Analysis of Pharmacokinetic & Pharmacodynamic Models in Oral and Transdermal Dosage Forms

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Abstract

Bioavailability is a pharmacokinetic term which refers to the extent and speed of absorption of the chemicals content in it. After the absorption the drug plays the important role in which the body react i.e. the pharmacodynamics process. Oral drugs, Transdermal drugs, Lipophilic drugs and combined oral drugs all plays the different role after being absorbed and the mode of absorption is also different through various research. The pharmacokinetic parameters (AUC), (Cmax) and dynamic models express the process of drug ADME reports. Various sample analysis is also being done through various instrumentation and databases. Researches and reports reveal the various side effects of few drugs which are taken orally as well as transdermally and the combine effects are being taken into consideration. The main aim is to analyze the process of drug absorption through various parameters, different instruments and mention the side effects after absorptions.

Keywords: Pharmacokinetics; Pharmacodynamics; Oral drugs; Transdermal; Bioavailability; Bioequivalence; Lipophilic

Introduction

Pharmacokinetic studies is based on a traditional intensive design model which usually conducted using carefully selected volunteer subjects, a controlled experimental design, and collection of multiple blood samples [1]. Measurements of drug and metabolite with pharmacokinetic models determine parameters like elimination half-life, volume of distribution, and clearance which is also known as Bioavailability. It is a pharmacokinetic term that describes the rate and extent to which the drug ingredient is absorbed from a drug product and becomes available in the systemic circulation [2]. Bioavailability is also a pharmaceutical form refers to the extent and speed of absorption of the active principle contained in it [3]. But studies assess the relative fraction of the orally administered dose that is absorbed into the systemic circulation when compared to the bioavailability data for a solution, suspension, or intravenous dosage form and provide pharmacokinetic information related to distribution, elimination, effects of nutrients on absorption of the drug, dose proportionality, linearity in pharmacokinetics of the active moiety and appropriate inactive moiety [4]. Rather Bioavailability of drug depend upon the gastric emptying time, pH of the stomach, rate of metabolism and other individual variations for the pharmacokinetic pathway inside the body, these characteristics plays a very minor role [5]. Some drugs are too painful such as diagnosis and therapeutic approaches for pediatric cancer; in this approach analgosedation is performed under intensive care. Prophylactic approaches used to acute the side effects [6].

Similarly, Bioequivalence studies are to demonstrate bioequivalence between a pharmaceutically equivalent generic drug product and the corresponding drug. Together with the determination of pharmaceutical equivalence, establishing bioequivalence allows a regulatory conclusion of therapeutic equivalence. Bioequivalence studies compare the systemic exposure profile of a test drug product to that of a reference drug product. Two pharmaceutical forms are said bioequivalent when, the drug being administered to the same individual, in the same experimental conditions and at the same dose, showed no significant differences in relation to bioavailability [7]. These studies are important in the development of inhaled medications and delivery devices.

For inhaled medications, bioequivalence ensures that equal doses of different agents of the same class, or different formulations of the same medication (i.e. powdered or aerosolized), produce equivalent pharmacodynamics effects [8]. Pharmacodynamics is the study of the biochemical and physiological effects of drugs on the body or on microorganisms or parasites within or on the body and the mechanisms of drug action and the relationship between drug concentration and effect [9]. Its clinical efficacy studies are considered the most useful tool to assess bioequivalence of different inhaled medications or different inhalation devices [8]. Pharmacodynamics is often summarized as the study of what a drug does to the body, whereas pharmacokinetics is the study of what the body does to a drug [9].

Pharmaco-kinetic-dynamic model

Pharmacokinetics is the discipline that applies mathematical models to describe and predict the time course of drug concentrations in body fluids, whereas pharmacodynamics refers to the time course and intensity of drug effects on the organism, whether human or experimental animal. Both evolve a technique for measuring the drug concentration to accurate and sensitive way. A kinetic-dynamic study in clinical psychopharmacology typically involves medication administration (usually under placebo-controlled, double-blind laboratory conditions) followed by quantitation of both drug concentration and clinical effect at multiple times after dosing. Pharmacokinetic and pharmacodynamics relationship evaluates separately and later its evaluation is recorded graphically as well as mathematically [1]. Bioavailability and Bioequivalence may be determined using both plasma concentrations.

