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Systematic Investigation of the Molecular Descriptors for the Bioavailability of Oral Drugs

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KEYWORDS

Oral drugs;

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Fraction Lipophilicity Index (FLI);

Log S; NLEM 2022; Biopharmaceutical Classification System (BCS)

ABSTRACT:

The molecular descriptors for predicting the drug-likeness of a small molecule was first proposed by Lipinski. While the lipinski rule of five describes four key physicochemical properties or molecular descriptors such as molecular weight, partition coefficient (Log P), hydrogen bond donors and hydrogen bond acceptors for good absorption and permeability of oral drugs, other rules such as the Veber's, Ghose, Egan's and Muegge's suggest many other key descriptors for better absorption of oral drugs. The aim of this study is to understand the correlation between the various molecular descriptors or a combination of descriptors and their influence on the bioavailability of oral drugs. For this study, structurally diverse, orally administered drugs from diverse therapeutic categories were selected primarily from the National list of Essential Medicines 2022, India [https://www.who.int/publications/m/item/india--national-list-of-essential-medicines-2022-english)] for the first time. As the dataset included neutral, acidic and basic oral drugs, in addition to log P, pH-dependent distribution coefficient (log D) at different physiologically relevant pH are also considered. Using Fraction Lipophilicity Index (FLI) which combines log P and log D as a new measure of permeability and log S as a measure of solubility, an attempt to predict Biopharmaceutical Classification System (BCS) classes of the oral drugs from the national list of essential medicines resulted in successful prediction of 70% of oral drugs into class 1 and class 2. Such an attempt is expected to provide early bioavailability profiles of drug-like small molecules and eventually narrow the search space for experimental validation.

1. Introduction

Among the different routes of drug administration, oral route is often preferred due to its non-invasive nature, cost effectiveness, unsupervised administration procedure, availability in varying dosage forms and reduced side effects. It is well known that molecular weight is an important descriptor that determines both the absorption and bioavailability of oral drugs. While low molecular weight drugs have better permeability and large absorption area making them suitable candidates for oral administration, high molecular weight natural product drugs such as macrolide antibiotics & peptides are gaining attention in the recent times [1,2]. The bioavailability of high molecular weight natural product drugs is primarily due to their conformational flexibility and their ability to form intra molecular hydrogen bonds [3] whereby they are able to expose non polar groups enabling membrane permeability while in polar environments they expose polar groups making them soluble. It is due to this 'chameleonic character' as already described in 1970 [4] of the high molecular weight macrolide antibiotics and peptides, they have better absorption and bioavailability. In addition to molecular weight, optimal lipophilicity and hydrogen bonding capability also determines the absorption and bioavailability of oral drugs [5-7]. In this regards, octanol/water partition coefficient (logP) is a widely used measure of lipophilicity and number of hydrogen bond donors and acceptors define the hydrogen bonding capability of the oral drug.

The pharmacokinetic properties or ADMET properties define absorption of a drug and its distribution within the human body while the pharmacodynamics refers to the bioavailability of the drug for specific therapeutic

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activity. Drug likeness of any molecule are guided by well-defined rules such as Lipinski, Veber's, Ghose, Egan's and Muegge's rules [8-11]. Ten different molecular descriptors with thresholds are defined by these five rules for a molecule to qualify to be an oral drug. While majority of the FDA approved drugs obey the thresholds defined by these rules, exceptions to these rules do exist [5]. A study on the physicochemical properties of FDA approved oral drugs from 2000-2022 suggests that deviations observed on the pharmacokinetic properties are often compensated by improved potency of the oral drugs [5]. A recent analysis on the FDA-approved macrocyclic drugs which often come under the classification of beyond the rule of 5 drugs, suggested that 30-40 % of the macrocyclic drugs are orally bioavailable. Their investigation also suggested that a combination of molecular descriptors which they call as bimolecular descriptor model would be effective in differentiating oral from parenteral routes of administration of macrocycles [2].

In the wake of rising drug resistance, screening of several hundreds of molecules for drug likeness properties becomes unavoidable and routine exercise. In such a scenario, experimental methods would be time consuming and expensive. Therefore, prediction of pharmacokinetic properties or ADMET properties using computational tools is an effective alternative. There are several computational tools (online/offline) available for calculating the molecular descriptors defined by the rules of drug likeness viz. These include ACD/Labs[14],Marvinsketch [15], SwissADME [16], Virtual Computational Chemistry Laboratory (VCCLAB)[17]etc. Among the several tools (free and licenced) available, we chose to use a licensed version of Marvinsketch as it was the widely used software by Drugbank, a knowledgebase hosting a detailed data of drug, drug target and action [7].

Biopharmaceutics Classification system (BCS) introduced in 1995, categorizes drugs based on solubility and permeability into 4 categories as these properties limit intestinal absorption after oral administration [18], [19]. BCS classification system sets the standards for immediate-release (IR) oral drugs. According to this classification, BCS Class I contains drugs with high solubility and high permeability (e.g. Paracetamol); Class II contains drugs with low solubility and high permeability (e.g. Diclofenac); Class III contains drugs with high solubility and low permeability (e.g. Metformin) and Class IV contains drugs with low solubility and low permeability (e.g. Cyclosporin).

Compounds with low solubility and low permeability results in low absorption and bioavailability leading to accumulation of drugs in the body resulting in increasing drug toxicity. Thus, toxicity of drug is another key player in safety, bioavailability and bioaccumulation [20]. According to Globally Harmonized System of classification of labelling of chemicals, based on the numeric criteria (LD_{50} values in mg/kg), drugs are classified into 6 toxicity classifications. Class I: Fatal if swallowed (LD_{50}<= 5), Class II: fatal if swallowed (5< LD_{50}<=50), Class III: toxic if swallowed (50< LD_{50}<=300), Class IV: harmful if swallowed (300< LD_{50}<=2000), Class V: may be harmful if swallowed (2000< LD_{50}<= 5000) and Class VI: non-toxic (LD_{50}> 5000) [20].

2. Objectives

In this analysis, a comprehensive computational investigation of ten molecular descriptors such as Molecular Weight, Hydrogen Bond donor (HBD), Hydrogen Bond Acceptor (HBA), log P (pH-independent partition coefficient), Number of Rotational Bond (NRB), Topological Polar Surface Area (TPSA), Molecular Refractivity (M.Ref), Number of Atoms (N.ATOMS), Number of Rings (N.RINGS), Fraction of sp^3 hybridized carbons (Fsp^3) defined by the five rules of drug likeness viz. was carried out using the list of oral drugs available in the National List of Essential Medicines, India 2022 (NLEM 2022) for the first time. Since the list of NLEM 2022 contains neutral, acidic and basic drugs, pH-independent partition coefficient (logP) and pH-dependent distribution coefficient (logD) were used as descriptors of lipophilicity. A study on the violations of the rules of drug likeness was carried out on the list of oral drugs in NLEM 2022 with an objective of understanding the acceptable violations to drug likeness of oral drugs.

A new lipophilicity index known as Fraction lipophilicity index (FLI) [21] that combines pH-independent log P and pH-dependent log D was used as a measure of lipophilicity and permeability to predict BCS and Toxicity classification of oral drugs based on their log S and FLI values. We could successfully classify 70% of drugs into correct BCS Classes. However, based on our efforts to predict toxicity classes, we observe that toxicity class prediction may require a combination of other molecular descriptors in addition to permeability and solubility.

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3. Methods

3.1 Dataset

240 oral drugs from 26 therapeutic categories were extracted from the National List of Essential Medicines (NLEM) 2022 [22]. The list of 26 therapeutic categories include: Medicines used in *Anaesthesia, (Analgesics, Antipyretics, Non-steroidal Anti-inflammatory Drugs) (NSAIDs)*, Medicines used to treat *Gout and Disease, Modifying Agents used in Rheumatoid Disorders, Anti-allergic and Medicines used in Anaphylaxis, Antidotes and Other Substances used in Management of Poisonings/Envenomation,* Medicines used in *Neurological Disorders, Anti-infective Medicines, Anti-cancer agents including Immuno-suppressive* and Medicines used in *Palliative Care, Medicines affecting Blood, Blood products and Plasma substitutes, Cardiovascular Medicines, Diagnostic agents, Dialysis components (Haemodialysis and Peritoneal Dialysis), Antiseptics and Disinfectants, Diuretics, Ear, Nose and Throat Medicines, Gastrointestinal Medicines, Hormones, other Endocrine Medicines and Contraceptives, Immunological , Medicines for Neonatal Care , Ophthalmological Medicines , Oxytocic and Anti-oxytocic, Medicines used in treatment of Psychiatric Disorders, Medicines acting on the Respiratory tract, Solutions correcting Water, Electrolyte disturbances and Acid-base Disturbance, Vitamins and Minerals, and Medicines for COVID 19 management*. Among these 26 categories, antibacterial and antifungal were merged into antimicrobial as there were few oral drugs in the NLEM 2022. Similarly, antimalarial and anti-parasitic were merged into anti-parasitic category. Therefore, the final analysis contains 23 therapeutic categories include Neonatal Care, Ophthalmological Medicines, Respiratory tract, Anaesthesia, Anti-leprosy Medicines, Diuretics, Anthelminthic, Medicines affecting Blood, Oxytocic and Anti-oxytocic, Vitamins and Minerals, Sexually transmitted diseases, Antidote, Gastrointestinal Drug, Psychotic Drugs, Tuberculosis Drug, Antiviral Medicines, Antimalarial Medicines, Hormones, other Endocrine Medicines and Contraceptives, Antipyretic and Anti-inflammatory, Antimicrobial, Cardiovascular Medicines, Neurological disorder, and Anti-cancer agents.

