Evaluation of the use of partition coefficients and molecular surface properties as predictors of drug absorption: a provisional biopharmaceutical classification of the list of national essential medicines of Pakistan

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ABSTRACT

Background and the purpose of the study: Partition coefficients (log D and log P) and molecular surface area (PSA) are potential predictors of the intestinal permeability of drugs. The aim of this investigation was to evaluate and compare these intestinal permeability indicators.

Methods: Aqueous solubility data were obtained from literature or calculated using ACD/Labs and ALOGPS. Permeability data were predicted based on log P, log D at pH 6.0 (log D₆₀), and PSA.

Results: Metoprolol’s log P, log D₆₀ and a PSA of <65 Å correctly predicted 55.9%, 50.8% and 54.2% of permeability classes, respectively. Labetalol’s log P, log D₆₀ and PSA correctly predicted 54.2%, 64.4% and 61% of permeability classes, respectively. Log D₆₀ correlated well (81%) with Caco-2 permeability (Pₐₚ). Of the list of national essential medicines, 135 orally administered drugs were classified into biopharmaceutical classification system (BCS). Of these, 57 (42.2%), 28 (20.7%), 44 (32.6%), and 6 (4.4%) were class I, II, III and IV respectively.

Conclusion: Log D₆₀ showed better prediction capability than log P. Metoprolol as permeability internal standard was more conservative than labetalol.

Keywords: Biopharmaceutical classification system, Permeability, log P, log D, PSA.

INTRODUCTION

Systemic bioavailability of an orally administered drug is largely dependent on its physicochemical properties and dosage formulation factors (1). Sophisticated modeling of the kinetics and dynamics of drug processes in the gastrointestinal tract subsequently led to the advent of the biopharmaceutical classification system (BCS) (2). According to the biowaiver, any possible variation in the bioavailability of a rapidly dissolving and highly soluble drug is attributed to physiological conditions rather than formulation and hence there is no logic in conducting a bioequivalence testing for such formulation (2). BCS offers a framework for development of pharmaceutical formulations. It has been estimated that the pharmaceutical industry can save $35 million annually through the applications of BCS (3). Assignment of the solubility and permeability classes of a drug is a laborious task. Lately, computational models to predict aqueous solubility and permeability through biological membranes have received considerable attention. The use of physicochemical properties in predicting in vivo behavior of drugs has many advantages including cost reduction; better control over protocol, reproducibility and avoidance of risk presented to human volunteers usually encountered in the bioequivalence studies (4). Molecular surface properties and partition coefficients have been used actively in construction of quantitative structure activity relationship (QSAR) models to predict intestinal permeability (2, 5-6).

This study reports for the first time an evaluation and comparison of pH-dependent and pH-independent n-octanol/water partition coefficients (log D and log P) and polar surface area (PSA) in prediction of intestinal permeability of drugs. The log D at physiologically relevant pH of 6.0 (log D₆₀) was used to provisionally classify the orally administered drugs on the list of national essential medicines (NEML) of Pakistan into BCS.

MATERIAL AND METHODS

The present revision of the NEML contains 335 medicines of different pharmacological classes (7). The highest dose of drug products available in oral dosage forms, i.e. oral tablets and capsules, were used.

Solubility

The dose number (Do) was calculated using equation 1:
**RESULTS AND DISCUSSION**

Previously the orally administered drugs on the World Health Organization (WHO) essential medicine list (EML) were provisionally classified into BCS (13-14). The NEML contained 135 orally administered drugs. It has been emphasized that the maximal administered dose to solubility ratio has a central role in the BCS (15). The NEML contained 89 drugs in common with the WHO’s EML while in term of doses, only 46 were similar.

Solubility correlation and class assignment

Lindenberg and colleagues classified 61 drugs with certainty on the basis of reliable practical solubility data. A total of 59 drugs were in common with Lindenberg’s list (13). ACD/Labs calculated solubility and predicted correctly that 51 (86.4%) of the solubility classes; whereas, data obtained from Drugbank and ALOGPS could correctly predict 76.3% and 78% of the drugs classified, respectively (Supplementary table 1). Solubility class assignment was compared to the WHO solubility classification (16). Of the 80 drugs in common, 66 drugs (82.5%) were classified in the same solubility classes, whereas, of the 14 drugs for which the solubility classes were different, 6 drugs were classified based on incomplete/ inconclusive data and 3 drugs had higher or lower doses on the NEML as compared to the WHO’s EML (Supplementary table 2).

Of the 135 drugs on the NEML, 15 (11.1%) drugs were classified according to their experimental solubility data obtained from Yalkowsky & He, of which 7 (46.7%) were classified as high soluble drug while the rest of 8 (53.3%) were classified as low soluble drugs. Additionally, 33 drugs (24.4%) were classified based on the solubility data obtained from Drugbank. Of these, 29 (87.9%) were classified as high solubility drugs while the rest of 4 (12.1%) were classified as low soluble drugs. The rest of 87 drugs (64.4%) were classified according to the ACD/Labs predicted soluble, of which, 66 (75.9%) were classified as high soluble drugs and 21 (24.1%) drug were assigned to low solubility class drugs (Table 1).

Permeability correlation and class assignment

Kasim and colleagues used metoprolol as internal standard indicating high permeability (14). Palm and colleagues showed that PSA of <60 Å ensured complete intestinal absorption (6); however, Kelder and colleagues showed drug intestinal permeation predominated by passive diffusion and paracellular route for drugs with PSA of less than 120 Å (17). When log \( D_{app} \) of -1.48, log \( P \) of 1.35, and a relaxed PSA of ≤65 Å were used to indicate high permeability of the 59 drugs in common with the Lindenberg’s list, cutoffs correctly predicted the permeability class of 30, 33 and 32 drugs (50.8%, 54.2% and 55.9%), respectively (Supplementary table 3). The fraction absorbed (Fa) of metoprolol (≥95%) is considerably even more conservative than permeability criteria (≥90%) of the Food and Drug Administration (FDA) (18). The use of labetalol as high permeable internal standard (Fa ≥90%) was evaluated using log \( D_{app} \) of -0.42, Log \( P \) of 2.31, and PSA of ≤95.6 Å. These cutoffs correctly predicted the permeability class of 38, 32, and 36 drugs (64.4%, 54.2% and 61%), respectively.

When WHO’s classification (16) where compared with the current classification in table 1; of the 80 drugs in common, 62 drugs (77.5%) were classified in the same permeability classes, whereas, of the 18 drugs for which the permeability classes were different, 11 could be correctly classified by their PSA values (Supplementary table 2).

To further verify the suitability of the permeability class assignment based on log \( D_{app} \), the Caco-2 monolayer permeability (\( P_{app} \)) values for a total of 22 drugs which were in common with a previous work...
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were obtained; these values were basically compiled from the literature. The $P_{\text{app}}$ value for labetalol was obtained from literature (15). Log $D_{6.0}$ correctly predicted the permeability class for 18 (81.8%) of the 22 drugs (Supplementary table 4). Furosemide, hydrochlorothiazide, saquinavir, and sulphasalazine were false positives. Similarly, the PSA of ≤95.6 Å (PSA of labetalol) correctly predicted the permeability class for 18 (81.8%) of the 22 drugs (Supplementary table 4). Acetylsalicylic acid, atenolol and zidovudine were false positives, whereas, digoxin was a false negative. The PSA of ≤65 Å correctly predicted only 15 (68.2%) out of the 22 drugs compared. In the study of Kasim and colleagues, the log $P$ of metoprolol correctly predicted 18 of 28 (64%) drugs (5).

The permeability classes were assigned using log $D_{6.0}$ in comparison to labetalol which was used as internal standard. In this classification, 128 (94.8%) of the 135 drugs on the NEML were classified, of these, 83 (64.8%) were assigned in high permeability, while the rest of 45 (35.2%) were assigned in low permeability classes. The rest of the 7 (5.2%) were classified according to their PSA values. Of these 2 (28.6%) were classified as high permeability drugs, while the rest of 5 (71.4%) were classified as low permeability drugs. The final BCS classification of the 135 orally administered drugs on the NEML is given in table 1 and class distribution is shown in figure 1.