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of a drug (pharmacokinetic parameters) and its pharmacological effects (pharmacodynamics parameters). However, drug concentrations(C) in blood/plasma, the active site or the peripheral compartment and the pharmacological effects (E) often follow a non-linear relationship, known as the Hill equation (equation below). As a result BA values obtained using pharmacokinetic and pharmacodynamics parameters may be substantially different.

\[ E = \frac{E_{\text{max}} \times C^n}{EC_{50} + C^n} \]

Emax is the maximal effect attributable to the drug; EC_{50} is the concentration producing 50% of the maximum effect and ‘n’ is Hill’s coefficient [10]. Beside this Pharmacokinetics depends upon the homogenization speed which may leads to 90% predetermined range (11) (Figure 1).

**Oral, Transdermal, Lipophilic administrations of drugs**

Transdermal is a route of administration wherein active ingredients are delivered across the skin for systemic distribution. Examples include transdermal patches used for medicine delivery, and transdermal implants used for medical or aesthetic purposes [12]. Transdermal route is known to reduce the adverse effects and increased bioavailability of drugs [13]. Drugs are normally taken orally as tablets or capsules. The drug (active substance) itself needs to be soluble in aqueous solution at a controlled rate. Such factors as particle size and crystal form can significantly affect dissolution. Fast dissolution is a prerequisite for their rate of absorption and bioavailability [14].

The main technologies to achieve the enhanced oral bioavailability of drugs with poor aqueous solubility include the use of micronization, nanosizing, crystal engineering, solid dispersions, cyclodextrins, solid lipid nanoparticles and other colloidal drug delivery systems such as microemulsions, self-emulsifying drug delivery systems, selfmicroemulsifying drug delivery systems and liposomes. Microemulsions are novel pharmaceutical formulations are thermodynamically stable, transparent, low viscosity, easy to prepare and isotropic dispersions designed to enhance the oral bioavailability of poorly soluble drugs [14].

There are many varieties of oral drugs which are formulated in different manner whether with lipophilic substance, biodegradable substance or a combination of other drugs. The way of action or delivery is fast as compared to transdermal. Transdermal deals with skin where oral delivery comes directly in contact with the body parts. Few examples of drugs are:

"Atorvastatin" (AT), a synthetic reversible inhibitor of the microsomal enzyme HMG-CoA reductase belongs to the second generation of statins. AT and its metabolites are substrates for CYP3A4, uridine diphospho glucuronosyltransferases (UGT1A1, UGT1A3), P glycoprotein (P-gp), organic anion-transporting polypeptide (OATP-C) and proton-monocarboxylic acid co-transporter (MCT). Losartan (LS) is an orally active, highly selective antagonist that blocks the binding of angiotensin II to the angiotensin II type 1 (AT1) receptor subtype without agonist properties. LS are very effective and safe in the treatment of hypertension. Three subjects were withdrawn from study due to adverse events such as dizziness and vomiting, pain in the left ear. CYP3A4 is also the major enzyme responsible for the conversion of AT to its metabolites. LS or its metabolite are not known to alter the activ-
zyme inhibition. Metabolism occurs by hydroxylation at the 5 position of the pyridyl side chain and conjugation of this product; by cyclodehydration; and by a sequence of reactions involving hydrolysis of the amide linkage, decarboxylation, ring contraction and N-demethylation [16].

“Pitavastatin” is a highly effective lipid-lowering drug with a distinctive metabolic pathway that has a low potential for drug interactions. When it enters the body it coagulates into metabolite Pitavastatin lactone which is observed after plasma validation [17]. Pitavastatin lactone is the chief metabolite of the drug.

Phytochemicals or plant extracts mixed with the present antibiotics gives more potential treatment against diseases such as: “Kumazasa cytoplasmic extract”. The antimicrobial activity (as MIC) of cytoplasmic extract from Kumazasa or each antibiotic (ampicillin: ABPC, vancomycin: VCM, clarithromycin: CAM, or tetracycline: TC) was measured against both Gram-positive and Gram-negative microbes. The Kumazasa-cytoplasmic extract (Kumazasa-CE) displayed a markedly potent antibacterial activity against Gram-positive bacteria such as Staphylococcus aureus, Enterococcus and Streptococcus pneumoniae [18].

