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Quantitative Structure Pharmacokinetic Relationship Using Artificial Neural Network: A Review

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ABSTRACT
Quantitative structure activity relationship (QSAR) has become a tool for designing in various areas like drugs, food additive, Pesticides, biochemical reactant, environmental pollutant and toxic products. In QSAR biological activity can be related with physicochemical properties and in QSPkR (Quantitative Structure Pharmacokinetic Relationship), pharmacokinetic properties can be related with physicochemical properties, relation found in terms of quantity. A number of literature and review article have been published on Quantitative structure pharmacokinetic relationship. But prediction of human pharmacokinetic properties of known and unknown is much difficult job in pharmaceutical industry. Pharmacokinetic data of animal cannot be put straightforward. Artificial neural network (ANN) is used to predict the pharmacokinetic properties. Artificial neural network has basic structure like biological brain and compose of neurons which are interconnected to each other. The present review not only compiles the literature of QSPkR using ANN, but gives detail about the physicochemical properties and artificial neural network.

Keywords: Artificial neural network, Quantitative Structure Pharmacokinetic Relationship, Statistics methods, Pharmacokinetic parameters.

INTRODUCTION

Virtual screening and combinatorial chemistry firmly established itself as a powerful technique in drug discovery efforts, particularly in lead discovery as well as lead optimization. Incorporation of medicinal chemistry knowledge and biopharmaceutical properties into library design is a prerequisite to rational drug design. [1] Recent advances in lead compound identification using high throughput and in silico techniques have allowed rapid identification of compounds exhibiting possible pharmacological effects at known drug receptor sites. [2] The use of combinatorial chemistry in drug design has drastically increased the number of compounds that can be synthesized.

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With the availability of software which is relatively inexpensive, powerful and computer hardware allows for the enumeration of large virtual librareraries. [3-6]
Application of computers [7-9] led the structure activity relationship from qualitative to a quantitative relationship. Quantitative structure activity relationship (QSAR) has become a tool for design of new drug. QSAR is used in various areas like drugs, food additives, pesticides, biochemical reactant, environmental pollutant and toxic products to design a new and safer drug or chemical. [10-12]
Quantitative structure activity relationship (QSAR) has become tool in design of new drug. The most successful approach which appears involves computing molecular descriptors (Physicochemical characteristics and topological parameter). This collection of descriptors is then subjected to a D-optimal design to select structure or structural building blocks to be included in creating a combinatorial library for biological evaluation. [13-14] In the free energy approach, Hansch used physicochemical properties and correlated with biological activity using regression analysis. The result of treatment was an equation which describes, in a quantitative manner the relationship between biological activities of compound with its chemical structure (Fig 1). QSAR

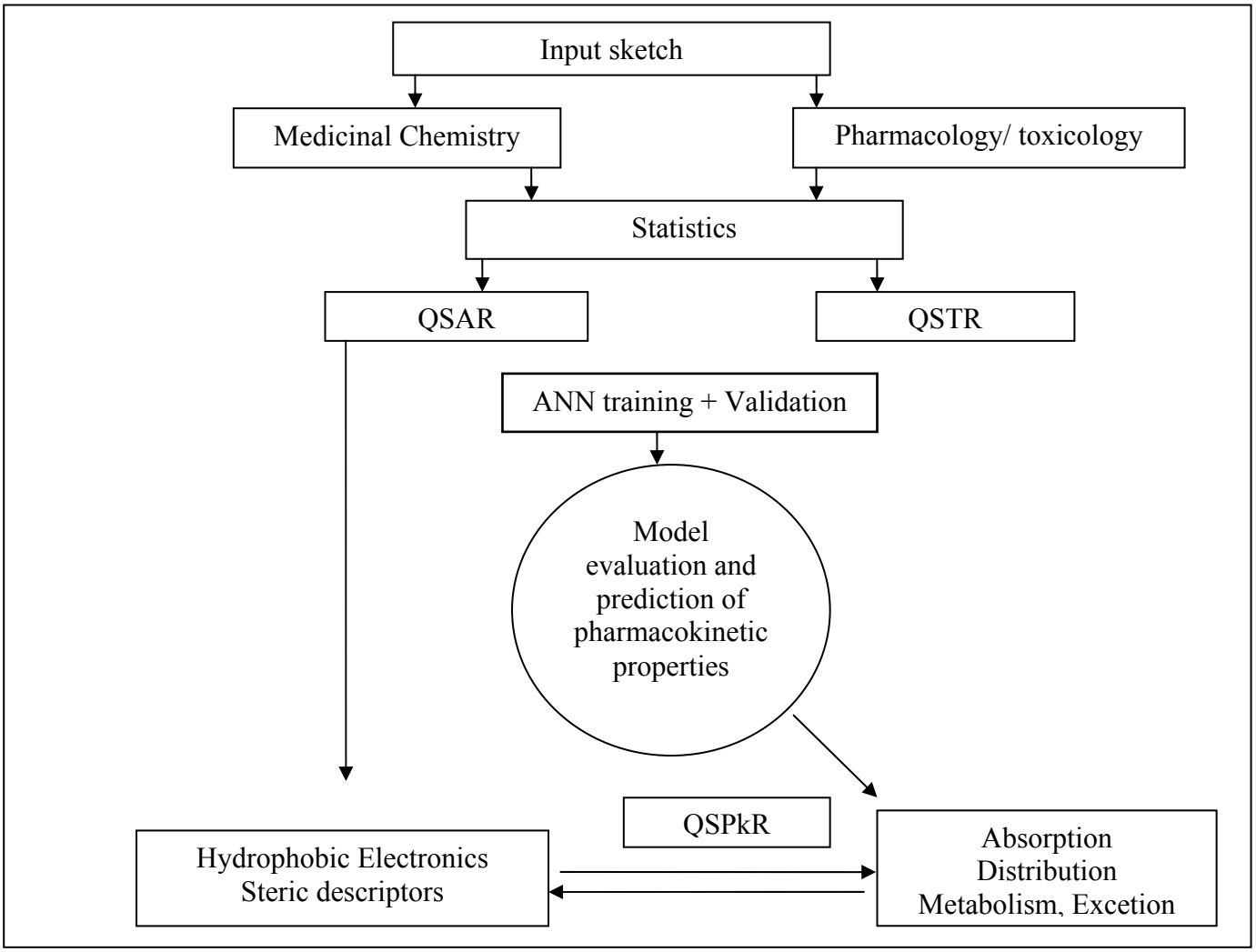

Fig. 1: Diagram showing the general procedure for Molecular Modeling

technique has been helpful in understanding of pharmacological activities based on structure and is important part of modern drug discovery activities. [15-18] Physiochemical properties can be calculated from experiment but it is time consuming and expensive. [19] Theoretical descriptors generated from the molecular structure of a compound have become popular now days. Over a thousand of these descriptors have been defined but all these are not equally useful. [20] Many of these descriptors have been successfully correlated with parameters such as boiling points of alkanes, octane isomers [21-22] aqueous solubility [23-24], plasma protein binding affinities [25] and enzyme inhibition property. [26-28] For design of drug requires prediction of both pharmacokinetic and pharmacodynamic properties. During the drug development process, prediction of human pharmacokinetic parameters such as clearance and volume of distribution is fundamental in the design, optimization and selection of lead drug candidates and in determination of optimal dosing regimens for early phase clinical trials. [29] For prediction of human pharmacokinetic parameters from animal data is far from straightforward while using appropriate pharmacokinetic allometric principles because there is great intrinsic difference between animal and human models and there is complexicity of human pharmacokinetic properties. [30-33] Prediction of pharmacokinetic properties is performed in-vitro or with various animal models which can be both time consuming and expensive. [34] Drug development often fails because of poor pharmacokinetic properties of drug candidates and results may not accurately reflect the human pharmacokinetic properties. [35] For minimizing the risk of such failure, selection of compound having pharmacokinetic properties is required in the early stages of a drug discovery programme. [36-37] As the pharmacokinetics is mechanism oriented science, most of pharmacokinetic model included a significant mechanistic element. Even the most common and two exponent models are based on assumption regarding the functional mechanism involved e.g. that the drug is transported by blood circulation (Central compartment) eliminated. [38] Screening for absorption, distribution, metabolism and excretion (ADME) properties and toxicity is often performed in-vitro or with various animals models which can be both time consuming and expensive. In addition existing model are limited by their high cost, intensive labor requirements, low throughput, and consumption of large amount of test sample. These limitations would be overcome by developing a reliable model for predicting pharmacokinetic parameter from easily measured physicochemical parameters. Partition coefficient had been utilized for prediction of pharmacokinetic property of Propylene glycol dipelargonate. [39] Prediction of human pharmacokinetic parameters is an area which needs lots of attention to aid in pharmaceutical product development. The complexity of prediction of drug input-drug effect systems makes such systems prime candidates for neural network analysis. Artificial neural network (ANN) has become popular in solving many complex nonlinear relationships that exist amongst data when dealing with drug data sets. [40]