3.2 Calculation of Molecular Descriptors:

Ten molecular descriptors described by the drug likeness rules such as Lipinski, Veber's, Ghose, Egan and Muegge's rules such as Molecular Weight, Hydrogen Bond donor (HBD), Hydrogen Bond Acceptor (HBA), log P (pH-independent partition coefficient), Number of Rotational Bond (NRB), Topological Polar Surface Area (TPSA), Molecular Refractivity (M.Ref), Number of Atoms (N.ATOMS), Number of Rings (N.RINGS), Fraction of sp^3 hybridized carbons (Fsp^3) were calculated using a licensed version of Marwinsketch (Version 25.3.6) from Chemaxon [15] a software that is widely used by Drugbank [8]. As the selected list of oral medicines include neutral, acidic and basic drugs, in addition to the calculation of pH independent partition coefficient (log P), pH-dependent distribution coefficient (log D) at various pH (1.5, 5.0, 6.5 and 7.4) was also calculated. Log S at pH 7.4 is calculated as a measure of solubility using Marwinsketch software [15].

3.3 Comparison between Experimental and Calculated Lipophilicity:

In order to verify whether the calculated Clog P and Clog D (7.4) values using Marwinsketch software are close to the experimentally determined Elog P and Elog D values, a scatter plot between the ClogP Vs ElogP was plotted for 108 drugs for which the Elog P values were already available [23]. Similary, ClogD (7.4) Vs Elog D was plotted for 28 drugs for which the Elog D values were available [24.] **Figure 1a and 1b** shows the comparison between the experimentally determined Elog P and Elog D with calculated Clog P and Clog D respectively. It is clear from the plots that there is a linear correlation with a correlation coefficient (**R^2 > 0.5**) suggesting a good correlation between the experimental and calculated lipophilicity values. In comparison to log P (**Figure 1a**), log $D_{7.4}$ (**Figure 1b**) shows a better correlation (with **R^2 = 0.931**) suggesting that Clog $D_{7.4}$ is a better descriptor of lipophilicity compared to Clog P.

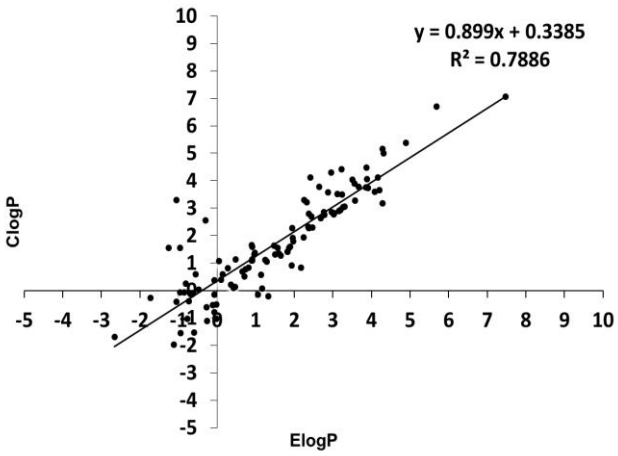

Figure 1a Plot of ClogP against Elog P. The ElogP values were taken from *Machatha SG & Yalkowsky SH, 2005.*

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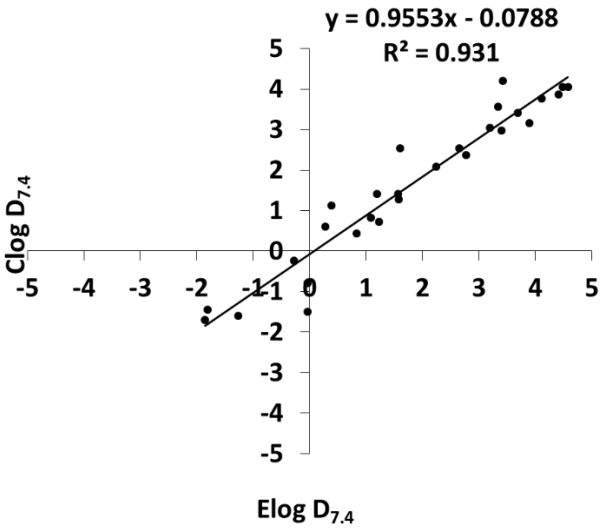

Figure 1b Plot of Clog $D_{7.4}$ against Elog $D_{7.4}$. The Elog $D_{7.4}$ were taken from *Axel Andrés .et.al., 2015*.

3.4 Calculation of Fraction Lipophilicity Index (FLI):

Fraction Lipophilicity Index (FLI) [21] is a molecular descriptor which is a combination of pH-independent partition coefficient (ClogP) and pH-dependent distribution coefficient (ClogD). It is calculated using the following formula:

$$\mathbf{FLI = (2*Clog\ P) - Clog\ D_{(pH)}}$$

CLog D values at pH 7.4 and 6.5 were used to calculate the FLI values as these pH values are close to intestinal pH range and hence influence intestinal absorption.

3.5 Prediction of Toxicity and BCS class:

The Toxicity of oral drugs were predicted using ProTox 3.0 software [20]. Due to their high molecular weight, toxicity class prediction using ProTox 3.0 was not possible for the following drugs: *Cyclosporin*, *Nystatin, Ivermectin, Tenofovir Alafenamide Frumarate, Tenofovir Disproxil Fumarate*. The BCS class of 190 oral drugs were extracted from the literature and used as reference for FLI Vs log S based BCS Class prediction. A representative list of 82 oral drugs and their BCS classes along with their citing literature are shown in **Table 1**.

4. Results & Discussions

4.1 Violation of Molecular Descriptor thresholds by Oral Drugs:

The absorption and bioavailability of small molecule drugs have been shown to obey certain accepted thresholds defined by the drug likeness rules defined by Lipinski's rule of five. However, certain natural products that violated the rule of five which were described under the category known as beyond the rule of five drugs (Ro5) still could be successfully used as oral drugs. From the National List of Essential Medicines (NLEM 2022) oral drugs (**240**) belonging to **26** therapeutic categories were extracted. Only **23** therapeutic categories were considered from NLEM 2022 oral drugs which include *Neonatal Care, Ophthalmological Medicines, Respiratory tract, Anaesthesia, Anti-leprosy Medicines, Diuretics, Anthelminthic, Medicines affecting Blood, Oxytocic and Anti-oxytocic, Vitamins and Minerals, Sexually transmitted diseases, Antidote, Gastrointestinal Drug, Tuberculosis Drug, Antiviral Medicines, Antimalarial Medicines, Hormones, other Endocrine Medicines and Contraceptives, Antipyretic and Anti-inflammatory, Antimicrobial, Cardiovascular Medicines, Neurological disorder, and Anti-cancer* agents [22].

From these, **11** therapeutic categories which had at least 10 oral drugs were chosen. These include *Gastrointestinal Drugs, Anticancer Drugs, Analgesic, Antipyretic and Anti-inflammatory Drugs, Antimicrobial Drugs (Antibacterial + Antifungal Drugs) , Antiviral Drugs (Antiviral + Covid 19 drugs), Neurological Disorder Drugs, Anti-tuberculosis Drugs, Antimalarial Drugs (Antiprotozoal +Antimalarial drugs), Cardiovascular Drugs, Hormones, other Endocrine Medicines and Contraceptives Drugs and Psychiatric Disorder Drugs.* Violation of molecular descriptor thresholds suggested by the five rules of drug likeness were calculated for the 11 categories of oral drugs. A bar graph showing the comparison of the number of drugs violating the rules of drug likeness to the total number of drugs in each of 11 therapeutic categories shows that antimicrobial drugs shows the maximum number of violations (**Figure 2).**

Table 1. *List of oral drugs with their BCS class mentioned from the literature*

S. No.	List of oral drugs	BCS Class	Citing literature[#]
1	Acetylsalicylic acid	**1**	25
2	Amlodipine	**1**	26
3	Chloroquine	**1**	27
4	Diethylcarbamazine	**1**	28
5	Hydroxychloroquine	**1**	29
6	Levetiracetam	**1**	30
7	Levodopa	**1**	31
8	Metronidazole	**1**	32