Literature often reported solubility data at room temperature. In contrast, the current solubility classification methodology yielded an acceptable accuracy of 86.4% and 78.3% for ACD/Labs and Drugbank solubility values respectively. Moreover, the current classification of solubility criteria were conservative since the solubility usually increases as a function of temperature, therefore, the solubility values at 37°C would be higher than the values used. In vivo human permeability investigations are expensive in terms of financial resources and technical allocations; and moreover are time consuming. Several reports described a certain correlation between physicochemical properties of drug molecules with intestinal absorption (6, 19-22). Linnankoski and colleagues suggested that passive diffusion predominates the routes of intestinal administration for the majority of the drugs (20). Although influx and efflux transporters have an important role in the absorption of some drugs, interestingly, for the majority of drugs the active transport is actually negligible (20). Most of the drugs available in the market are ionizable molecules; therefore, passive diffusion of these ionizable drugs is partly governed by their pKa values. Consequently, log $D$ at physiologically relevant pH should better reflect the overall distribution (ionized and unionized) of a drug (22, 23).

Recently, labetalol was suggested as a better internal standard in the permeability comparisons (24). The effective intestinal permeability ($P_{\text{app}}$) is typically the parameter reflecting both the rate and extent of intestinal absorption. In the current classification, labetalol was used as internal standard. In accordance with results of this study, Winiwater and colleagues found a correlation between $P_{\text{app}}$, log $D$ at pH of 5.5, PSA and hydrogen bond donors, the use of log $D_{6.0}$ gave better predictions than log $P$ (22). Similarly, Linnankoski and colleagues established a correlation between the intestinal absorption rate constant ($K_a$) with log $D_{6.0}$ and PSA (20).

Figure 1. Biopharmaceutical classification system with drugs on the list of national essential medicines of Pakistan.

| Solubility | Permeability |
|------------|--------------|
| High       | Low permeability |
| n=128      | (94.8%)       |
| Low        | High permeability |
| n=45       | (35.2%)       |

Class I:
- High solubility + Low permeability
- $n=44 (32.6\%)$

Class II:
- Low solubility + High permeability
- $n=28 (20.7\%)$

Class III:
- High solubility + High permeability
- $n=57 (42.2\%)$

Class IV:
- Low solubility + Low permeability
- $n=6 (4.4\%)$
Table 1. BCS classification of the orally administered drugs on the list of national essential medicines (NEML) of Pakistan with their therapeutic classes, maximum doses, experimental water solubility, predicted aqueous solubility (ACD/Labs), pH dependent solubility (pKa), log $D_{4.0}$, calculated PSA, and interaction with transporters in the intestine.

| Drug                  | Therapeutic class | Maximum dose (mg) | $D_{0^*}$ | $D_{0^+}$ | $D_{0^+}$ | pKa | Log $D_{4.0}$ | PSA | Transporters interaction | BCS classification |
|-----------------------|-------------------|-------------------|-----------|-----------|-----------|-----|---------------|-----|--------------------------|-------------------|
| Acetylsalicylic acid  | NSAID             | 300               | NA        | 0.0012    | 3.48      | -1.24| 63.6         | Pgp | High                     | Low               |
| Acyclovir             | Antiviral         | 200               | NA        | 2.1       | 9.18      | 1.89 | -1.76        | 109.83 OATP1, OATP3, OCT1 | Low               |
| Albendazole           | Anthelmintic      | 200               | NA        | 13.3      | 10.46     | 5.62 | 2.87         | 92.31 BCRP | Low                     | High              |
| Allopurinol           | anti-gout         | 300               | NA        | 0.03      | 9.2       | 2.4  | -3.81        | 74.69 NA | NA                       | High              |
| Amitriptyline         | Antipsychotic     | 50                | NA        | 0.16      | 8.58      | 1.58 | 1.07         | 156.79 NA | NA                       | High              |
| Amiodarone            | Antiarrhythmic    | 200               | 1.1       | NA        | 9.37      | 6.29 | 42.7         | MDR1 Low | High                    |
| Amitriptyline         | Antipsychotic     | 50                | NA        | 0.14      | 9.24      | 2.08 | 3.24         | NA High  | Low                     |
| Amiodarone            | Antiarrhythmic    | 200               | 1.1       | NA        | 9.37      | 6.29 | 42.7         | MDR1 Low | High                    |
| Amoxicillin           | Antibacterial     | 500               | NA        | 6.66      | 2.61      | 6.93 | -1.93        | 158.26 PEPT1 | Low Low IV               |
| Ampicillin            | Antibacterial     | 500               | 0.2       | 2.61      | 6.79      | -1.21| 138 PEPT1, OCTN2 | Low Low IV   |
| Anastrozole           | Anticancer        | 1                 | NA        | 0.008     | 4.78      | 0.77 | 78.3         | NA High  | High                    |
| Atenolol              | Antihypertensive  | 100               | NA        | 0.0004    | 13.88     | 9.17 | -2.73        | 84.58 MDR1 | High Low III             |
| Atropine sulphate     | Antispasmodic     | 1                 | NA        | 6.76E-06  | 9.88      | -1.52| 49.77 NA     | MDR1 Low | High                    |
| Azathioprine          | Anticancer        | 50                | 1.5       | 0.25      | -0.54     | 143  | NA           | Low Low IV |
| Bromocriptine         | Antiparkinsonism  | 2.5               | NA        | 0.11      | 9.61      | 6.45 | 4.52         | 118 MDR1 | High                    |
| Busulphan             | Anticancer        | 0.5               | NA        | 1.2E-06   | 9.88      | -1.52| 104 NA       | MDR1 Low | High                    |
| Bupropirl             | Antihypertensive  | 50                | NA        | 0.0002    | 3.82      | -2.02| 96.41 MDR1, PEPT1 | High Low III |
| Carbamazepine         | Antiepileptic     | 200               | NA        | 10        | 13.94     | 2.67 | 46.33 MDR1 | Low High II |
| Carbidopa             | Antiparkinsonism  | 25                | NA        | 0.1       | 3.4       | 7.91 | -2.71        | 116 NA  | High                     |
| Cefixime              | Antibacterial     | 100               | NA        | 0.03      | 2.1       | 2.86 | -3.72        | 238 NA  | High                     |
| Cefuroxime            | Antibacterial     | 250               | NA        | 3.52      | 2.59      | -4.47| 199 PEPT1    | Low Low IV |
| Cephalexin            | Antibacterial     | 500               | 0.04      | 3.12      | 6.8       | -2.22| 138 PEPT1, PEPT2, OCTN2 | High Low III |
| Cephradine            | Antibacterial     | 500               | 0.25      | 3.12      | 6.99      | -1.53| 138 OAT1, OCTN2, PEPT1 | High Low III |
| Chlorambucil          | Anticancer        | 2                 | 0.01      | 4.86      | 3.66      | 1.52 | 40.5 MRP1    | High High |
| Chloramphenicol       | Antibacterial     | 250               | NA        | 4.3       | 11.03     | 1.02 | 115.38 NA | High Low II |
| Chloroquine           | Antimalarial      | 150               | NA        | 0.02      | 10.48     | 1.2  | 28.16 MDR1 | High High |

Provisional biopharmaceutical classification of drugs on the list of national essential medicines (NEML) of Pakistan.
Table 1 (Cont)

| Drug               | Therapeutic class     | Maximum dose (mg) | Solubility | Permeability | BCS classification |
|--------------------|-----------------------|-------------------|------------|--------------|--------------------|
| Chlorpheniramine   | Antiallergic          | 4 NA              | 0.0003     | 9.33         | 0.49 16.13 NA      | High High I  |
| Chlorpromazine     | Antipsychotic         | 100 NA            | 0.44       | 9.43         | 2.28 31.78 MDR1, OCT1 | High High I  |
| Cimetidine         | Antiallergic          | 400 NA            | 0.14       | 6.73         | -1.14 114.19 MDR1, OCT1, OAT3, OCT1, OCT3, OCTN2 | High Low III |
| Ciprofloxacin      | Antibacterial         | 250 NA            | 0.77       | 2.74         | 8.76 -1.07 72.88 MDR1 | High Low III |
| Clofazimine        | Antileprosy           | 100 NA            | 412.4      | 6.24         | 5.72 39.99 MDR1    | Low High II  |
| Clomipramine       | Antipsychotic         | 25 NA             | 0.09       | 9.49         | 2.58 6.48 MDR1     | High High I  |
| Clotrimazole       | Antileprosy           | 100 NA            | 412.4      | 6.24         | 5.72 39.99 MDR1    | Low High II  |
| Cloxacillin        | Antibacterial         | 250 NA            | 0.07       | NA           | -0.81 138.04 PEPT1 | High Low III |
| Colchicine         | Anti-gout             | 0.5 NA            | 0.03       | NA           | 0.92 83.09 MDR1, OCT3 | High High I  |
| Cyclizine          | Antihistamine         | 50 NA             | 0.2        | 7.46         | 1.83 6.5 NA        | High High I  |
| Cyclophosphamide   | Anticancer            | 50 NA             | 0.002      | 4.09         | 0.23 51.38 MDR1    | High High I  |
| Cyclosporin        | Immunosuppressent     | 100 10            | NA NA 279  | BCRP, MDR1, MRP1, OATP1B1 | Low Low IV |
| Dapsone            | Antileprosy           | 50 NA             | 0.57       | 1.24         | 0.94 94.36 NA     | High High I  |
| Dexamethasone      | Antiallergic          | 0.5 NA            | 0.04       | 12.14        | 1.87 94.83 MDR1, OATP1A2 | High High I  |
| Diazepam           | Sedative              | 10 NA             | 2          | 3.4          | 2.96 32.67 MDR1    | Low High II  |
| Didanosine (ddi)   | Antiretroviral        | 400 NA            | 0.81       | 8.67 1.98    | -1.33 83.81 NA    | High Low III |
| Digerix            | Cardiostimulant       | 0.25 NA           | 0.002      | 13.5         | 0.85 203.06 MDR1, OATP1B3, OATP1C1, OATP4C1, OATP4C3, OATP4C4, OATP4C7 | High High I  |
| Diloxanide         | Anti-Amoebic          | 500 NA            | 1.08       | NA           | 1.62 40.54 NA     | Low High II  |
| Diltiazem          | Calcium channel blocker | 100 0.006      | 8.91       | 2.64         | 8.44 MDR1          | High High I  |
| Doxycycline        | Antibacterial         | 100 NA            | 0.54       | 4.5          | 9.32 -3.06 181.62 OAT1, OAT3, OAT4 | High Low III |
| Efavirenz          | Antiretroviral        | 50 NA             | 376.6      | 7.92         | 4.84 38.33 NA     | Low High II  |
| Enalapril          | Antihypertensive      | 10 0.002          | 3.75 5.53  | 0.02         | 9.59 MDR1, OATP1A2, PEPT1 | High High I  |
| Ergometrine        | Oxytocic              | 0.25 NA           | 0.00018    | NA           | -0.54 68.36 MDR1   | High Low III |
| Ergotamine         | Antimigraine          | 1 NA              | 0.4        | 9.62         | 7.2 1.99 118.21 MDR1 | High High I  |
| Erythromycin       | Antibacterial         | 500 NA            | 0.08       | 13.08        | 8.14 0.72 193.91 MDR1, MRP1, OAT2, OATP1A2 | High High I  |
| Ethambutol         | Anti-tuberculosis     | 400 NA            | 0.0016     | 9.6          | -3.23 64.52 NA    | High Low III |
| Ethosuximide       | Antiepileptic         | 250 NA            | 0.042      | 9.7          | 0.38 46.17 NA     | High High I  |
| Etoposide          | Anticancer            | 100 2             | 9.95       | 1.96         | 161 BCRT, MDR1-3-6-7, | Low High II  |
### Table 1 (Cont)

| Drug | Therapeutic class | Maximum dose (mg) | Do | Do | Do | pKa | Log D<sub>xy</sub> | PSA | Transporters interaction | Solubility class | Permeability class | BCS Class |
|------|-------------------|------------------|-----|-----|-----|-----|------------------|-----|------------------------|-----------------|------------------|----------|
| Fluoxetine | Antipsychotic | 20 | NA | 0.02 | 10.05 | NA | 21.3 | MDR1 | High | High | I |
| Flutamide | Anticancer | 250 | NA | 0.42 | 13.12 | NA | 74.9 | NA | High | High | I |
| Furosemide | Diuretic | 40 | NA | 0.02 | 3.04 | 0.26 | 131.01 | MRP2, OAT1, OAT3, OAT4, OCTN2 | High | High | I |
| Gentamycin | Antimicrobial | 300 | NA | 0.12 | 4.75 | 2.14 | 46.5 | NA | High | High | I |
| Gilbenclamide | Antidiabetic | 5 | NA | 1 | NA | 2.75 | 121.98 | BSEP, MDR1, MRP1, OATP2B1 | High | High | I |
| Griseofulvin | Antifungal | 500 | NA | 2985.07 | NA | 3.53 | 71.06 | NA | Low | High | II |
| Haloperidol | Antipsychotic | 5 | NA | 0.006 | 13.9 | 8.25 | 0.82 | 40.54 | MDR1 | High | High | I |
| Hydralazine | Antihypertensive | 25 | NA | 0.08 | NA | 0.56 | 63.83 | NA | High | High | I |
| Hydrochlorothiazide | Diuretic | 50 | NA | 0.48 | 8.95 | -0.07 | 135.12 | NA | High | High | I |
| Ibuprofen | NSAID | 600 | NA | 1.17 | 4.41 | 2.12 | 37.3 | MDR1, MRP1, MRP3, OAT1-4 | Low | High | II |
| Imipramine | Antipsychotic | 25 | 5.5 | 9.49 | 1.85 | 6.5 | MDR1, OCT2, OCT3 | Low | High | II |
| Indinavir | Antiretroviral | 400 | NA | 53.3 | 5.73 | 2.76 | 118.03 | MDR1, MRP1, MRP2, OATP1A2, OATP1B1 | Low | High | II |
| Indomethacin | NSAID | 25 | 6.25 | 4.17 | 0.3 | 68.5 | MDR1, MRP1-8, OAT1-4 | Low | High | II |
| Isoniazid | Anti-tuberculosis | 300 | NA | 0.01 | 11.27 | 3.79 | -0.89 | 68.01 | NA | High | Low | III |
| Isosorbide dinitrate | Antianginal | 10 | NA | 4.82E-05 | NA | -1.75 | 58.92 | NA | High | Low | III |
| Labetalol | Antihypertensive | 200 | NA | 0.04 | 7.91 | 9.2 | -0.42 | 95.6 | NA | High | High | I |
| Lamivudine (3tc) | Antiretroviral | 150 | NA | 0.17 | 13.83 | 4.41 | -0.71 | 113.45 | BCRP, MRP1 | High | Low | III |
| Levamisole | Anthelmintic | 40 | NA | 0.0067 | 8.81 | -0.15 | 40.9 | NA | High | High | I |
| Levodopa | Antiparkinsonian | 250 | NA | 0.09 | 2.24 | 9.3 | -0.27 | 103.78 | NA | High | High | I |
| Lisinopril | Antihypertensive | 20 | NA | 0.02 | 2.18 | 10.51 | -1.32 | 133 | MDR1, PEPT1 | High | Low | III |
| Losartan | Antihypertensive | 25 | NA | 0.49 | 4.24 | 3.1 | 0.89 | 92.5 | MDR1, OAT1 | High | High | I |
| Methadone | Anthelmintic | 100 | NA | 20 | 10.29 | 5.02 | 2.77 | 84.08 | MDR1 | Low | High | II |
| Mercaptopurine | Anticancer | 50 | 0.03 | 8.46 | 2.4 | 0.37 | 85.2 | MPV4, MPV5 | High | High | I |
| Metformin | Antidiabetic | 500 | NA | 0.02 | 13.1 | 4.31 | 88.99 | OCT1, OCT2 | High | Low | III |
| Methionine | Antifolate | 250 | NA | 0.04 | 2.23 | 9.26 | -2.13 | 86.8 | OCTN2 | High | Low | III |
| Methotrexate | Anticancer | 10 | NA | 6.20E-05 | 3.54 | 5.09 | NA | 211 | BCRP, MDR1, MRP1-7, OAT1-4, OATP1B1, OATP1B3, OATP1C1 | Low | High | III |
| Methyldopa | Antihypertensive | 500 | NA | 0.3 | 2.28 | 9.3 | -2.37 | 103.78 | PEPT1 | High | Low | III |
| Metoclopramide | Antiemetic | 10 | NA | 0.0002 | 13.28 | 9.62 | -7.8 | 67.59 | NA | High | Low | III |
Table 1 (Cont)

