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Review Article

COMPUTATIONAL APPROACHES RELATED TO DRUG DISPOSITION

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ABSTRACT

Drug disposition connects with the movement of drug molecules inside the body after administration irrespective with the route of administration. After entering the system, drug molecule and internal body systems comes under various pharmacokinetic interactions followed by observation of suitable biological activity. In this exhaustive process, physicochemical nature of the chemical substance and physiological nature of system makes this movement competitive. In this view, pharmacokinetic and toxic properties of the molecule regulates the destination of the molecule. Various computational processes are available for *in silico* pharmacokinetic assessment of drug molecule after absorption through biological membrane, distributed throughout the system based on the percent ionization or partition coefficient factors followed by biologically transformed into an another entity in presence of microsomal enzymes and finally excrete out from system using various cellular transport systems as well as related cellular toxicity behavior. In this chapter, we ensemble all the possible information related with the drug movement and related computational tools to understand the possible chemical and pathophysiological changes. Here detailed knowledge on database expedition, establishment of pharmacophore model, homology modelling based on sequence similarity, molecular docking study (rigid and flexible docking) and QSA_R/QSP_R study (with detailed process and available softwares) are provided. These diversely united informations actually helps a researcher to understand the factual movement of a drug molecule inside the system.

Keywords: Drug disposition, *In silico* pharmacokinetic parameter, Pharmacophore, QSA_R/QSP_R, Molecular docking, Homology modeling

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INTRODUCTION

Drug disposition means the change in the position of drug molecules after administration into the system [1, 2]. As per the pharmacological view: Drug is a substance which can cause positive or negative effect to the system. But in actual drug is a chemical substance comprised with a definite chemical structure. When a chemical substance goes into a system which itself governed by pH-partition hypothesis [3-5]. The disposition of drug molecule involves administration, distribution, metabolism, excretion and toxicity (ADMET) [6, 7]. Presence of different transporting proteins, nature of absorbing medium, pH, partition coefficient of the molecule, nature of microsomal enzyme, structural features of drug molecule, stereochemistry of the drug molecule are the directly correlated with disposition of the drug molecule [8, 9]. In the chapter, we are mainly focus on phases of drug disposition along with different computational methods/tools (molecular docking study, assessment of different databases, pharmacophore screening, *in silico* toxicity assessment, *in silico* determination of pharmacokinetic parameter) associated with disposition of drug molecule [10].

Search criteria

The keywords associated with search criteria of the manuscript were: role of ADME on drug disposition, availability of softwares for drug metabolism, availability of different active transporters related in drug disposition, exploration of different available databases related to drug distribution, pharmacophoric features development using different softwares, exploration of homology modelling softwares and standalone version, molecular docking process and its importance on drug receptor interaction and importance of QSAR/QSPR on drug disposition in different platforms such as: https://pubmed.ncbi.nlm.nih.gov/, https://www.sciencedirect.com/ with 10 y of timeline (2010-2020) as well as using different softwares such as: https://dtclab.webs.com/software-tools, https://www.click2drug.org/, http://zincpharmer.csb.pitt.edu/pharmer.html, http://bioinfo3d.cs.tau.ac.il/pharma/php.php, https://swissmodel.expasy.org/, https://blast.ncbi.nlm.nih.gov/Blast. cgi?PROGRAM =blastpandPAGE_TYPE=BlastSearchandLINK_LOC=blasthome.

Pharmacokinetic parameters associated with drug disposition

Absorption

After administration of the drug molecule, system processed the molecule through a series of biochemical reactions based on the structural features. In most of the cases, drug molecules absorb through a biological membrane following first order rate kinetics (direct correlation between increase in the drug concentration and plasma protein concentration) but when changes of drug concentration creates no positive impact on time interval, zero order chemical kinetics was followed (in saturated environment, no correlation between administrative dose increment and plasma protein concentration) [11]. Also stereoselective nature of drug molecule (R and S configuration) regulates the plasma protein concentration based on intravenous bolus dose [12]. There were two types of transporters available for transportation of drug molecules through membrane known as efflux and influx transporters, whereas efflux transporter systems belongs to ATP binding cassette and influx transporters belongs to solute linked carrier family [13]. These carrier systems were mainly found in major organs like liver, kidney, brain along with gastro-intestinal tract [14]. The permeation of drug molecule mainly depends upon solubility of the molecule in a specific environment. Initially BCS (Biopharmaceutics Classification System) was the preliminary scale to calculate the permeability of orally administered drugs (Class-I: High solubility and high permeability; Class-II: Low solubility and high permeability; Class-III: High solubility and low permeability and Class-IV: Low solubility and low permeability) [15]. In the next phase, calculation of MAD (Maximum Absorbable Dose) was developed based on solubility (S), volume of fluid (V_f), rate constant (K_a) and transition time (T_r).