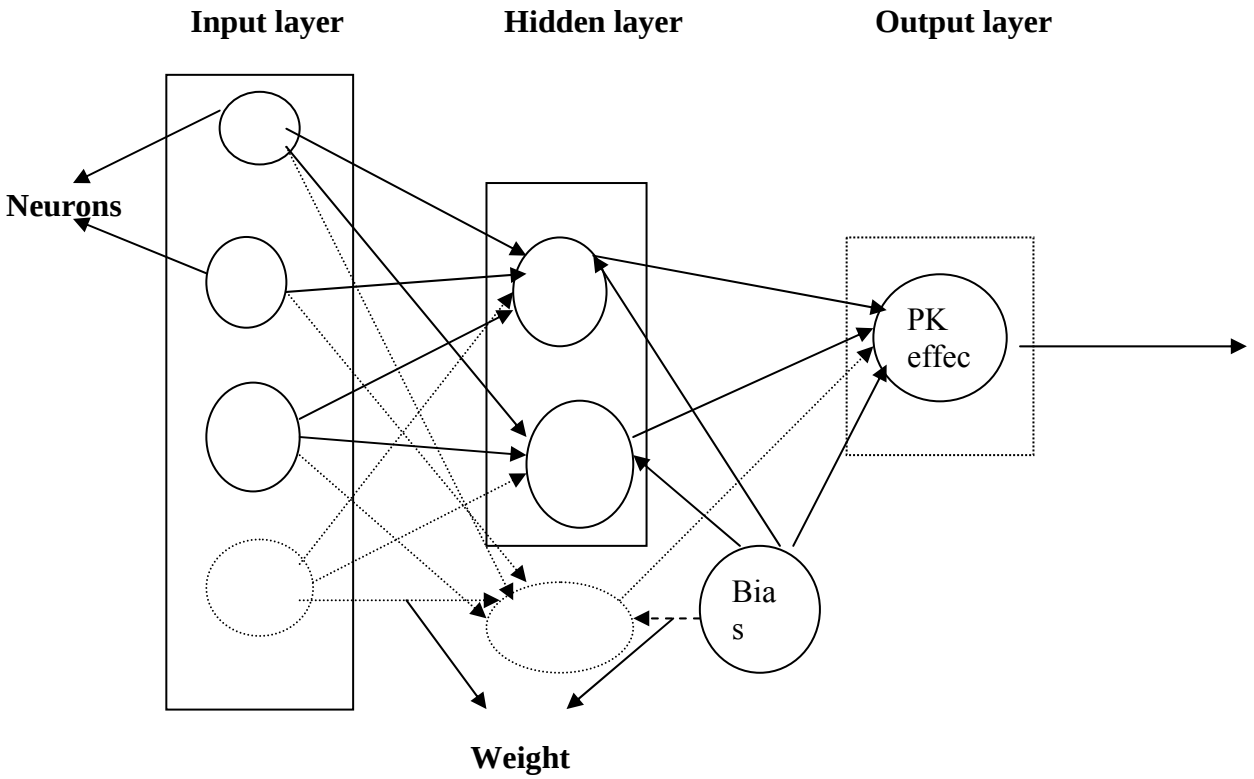

Fig. 2: Typical Artificial Neural Network (ANN)

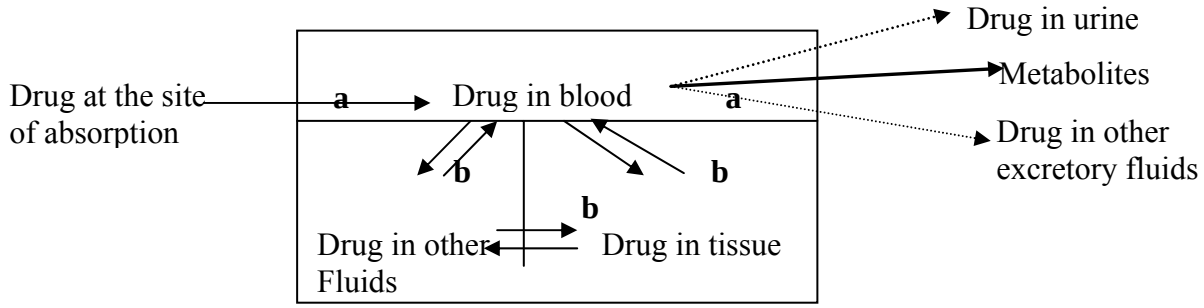

Fig. 3: Schematic diagram[125] of (a) absorption (b) distribution (c) elimination in humans

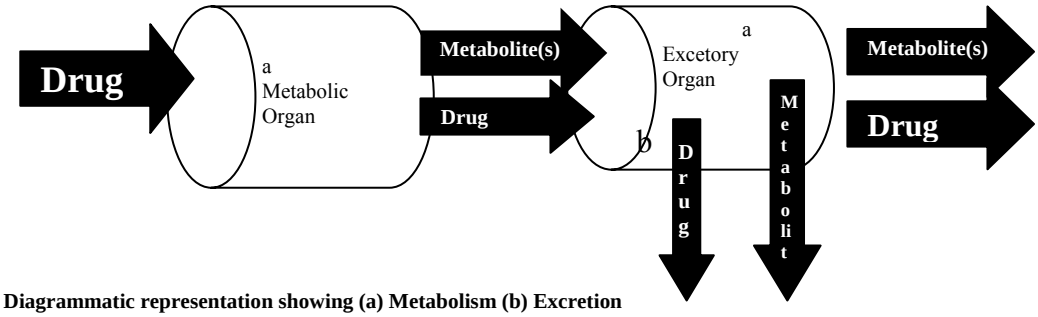

Fig. 4: Diagrammatic representation showing (a) Metabolism (b) Excretion

ANN is used widely for many studies due to their inherent nonlinearity and suitability for predictive applications. Moreover, Generalization ability of ANN makes them successful for construction of predictive model. Therefore, a number of workers have used artificial neural network (ANN) in prediction of pharmacokinetic parameters. [41-46] In many areas of pharmacy multilayer perceptron ANNs has been used. ANNs were used to monitor the pharmacodynamics of short-acting neuromuscular blockers in clinical setting. [47] ANNs were chosen for current studies

because it is fast and give controllable mechanism for prediction without the need of more costly biopharmaceutical data. When it is compared with conventional closed-loop controllers suggesting a potential use for ANN technique in clinical study. Both pharmacokinetics and pharmacodynamic relationships were analyzed using ANNs [48] in many studies ANN have been compared with common statistical technique such as multiple linear or polynomial regression analysis, nearest neighbor classifier, maximum likelihood estimation and Bayesian estimation. [49] The performance of ANN was reported to be comparable superior to that of other techniques. The advantages of ANN over statistical estimation technique is that no a prior knowledge of underlying statistical nature of problem is required and no simplifying assumption need to be made for application of this technique in a sparse data environment. [50] Neural network use an empirical approach for prediction and are based on observations of the system to discover relationships from the system recorded behavior. Neural computing is an attempt to build mathematical models that mimic the computing power of human brain. Like biological brain learning power depends on the connection between its neurons but not on the structure of neurons. Neural network has been used to model many complex problems in QSAR and QSPR studies. [51-53] Several attempts have been used to establish Quantitative structure pharmacokinetic relationship. [54-63] Gobburu [64] et al 1995 established QSPkR using artificial neural network. Quantitative structure activity/Quantitative structure pharmacokinetic relationship (QSAR/QSPkR) Modeling is used to establish mathematical expression correlating activity and Pharmacokinetic parameter to physicochemical properties of a congeneric series of compound. [65-68] QSAR approach has been used to predict the correlation and optimize molecular structures which are used to study and understand the mechanism of action of drugs. The general equation used for QSAR is:

$$BA = f(y)$$

Where BA represents biological acivity (usually reciprocal of a drug concentration producing a standard response such as 1/IC50). f(y) is a mathematical expression correlating biological activity with a matrix of structural parameter (y). If biological activity is replaced by pharmacokinetic, toxicity and metabolism, is known as QSPR, QSTR, and QSMR. For traditional Hansch analysis

$$F(y) = {}^{M}\sum a_i y_i + b$$

Where Yi are individual structural properties, ai are coefficients and b is a constant .both ai and b are obtained from multi linear regression analysis, providing the number of compounds exceeds the number of structural properties. [69] Many QSPR attempts have been established but these efforts have been less adapted than classical QSAR because of in appropriate data sets or phenomena is too complex to be depicted by model. [70]

Artificial neural network

Neural network are computational systems implemented in software or hardware that attempt to simulate the neurological processing abilities of biological systems, in particular brain. [71] ANN are the computational models that consist of number of simple processing unit that communicate by sending signal to each other over a large number of weighted connection. It is based on human brain in which neurons collect signal from other neuron or dendrites. [72] ANN contains mainly three layers: (1) input layer (2) hidden layer (3) Output layer (Fig. 2). The layer that receives the input from environment (i.e. independent variable of the system) is the input layer. The output layers nodes generate the dependent variable (i.e. output layer). The layers interconnecting the input and output layer are known as hidden layer. [73] The hidden and output neuron received an additional constant input called the 'bias'. The sigmoidal function was used as the neuron transfer or called as squashing function. [74] The total input, Xj to unit j is a linear function of outputs Y_i,of the units that are connected to j and of the weights, W_{ij}, on these connections.

$$X_j = \sum Y_i W_{ij}$$

The symbol W_{ij} denotes the weight associated with connection through which signal inpi enters the neuron j. [75] Neural work professional II/plus version 5 (Neuralware, Pittsburgh, PA) and was used to creat the neural network for prediction of peak and trough gentimicin concentration which is multilayer feed forward perceptron using the extended delta bar delta algorithm. [76-77] Model of human brain was drawn by soft computing and derives artificial intelligence (AI) sources including fuzzy logic, General regression neural network (GNN) and artificial neural network (ANN). [78] Yap [79] et al 2004 establish QSPkR using general regression neural network When population pharmacokinetic data is analyzed using NONMEM and ANN, ANN show less predictive error than NONMEM. [80] Neural network are most suitable to model the behavior of complex kinetic systems so it has been used to predict pharmacodynamics property of alfentanil drug. [81]

Descriptors

Descriptors may be scalar representation of an atom or a matrix. For Calculation of 3-D descriptor require lattice type information. There are currently over a thousand theoretical descriptors that have been applied to chemical and drug related problems. [82] There are two types of descriptors.

(1)Independent (2) Dependent

Independent descriptors

Independent descriptors are those which are not significantly linearly correlated with one another.eg topological, molar volume, molar refractivity etc.

Topological descriptors

Three dimensional structure of a molecule depends on the position of individual atom and the connection between them i.e. on its topology. Topology indices are numerical quantities derived from molecular graphs represent molecules. Topological indices have been used in connection and prediction of most molecular properties. [83] Wiener [84] *et al* 1947 proposed the first topological index based on distance matrix known as ***Wiener index*** and defined it for saturated hydrocarbons, the path number W as the sum of the number of bonds between all pairs of vertices; this index reflects the branching of molecule, may be calculated from the sum of the off diagonal elements of the distance matrix.

$$W = \sum_{i=1} dij \qquad i=1 \quad j=1$$

Connectivity index: Connectivity index introduced by randic [85] *et al* 1975

$$\chi^R = \sum (\delta i \delta j)^{-½}$$

δ is the vertex degree of adjacency matrix. Among topological index molecular connectivity has been used widely applied in simple and complex problems and relate it with boiling point, Molar refractivity and molar volume of alkanes, alkenes alcohol. [86] Kier and Hall connectivity indices called as chi (χ) indices developed to calculate zero-

and higher-order connectivity descriptors. [87-88] Many studies have been done correlating connectivity indices with physicochemical properties [89] and biological activity of mostly for structurally related compounds. Equation for both valence and non valence electrons.

$$\delta i^v = (Zi^v - Hi)/ (Zi - Zi^v - 1)$$

Zi is the atomic numberof i, δ_i^v values for non-hydrogen atom like C,N and O in various hybrid state Hi is the number of hydrogen bonded to atom I and Z_i^v is number of valence electrons for atom i. [90]

Balaban index (J) - The Balaban index J = J(G) of G (matrix) is defined as [91]

$$J = M/ (\mu+1) \sum(d_i.d_j)^{-0.5}$$

Where M is the number of bonds in G, μ is the cyclomatic number of G, and d_i (i = 1, 2, 3, N; N is the number of vertices in G) is the distance sum.