| Drug              | Therapeutic class | Maximum dose (mg) | Solubility | pKa | Permeability | BCS classification |
|-------------------|-------------------|-------------------|------------|-----|--------------|-------------------|
|                   |                   |                   | Da¹ Do¹    | Da¹ | Log Dm,6.0  | PTA V1 | Transporters interaction | Solubility class | Permeability class | BCS Class |
| Metronidazole     | Anti-Amoebic      | 400               | NA 0.2     | 2.58| -1.01       | 78.94 | NA                      | High    | Low    | III   |
| Morphine          | Analgesic         | 30 NA 0.0065      | 9.72 8.14  | -1.77 | 52.95       | MDR1  | High    | Low    | III   |
| Nalidixic acid    | Antibacterial     | 500 NA 0.73       | 1.2 5.95   | 0.33 | 70.5        | NA    | High    | High   | I     |
| Nelfinavir        | Antiretroviral    | 250 NA 291.54     | 9.58 7.53  | 5.44 | 127.2       | BCRP, MDR1, OATP1A2, OATP1B1 | Low    | High   | II    |
| Neostigmine       | Antidote          | 15 NA 0.00019     | NA 0.2     | NA  | -3.03       | 29.54 | MDR1      | High    | Low    | III   |
| Nevirapine        | Antiretroviral    | 200 NA 1.37       | 10.93 4.74 | 1.84 | 58.12       | NA    | Low    | High   | II    |
| Nicosamide        | Antihelmintic     | 500 NA 1801.8     | NA 0.2     | 5.4  | 95.15       | NA    | Low    | High   | II    |
| Nitrofurantoin    | Antibacterial     | 100 NA 0.28       | 7.69 1.2   | -0.41| 120.73      | NA    | High    | High   | I     |
| Nitroglycerin     | Antianginal       | 6.4 0.02          | NA 0.2     | 2.22 | 165         | NA    | High    | High   | I     |
| Nystatin          | Antifungal        | 200 NA 26.6       | NA 0.2     | NA  | 3.19       | 61.6  | MDR1      | Low    | High   | II    |
| Omeprazole        | Antulcer          | 20 NA 0.004       | 9.08 4.61  | 2.15 | 96.3        | BCRP, MDR1, MRP5 | High    | High   | I     |
| Paracetamol       | Analgesic         | 500 NA 0.19       | 9.86 0.34  | NA  | 49.33       | NA    | High    | High   | I     |
| Penicillamine     | Antidote          | 250 NA 0.096      | 2.13 11.54 | -1.57| 102.12      | NA    | High    | Low    | III   |
| Phenobarbital     | Antiepileptic     | 50 NA 0.18        | 7.88 1.66  | 1.66 | 75.27       | NA    | High    | High   | I     |
| Phenytoin         | Antiepileptic     | 100 NA 0.017      | 9.86 6.43  | -1.43| 58.4        | MDR1, OATP1A2, OAT1-3, OCT1-2 | High    | Low    | III   |
| Phentolamine      | Antidepressant    | 100 NA 4          | 8.33 2.52  | 58.2 | MDR1, MRP2  | Low   | High    | High   | II    |
| Prazosin          | Antihypertensive  | 2 NA 0.016        | 6.47 -1.25 | 107 | BCRP, MDR1, OCT1-3 | High    | Low    | III   |
| Pregabalin        | Anticonvulsant    | 5 NA 0.15         | 12.47 1.49 | 94.83| MDR1        | High   | High    | High   | I     |
| Primaquine        | Antimalarial      | 7.5 NA 0.00015    | 10.38 -0.41| 60.17| NA          | High   | High    | High   | I     |
| Procainamide      | Antiarrhythmic    | 250 NA 0.017      | 9.86 -1.43 | 58.4| MDR1, OATP1A2, OCT1-3, OCT1-2 | High    | Low    | III   |
| Procarbazine      | Anticancer        | 50 NA 0.0006      | 7.46 0.11  | 53.2 | NA          | High   | High    | High   | I     |
| Prochlorperazine  | Antipsychotic     | 5 1.34            | 7.82 2.42  | 35  | NA          | Low    | High    | High   | II    |
| Procyclidine      | Antiparkinsonism  | 5 NA 2.03         | 10.48 0.84 | 23.5 | NA          | Low    | High    | High   | II    |
| Promethazine      | Antifungal        | 25 NA 0.04        | 8.98 2.04  | 31.78| MDR1        | High   | High    | High   | I     |
| Propranolol       | Antihypertensive  | 160 NA 0.01        | 13.84 9.14 | 0.28| 41.49       | MDR1, NTCP, OCT2 | High    | High   | I     |
| Propylthiouracil  | Anticancer        | 100 NA 0.2        | 7.63 0.54  | 1.36 | 73.22       | NA    | High    | High   | I     |
| Pyrantel          | Antihelmintic     | 250 NA 0.012      | 10.97 -0.49| 43.84| NA          | High   | High    | High   | III   |
| Pyrazinamide      | Anti-tuberculosis | 500 NA 0.09       | 13.91 -0.37| 68.87| NA          | High   | High    | High   | I     |
| Pyridostigmine    | Muscle relaxant   | 60 NA 0.0005      | NA -4.31  | 29.54| NA          | High   | Low    | High   | III   |
Table 1 (Cont)

| Drug               | Therapeutic class | Maximum dose (mg) | Do² | Do³ | Do¹ | pKa | Log D₆⁺ | PSA² | Transporters interaction³ | Solubility class | Permeability class | BCS classification |
|--------------------|-------------------|-------------------|-----|-----|-----|-----|---------|------|-----------------------------|-----------------|---------------------|---------------------|
| Quinidine         | Antiarrhythmic    | 200               | 5.7 | NA  | 13.05 | 9.13 | 1.35   | 45.6 | BSEP, MDR1, OAT3, OATP1A2, OATP1B1, OCT1,2, OCTN1,2 | Low              | High                | II                  |
| Quinine           | Antimalarial      | 200               | NA  | 0.03| 13.05 | 9.13 | 0.54   | 45.59| MDR1, OATP1A2, OCT1,2, OCTN1,2 | High             | High                | I                   |
| Risperidone       | Antipsychotic     | 3                | NA  | 0.017| 7.91  | 1.01 | 61.9   | NA   | NA                           | High             | High                | I                   |
| Rifampicin        | Anti-tuberculosis | 600              | NA  | 1.71| NA    | -1.75| 217    | 202.26| MDR1, MRP1,2,3,5, OATP1A2, OATP1B1, OATP1B3, OATP2B1 | Low              | Low                 | IV                  |
| Ritonavir         | Antiretroviral    | 100              | NA  | 1063.8| 11.47| 3.48  | 5.28  | 166.75| BCRP, MDR1, MRP1,2, OATP1A2, OATP1B1 | Low              | High                | II                  |
| Salbutamol        | Antiallergic      | 4                | NA  | 0.000016| 0.83 | 9.22  | -2.84 | 72.72| NA                           | High             | Low                 | III                 |
| Saquinavir        | Antiretroviral    | 200              | NA  | 16   | NA    | 2.84  | 165.75| BCRP, MDR1,2, OATP1A2, OATP1B1 | Low              | High                | II                  |
| Selegiline        | Antiparkinsonism  | 5                | NA  | 0.78 | 7.53  | 1.42  | 3.2    | NA   | MDR1                         | High             | High                | I                   |
| Spironolactone    | Diuretic          | 100              | NA  | 44.3| NA    | 3.12  | 85.74  | MDR1 | Low                          | High             | High                | II                  |
| Stavudine (D4T)   | Antiretroviral    | 40               | NA  | 0.009| 9.57  | -0.86 | 78.87  | NA   | MDR1                         | High             | Low                 | III                 |
| Sulphasalazine    | Antibacterial     | 500              | NA  | 0.29| 2.88  | 1.86  | 0.35   | 149.69| NA                           | High             | High                | I                   |
| Tamoxifen         | Anticancer        | 20               | NA  | 479.04| 8.69 | 6.2    | 12.5  | BCRP, BSEP, MDR1 | Low              | High                | II                  |
| Theophylline      | Antiallergic      | 270              | NA  | 0.25| 8.6   | 1.05  | -0.18  | 69.3 | NA                           | High             | High                | I                   |
| Thiocetazone      | Anti-tuberculosis | 50               | NA  | 0.2 | NA    | NA    | 112    | NA   | MDR1                         | High             | Low                 | III                 |
| Thioacetazine     | Anti-tuberculosis | 40               | NA  | 0.004| 7.44 | 3.09  | -0.4   | 111  | MRP4                         | High             | High                | I                   |
| Tindazole         | Antifungal        | 500              | NA  | 0.0004| 7.44 | 3.09  | -0.4   | 106  | NA                           | High             | High                | I                   |
| Trifluperazine    | Antipsychotic     | 5                | NA  | 1.63| 7.82  | 4.04  | 35     | NA   | Low                          | High             | High                | II                  |
| Trimethoprim      | Antibacterial     | 300              | NA  | 0.17| 7.34  | -0.42 | 105.51 | MDR1 | High                         | High             | I                   |
| Valproic acid     | Antiepileptic     | 300              | NA  | 0.005| 4.82 | -1.65 | 100.27 | OAT3, OCTN2 | High             | Low                 | III                 |
| Verapamil         | Antihypertensive  | 240              | NA  | 0.85| 9.03  | 2.91  | 64     | OAT3, OCTN1,2, Pgp | High             | High                | I                   |
| Warfarin          | Anti-coagulant    | 5                | NA  | 0.01| 4.5   | 1.91  | 63.6   | NA   | High                         | High             | High                | I                   |
| Zalcitabine (DDC) | Antiretroviral    | 0.75             | NA  | 4.96E-07| 4.47 | -1.31 | 88.2 | NA | High                         | Low              | III                 |
| Zidovudine (ZDV)  | Antiretroviral    | 100              | NA  | 0.1 | NA    | -0.53 | 91.23  | PEPT1 | High                         | Low              | III                 |

1- Do (dose number) calculated from solubility data taken from ref. (9); 2- Do (dose number) calculated from solubility data taken from ref. (10); 3- Do (dose number) calculated from predicted solubility data, ACD/Labs; * The maximal dose strength on the list of national essential medicines of Pakistan; † pKa values were taken from ref. 12; ¶ Calculated log D₆⁺ values at pH 6 using ACD/Labs; ¥ PSA calculated from ACD/Labs; ‡ Transporter interaction taken from ref. 25; BCRP: Breast cancer resistance protein; BSEP: Bile salt export pump; MDR: Multidrug transporter; MRP: Multidrug resistance protein; NA: not available; OAT: Organic anion transporter; OATP: Organic anion-transporting polypeptide; OCTN: Organic cation transporter; OST: Organic solute transporter; PEPT: Peptide transporter; Pgp: P-glycoprotein.
Supplementary table 1: Solubility data correlation: ACD/Labs, experimental water solubility DrugBank, ALOGPS and reliable experimental solubility.

| Drug            | Dose (mg) | D1    | D2    | D3    | Solubility Class 1 | Solubility Class 2 | Solubility Class 3 | Reliable experimental solubility* |
|-----------------|-----------|-------|-------|-------|--------------------|--------------------|--------------------|-----------------------------------|
| Abacavir        | 300       | 2.9268293 | 0.0155844 | 0.99173554 | Low | High | High | High |
| Acetylsalicylic Acid | 500       | 0.002 | 0.437826 | 1.36986301 | High | Low | High | Low |
| Aciclovir       | 200       | 2.1052632 | 0.4938272 | 0.08810573 | Low | High | High | High |
| Alfopurinol     | 100       | 0.0101807 | 0.7029877 | 0.06802721 | High | High | High | High |
| Amiloride       | 5         | 0.1666667 | 0.01639344 | 0.99173554 | High | High | High | High |
| Atenolol        | 100       | 0.0004 | 0.0296296 | 0.93240093 | High | High | High | High |
| Captopril       | 25        | 0.0001 | 0.0212389 | 0.93240093 | High | High | High | High |
| Carbamazepine   | 200       | 10 | 45.19774 | 5.26315789 | Low | Low | Low | Low |
| Chloramphenicol | 250       | 4.3478261 | 0.4 | 2.1691974 | Low | High | High | High |
| Chloroquine     | 150       | 0.0203035 | 56.603774 | 34.2857143 | High | Low | Low | Low |
| Cimetidine      | 200       | 0.0722022 | 0.16 | 0.98039216 | High | High | High | High |
| Cloxacillin     | 1000      | 0.2605049 | 287.76978 | 75.1879699 | High | Low | Low | Low |
| Codeine         | 30        | 0.0028714 | 4.4E-05 | 0.07246377 | High | High | High | High |
| Colchicine      | 25        | 0.0011682 | 0.002 | 0.00662252 | High | High | High | High |
| Dapsone         | 100       | 1.1428571 | 1.0526316 | 1.4084507 | Low | Low | Low | Low |
| Diazepam        | 5         | 1 | 0.4 | 1.63934426 | High | Low | High | High |
| Diclofenac      | 100       | 0.0203035 | 56.603774 | 34.2857143 | High | Low | Low | Low |
| Diclofenac      | 100       | 0.0203035 | 56.603774 | 34.2857143 | High | Low | Low | Low |
| Erythromycin    | 100       | 0.0011682 | 0.002 | 0.00662252 | High | High | High | High |
| Flurofen        | 100       | 0.0203035 | 56.603774 | 34.2857143 | High | Low | Low | Low |
| Fluoxetine      | 100       | 0.0203035 | 56.603774 | 34.2857143 | High | Low | Low | Low |
| Griseofulvin    | 250       | 1492.5373 | 115.74074 | 19.8412698 | High | Low | Low | Low |
| Hydralazine     | 50        | 0.1724138 | 0.0757558 | 0.93240093 | High | High | High | High |
| Hydrochlorothiazide | 25        | 0.2439024 | 0.1428571 | 0.0464286 | High | High | High | High |
| Ibuprofen       | 100       | 0.0942507 | 23.562677 | 0.3030303 | High | Low | Low | Low |
| Indinavir       | 100       | 0.1666667 | 0.01639344 | 0.99173554 | High | High | High | High |
| Levodopa        | 50        | 0.7407407 | 200 | 0.14388489 | High | Low | Low | Low |
| Levonorgestrel  | 40        | 0.0230548 | 26.6666667 | 1.3559222 | High | Low | Low | Low |
| Levotyroxine    | 0.1       | 0.0997506 | 0.0038095 | 0.04454343 | High | High | High | High |
| Metformin       | 500       | 0.002 | 0.8888889 | 0.93240093 | High | High | High | High |
| Methyldopa      | 250       | 0.149925 | 0.44247788 | 0.93240093 | High | High | High | High |
| Metronidazole   | 500       | 0.2816901 | 84.459459 | 0.808 | High | Low | High | High |
| Nelfinavir      | 250       | 591.54519 | 523.560209 | 0.96385542 | High | Low | Low | Low |
| Nifedipine      | 10        | 1.3333333 | 2.25988701 | 0.96385542 | High | Low | Low | Low |
| Nitrofurantoin  | 100       | 0.2857143 | 5.0327126 | 0.96385542 | High | Low | Low | Low |
| Paracetamol     | 50        | 0.1966568 | 0.1428571 | 0.48192771 | High | High | High | High |
| Penicillamine   | 250       | 0.0968054 | 0.009009 | 0.21505376 | High | High | High | High |
| Penicillin V    | 250       | 0.0125723 | 1 | 2.02064317 | High | Low | Low | Low |
| Phenobarbital   | 100       | 0.625 | 2.3603604 | 1.44927536 | High | High | Low | Low |
| Phenytoin       | 100       | 4 | 12.5 | 5.6287904 | Low | Low | Low | Low |
| Prednisolone    | 5         | 0.1538462 | 0.0896861 | 0.08368201 | High | High | High | High |
| Primaquine      | 15        | 0.0003165 | 1.06382979 | 0.93240093 | High | High | High | High |
### Supplementary table 1 (Cont)

| Drug                  | Dose (mg) | D[^1] | D[^2] | D[^3] | Solubility Class 1 | Solubility Class 2 | Solubility Class 3 | Reliable experimental solubility[^a] |
|-----------------------|-----------|-------|-------|-------|--------------------|--------------------|--------------------|-------------------------------------|
| Promethazine          | 25        | 0.0478469 | 4.08163265 | High | Low                | High               | High                |                                     |
| Propranolol           | 40        | 0.0029602 | 2.2857143 | High | Low                | Low                | Low                |                                     |
| Propylthiouracil      | 50        | 0.1149425 | 0.1666667 | High | High               | High               | High                |                                     |
| Pyrazinamide          | 400       | 0.0759734 | 0.1066667 | High | High               | High               | High                |                                     |
| Pyridostigmine        | 60        | 0.0005417 | 0.23076923 | High | High               | High               | High                |                                     |
| Riboflavin            | 5         | 0.0001868 | 0.2361275 | High | High               | High               | High                |                                     |
| Ritonavir             | 100       | 1063.8298 | 317.460317 | Low  | Low                | Low                | Low                |                                     |
| Salbutamol            | 4         | 0.000016  | 5.3333333 | 0.0074416 | High               | Low                | High                |                                     |
| Saquinavir            | 200       | 16      | 323.88664 | Low  | Low                | Low                | Low                |                                     |
| Stavudine             | 40        | 0.0091376 | 0.016   | 0.00395062 | High               | High               | High                |                                     |
| Sulfamethoxazole      | 400       | 1.509434 | 2.6229508 | 3.4858387 | Low                | Low                | Low                |                                     |
| Theophylline          | 300       | 0.2836879 | 0.24    | 0.05240175 | High               | High               | High                |                                     |
| Thiamine              | 5         | 0.0009126 | 0.0004  | 15.0718954 | High               | Low                | High                |                                     |
| Trimethoprim          | 200       | 0.1152738 | 0.0661157 | 1.30081301 | High               | High               | Low                |                                     |
| Valproic Acid         | 500       | 0.0091258 | 0.004   | 150.718954 | High               | High               | Low                |                                     |
| Zidovudine            | 300       | 0.3243243 | 0.024   | 0.07361963 | High               | High               | High                |                                     |

[^1]: Do (dose number) calculated from predicted solubility data, ACD/Labs; 2 Do (dose number) calculated from solubility data obtained from DrugBank database; 3 Do (dose number) calculated from predicted solubility data, ALOGPS; Θ Reliable experimental solubility, were taken from ref. 13.

### Supplementary table 2: Solubility and permeability classification comparing the list of national essential medicines (NEML) of Pakistan and classification of the WHO’s essential medicines model list (EML)

| Drug                  | WHO[^b] Dose (mg) | NEML[^b] Dose (mg) | WHO[^b] Solubility class | NEML[^b] Solubility class | Comment | WHO[^c] Permeability class | NEML[^c] Permeability class | Comment |
|-----------------------|-------------------|--------------------|--------------------------|--------------------------|---------|---------------------------|----------------------------|---------|
| Acetylsalicylic acid  | 500               | 300                | High                     | High                     | High    | Low                       | Low                       | classified as low permeability drug based on reliable data[^c]; log D[^5] indicated low permeability, whereas, PSA was lower than that of labetalol |
| Aciclovir             | 200               | 200                | High                     | Low                      | Low     | Low                       | Low                       |                                     |
| Albendazole           | 400               | 200                | Low                      | Low                      | inconclusive | High |                       |                           |                                     |
| Allopurinol           | 100               | 300                | High                     | High                     | High    | Low                       | Low                       | classified as low permeability drug based on reliable data[^c]; log D[^5] indicated low permeability, whereas, PSA was lower than that of labetalol |
| Amiloride             | 5                 | 5                  | High                     | High                     | High    | High                       | High                       |                                     |
| Amitriptyline         | 25                | 50                 | High                     | High                     | High    | High                       | High                       |                                     |
| Drug            | WHO § Dose (mg) | WHO § Solubility class | NELM Solubility class | Comment                                                                 | WHO § Permeability class | NELM Permeability class | Comment                                                                                   |
|----------------|-----------------|------------------------|-----------------------|--------------------------------------------------------------------------|--------------------------|-------------------------|-------------------------------------------------------------------------------------------|
| Amlodipine     | 5               | High                   | High                  | High                                                                      | High                     | High                    | High                                                                                      |
| Amoxicillin    | 500             | High                   | Low                   | classified as high solubility based on incomplete data*                  | High                     | Low                     | Classified as high permeability based on incomplete data*; both log $D_{6.0}$ and PSA indicated low permeability |
| Atenolol       | 100             | High                   | High                  | Low                                                                       | Low                      | Low                     | Low                                                                                      |
| Carbamazepine  | 200             | Low                    | Low                   | Low                                                                       | High                     | High                    | NEML dose is lower than that of WHO                                                        |
| Cefixime       | 400             | Low                    | High                  | inconclusive                                                              | low                      | Low                     | Classified as low permeability based on reliable data*; PSA can indicate low permeability |
| Chloramphenicol| 250             | High                   | Low                   | Low                                                                       | Low                      | High                    |                                                                                           |
| Chloroquine    | 150             | High                   | High                  | High                                                                      | High                     | High                    |                                                                                           |
| Chlorphenamine | 4               | High                   | High                  | inconclusive                                                              | High                     | High                    |                                                                                           |
| Chlorpromazine | 100             | High                   | High                  | inconclusive                                                              | High                     | High                    |                                                                                           |
| Ciprofloxacin  | 250             | High                   | High                  | inconclusive                                                              | Low                      | Low                     |                                                                                           |
| Clomipramine   | 25              | High                   | High                  | inconclusive                                                              | High                     | High                    |                                                                                           |
| Cloxacinil     | 1000            | High                   | High                  | Low                                                                       | Low                      | Low                     |                                                                                           |
| Dapsone        | 100             | Low                    | High                  | NELM dose is lower than that of WHO                                       | High                     | High                    |                                                                                           |
| Diazepam       | 5               | High                   | Low                   | NELM dose is higher than that of WHO                                       | High                     | High                    |                                                                                           |
| Didanosine     | 400             | High                   | High                  | Low                                                                       | Low                      | Low                     |                                                                                           |
| Digoxin        | 0.25            | High                   | High                  |                             | High                     | High                    |                                                                                           |
| Diloxanide     | 500             | Low                    | Low                   | inconclusive                                                              | High                     | High                    |                                                                                           |
| Doxycycline    | 100             | High                   | High                  | High                                                                      | Low                      | Low                     | Classified as low permeability drug based on reliable data*; both log $D_{6.0}$ and PSA indicated low permeability |
| Efavirenz      | 200             | Low                    | Low                   | inconclusive                                                              | High                     | High                    | Both log $D_{6.0}$ and PSA indicated high permeability                                    |
| Enalapril      | 2.5             | High                   | High                  | Low                                                                       | High                     | High                    |                                                                                           |
Supplementary table 2 (Cont)

| Drug          | WHO\textsuperscript{¶} Dose (mg) | NEML Dose (mg) | WHO\textsuperscript{¶} Solubility class | NEML Solubility class | Comment | WHO\textsuperscript{¶} Permeability class | NEML Permeability class | Comment |
|---------------|----------------------------------|----------------|-----------------------------------------|-----------------------|---------|-------------------------------------|-----------------------|---------|
| Erythromycin  | 250                              | 500            | Low                                     | High                  | classified as low solubility based on incomplete data\* | Low                   | High     | Classified as low permeability based on incomplete data\*; PSA can indicate low permeability |
| Ethambutol    | 400                              | 400            | High                                    | High                  | Low     | Low                                 | Low                   | Low     |
| Furosemide    | 40                               | 40             | Low                                     | High                  | inconclusive | High     | |
| Glibenclamide | 5                                | 5              | Low                                     | High                  | inconclusive | High     | |
| Griseofulvin  | 250                              | 500            | Low                                     | Low                   | High     | High                                 | High                   | |
| Haloperidol   | 2                                | 5              | inconclusive                            | High                  | Low     | High                                 | Low                   | |
| Hydralazine   | 50                               | 25             | High                                    | High                  | Low     | High                                 | Low                   | |
| Hydrochlorothiazide | 25                      | 50            | High                                    | High                  | Low     | High                                 | Low                   | |
| Ibuprofen     | 400                              | 600            | Low                                     | Low                   | High     | High                                 | High                   | |
| Indinavir sulfate | 400                     | 400           | Low                                     | Low                   | inconclusive | High     | |
| Isoniazid     | 300                              | 300            | High                                    | High                  | inconclusive | Low     | |
| Isosorbide dinitrate | 5                        | 10            | High                                    | High                  | inconclusive | Low     | |
| Lamivudine    | 150                              | 150            | High                                    | High                  | High     | Low                                  | High                   | |
| Levasimole    | 150                              | 40             | High                                    | High                  | inconclusive | High     | |
| Levodopa      | 250                              | 250            | High                                    | High                  | High     | High                                 | High                   | |
| Carbidopa     | 25                               | 25             | High                                    | High                  | inconclusive | Low     | |
| Mebendazole   | 500                              | 100            | Low                                     | Low                   | inconclusive | High     | |
| DL-methionine | 250                              | 250            | High                                    | High                  | High     | Low                                  | Low                   | |
| Metformin     | 500                              | 500            | High                                    | High                  | Low     | Low                                 | Low                   | |
| Methylidopa   | 250                              | 500            | High                                    | High                  | Low     | Low                                 | Low                   | |
| Drug          | WHO § Dose (mg) | NEML Dose (mg) | WHO § Solubility class | NEML Solubility class | Comment                  | WHO § Permeability class | NEML Permeability class | Comment                  |
|--------------|----------------|----------------|------------------------|-----------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Metoclopramide | 10             | 10             | High                   | High                  | Low                      | Low                      |                          |                          |
| Metronidazole | 500            | 400            | High                   | High                  | High                     | Low                      | Classifed as high permeability drug based on reliable data*; PSA can indicate low permeability |
| Morphine     | 10             | 30             | High                   | High                  | inconclusive             | Low                      |                          |                          |
| Nelfinavir    | 250            | 250            | inconclusive           | Low                   | inconclusive             | High                      |                          |                          |
| Neostigmine  | 15             | 15             | High                   | High                  | Low                      | Low                      |                          |                          |
| Nevirapine   | 200            | 200            | Low                    | Low                   | High                     | High                      |                          |                          |
| Niclosamide  | 500            | 500            | Low                    | Low                   | inconclusive             | High                      |                          |                          |
| Nitrofurantoin | 100           | 100            | Low                    | High                  | High                     | High                      |                          |                          |
| Nystatin     | 200            | 200            | inconclusive           | Low                   | inconclusive             | High                      |                          |                          |
| Paracetamol  | 500            | 500            | High                   | High                  | High                     | High                      |                          |                          |
| Penicillamine | 250            | 250            | High                   | High                  | Low                      | Low                      |                          |                          |
| Phenobarbital | 100            | 30             | High                   | High                  | High                     | High                      |                          |                          |
| Penicillin v | 250            | 500            | High                   | High                  | High                     | Low                      | Classified as high permeability drug based on reliable data*; both log \( D_{6.0} \) and PSA indicated low permeability |
| Phenytion    | 100            | 100            | Low                    | Low                   | High                     | High                      |                          |                          |
| Prednisolone | 25             | 5              | High                   | High                  | High                     | High                      |                          |                          |
| Primaquine   | 15             | 7.5            | High                   | High                  | High                     | High                      |                          |                          |
| Promethazine | 25             | 25             | High                   | High                  | High                     | High                      |                          |                          |
| Propranolol  | 40             | 160            | High                   | High                  | High                     | High                      |                          |                          |
| Propylthiouracil | 50         | 100            | High                   | High                  | High                     | High                      |                          |                          |
| Pyrantel     | 250            | 250            | Low                    | High                  | classified as low solubility based on inconclusive data* | inconclusive             | Low                      |                          |
| Pyrazinamide | 400            | 500            | High                   | High                  | inconclusive             | High                      |                          |                          |
| Quinine      | 300            | 200            | High                   | High                  | High                     | High                      |                          |                          |
| Rifampicin   | 300            | 600            | Low                    | Low                   | High                     | Low                      | Classified as high permeability based on incomplete data*; both log \( D_{6.0} \) and PSA indicated low permeability |
| Ritonavir    | 100            | 100            | Low                    | Low                   | inconclusive             | High                      |                          |                          |
| Salbutamol   | 4              | 4              | High                   | High                  | Low                      | Low                      |                          |                          |
| Saquinavir   | 200            | 200            | Low                    | inconclusive           | High                     | High                      |                          |                          |
| Spironolactone | 25           | 100            | inconclusive           | Low                   | inconclusive             | High                      |                          |                          |
Partition coefficients and molecular surface properties as predictors of drug absorption

Supplementary table 2 (Cont)

| Drug                  | WHO \* Dose (mg) | NELM Dose (mg) | WHO \* Solubility class | NELM Solubility class | Comment | WHO \* Permeability class | NELM Permeability class | Comment                          |
|-----------------------|------------------|----------------|-------------------------|-----------------------|---------|---------------------------|------------------------|----------------------------------|
| Stavudine (d4t)       | 40               | 40             | High                    | High                  | High    | Low                       | PSA can indicate high permeability |
| Sulphasalazine        | 500              | 500            | Low                     | High                  | Low     | High                      | Low; PSA can indicate low permeability |
| Trimethoprim          | 200              | 300            | Low                     | High                  | High    | High                      | Classified as high permeability based on reliable data; both log \(D_{6.0}\) and PSA indicated low permeability |
| Valproic acid         | 500              | 300            | High                    | High                  | High    | Low                       | Classified as high permeability drug based on reliable data; both log \(D_{6.0}\) and PSA indicated low permeability |
| Verapamil             | 80               | 240            | Low                     | High                  | High    | High                      | Classified as low solubility based on inconclusive data* |
| Warfarin              | 5                | 5              | High                    | High                  | High    | High                      | Classified as high permeability drug based on reliable data*; PSA can indicate high permeability |
| Zidovudine (zdv)      | 300              | 100            | High                    | High                  | High    | Low                       | PSA can indicate high permeability |

\* Ref. (13); ¶ Ref. (16)

Supplementary table 3: Comparison of Permeability prediction based on log \(P\), log \(D_{6.0}\) and PSA, by using metoprolol or labetalol as internal standard.

| Drug                  | Log \(P\) | Log \(D_{6.0}\) | PSA | Internal standard: Metoprolol | Internal standard: Labetalol | Reliable experimental solubility* |
|-----------------------|-----------|-----------------|-----|-------------------------------|-------------------------------|----------------------------------|
|                        |           |                 |     | \(P\) cutoff \("1.35\") | \(D_{6.0}\) cutoff \("-1.48\") | \(PSA\) cutoff \("65\") | \(P\) cutoff \("2.31\") | \(D_{6.0}\) cutoff \("-0.42\") | \(PSA\) cutoff \("95.6\") |                               |
| Abacavir               | 0.72      | 0.03            | 96.95 | Low                           | Low                           | Low                             | Low | Low | Low | Low |                     |
| Acetylsalicylic Acid   | 1.19      | -1.24           | 63.6  | Low                           | Low                           | Low                             | Low | High | Low | Low |                     |
| Aclclovir              | -1.76     | -1.76           | 109.83 | Low                           | Low                           | Low                             | Low | Low | Low | Low |                     |
| Allopurinol           | -1.33     | -3.81           | 74.69  | Low                           | Low                           | Low                             | Low | Low | Low | Low |                     |
| Amiloride              | 1.08      | 1.07            | 156.79 | Low                           | Low                           | Low                             | Low | High | Low | High |                     |
| Atenolol               | 0.1       | -2.73           | 84.58  | Low                           | Low                           | Low                             | Low | Low | Low | High |                     |
| Captopril             | 0.27      | -2.02           | 96.41  | Low                           | Low                           | Low                             | Low | Low | Low | Low |                     |
| Carbamazepine         | 2.67      | 2.67            | 46.33  | High                          | High                          | High                            | High | High | High | High |                     |
| Chloramphenicol       | 1.02      | 1.02            | 115.38 | Low                           | Low                           | Low                             | Low | Low | Low | Low |                     |
| Chloroquine           | 4.69      | 1.2             | 28.16  | High                          | High                          | High                            | High | High | High | High |                     |
| Cimetidine            | 0.26      | -1.14           | 114.19 | Low                           | Low                           | Low                             | Low | Low | Low | Low |                     |
| Clobazam             | 2.53      | -0.81           | 138.04 | High                          | Low                           | High                            | Low | Low | Low | Low |                     |
| Codeine               | 1.2       | -0.99           | 41.93  | Low                           | Low                           | Low                             | Low | Low | Low | High |                     |
| Colchicine           | 0.92      | 0.92            | 83.09  | Low                           | Low                           | Low                             | Low | Low | Low | Low |                     |
| Cyclophosphamide      | 0.23      | 0.23            | 51.38  | Low                           | Low                           | Low                             | Low | Low | Low | High |                     |

" Rel. (13); ¶ Ref. (16)
### Supplementary table 3 (Cont)

| Drug               | Log P | Log $D_{60}$ | PSA | Log P cutoff $^*$ | Log $D_{60}$ cutoff $^*$ | PSA cutoff $^*$ | Reliable experimental solubility$^{10}$ |
|--------------------|-------|--------------|-----|-----------------|--------------------------|----------------|----------------------------------------|
| Dapsone            | 0.94  | 0.94         | 94.56 | Low             | Low                      | Low            | High | High | High |
| Diazepam           | 2.96  | 2.96         | 32.67 | High            | High                     | High           | High | High | High |
| Digoxin            | 0.85  | 0.85         | 203.06 | Low              | Low                      | Low            | High | Low | High |
| Doxycycline        | -0.54 | -3.06        | 181.62 | Low              | Low                      | Low            | Low | Low | High |
| Ergotamine         | 3.58  | 1.99         | 118.21 | High             | High                     | High           | Low | High | High |
| Fluconazole        | 0.5   | 0.5          | 71.79  | Low              | Low                      | Low            | Low | Low | High |
| Furosemide         | 3     | 0.26         | 131.01 | High             | High                     | Low            | High | Low | Low |
| Griseofulvin       | 3.53  | 3.53         | 71.06  | High             | High                     | High           | High | High | High |
| Hydralazine        | 1     | 0.56         | 63.83  | Low              | Low                      | Low            | Low | Low | High |
| Hydrochlorothiazide| -0.07 | -0.07        | 135.12 | Low              | Low                      | Low            | Low | Low | High |
| Ibuprofen          | 3.72  | 2.12         | 37.3   | High             | High                     | High           | High | High | High |
| Indinavir          | 2.88  | 2.76         | 118.03 | High             | High                     | High           | Low | Low | Low |
| Levodopa           | -0.22 | -0.27        | 103.78 | Low              | Low                      | Low            | Low | Low | High |
| Levonorgestrel     | 3.92  | 3.92         | 37.3   | High             | High                     | High           | High | High | High |
| Levothyrirxine     | 5.93  | 3.38         | 92.78  | High             | High                     | Low            | Low | Low | High |
| Metformin          | -2.31 | -4.31        | 88.99  | Low              | Low                      | Low            | Low | Low | High |
| Methyldopan        | 0.12  | -2.37        | 103.78 | Low              | Low                      | Low            | Low | Low | Low |
| Metronidazole      | -1.01 | -1.01        | 78.94  | Low              | Low                      | Low            | Low | Low | High |
| Nelfinavir         | 6.98  | 5.44         | 127.2  | High             | High                     | Low            | Low | Low | Low |
| Nifedipine         | 2.97  | 2.96         | 110.45 | High             | High                     | Low            | Low | Low | High |
| Nitrofuranotin     | -0.4  | -0.41        | 120.73 | Low              | Low                      | Low            | Low | Low | High |
| Paracetamol        | 0.34  | 0.34         | 49.33  | Low              | High                     | Low            | High | Low | Low |
| Penicillamine      | 0.93  | -1.57        | 102.12 | Low              | Low                      | Low            | Low | Low | Low |
| Penicillin V       | 1.88  | -1.47        | 121.24 | Low              | Low                      | Low            | Low | Low | High |
| Phenoxybarbital    | 1.67  | 1.66         | 75.27  | High             | High                     | Low            | High | High | High |
| Phenothiazine      | 2.52  | 2.52         | 58.2   | High             | High                     | High           | High | High | High |
| Prednisolone       | 1.49  | 1.49         | 94.83  | High             | High                     | Low            | Low | Low | High |
| Primaquine         | 2.67  | -0.41        | 60.17  | High             | Low                      | High           | High | High | High |
| Promethazine       | 4.78  | 2.04         | 31.78  | High             | High                     | High           | Low | High | Low |
| Propranolol        | 3.1   | 0.28         | 41.49  | Low              | High                     | High           | High | High | High |
| Propylthiouracil   | 1.37  | 1.36         | 73.22  | Low              | Low                      | Low            | Low | Low | High |
| Pyrazinamide       | -0.37 | -0.37        | 68.87  | Low              | Low                      | Low            | Low | Low | High |
| Pyridostigmine     | -4.31 | -4.31        | 29.54  | Low              | High                     | Low            | High | Low |
| Riboflavin         | -2.02 | -3.48        | 155.05 | Low              | Low                      | Low            | Low | Low | Low |
| Ritonavir          | 5.28  | 5.28         | 202.26 | High             | High                     | Low            | Low | Low | Low |
| Salbutamol         | 0.01  | -2.84        | 72.72  | Low              | Low                      | Low            | Low | Low | High |
| Saquinavir         | 4.44  | 2.84         | 166.75 | High             | High                     | Low            | Low | Low | High |
| Stavudine          | -0.86 | -0.86        | 78.87  | Low              | Low                      | Low            | Low | Low | High |
| Sulfamethoxazole   | 0.89  | 0.49         | 106.6  | Low              | Low                      | Low            | Low | Low | High |
| Theophylline       | -0.17 | -0.18        | 69.3   | Low              | Low                      | Low            | Low | Low | High |
| Thiamine           | -1.61 | -1.65        | 100.27 | Low              | Low                      | Low            | Low | Low | Low |
| Trimethoprim       | 0.79  | -0.42        | 105.51 | Low              | Low                      | Low            | Low | Low | High |
| Valproic Acid      | -1.61 | -1.65        | 100.27 | Low              | Low                      | Low            | Low | Low | High |
| Zidovudine         | -0.53 | -0.53        | 91.23  | Low              | Low                      | Low            | Low | Low | High |
CONCLUSION

Within the limitations of our investigation, the following conclusions can be drawn. First, log $D_{6.0}$ showed better prediction capability than log $P_p$.

Second, metoprolol was conservative permeability internal standard as compared to labetalol. Finally, models combining log $D$ and PSA can have the best permeability prediction capabilities.

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