$$MAD = S \times K_a \times V_f \times T_r \text{ --------- (i)}$$

$$SLAD = S_i \times V_f \times M \text{ --------- (ii)}$$

Based on the calculation of fast state simulated intestinal fluid (FaSSIF) and solubility limited absorbable dose (SLAD) values a new developability classification system (DCS) was established (Where S_i= solubility through small intestine and M = permeability factor). As per this DCS system, Class-II of BCS (good permeation in poor

solubility) was further divided into Class-IIa (dissolution rate limiting) and Class-IIb (solubility rate limiting) [16]. In this context, solubility of drug molecules through an aqueous medium (Log S) was also a critical parameter to establish. Log S is the 10 base logarithm value of solubility of a molecule in mol/l unit. As we know solubility and solubility product values were performed at℃25 temperature, same was followed in the prediction of Log S value.

$$\text{Log S} = \text{Log}_{10}\,(\text{S}) \text{ -------- (iii)}$$

As we know, maximum drug molecules were weakly acidic or basic in coarse of its pharmacological activities. So for the prediction of Log S value, pH of the environment and pKa value of the molecule plays an important role [17]. If the molecule was solubilize in a solvent at isoelectric point, solubility decrease but same molecule tends to from an ionic derivative or zwitterion at a particular pH of solvent, solubility increased. This behavior was well observed in amino acid (fig. 1). In the prediction of pKa value of a drug molecule at a particular pH was predicted using various multiple linear regression as well as MoKa like standalone predicting tools (https://www.moldiscovery.com/software/moka/), CHARMM based pKa calculation, H++Poisson-Boltzmann based pKa calculations (http://biophysics.cs.vt.edu/), MCCE Multi-Conformation Continuum Electrostatics pKa calculation (https://gunnerlab.github.io/Stable-MCCE/pkaexample/), PROPKA pKa predictor (https://pypi.org/project/propka/) etc.

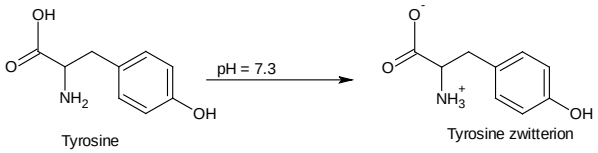

Fig. 1: Zwitterion formation of tyrosine

According to QSPR (Quantitative Structure Property Relationship) prediction of Log S (solubility) of an unknown structure was depend upon various descriptors such as molecular weight, melting point type of atoms, partial charges on atom, lipophilicity (Log P), molar refractivity, number of hydrogen bond acceptor or donor atoms including some newer descriptor like electrostatic potential surface area value [18]. Among the descriptors, Log P value plays an important role. Lipophilicity influenced a series of pharmacokinetic behavior including movement through cellular membranes and portal systems. Log P directly related with hydrophobic nature of unionized portion of the molecule. ALOGP (Atomic Log P), XLOGP (X Log P), MLOGP (Moriguchi's method of Log P) and CLOGP (Compound Log P) are different available tools for predicting Log P values of small molecules. ALOGP collectively express the contributions of each atoms on partition coefficient prediction, XLOGP was one step higher version of ALOGP (include both atom and its neighboring species), MLOGP observed with prediction of Log P value using solvation and molecular dynamics and finally CLOGP values showed the prediction of Log P using fragment based analysis, electronic nature and orbital nature of the molecule. Among these ALOGP and CLOGP are highly acceptable [19, 20]. In the other hand, permeation through a biological membrane is equally important for drug molecule. In this context, Caco-2 cell line (immobilized human colorectal adenocarcinoma), STELLA simulation model (considering particle size and diffusion) and parallel artificial membrane permeability assay (PAMPA) model (considering lipid fused membrane separated between acceptor and donor compartments) are the highly used intestinal epithelial membrane model to predict permeation characteristics [21]. Furthermore, physiologically based pharmacokinetic/ biopharmaceutics model considered GastroPlus software is available to predict total pharmacokinetic behavior of a drug molecule including *in vitro-in vivo* extrapolation, interactions with transporter system, plasma concentration of drug as well as compartmental and non-compartmental pharmacokinetic model after intravenous or oral administration [22].

Distribution

After absorption, then the molecule goes through different lipid layer and cellular membranes based on enantioselectivity. Enantioselectivity governs both concentration of drug on plasma and volume of distribution. As we know molecular structure and electronic configuration of the molecule were directly correlated with nature of microsomal enzymes (CYP 3A4, CYP 2C9, CYP 2D6, CYP 2C19, CYP 1A2), Log PCaCO2 cell permeability. As we know volume of distribution (V_d) resembles with the dose of drug present in the body and plasma concentration. The distribution of drug molecules also observed with greater dependency on extent of plasma protein concentration and protein binding nature [23]. Most of the drugs were interacted with albumin, α1-acid glycoprotein and different lipoproteins. Among them, acidic drugs goes through albumin binding whereas basic drugs tends to glycoprotein and lipoprotein bound. If the drug molecule present as unionized weak acid (HA) form (fig. 2), it can easily cross non-polar cellular membrane without entering the aqueous medium but if the molecule enters in the system as protonated form (BH^+) turns into unionized form (B) easily cross the membrane [24].