The cyclomatic number μ = μ(G) of a cyclic graph G is equal to the minimum number of edges necessary to be erased from G in order to transform it into the related acyclic graph. In case of monocyclic graph μ = 1 otherwise it is calculated by means of the following expression

$$M = M-N+1$$

Van der Waal radius and volume

Each atom of molecule represent as a sphere which is centered at the equilibrium position of the atomic nucleus with a radius equal to vander waal radius (rw) is a function of the electron density distribution around each atom .Van der waal surface area may be defined as the surface of intersection of all van der waals sphere in the molecule, while the van der waal volume is represented by volume contained by surface. [92]

Verloop parameter

These parameters are evaluated by measuring the dimensions of substituents in a restricted number of directions.Verloop [93] *et al* 1976 defined four width parameters B_1, B_2, B_3 and B_4 determined by rotations of the substituents arrround the X-axis.B_1 (minimum width parameter) was determined as the smallest distance to X-axis of the substituent tangential planes perpendicular to 2-coordinates.The additional parameters B_2, B_3 and B_4 were derived in such a way that represent the width parameters in four rectangular directions.

Molar refractivity

The molar refractivity (MR) is given by

$$MR: (n^2-1) MW/ (n^2+2) d$$

MW is the molecular weight is the density and n is the refractive index. The refractive index does not vary much from one organic compound to another and as the molecular weight divided by the density equals the volume, MR gives some indication of steric bulk of a molecule. The presence of the refractive index term also provides a connection to the polarisibility of a molecule. [94]

Parachor

Parachor parameter is related to molar refractivity and it is defined by sugden [95] *et al* 1924

$$Pr = \gamma^{1/4} M/ (d-d^1)$$

Where d and d^1 are the densities of a liquid and vapor respectively and γ is the surface tension in dyne/cm^2 at the same temperature. When vapor density is negligibly small in comparison with that of liquid, the relationship reduces to

$$Pr = \gamma^{1/4} M/d$$

Log P

Lipophillicity is an important parameter for drug disposition and drug activity. [96-98] Partition coefficient is an important property because it measure lipophillicity and hydrophillicity of a drug. More the partition coefficient, more the drug is hydrophilic. [99] Partition coefficient can be determined by Shake-flask method. [100-101]

$$\text{Log P} = \log \frac{[C]org}{[C]aq.}$$

Log p can be calculated from chromatography. [102] Neural network is also used for prediction of lipophillicity of compounds. [103] Many studies have been established for correlating biological activity with lipophillic parameters. [104-106]

Dependent descriptors and their relationship

Dependent descriptors are those which depends on the independent descriptors all pharmacokinetic properties are included in this descriptors

Pharmacokinetic properties

It is defined as the kinetics of drugs absorption, distribution, metabolism and excretion and their relationship with pharmacologic, therapeutic or toxicological response in men and animals. [107]

Absorption

Absorption is defined as the process by which unchanged drugs proceeds from site of administration to the site of measurement with in the body. Absorption at the site of administration can influence bioavailability. When the drugs are given with the intravenous route, it does not undergo dissolution and absorption. The major causes of differences in absorption of drug from various products are dissolution. Absorption follows two step processes (Fig. 3)

$$\text{Drug in product} \xrightarrow{\text{Dissolution}} \text{Drug in solution} \xrightarrow{\text{Entry into the body}} \text{Absorbed drug}$$

In this two situation has been considered. One in which dissolution is much faster than is entry of drug into the body. The drugs which are administered in the solid form, the first of drug process are dissolution in aqueous media. It follows the Noyes –Whitney equation:

$$\text{Rate of dissolution} = \frac{DA}{\delta}(S-C)$$

D = Diffusion coefficient of solute
δ = Thickness of stagnant diffusion layer and
C = Concentration of solute in bulk solution
A = Surface area
S = Solubility

This equation gives the relationship between the rate of dissolution with the surface area and solubility. Dissolution is rate limiting process; A remains constant and maintained sink condition. [108] Gao et al 2002 relates aqueous solubility with log p.

$$\log Sw = 2.34 - 0.41 \log p - 0.24b\_ar + 0.35\ {}^0\chi^v_C - 0.31\ {}^1\chi_C - 0.83\ {}^1K^{\alpha} + 0.34\ {}^2K^{\alpha} \qquad (r^2 = 0.92)$$

The prediction of human intestinal absorption is a major goal in design, optimization and selection of candidates for development of oral drugs. [109] Many QSAR studies have been established to show their importance in prediction of intestinal absorption. [110-115] The bioavailability of a drug and its access to the therapeutic target are important considerations in rational drug design. Before the drug can elicit an effect, for example if it is orally administered, it usually has to pass through a series of barriers (e.g. biological membranes) either by passive diffusion and/or carrier-mediated uptake. Depending on the route of the

administration of the drug and the location of the target site, the pH of the environments that the compound is exposed to may vary considerably. Some examples of physiological pH values are as follows: stomach 2.0, kidneys 4.2, small intestine (food 5.0; fasted 6.8), duodenal mucus 5.5, plasma 7.4. In this context, the affinity of the drug molecule for the target of interest and its ability to partition into a lipophillic environment at different pH values has to be quantified for a proper prediction of its ability to interact with the biological target and hence to be efficacious. [116] The rule of five is used widely for screening in combinatorial chemistry. According to this rule the compound are seemed to have poor absorption if it satisfies any two of condition of following rule:

(1) Molecular weight>500 (2) No. of hydrogen bond donor >5 (a donor being any O-H or N-H groups (3) No. of hydrogen bond acceptor>10 (an acceptor being any O or N including these in donor groups (4) clog p>5.0. [117] Palm [118] et al 1996 correlated the molecular surface properties with drug absorption and show a good correlation (r2= 0.94). Wessel *et al* 1998 predict human absorption from molecular descriptor of 67 structurally different drug and drug like compound using the artificial neural network. The choice of parameter is important aspect in QSPkR study. Cmax, Tmax, AUC are important parameter for drug absorption and directly relates with the lipophillicity [119] but these are more complex because it involves distribution and elimination other than absorption. The equation which are used for this.

$$C = \frac{FDKa}{V(Ka-K)}(e^{-kt}-e^{-kat})$$

$$FD = (Cl)(AUC)$$

$$Cl = KV$$

$$Tmax = \frac{In(Ka/k}{Ka-K}$$

$$Cmax = \frac{FD(Ka)^{(k/Ka-K)}}{V\ K_{(k/ka-k)}}$$

Where C is concentration of drug in plasma, K and Ka are elimination absorption rate constant.Winiwarter [120] et al 1998 used a combination of experimental and theoretical descriptors for prediction of human intestinal absorption of drugs. Theoretical descriptors have been established for a number of structure-bioavailability relationships. One model constructed for 232 commercial drugs classified compounds into four classes according to their predicted bioavailability. [121]

Distribution and Plasma protein binding

Distribution is defined as the reversible transfer of a drug between the blood and extra vascular fluids and tissues. Distribution of a drug is not uniform throughout the body because different tissues receive the drug from plasma at different rates and to different extent [122] after absorption drug enters into the distribution where it is distributed reversibly among the extra vascular tissue and blood.

Volume of distribution

Presuming that the body behaves as a single homogenous compartment with volume V into which drug gets immediately and uniformly distributed.

$$\mathbf{V} = \frac{\text{Dose administred i.v}}{\text{Plasma concentration}}$$

The extent of distribution of a drug depends on its lipid solubility (log p), ionization at physiological pH, extent of binding to plasma and tissue proteins and differences in regional blood flow. [123] Apparent volume of distribution or volume of distribution of the unbound fraction (fu) can provide useful clinical information because it is generally considered that the unbound fraction of a drug is responsible for the pharmacological action. Volume of distribution for 45 structurally unrelated drugs has been performed. [124] The partitioning of a drug between tissue and blood describe the distribution of drug under steady state conditions is an important pharmacokinetic property. Extent of partitioning is given by the ***partition coefficient***, P_{tb} is defined as follows:

$$P_{tb} = C_t / C_b$$

Where *Ct* is the concentration of drug in the tissue of interest and *Cb* is the drug concentration in the blood. [125-126] When ANN compared with mechanistic model demonstrated that both techniques were able to provide acceptable models for prediction of log *P* and tissue-to-unbound plasma concentrations for series of analogues. Herman *et al* 1994 used 17 noncongenric drugs to predict the various distribution parameters from physicochemical properties, including molecular weight, intrinsic solubility, aqueous solubility etc.

Plasma protein binding

Most of the administered drugs are retained by plasma protein, which act as major drug storage sites. The stored drug is in equilibrium with the free drug in plasma and is released as the free drug concentration fall below the therapeutic value. [127] Albumin, lipoproteins glycoprotein are the proteins from which the drug mainly bind reversibly and affects the pharmacokinetics and pharmacodynamics of drug. [128-130] It is clear from many studies that lipophillicity (log p) is an important parameter for plasma protein binding but other physicochemical parameters (pka, σ) also affect the protein binding. [131] Seedhar et al [132-133] used aniline & non –steroidal anti-inflammatory drugs for quantitative structure protein binding relationship (QSPBR) and found that steric parameter are highly correlated with plasma protein binding in both cases. The equations obtained in study of aniline and non-steroidal anti-inflammatory drugs:

$\text{Log } K = 0.220\,{}^{1}\chi_{ar} + 1.603$ R= 0.990

$\text{Log } K_1 = 56.13\ I^{D} - 33.04\,{}^{1}\chi + 3.87P_9 - 739.97$ R= 0.951

Thus size of drug molecule and electrostatic interactions plays important role in plasma protein binding. Many relationships have been established between molecular structure and protein binding. [134]

Metabolism and Elimination

Knowledge of the metabolic fate and tissue half-life of drugs and xenobiotics is of critical importance to the understanding of their mode of action and for validation of toxicological studies. Elimination can be related to molecular structure with elimination half life. Biotransformation or Metabolism is the chemical conversion of parent drug into its metabolites. As with enterohepatic cycling, this metabolic interconversion is a route of elimination only to the extent that the metabolites is excreted or otherwise irreversibly lost from the body. Metabolism is divided into two phase: Phase1 and phase 2 (Fig. 4). Many enzymes are involved in metabolism make it complex. One approach in structure metabolism relationship modeling characterize molecule interact with one of specific enzyme. [135] Flavonoid derivatives made use of quantum chemical descriptors to inhibit the CYP 1A2. [136] One study examined urinary excretion of glucuronide conjugates, glycine conjugates, and unchanged parent drug for 22 benzoic acid derivatives. [137] Many structure metabolism relationships have been limited because it

involves simple models of calculation of conformational space filling properties or by standard substituent effects. [138-139]

Clearance

Clearance relates the rate of elimination to the plasma concentration and is an important elimination parameter. [140] It is defined as the hypothetical volume of body fluids containing drug from which the drug is removed or cleared completely in a specific period of time

Clearance = elimination rate/Plasma drug concentration

Schneider [141] *et al.* 1999 study a larger data set of more structurally diverse drugs to develop a model for *in vivo* hepatic clearance. Clearance due to a single organ is given as the product of the blood flow to that organ and the extraction ratio:

$$Cl = \frac{Q.C_A - C_V}{C_A} = Q.ER$$

Q is blood flow to the organ, C_A is concentration of drug in arterial blood, C_V is concentration of drug in venous blood and is extraction ratio. The extraction ratio is the ratio of the rate of elimination of a drug to the input rate of the drug to an organ. Thus, the higher the extraction ratio the more drugs is eliminated and the less passes through the eliminating organ intact. Wajima [142] *et al* 2002 predicted new regression equation of human clearance from animal data and molecular structural parameters. Oral clearance is one of most important pharmacokinetic parameters for characterizing drug pharmacokinetics and is related to metabolism, renal excretion and bioavailability of drug. Predicting oral clearance is more difficult than predicting clearance after intravenous administration because oral clearance includes an absorption process and a first pass effect. [143] Clearance (CL), apparent volume of drug distribution (V (ap)), fractal clearance (CL (f)), and fractal volume (v (f)), for a series of 23 cephalosporins used for the quantitative structure pharmacokinetic prediction. CL and CL (f) expressed similar performance while the predictive performance of v (f) was much higher than that of V (ap). [144-145]

This article gives the overview of the possible use of pharmacokinetic parameters in quantitative drug design. QSAR and QSPR (quantitative methods) apply for solving of toxicological problems which are related to the drugs. We have used models to describe the complex interdependency of pharmacokinetic parameters. Physiologically based pharmacokinetic modeling describes the whole body by a number of anatomical compartments. In a more general way, simultaneous modeling of the pharmacokinetic and pharmacodynamic phases of drug action has been reported. QSAR help in predicting the limiting factors to understand drug action in the whole body. Each step in drug action should be analyzed by using a quantitative method. The information obtained from Quantitative Structure estimation is worth the efforts but it is time consuming. QSPkR helps in designing of more rational drug design in the development of drugs. From this article it is cleared that the pharmacokinetic parameters can be useful but when it use properly.

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