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9	Nicotine	**1**	33
10	Ondansetron	**1**	34
11	Primaquine	**1**	35
12	Propranolol	**1**	36
13	Quinine	**1**	36
14	Salbutamol	**1**	37
15	Sulphadoxine	**1**	38
16	Tramadol	**1**	39
17	Tranexamic acid	**1**	40
18	Verapamil	**1**	41
19	Warfarin	**1**	42
20	Zidovudine	**1**	43
21	Carbidopa	**1,3**	44
22	Cefuroxime	**1,3**	44
23	Escitalopram	**1,3**	44
24	Albendazole	**2**	45
25	Atazanavir	**2**	46
26	Atorvastatin	**2**	47
27	Cefadroxil	**2**	48
28	Clofazimine	**2**	49
29	Clonazepam	**2**	50
30	Clopidogrel	**2**	51
31	Clozapine	**2**	52
32	Cyclosporine	**2**	53
33	Dapsone	**2**	54
34	Domperidone	**2**	55
35	Ethionamide	**2**	56
36	Flunarizine	**2**	57
37	Gefitinib	**2**	58
38	Glimepiride	**2**	59
39	Griseofulvin	**2**	60
40	Itraconazole	**2**	61
41	Loperamide	**2**	62
42	Lumefantrine	**2**	63
43	Melphalan	**2**	64
44	Montelukast	**2**	65
45	Mycophenolate mofetil	**2**	66
46	Nevirapine	**2**	67
47	Nifedipine	**2**	68
48	Ormeloxifene	**2**	69
49	Praziquantel	**2**	70
50	Ramipril	**2**	71
51	Rifampicin	**2**	72
52	Tacrolimus	**2**	73
53	Trihexyphenidyl	**2**	74
54	Trimethoprim	**2**	75
55	Ciprofloxacin	**2,3**	44
56	Co-trimoxazole	**2,3**	76
57	Amoxicillin	**2,4**	44
58	Azathioprine	**2,4**	44
59	Dabigatran	**2,4**	44
60	Ascorbic acid	**3**	77
61	Baclofen	**3**	78
62	Chlorambucil	**3**	79
63	Clavulanic acid	**3**	80
64	Cloxacillin	**3**	81
65	Cycloserine	**3**	82
66	Enalapril	**3**	83
67	Entecavir	**3**	84
68	Ethambutol	**3**	85
69	Isoniazid	**3**	86
70	Lamivudine	**3**	87
71	Levothyroxine	**3**	88
72	Metoclopramide	**3**	89
73	Naloxone	**3**	90
74	Paraaminosalicylic acid	**3**	91
75	Riboflavin	**3**	92
76	Sumatriptan	**3**	93
77	Vancomycin	**3**	94
78	All-trans retinoic acid	**4**	95
79	Lopinavir	**4**	96
80	Mifepristone	**4**	97
81	Nystatin	**4**	98
82	Sulphamethoxazole	**4**	99

Table 2 shows the number of violations of the molecular descriptors in each therapeutic category. It is clear from the table that Fsp3 is the molecular descriptor that is most violated by all the 11 therapeutic category of drugs with *Anticancer drugs* and *Neurological disorders* topping the list. Violation to molecular weight thresholds is also

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more prevalent in all the 11 therapeutic categories *Anticancer* and *Antituberculosis drugs* topping the list.

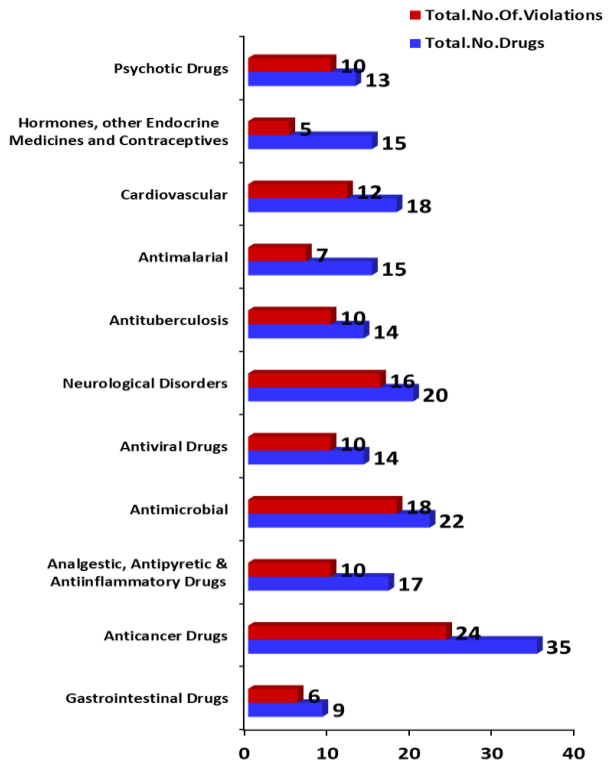
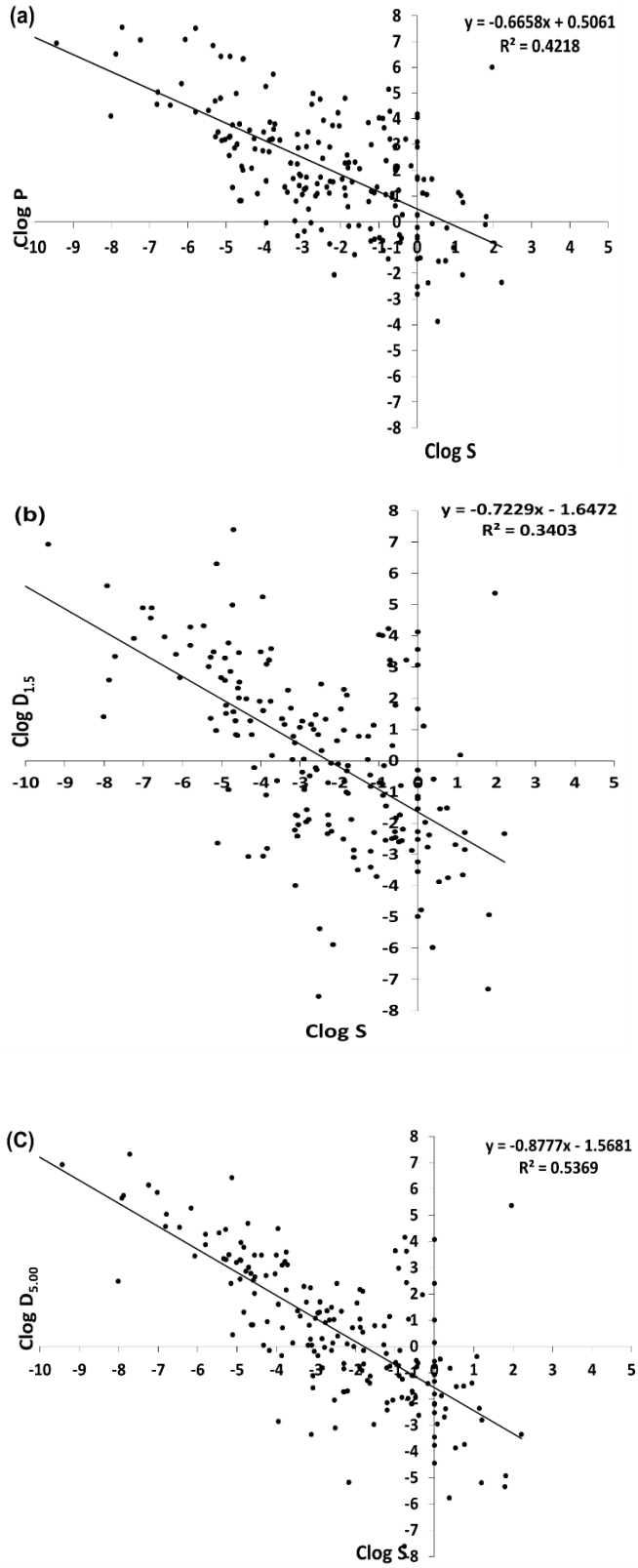