“Cyclobenzaprine hydrochloride” is a centrally acting muscle relaxant. Cyclobenzaprine improves global functioning of patients with fibromyalgia with a modest improvement in sleep quality. The relative bioavailability between Cyclobenzaprine and caffeine is analyzed for the excellent pharmacodynamics study [19]. Drug and metabolite plays an important role when combined each other. The rate of bioavailability is same but the measurement range depends upon the test and references used. Two formulations differ in their extent of absorption. Parent drug data are more sensitive to detect differences in the rate of absorption. Example cyclobenzaprine hydrochloride and caffeine [20].

“Tetrahydrofuran”, “oxymatrine” and “phospholipids” were resolved into the medium, oxymatrine phospholipid complex was formed. After administration of the complex it shows the increase absorption in gastrointestinal tract and pharmacokinetic dynamic studies done [21].

“Pentoxifylline” (PX) (1-[5-oxohexyl]-3, 7-dimethylxantine) is an anti-inflammatory agent with a broad antimicrobial spectrum against gram positive and gram-negative bacteria and is considered safe. The bacteriostatic feature includes good oral absorption and lack of metabolism resistance and treatment failure despite 100% adherence to the treatment regimen. The bioavailability of rifampicin from the formulations can also be explained on the basis of physiochemical properties of the drugs and dosage forms. Since rifampicin tablets are film coated, this dosage form presents all the potential problems of compressed tablets that impose a physical barrier between the gastrointestinal fluid and tablet containing the drug [5].
“Valsartan”, an angiotensin receptor blocker (ARB), is a widely used antihypertensive drug approved worldwide either as monotherapy or in combination with other antihypertensive agents. The pharmacokinetics of valsartan is linear and dose proportional across a wide dose range (80–320 mg). Valsartan is rapidly absorbed after oral administration, reaching peak plasma concentration (Cmax). The oral bioavailability of valsartan is only 23% and about 95% is bound to serum proteins mainly albumin [32].

Combination contraceptives like “Ethinylestradiol” are used to prevent pregnancy in women. Ethinylestradiol is rapidly and completely absorbed from the gastrointestinal tract. Ethinylestradiol undergoes extensive first-pass metabolism, and its absolute bioavailability is approximately 40%-60%. After single oral administration, peak plasma concentrations of ethinylestradiol are reached and changes. “Gestodene” has been combined with low doses of ethinylestradiol to provide low-dose combination oral contraceptive (COC) preparations. While low-dose COCs are the most widely prescribed form of oral contraceptive and have a low failure rate in terms of unintended pregnancies, approximately 50% of all women who begin taking oral contraceptives discontinue their use within one year. Gestodene is rapidly and completely absorbed from the GI tract with peak plasma concentration occurring in about 1-2 hours. Gestodene is extensively metabolised in the liver but does not undergo significant first pass metabolism [33].

“Flurbiprofen” is a non-selective cyclo-oxygenase inhibitor and member of a series of alkanolic acid derivatives and has shown to have anti-inflammatory and analgesic activity. Flurbiprofen has also caused a dose dependent inhibition of collagen-induced platelet aggregation in patients with platelet-rich plasma [34].

“Candesartan” cilexetil administered orally, which is completely converted during enteric absorption to the active compound, candesartan. Candesartan cilexetil is rapidly and completely hydrolysed to the active compound candesartan during absorption from the gastrointestinal tract. Candesartan is a potent, long-acting, selective angiotensin II AT1 receptor blocker which is well-tolerated and effective with a once-daily dosing regimen in hypertensive patients. “Felodipine” is a calcium antagonist, within the dihydropyridine group, which lowers blood pressure by a selective action on the vascular smooth muscle in the resistance vessels. This benefit is abolished by the poor bioavailability of the drug, which—although being almost completely absorbed from the gastrointestinal tract—is only 15% bioavailable after oral administration. The poor oral bioavailability of felodipine was attributable to its extensive first-pass metabolism and the very low water solubility of the drug [35].

“Metformin hydrochloride” (N, N-Dimethyl-Imido-diaimidic diamide hydrochloride) is an oral antihyperglycaemic agent that improves glucose control in patients with type 2 diabetes by lowering both basal and postprandial plasma glucose level. Metformin HCl decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization [36].

“Nevirapine” (NVP) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that binds to the membrane of the HIV virus inhibiting viral replication. It also probably inactivates cell free virions present in the genital tract and in human milk. Nevirapine is well absorbed by mouth, widely distributed, penetrates the cells very well because it is lipophilic, rapidly transferred across the placenta. A substantial quantity of drug appears in breast milk [37].

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metabolite of CDP-choline to evaluate the characteristics of the pharmacokinetics and bioequivalence of CDP-choline oral preparations [44].

“Fenoterol” is a B2 adrenergic agonist, which is effective bronchodilator in animals and humans when given by inhalation or oral route. Following the administration of several B2 stimulants oral or inhaled, fenoterol is superior to isopenoline, orciprenaline and salbutamol in protecting against bronchospasm and is longer acting. Fenoterol is rapidly absorbed following oral ingestion or inhalation. Its oral bioavailability is low, only 2%. It is rapidly metabolized to sulphate and glucuronide conjugates. Therefore, the development of transdermal controlled drug delivery system of fenoterol without adverse effects which could occur when administered orally is very important [45].

“Quetiapine” is rapidly absorbed in the gastrointestinal tract, and its absorption is unaffected by food [46]. Quetiapine is indicated for the treatment of schizophrenia and bipolar disorder. Quetiapine is metabolized by the liver [3].

“Cefdinir” is one of the third generation cephalosporins which have broad spectrum antibacterial activity. Cefdinir dispersible tablet disintegrates very fast and disperses homogenously, it is easily to be absorbed and highly effective [47].

Minocycline is more lipid soluble than doxycycline and the other tetracyclines and widely distributed in body tissues and fluids, but the penetration into the CSF (Cerebrospinal Fluid) is relatively poor. It crosses the placenta and is distributed into breast milk [2].

“Acylovir” is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV). Absorption of acyclovir from the gastrointestinal tract is variable and incomplete; 10%-30% of an oral dose may be absorbed. This poor systemic bioavailability is considered to be a result of the characteristics of the drug itself and not its delivery vehicle. Because of its high hydrophilic nature, absorption of acyclovir occurs mainly by passive diffusion mechanism and it is slow, variable and incomplete manner. Therefore, acyclovir is replaced with its prodrug valacyclovir, the L-valyl ester of acyclovir has been used orally to increase the systemic bioavailability. Acyclovir is well tolerated whether administrated by ocular, topical, oral or intravenous routes [48].

“Esomeprazole” is absorbed rapidly after oral administration. Esomeprazole is metabolized extensively in the liver by two cytochrome P450 isoenzymes to metabolites devoid of antisecretory activity. The drug is primarily metabolized by CYP2C19 to hydroxyl and desmethyl metabolites and to a lesser degree by CYP3A4 to sulfone metabolites [49].

“Omalizumab” (XOLAIR®) is a recombinant DNA-derived humanized IgG monoclonal antibody that selectively binds to human IgE. Omalizumab has been approved as an add-on therapy in adults, adolescents and children (≥6 years) for the treatment of IgE-mediated severe allergic asthma in the EU, and in adults and adolescents (≥12 years) with moderate-to-severe allergic asthma in the US. Omalizumab was first launched as a sterile, white, preservative free, lyophilized powder in a single-use vial that has to be reconstituted with sterile water for injection. The solution should be administered immediately after reconstitution. Omalizumab exerts its pharmacological effect by binding to circulating IgE, whatever its allergen specificity, and prevents subsequent IgE-mediated responses [50].

The mean absolute bioavailability of orally administered “desvenlafaxine” in humans is 80%; the concentrations of (R)- and (S)-desvenlafaxine enantiomers in all plasma samples assayed were approximately equal, and demonstrated similar pharmacokinetic parameters [51].

“Imatinib mesylate” is the first and only effective drug for the treatment of gastrointestinal stromal tumour (GIST) at present. The constitutive activation of KIT receptor tyrosine kinase is critical in the pathogenesis of GISTs. Imatinib is rapidly absorbed after oral administration with a peak plasma concentration occurring at 2-4 hours. Additionally, Imatinib absorption is not significantly affected by food [52].

“Paracetamol” is well absorbed from the gastrointestinal tract and it relatively poorly binds to blood proteins (20%-50%). A part of the ingested drug dose is coupled in liver with glucuronic acid (60%), active sulfonic acid or glycine, and excreted with urine in the form of such compounds. Accumulation of this metabolite can lead to liver necrosis for a long-term [53].

“Gabapentin” can be actively transported across the brain–blood barrier and the gut via the L-system amino acid transporter, which recognizes L-isoleucine, L-leucine, Lphenylalanine and L-valine. Gabapentin has some lipophilicity and readily crosses the blood-brain barrier. Its volume of distribution is large, estimated as 50 to 60 L in healthy volunteers. The drug is not bound to human plasma proteins [7].

“Capecitabine” is administrated orally, morning and evening. Capecitabine is an adjuvant treatment for colon cancer and for the treatment of metastatic breast cancer in particular patients whose pathology did not improve during treatment with other therapeutic agents [54].

“Rapamycin” released from ReGel exhibited antiproliferative activity similar to the free Drug. ReGel is thermosensitive which allows for easy mixing with rapamycin and also easy injection into the physiologic site of interest. Basically drug is used after grafting of the body parts which is applied transdermally [55].

“Aceclofenac”, a nonsteroidal anti-inflammatory drug (NSAID) has been recommended orally for the treatment of various kinds of pain, inflammation, rheumatoid arthritis and osteoarthritis oral administration of aceclofenac causes gastrointestinal (GI) ulcers and GI bleeding. Transdermal route is known to reduce these adverse effects and increased bioavailability of drugs [13]. Nanoemulsion or nanocarriers improve solubility and dissolution of the lipophilic drug aceclofenac [56].

“Vedolizumab” is a gut-selective biologic that has shown efficacy in ulcerative colitis (UC) and Crohn’s disease (CD). Vedolizumab demonstrates dose-proportional pharmacokinetics and maximally saturated α(4) β(7) receptors over the tested dose range. Vedolizumab treatment reduced fecal calprotectin levels compared with placebo process [57].

“Xanthohumol” (XN), a dietary flavonoid found in hops, may have health-protective actions against cardiovascular disease and type 2 diabetes. The pharmacokinetic approach shows intravenous and injection or oral intake of low ,high dose is applicable. But the approach is applicable for oral intake [58].

“Dasatinib” a cancer drug orally ingested. The drug interaction between the dasatinib and gastric acid suppressants shows the pharmacokinetic analysis details of the drug act. Administration of an acid suppressant such as famotidine, nizatidine, and lansoprazole can decrease the absorption of dasatinib from the gastrointestinal tract, thereby resulting in a significant decrease in the plasma concentration of da-
The combination of dasatinib and an acid suppressant requires careful therapeutic drug monitoring of the dasatinib plasma concentration to ensure effective patient exposure to the drug [59].

Docosahexaenoic acid (DHA) and DHA-containing ethanolamine plasmalogens (PlsEtn) are decreased in the brain, liver and the circulation in Alzheimer’s disease (AD). Peroxosomal deficits is a process that probably starts early in the AD. An ether lipid precursor of plasmalogens is orally bioavailable augmenting the circulating levels of unesterified DHA and DHA-containing PlsEtn and PtdEtn. Phosphatidylthanolamines were generated via de-alkylation/re-acylation reactions [60].

Sagopilone identifies and preferentially used for the treatment of taxane-resistant cancer. Sagopilone intravenous infusion leads to dose-limiting toxicity (DLT) which shows peripheral sensory neuropathy. Pharmacokinetic data for sagopilone gives no accumulation after repeated administration which will help define the treatment of advanced tumors in more extensive clinical trials [61].

Dalfampridine is a novel drug with a unique mechanism for the symptomatic management of multiple sclerosis (MS). Dalfampridine blocks potassium channels on demyelinated neurons and allows normal electrical conduction, thus improving locomotor difficulty. Dalfampridine is rapidly absorbed after oral administration, reaching its peak plasma concentration. Dalfampridine is not an inhibitor or inducer of a major cytochrome P-450 isozyme. Dalfampridine side effects are insomnia, dizziness, headache, nausea, and weakness [62].

Pharmacokinetics & dynamic analysis

The plasma concentration obtained from metabolites was fed with computer software BASICA®, WinNonlin software etc. This determines the pharmacokinetics parameters. The maximum metabolites (i.e. T & TG) concentrations (Cmax) and the corresponding peak time (Tmax) were determined by checking the individual drug plasma concentration– time profiles [27,30]. Immediately after the administration of the drug, pharmacokinetic parameters it straight away followed when pharmacodynamics parameters are used for BA and BE determination [11]. The pharmacokinetics analysis was Individual plasma concentration-time curves were constructed, Cmax and Tmax were directly obtained from the curve. AUC from time 0 (baseline) to 24 hours (AUC0-24) was calculated using the trapezoidal rule. From the terminal log-decay phase, elimination rate constant (ke) was estimated using linear regression, and t1/2 was estimated using the following equation:

\[ t_{1/2} = \frac{\ln 2}{ke} \]

Where In was defined as the natural log;

And extrapolation of AUC from baseline to infinity (AUCinf) was calculated as follows:

\[ AUC_{inf} = AUC_{0-24} + \frac{(C_{24}/ke)}{ke} \]

Where C_{24} was defined as concentration at 24 hours [65].

The two formulation analysis can also be done by the database searches. Some drugs whose formulations are different in such case the database searches helps in analyze the bioequivalence rate and approaches. The AUC value determines the possibility of reaction. The variability depends on the concentration of the drug and the overall bioavailability which may vary [66]. Drug interaction leads to different reaction, similarly in hepatic allograft the drug pharmacokinetic analysis shows orally ingested drug has highly predictive AUC. The concentration of the drug, efficacy and adverse reaction along with the time normalization is important in predicting the data [67].

Sample analysis

The blood samples are the most useful sample for drug metabolism test and qualification test. The urine samples are also the good collected sample for drug test. Plasma concentrations determined through the method validated by liquid chromatography-mass spectrometry (LC-MS/MS), HPLC. The mass spectrometer was equipped with negative electrospray source (ESI) by using multiple reactions monitoring (MRM) mode.

Pharmacokinetics/pharmacodynamics and statistical analysis is carried out by using the software GraphPad Prism® version 4.0, WinNolin® version 5.0.1, EquivTest” version 2 and Microsoft Excel”. The bioanalytical method was validated for specificity, selectivity, linearity, precision, accuracy, recovery of extraction and stability according to the US FDA guidance. Liquid chromatography tandem mass spectrometry was also used to determine plasma drug concentrations [42,68]. The overall sampling time is long enough to describe the pharmacokinetic profile of investigated drugs after oral administration of formulations [68]. Drug administration involves homogenization speed which effects the drug pharmacokinetics when used as a suspension formulation [11]. Pharmacokinetic and pharmacodynamic analysis for some erythromycin or intravenous sample of plasma can also be done through ELISA [69].
Discussion

Overall idea of route of administration of drug is being observed. The oral administration overcomes the mode of transmission of drug through transdermal procedure. Few poorly soluble drugs can be incorporated in the oil phase to enhance their oral bioavailability. One of the challenges in formulating microemulsions, SEDDS or SMEDDS (isotropic solutions of oil) is the limited availability of formulation components. The excellent research reports enhanced oral bioavailability of poorly soluble drugs [14]. The biotechnologically modified administrations of Calcium in body through natural source like carrot, phytochemicals from spices, are the different source of administration to the body [70,71].

Discovery and drug development often have different solubility screening requirements and methodologies have been developed to meet the needs of these different stages [73]. Side effects of the drugs are followed by the Table 1.

Conclusion

Novel strategy of a drug is to increase the affinity and protection to health. Drug administration can be done through different strategies which are pharmacokinetically accepted. The pharmacokinetic interaction involves the modification of drug towards its affinity where pharmacodynamics interaction is done with inhibition and enhancement. Whether the drug is orally absorbed or transdermally there effects are different and protect the body. Beside this drug brings the side effects unusually which enhance and helps to produce the better formulated drug which will be kinetically and dynamically a useful one.

Table 1: The following table contains the name of the drugs, its mode of absorption and the side effects after being fully absorbed by the body [75].

| Serial no | Name of the Drugs | Mode of Absorption | Side Effects of the drugs |
|-----------|-------------------|--------------------|---------------------------|
| 1         | Aceclofenac       | