).
The calculated values of dosages along with suggested dosage for NSAID and Antihistamines is reported in Tables III and IV.

Table III: Anti- Inflammatory[10, 11] (NSAID): Average value of K= 1.155

S.No	Compound	D (calculated) (mg/day)	D (suggested) (mg/day)	Toxic Effects
1	Indometacin	200	112.5	Swelling of face, Cardiovascular thrombotic events
2	Sulindac	400	350	Abdomen pain, dizziness,
3	Dichlofenac	150	250	Nausea, vomiting, skin rash
4	Flurbiprofen	200	200	Abdominal or stomach cramps
5	Diflunisal	1500	1250	Coma, tachycardia
6	Rofecoxib	25	25	Insomnia, anxiety

Table IV: Antihistamines, Average value of K=1.129

S.No	Compound	D(mg/day) (Calculated)	D(mg/day) (Suggested)	Toxic effects
1	Diphenhydramine	100	125	Cardiac dysrhythmia, sinus
2	Chloropheniramine Maleate	24	30	Respiratory depression
3	Hydroxizine	95.49	50-100	Mild drowsiness, dry mouth
4	Cyclizine	39.72	50	Xerostomia, blurred vision
5	Ketotifen	3.508	3.5	Head ache, weight gain
6	Astimizole	13.50	10.0	Hypotension, dizziness

Results and Discussions : The dosages calculated by eqn.(2) and reported in tables III and IV reveal that the dosages agreed mostly in order of magnitude and more closely in some compounds like Flurbiprofen, Hydroxizine and Ketotifen.

But in some cases like Diflunisal and Diclofenac, the difference is much marked. This difference might be attributed to errors in values of PB, BA and mostly L.

The inference from the present paper is that, the investigators in the field of medical physics are provided with an entirely new, facile and elegant method of estimating dosages from the knowledge of simple molecular structure and data on medicinal parameters. The drug activity is reflected in its refractive, diamagnetic properties. A drug with high polarizability, diamagnetic susceptibility and Q will have little surface area of cross-section of molecule for reaction and hence needs to be monitored in less quantity. Any excess dosage might lead to imbalance in electron transport properties of drugs and result in undesirable toxic effects.

Thus the present method compares favorably well with already existing methods and is preferable to them which are both sophisticated and costly or involve tedious theoretical deliberations.

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References:

1. Murthy,V.R, Raghuram,D.V and Murthy,P.N. "Drug dosage, activity, studies of antimalarials by physical methods – II", ISSN 0973-2063 Bioinformation 2(1): 12-16 (2007).
2. Murthy,V.R, Raghuram,D.V and Murthy,P.N. "Drug dosage activity of anti-inflammatory drugs (NSAID). A novel physical approach", Romanian J.Biophys., Vol 17, No. 4, P 247-257, BUCHAREST, 2007.
3. Srinivasulu.M, Ph.D Thesis, "Studies in optical and related properties of a few molecules of medical importance "S.K University,(AP).(1996).
4. Suresh Babu.M, Ph.D Thesis, "Diamagnetic susceptibilities and related properties of plant drug molecules". S.K. University (AP),(2000).
5. Phaniraja Rao.B, Ph.D Thesis, "Optical and related properties of few medically important molecular systems," S.K. University (AP),(2001).
6. Ramesh Babu.S, M.Phil Dissertation, "Physical properties and medical activity of a few antibiotics". S.K. University (AP),(2001).
7. Nagalakshmi.B, M.phil dissertation, "Optical studies in medical diagnosis", S.K. University (AP),(2003).
8. Kavitha.S, M.Phil dissertation, "Physical studies in medicinal compounds", Acharya Nagarjuna University (AP),(2005).
9. Raghuram.D.V, Ph.D Thesis, "Physical studies, activity and dosage of medicinal compounds," Acharya Nagarjuna University (AP),(2007).
10. Murthy,V.R, Raghuram,D.V and Prasad, P.M. "Molecular characterization: Retrospective and prospective", P 215-225 Recent advances in Material Sciences. ISBN 978-93-87769-51-9.
11. Murthy,V.R, Raghuram,D.V and Prasad, P.M. "A Novel approach to drug dosage activity of Antidepressant", P 226-238 Recent advances in Material Sciences. ISBN 978-93-87769-51-9.

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