Figure 2 Comparison of the number of drugs violating the rules of drug likeness to the total number of oral drugs in each therapeutic category

4.2 Correlation between ClogS and Lipophilicity descriptors Clog P AND Clog D at various pH:

The octanol/water partition coefficient has been an accepted measure of lipophilicity of oral drugs for ages. However, it has been shown to be a good measure of lipophilicity for neutral drugs. It has already been shown that the distribution coefficient is a better descriptor of lipophilicity for acidic or neutral drugs [R – cite the paper with the title when to use log P Vs log D]. A plot of Clog P Vs Clog S of all the 242 oral drugs (**Figure 3a**) shows that there is poor correlation between the two measures ($\mathbf{R^2 = 0.4218}$). A plot of Clog D at various pH against Clog S (**Figures 3b, 3c, 3d & 3e**) suggests that the correlation between the two measures is best at pH 6.5 ($\mathbf{R^2 = 0.6141}$) and 7.4 ($\mathbf{R^2 = 0.6047}$) which is favourable



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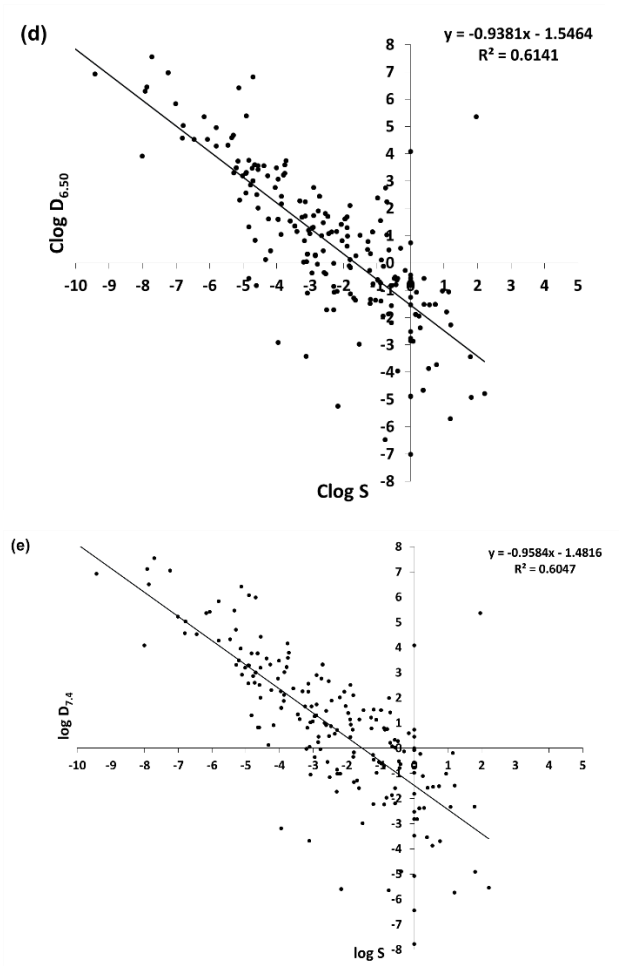

Figure 3. (a) Plot of Clog S Vs Clog P. **(b)** Plot of Clog $D_{1.5}$ Vs Clog S. **(c)** Plot of Clog $D_{5.00}$ and Clog S. **(d)** Plot of Clog $D_{6.50}$ and Clog S. **(e)** Plot of Clog $D_{7.40}$ and Clog S.

for gastrointestinal absorption. Hence, it is clear from the analysis that Clog D values at pH 6.5 and 7.4 is a good measure of lipophilicity.

4.3 Prediction of BCS classification of NLEM 2022 oral drugs based on $FLI_{7.4}$ AND Clog S:

The BCS classes of the **190** non-redundant set of oral drugs were noted from the literature. Those drugs belonging to single BCS classes were considered for the current analysis. Based on the FLI and log S thresholds, the oral drugs were classified into four BCS Categories as follows: **Class 1** ($FLI_{7.4}$ **> 0; log** $S_{7.4}$ **>= -2**); **Class 2** ($FLI_{7.4}$ **> 0; log** $S_{7.4}$ **< -2**); **Class 3** ($FLI_{7.4}$ **<0; log** $S_{7.4}$ **>= -2**) and **Class 4** ($FLI_{7.4}$ **< 0; log** $S_{7.4}$ **<= -2**). Thus, a plot of $FLI_{(7.4)}$ Vs Clog $S_{7.4}$ for the **52** oral drugs resulted in the distribution of the drugs into four quadrants with the X-axis reference shifted to Clog $S_{7.4}$ = -2 (**Figure 4**). Based on the scatter plot, it can be seen that **18** drugs belonged to class 1 (●, *filled circles*), **31** oral drugs belonged to class 2 (□, *open squares*), **3** oral drugs belonged to class 3 (**Δ**, *open triangles*), and only few oral drugs of class 4 was available in the NLEM 2022. All these predictions matched with the literature. Thus, 70% of drugs could be successfully classified into known BCS classes.

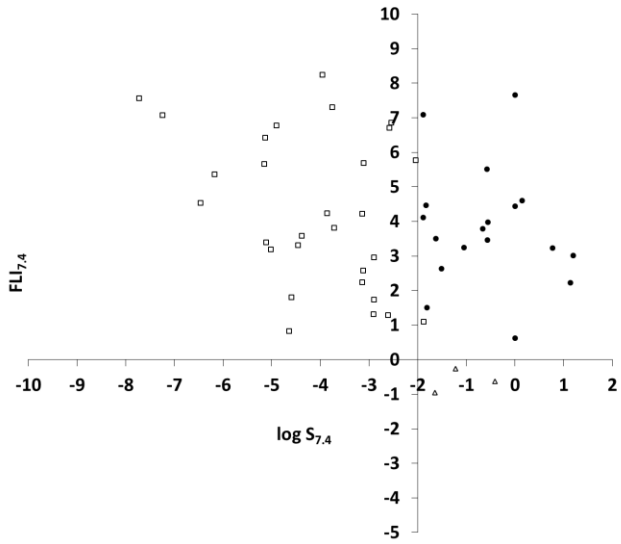

Figure 4. Plot of $FLI_{7.4}$ and Clog $S_{(7.4)}$ for BCS Classification of oral drugs. **class 1** (●, filled circles); **class 2** (□, open squares); **class 3** (**Δ**, open triangles).

4.4 Toxicity classification of Oral drugs:

An optimal balance between lipophilicity and solubility is important for absorption and bioavailability of oral drugs. When this balance is altered, it might lead to accumulation of drugs in the body resulting in increased

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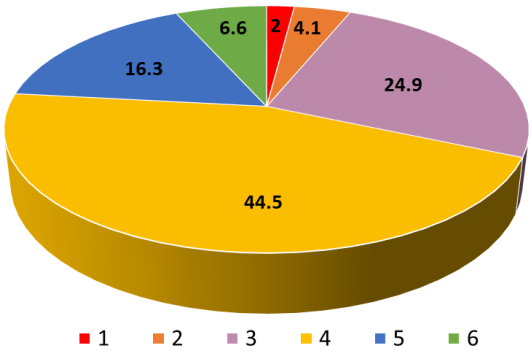

Figure 5. Toxicity class distribution (%) in NLEM 2022 list of oral drugs

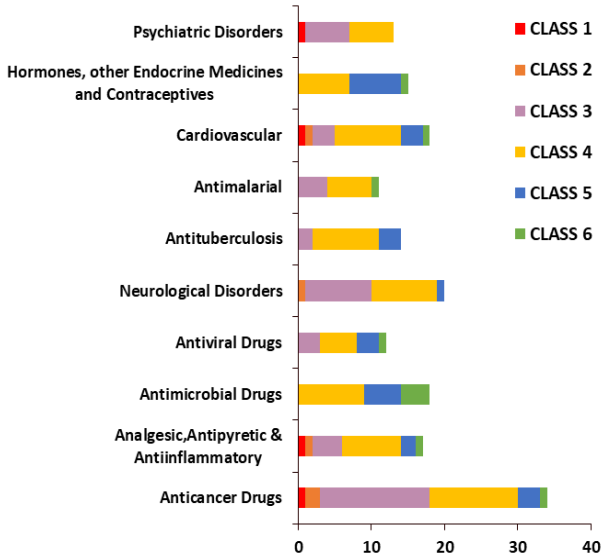

Figure 6. Distribution of toxicity classes in various therapeutic categories

toxicity. Thus, toxicity classification is an important parameter for oral drugs absorption and bioavailability. Drugs belonging to Toxicity classes greater than or equal to 4 are known to be safer for human consumption and those below class 4 are highly toxic. An analysis on the toxicity class distribution of oral drugs in the NLEM 2022 list (Figure 5) suggested that 44.5% belonged to toxicity Class 4. Analysis on the distribution of toxicity classes in different therapeutic categories (Figure 6) suggests that few oral drugs from Anticancer Drugs, Analgesic, Antipyretic and Anti-inflammatory Drugs, Cardiovascular Drugs, and Psychiatric Disorder Drugs categories belonged to Class 1.

5. Conclusion

A systematic and comprehensive investigation on the molecular descriptors of oral drugs in the National List of Essential Medicines, India 2022 (NLEM 2022) is presented here. An analysis on the violations of the molecular descriptors of the five rules of drug likeness suggested that the molecular weight and Fsp3 are the two molecular descriptors often violated by the oral drugs. Such an analysis is suggested to provide a knowledge based evidence for allowed deviations in molecular descriptors. While the Fsp3 is violated by almost all the therapeutic category of oral drugs, molecular weight violations are most prevalent in antimicrobial oral drugs. A closer analysis suggested that these antimicrobials predominantly belonged to macrocyclic antibiotics and cyclic peptides from natural sources. A thorough analysis of the literature further suggested that the natural product antibiotics possess chameleonic behaviour due to which they have optimal permeability across member as well as solubility in aqueous environment.

A comparative analysis on the correlation between Clog P (pH-independent partition coefficient) Vs Clog S and Clog D (pH-dependent distribution coefficient) Vs Clog S suggested that Clog D at pH 6.5 and 7.4 are better descriptors of lipophilicity than Clog P. An attempt to classify the oral drugs based on $FLI_{7.4}$ Vs Clog $S_{7.4}$ for which the BCS Classes were already known from literature resulted with a success rate of **70%**. Toxicity class predictions of the 240 oral drugs suggest that the essential medicines in the list often belong to the toxicity **Class 4.** Although, this analysis could successfully classify the drugs into specific BCS Classes based on $FLI_{7.4}$ and Clog $S_{7.4}$, it could not classify them into toxicity classes. Hence, it can be understood that oral drug toxicity classification probably involves the influence of several molecular descriptors or a combination of them beyond permeability and solubility.

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Conflict of Interest

The authors declare no competing interests.

Author Contributions

VKP: Data curation, formal analysis. **BSV:** Project administration and supervision. **VSG:** Conceptualization, Methodology, Resources, project administration, writing original draft.

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Table 2 *Number of drugs with violation of molecular descriptors in each therapeutic category*

MOLECULAR DESCRIPTORS	M.W	HBD	HBA	log P	NRB	TPSA	M.REF	N.ATOMS	N.RINGS	FSP3
Threshold	<500, 160-140, 200-600	<=5	<=5, <=10	<5, =5.88, (-2 to -5)	<=10, <=15	<=140, <=131.6, <=150	(40 to 130)	(20 to 70)	<=7	>0.40
Therapeutic Category	-	-	-	-	-	-	-	-	-	-
Gastrointestinal Drugs	1	1	1	2	0	1	0	1	0	4
Anticancer Drugs	8	1	4	5	1	5	6	5	0	19
Analgestic, Antipyretic & Antiinflammatory	3	0	1	1	0	2	0	1	0	10
Antimicrobial	6	3	4	8	3	9	5	6	1	10
Antiviral	3	0	0	2	2	3	2	2	0	5
Neurological Disorders	5	0	0	2	0	0	0	0	0	14
Antituberculosis	8	0	2	5	0	2	7	6	0	6
Antimalarial	3	0	1	3	1	1	1	1	0	3
Cardiovascular	4	1	1	3	3	3	6	2	0	8
Hormones, other Endocrine Medicines and Contraceptives	3	0	0	3	0	0	2	0	0	2
Psychiatric Disorders	1	0	0	0	0	0	0	0	0	9

The thresholds are colour coded for different rules as follows: Lipinski, Veber's, Ghose, Egan's and Mueggue's.

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