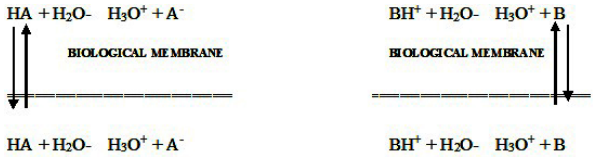

Fig. 2: Fate of unionized and ionized weakly acidic drug on lipid barrier

The distribution of drug molecules consults with crossing various plasma membrane and blood brain barrier (BBb) [25]. BBb composed of three cellular portions such as endothelial cell, end feet astrocyte and pericyte. In this structure tight junction (tj) proteins plays an important role in the transportation of ions, water and solutes through the paracellular pathway [26]. Blood brain barrier permeation was determined by various models like recurrent neural network-BBb permeability (RNN-BBb model) [27], human blood-brain barrier model and SynBBB 3D blood brain barrier model. Topological polar surface area (TPSA), passive permeability factor (Log PS), partition coefficient value (Log P) and Log D (distribution coefficient for an ionized weakly acidic drug at a particular pH) were the factors associated with the permeation of blood brain barrier [28].

Permeation through BBb was calculated by three different processes using polar surface area (PSA) value of the molecule, calculation of Log BB value using the following equation:

$$\text{Log BB} = (-)\ 0.0148\ \text{PSA} + 0.152\ \text{Log P} + 0.139 \text{ -------- (iv)}$$

As well as by passive permeability factor (PS)

$$\text{Log PS} = (-)\ 2.712 + 0.312\ \text{Log D} \text{ ------- (v)}$$

Furthermore, the permeation of drug molecule through BBb regulated by the composition and nature of tj proteins such as claudin and occluding [29]. Claudin and occludin were both tetraspan membrane proteins composed of two extracellular loops and domains with one intracellular domain with molecular weight of 60 KDa and (20-27) KDa; respectively. OSP/claudin-11, PMP22/gas-3 and OAP-1/TSPAN-3 were the most prominent tj present in myelin sheath of nerve endings and sertoli cells. The assessment of tj protein claudin-5 was identified using *in vitro* formaldehyde cross linking study and outcomes showed five dimer played an essential role in trans membrane exchange of ions based on leucine residue interaction with extracellular loop of the protein. Another pathway (leak pathway) associated with tj protein was evolved with time considering the structural permeation corresponded with epithelial membrane electrical conductance along with membrane dynamics related to bicellular opening of strands and tricellular pores [30].

Metabolism

After proper distribution of drug molecules, biotransformation or metabolism in the hepatic and extra hepatic tissues is next crucial step to understand. The biotransformation of different xenobiotic followed four different transformation techniques such as: eliminate without change in structure (structures composed of highly polar groups such as carboxylic acid, quaternary amine or it may be volatile in nature), retained in system without any chemical transformation (molecules comprised of highly lipophilic groups, also responsible for redistribution) [31], readily structural modification (proper balance in hydrophilic and lipophilic nature of the structure, presence of carboxylic acid, hydroxyl, thiol etc groups using conjugation reactions (glucoronide or glutathione) or different phase-I reactions such as oxidation, reduction, azo-reduction etc) [32] and transformation based on enzymatic action (biotransformation in presence of microsomal enzyme under cytochrome oxidase category). Initially Lipinski Rule of Five regulated the total business of drug development. But after the development of higher molecular weight (greater than 500 Da) molecules, this rule became obsolete; this phase followed by development of new age descriptors such as sum of atom-type electrotopological state, verage Broto-Moreau autocorrelation descriptor related to polarizability, extended topochemical atom descriptors, McGowan volume, molecular linear free energy relation descriptors etc. (HOMO-LUMO) and other electronic descriptors [33]. In the assessment of interactions between drug molecules and metabolizing enzymes, pharmacophore modelling, partial least square (PLS) coefficient analysis and calculation of ADMET profile plays a pivotal role. In the early stages of drug discovery, assessment of pharmacokinetic-toxicity profile of a molecule is the most important work followed by pharmacophore and QSA_R/QSP_R model generation. Furthermore, assessment of receptor structure was also important [34]. The similarity in structures and distance between essential groups showcased a new computational possibility in the view of biotransformation, as well as PLS discriminant analysis sets up a map using possible similarity utilizing presence of hydrogen bond donor/acceptor groups, hydrophobic interactive groups and presence of positive ions [35]. But if the receptor structure was not available then using FASTA (FAST Alignment Tool) sequence of DNA (Deoxyribo Nucleic Acid) or nucleotide or protein and BLAST (Basic Local Alignment Search Tool) tool, a new full grown protein including groves and helix was developed [36-37]. In this view, various crystal structures of cytochrome P450 microsomal enzymes (5VEU, 5JQV, 2RFB, 2RFC, 6OOW, 6OOX, 6WGW, 6U31, 6U30, 6U3K, CPQX, CPQS) were procured from various sources such as *Homo sapiens*, *Picrophilus torridus*, *Rhodopseudomonas palustris HaA2*, *Novosphingobium aromaticivorans*, etc available in protein data bank (www.rcsb.org). There were lots of computational models available for the computation and prediction of drug metabolism factors (molecular descriptors) such as: ADMET predictor (http://www.simulations-plus.com/software/admet-property-prediction-qsar, ChemAxon (https://www.chemaxon.com/products/calculator-plugins/), Codessa (http://www.codessa-pro.com/), Corina Symphony (https://www.mn-am.com/products/corinasymphony), DRAGON (https://chm.kode-solutions.net/products_dragon.php), E-Dragon (http://www.vcclab.org/lab/edragon/), MOE (http://www.chemcomp.com/MOE-Cheminformatics_and_QSAR.html), Molconn (http://www.edusoft-lc.com/molconn/), PaDEL (http://www.yapcwsoft.com/dd/padeldescriptor/), QikProp (https://www.schrodinger.com/qikprop/), ACD Labs (https://www.acdlabs.com/products/percepta/), etc [38]. Most of these softwares were commercial but E-Dragon, PaDEL and ACD Labs were free standalone softwares. Furthermore in the automated pharmacophore model generation category: Catalyst, DISCO (based on distance comparison) and GASP (based on genetic algorithmic search) techniques were widely used. Catalyst system of automation was divided into HipHop and HypoGen. HipHop was the pharmacophore model generation using similarity index between molecules whereas HyoGen model consulted with the quantitative property data of the active structures [39]. In both the cases, hydrogen bond acceptor/donor groups, hydrophobic portions and positive/negative ions were used as parameters. In case of DISCO pharmacophore automation model generation, ligand and site both were important (fig. 3). Ligands include same features as catalyst whereas presence of interactive space, heavy atoms and flexibility in receptor dominate the pharmacophore development. Further in case of GASP, molecules were considered as single entity with frequent randomized orientations and finally chosen molecule must have least number of pharmacophoric features [40]. Also, a group of scientist developed a new generation pharmacophore model (truly focused pharmacophore model) using macromolecular interactive forces and clustering techniques based on density based algorithmic searches [41].

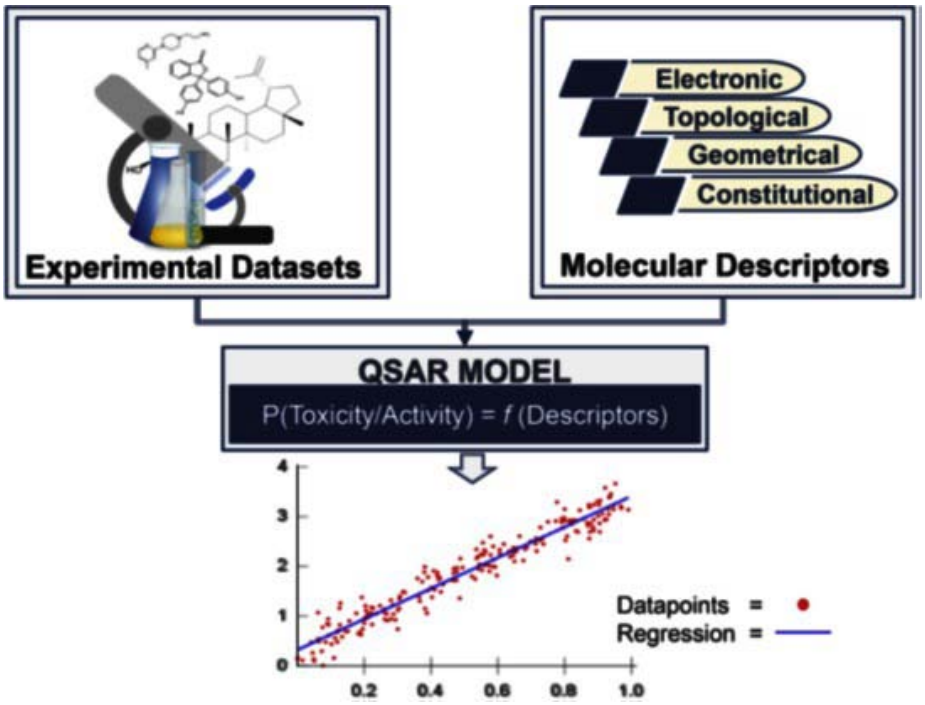

Fig. 3: Stages of QSAR model generation [33]

Excretion

Biliary and renal excretions were the primary routes of excretion of drug molecules after proper metabolism [42]. In this process, polar compounds were excreted more efficiently than lipophilic molecules involving kidney and liver as major organs. Excretion and reabsorption were linked with other as two side of coins, both were pH dependent and weakly acidic or basic environment of the molecules [43]. In the process of computation and prediction of drug molecules, partial least square analysis was applied to database consisted of 754 molecules correlated with biotransformation. This process was validated with enhanced leave analog structural, therapeutic, ionization class out and geometric mean fold error metrics. The positive factor of the model was prediction of neutral compound excretions near about pH 7.5. Another model was developed using support vector machine and a group of molecules (141), followed by mining of metabolism like descriptors (CPathPred, SVM descriptor). These SVM descriptors created a positive impact of elimination of xenobiotic. Furthermore, a new model was established with a large number of data focusing on unchanged eliminated drug in urine and renal clearance data with greater productivity for drug excretion prediction [44].

Active transport

Active transport (up-hill transport) of drug molecules plays an essential role in transportation of molecules against the concentration gradient and natural thermodynamic fluidity. As this was an energy regulated step, so some suitable inorganic ions, enzymes, proteins acts as support system [45]. As earlier discussed, adenosine triphosphate dependent binding cassette and solute carrier system were the main types of active transporter system. The energy dependent system was used energy for enhanced permeation of membrane whereas other system was depend upon energy dependent sodium potassium ion gated proton pump system [46]. P-glycoprotein, BCRp (breast cancer resistance protein), nucleoside transporters, hPEPt1 (human peptide transporter-1), ASBt (apical sodium-dependent bile acid transporter), OCt (organic cation transporter), OATP (organic-anion-transporting polypeptides), BBb-Choline (blood brain barrier choline system) were some important carrier systems related to biomolecules [47].

P-glycoprotein (P-Gp)

P-Gp was primarily belongs to energy dependent cassette related to multi drug resistant system, mainly available in gastrointestinal tract, blood, brain, testes and placenta and it had a prominent role in movement of drug molecules in system [48]. In the movement of drug molecules from systemic circulation to brain stem as well as from lumen to epithelial cell, cellular uptake was always try to decrease the systemic concentration, P-Gp created a barrier in this format. The experimental correlation data between *in vitro* and *in vivo* P-Gp related experiments showed that noticeable relation was observed during data extrapolation. Furthermore, P-Gp was also impacted on drug-drug interactions by interacting with cytochrome P450 (3A4) microsomal enzyme. Bioavailability of drugs was also effected by P-Gp (inducer or inhibitor) as rifampicin (P-Gp inducer) minimized bioavailability whereas verapamil (P-Gp inhibitor) increase bioavailability of related drugs [49].

BCRp (Breast cancer resistance protein)

Breast cancer resistance protein (BCRp) composed of 655 amino acids and widely distributed in stem cells, cancerous cells, liver, intestine and placenta. BCRp was worked as high gradient transporting system with greater specification for molecules with negative or positive charge, organic anion and conjugated sulfates. This system effectively worked for fetus protection, biliary elimination, and decrease in reabsorption through kidney as well as protection of stem cells. In this fashion, anticancer drugs, toxins, endogenous substances were behave as substrate whereas multidrug resistant modulators were the inhibitors of this transporting system. In this text, Fumitremorgin-C was the chemical substance which can reversed the drug resistance due to BRCp activity [50].

Nucleoside transporter

Nucleoside transporters were responsible for the transportation of nucleosides (deoxyribo/ribo nucleic acid synthesis starting material) as well as regulate the energy dependent neuronal modulation especially transportation of blood to retina. This system was classified into sodium ion dependent and independent transporting systems [51]. These drugs were mainly prodrug in nature, so travelling from administration to destination, these transporter systems showed a positive impact. Nucleoside transporter system was further divided into concentrative (CNT_{1-3}), carrier (solute) ($28A_{1-3}$) and equilibrium oriented (EN_{T1-2}, $SLC29_{A1-2}$). CNT_{1-3} system located in renal epithelium and both EN_{T1-2}, $SLC29_{A1-2}$ were available in basolateral membrane [52].

hPEPt1 (human peptide transporter-1)

Human peptide transporter belongs to peptide transporter (solute carrier-15A1 system), which was mainly used for transport of oligopeptide with the exchange of sodium and hydrogen ions, associated with transportation of antibiotics, antiviral and antihypertensive agents as well as movement of nitrogen throughout the body [53]. This system mainly located in apical membrane of small intestine. In this context oral hypoglycemic agents (sulfonylureas, biguanides and others) inhibited the transporting system [54].

ASBt (apical sodium-dependent bile acid transporter)

ASBt belongs to solute carrier (10A2) transporting system and mainly located in chromosome 13q33 genes with 22.8 kilobyte deoxyribonucleic acid. This carrier system observed with presence of 348 amino acids with 38 kilo dalton of molecular weight. The system comprised two glycosylation sites at N_{10} and N_{328}. ASBt was responsible for transportation and reabsorption of bile acids from gut lumen as well as active against liver disease, hyperglycemia and hyperlipoproteinemia [55].

OCt (organic cation transporter)

OCt system responsible for movement of organic cations (dopamine, quinine) at physiological pH. OCt system comprised of (550-560) amino acids with three subtypes (OCt_{1-3}) with 12 transmembrane alpha helices (intracellular loop) and large extracellular loop with proper glycosylation factors [56]. This transporting system directly related to uptake of hydrophilic compounds.

OAtp (organic-anion-transporting polypeptides)

OAtp system belongs to solute sodium ion dependent carrier superfamily responsible for transportation of amphipathic endogenous, exogenous organic compounds and intestinal absorption of drugs. It has four subtypes as OAtp1B1, OAtp1B3, OAtp2B1 and OAtp1A2. This family mainly located in liver, intestine, kidney, brain and placenta. The first two types were responsible for hepatocellular drug uptake and later two were related to intestinal absorption [57].

BBb-Choline transporter (blood brain barrier choline system)

After entering body, choline reached brain through semi-permeable blood brain barrier using sodium ion dependent and passive diffusion processes. This transporting system was also belongs solute carrier system, responsible for biosynthesis of acetylcholine from choline. This transporting system has two subtypes as choline transporter (Cht) 1 and 2; among them Cht2 was responsible for oxidation of choline in mitochondria [58] whereas Cht1 was responsible for choline from extracellular system. Hemicholinium blocks the activity profile of Cht 1 and 2 [59].

Computational models associated with drug-transporter interactions

In the computation and prediction of drug-transporter interaction, exploration of database, generation of pharmacophore model, homology modelling, molecular docking study and QSA_R/QSP_R model generation are the most important models.

Exploration of database

There are lots of database available related with structural features of drug molecules and pharmacological activities. Databases are mainly helpful for the exploration of molecules based on their

properties, disease types and toxicity profile [60]. These collective information helps a researcher or student for the development of newer molecules with greater activity and lesser toxicity. Experimental pKa, Phys-chem EPISUITE, ADME database, Bioconcentration NITE, ZINC and Pubchem are some database related with drug disposition and toxicity.

Experimental pKa database

This database represents the pKa values (dissociation constant of acid or bases in aqueous environment) procured from 5647 and 8060 organic acids and bases, respectively [61].

Phys-chem EPISUITE database

This database belongs to estimation program interface under environment protection agency and associated with calculation of physicochemical properties using values of octanol-water partition coefficient, gas phase rate of reactions associated with various oxidants, value of henry law constant value using air-water partition coefficient, calculation of boiling point, melting point and vapor pressure, percentage of degradation of substance in absence or presence of oxygen. This database was constituted with more than forty thousand molecules [62].

ADME database

This database directly reflects the detailed information about molecules (induce or inhibit a system) and role of metabolic enzymes with other biotransformation factors. In this context, role of cytochrome P450 microsomal enzyme, uridine diphosphate glucuronyltransferase, glutathione-S-transferase and flavin monooxygenase on biotransformation of a drug molecule as well as clinical trial data with pharmacological factors (maximum concentration need for activity with time response) are assessed and tabulated for researchers.

Bioconcentration NITE database

Bioconcentration factor is directly related with accumulation of organic or inorganic contaminants inside a biological system in dissolved form [63]. The accumulation depends upon absorption of the molecule via active or passive transport, interaction with living system via dipole-dipole or Van der Waal force followed by reaction and accumulation. This database contained with huge number of chemical structures with bioconcentration factor in relation with toxicity. In the calculation of bioaccumulation factor, partition coefficient, solubility are the key factors [64].

ZINC database

This database is mainly a collection hub of more than thirty five million commercially available drugs with their possible physicochemical and pharmacophoric features. This database also sense a correlation between molecules and their probable biological activity [65].

Pubchem database

This database represent a collection of drug molecules along with its biological assay results, mainly obtained from various commercial database vendors (more than eighty). The database is maintained by National Centre Biotechnological Information. Here chemical structure, nomenclature, partition coefficient data and other physicochemical parameters are included [66].

Pharmacophore model generation

Pharmacophore is the three dimensional similarity between a group of similar to very diversely structured molecular group in respect of the biological activity. Pharmacophore model represents the structural points and distance between most important structural features, in this context biological activity plays an essential role. In the pharmacophore model generation, Drug Discovery studio, Ligandscout, ZINC Pharmer and Pharmagist are the mostly used softwares. Among them, Drug Discovery studio and Ligandscout are the commercial softwares whereas ZINC Pharmer and Pharmagist are freely available softwares. In the assessment of pharmacophoric features, structures are input in Sybl mol2 format. In the fig. 4, the pharmacophoric features of aspirin and acetaminophen showed that presence of two hydrophobic regions (green color), one aromatic region (purple color), one negative ion group (red color), four hydrogen bond acceptor regions (yellow color) and one aromatic group (purple color), two hydrophobic regions (green color), two hydrogen bond donor atoms (white color) and two hydrogen bond acceptor atoms (yellow color) [67].

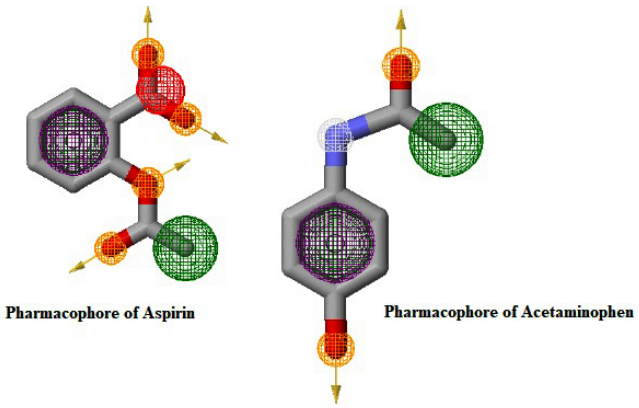

Fig. 4: Pharmacophoric features of aspirin and acetaminophen [67]

But when collectively submit a group of substances (similar to diverse group) in PharmaGist server panel (minimum 5 and maximum 30 structures at a time), then it not only search the similarity between the structures as well as calculate the possible bond distance between the features using Drug Discovery studio visualizer software. Here we put in an example with a bunch of molecules (aspirin, acetaminophen, ibuprofen, indomethacin and naproxen) to create a model using PharmaGist. The outcomes showed that only four spatial features are responsible for activity (one aromatic center, one negative ion center and two hydrogen bond acceptor points) (fig. 5) with proper distance measurements in angstrom [68].

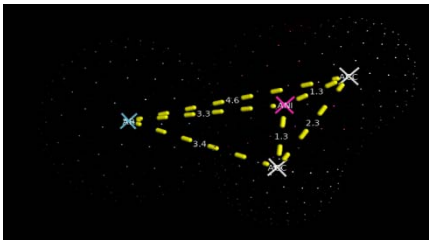

Fig. 5: Common structural features between five anti-inflammatory agents [68]

Homology modelling

In some cases, receptor or protein structure is not available then using FASTA or UniProt sequence and swiss pdb viewer (https://swissmodel.expasy.org/interactive) [69]. FASTA sequence was obtained from Protein Similarity Search (https://www.ebi.ac.uk/Tools/sss/fasta/) and UniProt sequence was obtained from https://www.uniprot.org/. Finally, a new protein was developed using similarity index and BLAST. In the example, we use FASTA sequence of alpha amylase (P0DUB6 source *Homo sapiens*) followed by searching of relative templates and finally based on GMQE (Global Model Quality Estimation), QMEAN (Global Model Quality Estimation) and sequence similarity, a new protein model was developed (fig. 6) [70].

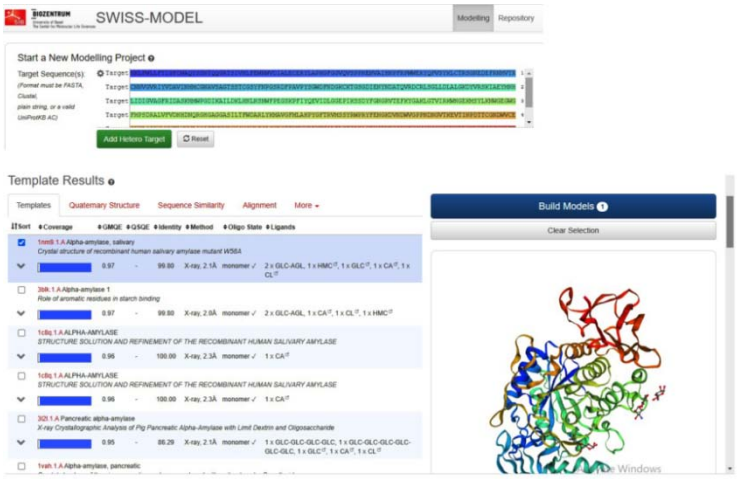

Fig. 6: Development of homology model [69, 70]

Molecular docking study

Molecular docking study is the process to identify the molecular interactions between drug molecule and receptor, which corresponds with the biological activity. As we know, small molecule and receptor (protein or enzyme) or two proteins were docked to affirm the pose of interactions. Molecular docking study was divided into rigid and flexible docking. This study plays a pivotal role in terms of pharmacokinetic behavior and biological activity. There are ample of softwares available to study the docking interactions. Rigid molecular docking study showed the favored conformations with free energy assessment and electrostatic interactions between chemical structure and receptor. In this process, fast Fourier transformation and spherical harmony of the three dimensional structure of the receptor plays the most important role. This knowledge was utilized in FRODOCK (software), whereas desolvation energy and grid based knowledge were used in ZDOCK and MEGADOCK softwares, respectively. The science of translation and rotation of chemical structure were considered in Cell-Dock whereas resolution per grid volume was used in FTDock platform [71].

In case of flexible docking, the three dimensional movements of ligands were considered with (6+N) special orientations as per Monte Carlo simulation process. Flexible docking process was studied using four different strategies such as Monte Carlo molecular dynamic simulation, in-site combinatorial searching, building of ligand molecules and site assessment with fragmentation. In this docking process, grid space volume, relative mean standard deviation and receptor active pocket analysis are the important factors. AutoDocK Vina (free version) is the most useful software in this process, several other softwares such as GLIDE, GOLD, MedusaDock etc are also available (commercial standalone version). In this context, we focused on the process of molecular docking using AUTODOCK Vina software interface. The methodology of molecular docking study involves preparation of receptor, preparation of ligand molecule, grid measurement followed by drug-receptor interaction and visualization of the docking pose using Pymol console [72].

In the preparation of receptor portion, initially receptors were procured from www. rcsb. org (Protein Data Bank) or generation of resemble protein structure using homology modelling. Then all the water molecules and co-crystallized ligands were removed from the receptor followed by addition of gasteiger charges and saved in. pdbqt format. In case of ligand preparation, addition of rotation and charges were the necessary added effects in the ligand and saved in. pdbqt format. Finally based on the interactive residues, grid space volume and exhaustiveness were set and performed the iterated interactions. In the fig. 7, the molecular docking pose diagram showed the possible interaction between the nearby amino acids (ARG 817) and some part of the ligand within the receptor voxel. Finally a tabulated energy data (Kcal/mole) with relative mean standard deviation value were obtained [73]. Then we perform the same process with standard molecule and compare the score and interaction.

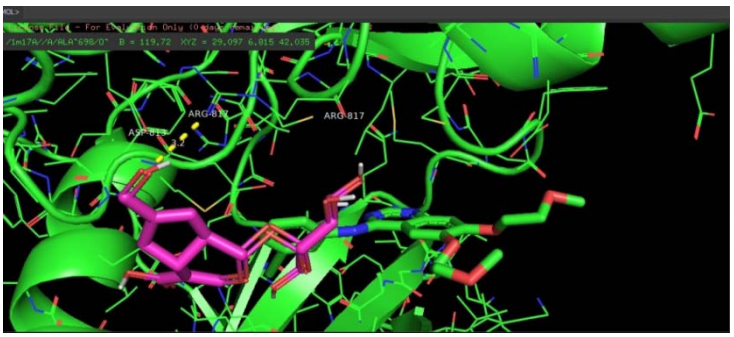

Fig. 7: Molecular docking interaction [71, 72]

Quantitative structure activity/property relationship (QSA_R/QSP_R)

QSA_R/QSP_R is basically a statistical approach between activity/property (physicochemical) and structural features including $CoMF_A$ (Comparative Molecular Field Analysis) and $CoMSI_A$ (Comparative Molecular Structural Indices Analysis) using multiple linear regression, partial least square or principal component analysis methods. This technique has several types such as 0D QSA_R (possible descriptors are molecular weight and types of atoms present), 1D QSA_R (consists of molecular fragmentation descriptors such as functional groups, number of rings, bonds, substituent etc), 2D QSA_R (consist of bonding information), 3D QSA_R (consist of three dimensional molecular information such as shape, steric factors), 4D QSA_R (previous all descriptors with possibility of conformer generation and grid factors), 5D QSA_R (information of molecular dynamics are also included), 6D QSA_R (information of solvation theorem are also introduced), 7D QSA_R (real and virtual target analysis along with all information are include) and hologram QSA_R (where molecular fragments and cyclic redundancy check algorithm are used to develop the hologram of the structure followed by correlated with activity) [74]. In this techniques, types of descriptors also plays an important role. Here, fragment based descriptor, total molecule descriptor, topological descriptor (Wiener index, Randic index, E_{HOMO} and E_{LUMO}), geometric descriptor (Van der Waal volume, molecular surface area) and constitutional descriptors (molar volume, Kier-Hall index, Balaban index, kappa shape index, E-state, Moran/Geary autocorrelation descriptor, Ghose-Crippen molar refractivity) are mainly counted in study [75-76]. The process of model generation involves a series of data processing such as: i. Preparation of dataset (using database or experimental data), ii. Calculations of descriptors (using DRAGON, E-Dragon, PADEL softwares), iii. Normalization of data volume (minimize data exhaustiveness and remove near about data) [77-78], iv. Checking of MODelability index (threshold value 0.65 for model generation), v. Data pretreatment and dataset division into training and test set using Euclidean distance, Kennard-stone process, vi. Model preparation using multiple linear regression process [79], vii. Validation of generated model using Golbraikh-Tropsha acceptance criteria, k-fold cross validation, leave one out, viii. Applicability domain analysis using Euclidean distance and Mahalanobis distance [80-81].

Future scope

The collective information from all sources helps a researcher to visualize the possible movement of a drug molecule inside the body system. So in future if we approach the *in silico* behavior of a drug-drug or drug-receptor interactions along with other relative tools for drug discovery, then the process become more robust and reproducible as well as every step will statistically justified, so the chances of error or false claim will less, which will produce a molecule or formulation more fruitful for mankind.

CONCLUSION

This chapter mainly focused on the journey of a drug molecule inside the body. In this intriguing viewing process, various pathophysiological aspects help us to know or visualize the path of a drug molecule in achieving the ultimate goal. When a drug molecule enters our system, system treat the substance as foreign material, so it always try to expel out the substance and in this expelling process both molecule and body system comes under an iterative process and finally some positive or negative effect is observed by the system. In this fate determining process, physicochemical nature of the chemical substance and physiological environment (composition) of system makes this movement more interesting. In this context, pharmacokinetic features along with toxicity profile of the drug substance regulate the ultimate fate of the molecule. Nowadays various computational processes are considered such as *in silico* assessment of drug molecule after absorption through biological membrane, distribute throughout the system based on the percent ionization or partition coefficient factors followed by biologically transformed into an another entity in presence of microsomal enzymes and finally excrete out from system using various cellular transport systems. In some cases, based on the chemical nature and nature of interactions triggered the toxic behavior of the substance. In this chapter, we discussed all the possible factors related with the movement of a drug molecule as well as positioned on various computational tools to assess the chemical changes of the drug molecule. So we focused on detailed computational studies related to drug disposition behavior such as database mining, pharmacophore model generation, homology modelling, molecular docking study and QSA_R/QSP_R study.

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CONFLICT OF INTERESTS

Declared none

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