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Quantifying drug primary mechanism of action parameter in HIV (viral) dynamics

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Abstract

Surface thermodynamics concept was used to quantify drug primary mechanism of action parameter in control infectivity of viral dynamics. The methodology involved expressing interfacial energetics of Hamaker constant, a thermodynamic tool capable of being optimized for disease extinction as drug primary mechanism of action parameter in control infectivity of viral dynamics. The expressed drug primary mechanism of action parameter and the associated drug primary mechanism of action are quantified from imported Hamaker constants data of experimental drugs. The drug primary mechanism of action parameter β_{1T} quantified from the imported drug experimental data which are all greater than 1 and vary from $1.0228\left({}^{mL}/_{copies.d.mg}\right)$ for drug Efavirenz tablets (D4) to $1.0683\left({}^{mL}/_{copies.d.mg}\right)$ for drug Nevirapine tablets (D3). These gave rise to associated drug primary mechanism of action with values varying from $0.0632\left({}^{mL}/_{copies.d.}\right)$ for drug Lamivudine tablets (D5) to $0.2757\left({}^{mL}/_{copies.d.}\right)$ for the combinational drugs Lamivudine, Nevirapine & Zidovudine (D1). A greater than 1 value of drug primary mechanism of action parameter imply the existence of net van der Waals forces which indicate a possible repulsion of HIV viral particles that invade blood cells (lymphocyte). As in functional controlled viral dynamics, an associated increase in CD4 count is expected as a result of decrease in viral load. This finding could be utilised by Pharmaceutical industries in the drug design to optimize the drug primary mechanism of action parameter for possible extinction of HIV infection.

Keywords: Human immunodeficiency virus, Drug mechanism of action, Interfacial energetics, Hamaker constant

1. Introduction

Viruses multiply by using the host cell's synthesizing machinery to cause the synthesis of viral building blocks, which then self-assemble into new viruses that are released into the environment. A virus is a small agent that is only able to replicate itself inside the living cells of an organism. They are not susceptible to the action of antibodies (Khanal & Shrestha, 2013). Viruses are found in almost every ecosystem on earth and known to infect most types of organisms, including bacteria, fungi, plants, vertebrates, etc. Several virus diseases are common in humans, wild and domestic animals or crop plants. Some common human diseases such as cold, influenza, chickenpox and cold sores are caused by viruses. There are currently twenty one families of viruses known to cause diseases in humans, including human immunodeficiency virus (HIV), Hepatitis, Herpes Simplex, Measles, etc. These have continued to plague humans (Lai, 2014).

The mechanisms by which viruses cause diseases in an organism depend largely on the viral species (Smith, 1972). Viruses can usually cause damage in the host via cell lysis, production of toxic substances and cell transformation (Doitsh & Greene, 2016). When a virus enters a cell and completes its normal replication cycle, the host cell may undergo lysis due to a physical internal pressure exerted by multiplying virus or immune response. During the course of virus replication, many cytotoxic viral components as well as by-products of viral replication accumulate

in the cell (Klatt, 2015). Cell lysis and cytotoxic components cause death of the cell (Lai, 2014). Some viruses can cause lifelong or chronic infections where viruses continue to replicate in the body despite the host's defence mechanisms.

HIV, as one of the most intensively studied viral infections, now has massive drug development efforts starting soon after identification of the virus with twenty seven (27) different antiretroviral drugs (Hill, Rosenbloom, Nowark, & Siliciano, 2018), capable of halting viral replication and preventing transmission and progression to AIDS but still without a cure. Variability in response to therapy has made some individuals experience virologic failure on therapy that is highly effective on others. Under the use of Highly Active Anti Retroviral Therapy (HAART), transient rebounds of plasma viremia have also remained a problem (Jeffry, 2006). Most viral diseases have the ability to develop resistance. About ten billion new viral particles of HIV can be generated daily, in chronic cases (Omenyi, 2005). Ronsard *et al.*, in (Santoro & Perno, 2013), noted that a rate-limiting factor in the management of HIV infections, is the plethora of genetic variations in infectivity leading to failure of clinical trials. Virus infectivity in HIV infection is observed to vary (Ganusov, Neher & Perelson, 2012). Clinical solution to the problem of HIV is hampered by the rapid genetic mutation of HIV.

The problem therefore is the difficulty in the determination of a new knowledge in HIV/drug interactions required by drug manufacturers that would translate to production of more effective drugs. The identification of the actual mechanisms of virus/blood interactions parameters within the existing mathematical models has not been easy. A very serious problem in the mathematical modelling is the unavailability of experimental data on HIV/blood interactions. In this paper, the virus/blood interaction parameters required for complete solution of the model equations, will be quantified in terms of the interfacial energetics and amount of drugs required estimated.

2. Literature Survey

2.1 Surface Thermodynamic Principles

In the virus life cycle (replication cycle) the most crucial stage is the first stage, the binding (attachment) stage. It is a stage without which the HIV life cycle would be cut short. Now at entry to the body, the viral particle is attracted to a cell (lymphocyte) with the appropriate CD4 receptor molecules where it attaches (binds) and by fusion to a susceptible cell membrane or by endocytosis (an energy using up process) and then enters the cell. Fusion of the viral and host membranes is a critical step during infection by membrane enclosed viruses like HIV and influenza. The probability of infection is a function of both the number of infective HIV virions in the body fluid which contacts the host as well as the number of cells available at the site of contact that have appropriate CD4 receptors (Klatt, 2015: Sundquist & Kraussilich, 2012). This probability could only be attained as a result of the unavoidable contact between the virion and the lymphocyte. The interaction between particles, a virus and the surface of the lymphocyte is controlled by a balance between electrostatic repulsion – van der Waals attraction mechanism, resulting in an adhesive energy which can be expressed as equation (1) (Omenyi, 1978).

$$\Delta F_{PLS}^{adh}(d_0) = \gamma_{PS} - \gamma_{PL} - \gamma_{SL} \quad (1)$$

Where ΔF^{adh} is the thermodynamic free energy of adhesion, integrated from infinity to the equilibrium separation distance d_o; γ_{PS} is the interfacial free energy between *P* (representing the virus) and *S* (lymphocyte), γ_{PL} is that between P and L (where *L* is the plasma) and γ_{SL} is that between S and L.

Similar equations can be obtained for interactions between the individual components as,

$$\Delta F_{ij}^{adh}(d_0) = \gamma_{ij} + \gamma_{iv} + \gamma_{jv} \quad (2)$$

For all given combinations, ΔF^{adh} could be expressed in terms of van der Waals energy thereby making surface free energy or energy of interaction a function of attraction between different particles suspended in a liquid medium given equation (3) (Omenyi, 1978).

$$\Delta F_{ij}^{adh}(d_0) = -\left[\frac{A_{ij}}{12\pi {d_0}^2}\right] \quad (3)$$

$$\Delta F_{PLS}^{adh}(d_0) = -\left[\frac{A_{PLS}}{12\pi {d_0}^2}\right] \quad (4)$$

Where A_{ij} is Hamaker constant between two surfaces i and j, A_{PLS} is the Hamaker coefficient for interaction between two surfaces P and S separated by a liquid medium L, and

$$A_{ij} \cong \sqrt{A_{ii}A_{jj}} \quad (5)$$

For a combination of attraction of two materials P and S, with material medium 3 in-between them Hamaker (1937) also has it that

$$A_{PLS} = A_{PS} + A_{LL} - A_{PL} - A_{SL} \quad (6)$$

Dzyaloshinskii, Liftshitz, & Pitaevaskii (1961) applied an alternative derivation of van der Waals forces between solid bodies due to limitations of Hamaker's approach since the interaction between solids on the basis of their macroscopic properties considers the screening and other effects in their calculations. Some authors, Visser (1975); Ninham & Parsegian (1970); Nir, *et al*., (1972); Israelachivili (1972) approximated the Lifshitz's equation. It was observed that the results are identical while starting at a different position at zero frequency for a group of materials like polymers. While analysing the absorption data of polystyrene, the value of A_{11} was expressed as

$$A_{11} = 2.5\left[\frac{\varepsilon_{10}-1}{\varepsilon_{10}+1}\right]^2 = 2.5\left[\frac{n^2-1}{n^2+1}\right]^2 \quad (7)$$

Both the dielectric constant, ε_{10} and the refractive index, n of the polymer at zero frequency which are the bulk materials properties can easily be obtained. Robinson (1952) had established

$$n = \left[\frac{1-R^{1/2}}{1+R^{1/2}}\right] \quad (8)$$

Where R, is the reflectance and,

$$R = 1 - T - \bar{a} \quad (9)$$

T is the transmittance is expressed as

$$T = 10^{-\bar{a}} \quad (10)$$

$\bar{a}$ is the absorbance and can be obtained through spectrophotometric experiment.
What one needs to do therefore is measure the dielectric constants as a function of wavelength.

2.2 Control Infectivity Parameter

The basic model adopted for this study is that due to (Bonhoeffer, May, Shaw, & Nowak., 1997),

$$\begin{aligned} \dot{x} &= \lambda - dx - \beta xv, \\ \dot{y} &= \beta xv - ay, \\ \dot{v} &= ky - uv. \end{aligned} \quad (11)$$

The interaction between the virus *v* and the lymphocyte *x* is clearly given as *xv* and the appropriate infectivity parameter is β. Clearly seen from literature, when there is therapy (control), infectivity can be reduced with application of drugs. Two approaches are evident. The first is a function of the efficiency of drugs and the infectivity clearly shown in equation (12).

$$\beta_c = \beta_0(1 - \eta) \quad (12)$$

η is drug (response) efficiency.

The second approach due to (Costanza *et al.* cited in Rivadeneira, *et al.*, 2014) gave control interaction parameter β_C, under therapy as

$$\beta_C = (\beta_0 - \beta_1 u - \beta_2 u^2) \qquad (13)$$

It is an empirical approximation for pharmacodynamic (concerned with the effects of drugs and the mechanisms of their action, that is, how a drug works) and pharmacokinetic (study of effects of the body on the actions of a drug, basically the time course of drug absorption) equations used to relate the real dose with its efficiency. The first term of the equation (13) is the disease mechanism of action term (infectivity) that is, virus mechanism of action term commonly known as disease interaction term, the second term is the drug primary (dominant) mechanism of action term while the third term is the drug secondary mechanism of action term with β_2 being identified as a function of β_1. β_0 is actual disease mechanism of action (infectivity), β_1 drug primary mechanism of action parameter and has value greater than one, β_2 is drug secondary mechanism of action parameter and has maximum value of one, u is drug amount.

2.3 Drug Response and Dose Relationship

In line with assertions by Peper (2009), that the dose-response curve postulates that a change in drug dose either by way of additives or change in molecular composition will produce a proportionate and predictable change in drug effect (response), and by (Gupta, 2016), that the graded or gradual dose-response involves a continuous change in the effects (response) with changing doses, (Gupta, 2016) showed that a more linear presentation of data in therapeutic window (that is a range of doses of drugs that elicits a therapeutic response) was observed in a typical dose-response plot as in figure 1.

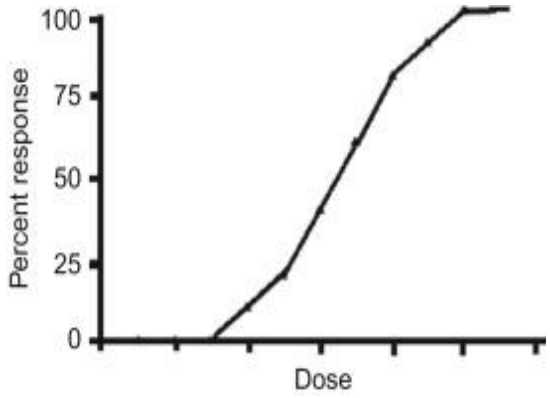

Figure 1: Relationship between drugs dose and response (Gupta, 2016).

Again, there is a correlation between drug response and drug mechanism of action. Ani, (2016) had established a direct evidence correlation between a coating effectiveness therapeutic response and the drug surface free energy, a drug primary mechanism of action. From all shown above, little or no effort has been put into understanding the drug mechanism of action against virus binding effects on the lymphocytes in the studies on mathematical modelling so far reported. In this paper therefore, the drug mechanism of action requisite for counteracting virus/blood interaction parameter, will be expressed using interfacial energetics concepts and quantified.

In this work, only drug primary mechanism of action in antiretroviral drugs environment required to counteract HIV/human blood interactions is considered with the use of van der Waals forces as analytical tool. Data is imported from available literature to quantify interfacial energetics parameter hence drug primary mechanism of action. Drug secondary mechanism of action may not be sought for as it has been found to be function of interfacial energetics parameter. This work will be valued by those in the pharmaceutical industry who are involved in antiretroviral drug design and production, clinicians and HIV/AIDS patients based on appropriate information of surface thermodynamics.

3.0 Material and methods

3.1 Material and data

This study involved expressing and quantification of drug primary mechanism of action parameter hence drug primary mechanism of action using interfacial energetics from Ilo (2021) to express the drug dominant or primary mechanism of action parameter β_1. The data used to quantify the expression obtained include experimental results of Antiretroviral drugs (Ani, 2016). The drugs information are presented in plate 1 and table 1.



Plate 1. Photographs of the drugs whose experimental data were used (Ani, 2016).

Table 1 shows details of the five antiretroviral drugs that their experimental data were used in this study. Dilution experiment by Ani (2016) that was based on average volume of human blood, determined the amount of drugs required for his experiments as follows: drug one 0.26(mg), drug two 0.24(mg), drug three 0.08(mg), drug four 0.12 and drug five 0.06(mg). These amounts of drugs are represented by u in equation (13).

Table 1: Details of five antiretroviral drugs whose experimental data were used (Ani, 2016).

Drug	Tablets	Batch Number	Expiration Date	Company
D1	Lamivudine, Nevirapine & Zidovudine	7220929	01/2016	Strides Arcolab Limited
D2	Tenofovir, Lamivudine & Efavirenz	3018522	09/ 2015	Mylan Laboratories Limited
D3	Nevirapine	7216348	04/2015	Strides Arcolab Limited
D4	Efavirenz	E121035A	07/2015	Hetero Labs Limited
D5	Lamivudine	LEX-023	04/2018	Mcneil & Drugs

3.2 Drug Primary Mechanism of Action Parameter β_1

Two detailed studies of drug action in HIV infection at drug intervention by Achebe (2010) of van der Waals forces which revealed that Hamaker coefficient A_{PLS} expressed in equation (14) could attain a negative value, that is $A_{PLS} < 0$, leading to repulsion of interacting cells (HIV and lymphocytes) and by Ani *et al.*, (2015) and Ani (2016) on absorbance characteristics of both the drugs and blood which revealed that coating effectiveness, η_a is a function of drug surface free energy and could attain a maximum 100% value, hence the drug becomes effective HIV blockers by being able to effectively coat the surfaces of the lymphocyte for repulsion of interacting cells (HIV and lymphocytes) could be of great value in expressing the drug primary mechanism of action parameter β_1.

Hamaker constant being a function of surface free energy, as also shown by equations (1) to (6) therefore, coating effectiveness, η_a is a function of Hamaker coefficient A_{PLS} as also observed in (Ani, 2016). This implies that equation (14) could be used to express the drug primary mechanism of action parameters β_1 since it is on it that the coating effectiveness depends. A positive value of A_{PLS} ($A_{PLS} > 0$) implies that the net van der Waals interaction between particles, virus (P) and cell (S) all immersed in the plasma (L), is attractive**.** Equation (14) expresses the idea of the energy required to prevent adhesion and prevent virus penetration into the cell per mass of drug used, $A_{PLS} < 0$, (Achebe, 2010).

$$A_{PLS} = A_{PS} + A_{LL} - A_{PL} - A_{SL} < 0 \quad (14)$$

Thus, transition from energy of attraction to energy of repulsion is evident in equation (15).

$$A_{PLS} = A_{PS} + A_{LL} - A_{PL} - A_{SL} = 0 \quad (15)$$

That is,

$$A_{PS} + A_{LL} = A_{PL} + A_{SL} \quad (16)$$

and

$$\frac{(A_{PL}+A_{SL})}{(A_{PS}+A_{LL})} = 1 \quad (17)$$

If

$$\frac{(A_{PL}+A_{SL})}{(A_{PS}+A_{LL})} < 1 \quad (18)$$

Then corresponding Hamaker coefficient A_{PLS} is positive i.e., attraction occurs. This is the condition generally encountered in HIV/blood interaction in the absence of antiretroviral drugs.

If however,

$$\frac{(A_{PL}+A_{SL})}{(A_{PS}+A_{LL})} > 1 \quad (19)$$

Then the corresponding Hamaker coefficient A_{PLS} is negative i.e., repulsion occurs. This is energy driven process and is the condition generally encountered in HIV/blood interaction in the presence of antiretroviral drugs per viral attack on the lymphocyte. Thus, denote

$$\beta_{1T} = \frac{(A_{PL}+A_{SL})}{(A_{PS}+A_{LL})} \quad (20)$$

Note,

$$A_{PS} \cong \sqrt{A_{PP}A_{SS}} \quad (21)$$
$$A_{PL} \cong \sqrt{A_{PP}A_{LL}} \quad (22)$$
$$A_{SL} \cong \sqrt{A_{SS}A_{LL}} \quad (23)$$

With these equations, interfacial energetics of Hamaker constants for both particles of virus(*p*), lymphocyte(*s*) and serum(*L*) can be calculated with available imported data hence β_{1T}. From equation (19), $\boldsymbol{\beta_{1T}}$ has a value of greater than 1, hence the dominant parameter. The parameter β_{1T}, the drug interaction energy interplay (energetics) expressed the dominant mechanism of action parameter that actually drives the effects of drugs. The higher the β_{1T}, the greater tendency to drive the effectiveness of drugs to 100% as implied by (Ani *et al.,* 2015; Ani, 2016).

Therefore, to account for effect of every amount of drug, the drug main mechanism of action is a product of β_{1T} and mass, u of drug in the unit volume of blood.

4.0 Results and Discussions

4.1 Quantification of Drug Primary (Dominant) Mechanism of Action Parameter, β_{1T}.

Individual Hamaker constants are obtained from Ani (2016) and in combination with equations (21), (22) and (23), substituted into equation (20) to calculate drug primary (dominant) mechanism of action parameter, β_{1T} as seen in table 2. The data are presented in Table 2. Table 2 shows the computed A_{pL}, the Hamaker constant for both particles of virus (p) and serum (L), A_{sL} the Hamaker constant for both particles of lymphocyte (s) and serum (L), A_{ps}, the Hamaker constant for both particles of virus (p) and lymphocyte (s), the drug interaction energetics parameter (primary mechanism of action parameter) β_{1T} and primary (dominant) mechanism of action for each drug. A look at the table 2 shows that the drug interfacial energetics parameter β_{1T} for each of the drugs is greater than one as expected from equation (19). This confirms actually the expectation of equation (19) for any drug. The primary (dominant) mechanism of action $\beta_{1T}u$ is also shown clearly from second term of equation (13) as a function of drug interfacial energetics parameter and the amount of drug. As stated earlier, the values are obtained per copies of virus in millilitre of blood on a daily basis, per unit amount of drug obtained from the dilution experiment of (Ani, 2016).

Table 2: Drug primary mechanism (interaction energetics) parameter (β_{1T}) and primary (dominant) mechanism of action ($\beta_{1T}u$) table.

Variable	A_{pL} $\left(mL/_{copies.d.mg}\right)*(10^{-22}J)$	A_{sL} $\left(mL/_{copies.d.mg}\right)*(10^{-22}J)$	A_{ps} $(10^{-22}J)$	β_{1T} $\left(mL/_{copies.d.mg}\right)$	$\beta_{1T}u$ $\left(mL/_{copies.d.}\right)$
D1	3.5635	7.3797	5.7314	1.0604	0.2757
D2	4.4548	7.7521	6.0464	1.0382	0.2492
D3	3.0514	6.5898	5.0176	1.0683	0.0855
D4	4.3101	6.9618	6.1080	1.0228	0.1227
D5	3.7546	7.3464	5.7239	1.0529	0.0632

Again, plots of various amounts of drugs (varied doses) with corresponding or associated drug primary mechanism of action based on second term of equation (13) are shown in Figure 2. Figure 2 shows plots of drugs primary mechanism of action versus amount of drug for drugs one, two, three, four and five. As expected, there is a common trend in the progression. There is somewhat proportionate increase in drug primary mechanism of action in response to increase in amount of drugs in line with assertions by (Peper, 2009), that the dose-response curve postulates that a change in drug dose will produce a proportionate and predictable change in drug effect, and by (Gupta, 2016), that the graded or gradual dose-response involves a continuous change in the effects with changing doses in a more linear presentation of data, as observed in figure 1.

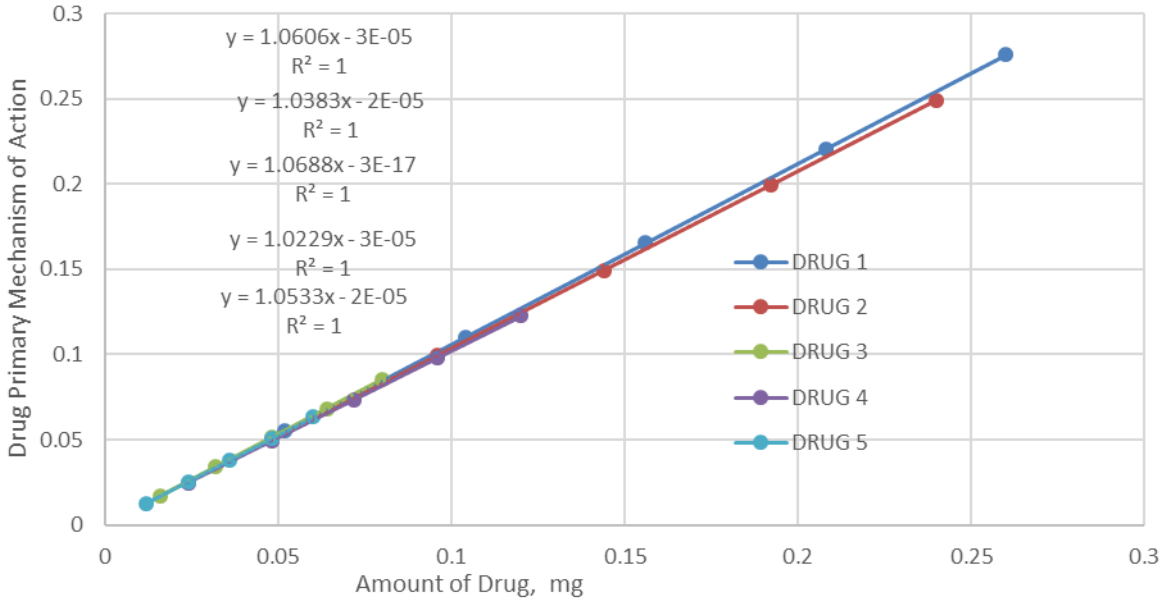

Figure 2: Plot of the drugs primary mechanism of action versus drug amount.

The slope of each plot of figure 2 indicates the individual drug mechanism of action parameter, β_{1T}, as 1.0606, 1.0383, 1.0688, 1.0229 and 1.0533 $\left({}^{mL}/_{copies.d.mg}\right)$ respectively for drugs 1 to 5. A look at table 2 shows that these values are virtually the same. This shows clearly the primary mechanism of action parameter as the steepness of the slope has some correlation with the drug's effectiveness. Drug four has the least slope hence least quantified drug primary mechanism of action parameter and it is the drug with least coating effectiveness and is least effective clinically, according to findings by (Ani, 2016). The negative intercept which ranged from $3 * 10^{-17}$ to $3 * 10^{-5}$ (see plot area of figure 2) speaks of therapeutic window (that is a range of doses of drugs that elicit a therapeutic response) as was observed in a typical dose-response plot of figure 1 in the literature survey.

The values of β_{1T} can also be presented on a bar chart as shown on figure 3. From figure 3 it is obvious that the quantified primary mechanism of action parameters for all the drugs are greater than one as expected, with that of drug 4 being the lowest. This shows that the expression of equation (19) by Ilo (2021) is quite suitable for the second term parameter of equation (13) by (Costanza *et al.* cited in Rivadeneira, *et al.*, 2014).

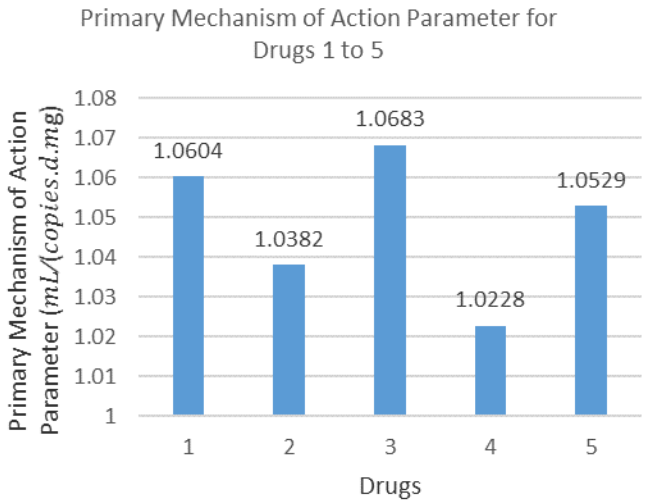

Figure 3: Greater than one bars of primary mechanism of action parameter of the five drugs (Ilo, 2021)

One thing is evident in figure 3. All the bars representing drug mechanism of action parameter the drugs are greater than one. Each of bars actually affirms or validates equation (14) by (Achebe, 2010) hence equation (19).

5.0 Conclusion

In this study, control infectivity which had hitherto been arbitrarily used and assigned values by researchers based on some reasoning, has been given a physical meaning by thermodynamically expressing it and showing clearly the drugs mechanisms of action and hence drugs primary mechanism of action parameter and secondary mechanism of action parameter. This avoids arbitrariness in assigned values. The notion in principle that drug primary mechanism of action parameter is greater than one (1) is validated. The drug primary mechanism of action parameter for the imported experimental drugs gave $1.0604, 1.0382, 1.0683, 1.0228$ and 1.0529 $\left({}^{mL}/_{copies.d.mg}\right)$ respectively for each of the five drugs. These gave rise to associated drug primary mechanism of action as 0.2757, 0.2492, 0.0855, 0.1227 and 0.0632 $\left({}^{mL}/_{copies.d.}\right)$ respectively for each of the five drugs. The result of this novel research is another mile stone in the sands of time for solution to myriads of problems facing humanity using surface thermodynamics and in particular in the area of biological processes in the quest to unravel HIV-blood interaction plethora of variations. A greater than one (1) in value for each drug primary mechanism of action parameter showed a repulsive ability or potential between the virus and lymphocyte. Note that a less than one (1) in value of the drug primary mechanism of action parameter means attraction between virus and lymphocyte, a condition generally encountered in HIV-blood interaction in the absence of antiretroviral drugs. This approach should be explored towards finding a lasting solution or vaccine to other viral diseases like ebola, lassa fever, e.t.c.

6.0 Recommendation

The expression and subsequent quantification of drug primary mechanisms of action parameter with interfacial energetics is a novel one. The disease control input in terms of amount of drugs in HIV viral dynamics model evident in drug primary mechanisms of action is also something new. Drug designers should try this approach to certify its validity. Having drug primary mechanism of action parameter value to the requisite greater than one (1) value and the additive material profiling is a necessity in further studies. An option of preventing or counteracting HIV-blood interaction could be achieved by quantifying adhesion coefficient and the drug primary mechanism of action to the desired greater than one (1) value with an appropriate inoculant or additives. The application of this study in pharmaceutical industries, in the area of drug design and in clinical studies cannot be overemphasized.

Nomenclature

Infectivity β, $\left({}^{mL}/_{copies.d}\right)$, Uninfected (susceptible) Cell x, $\left({}^{cells}/_{\square L}\right)$, Infected Cell y, $\left({}^{cells}/_{\square L}\right)$, Viral Load v, $\left({}^{copies}/_{mL}\right)$.

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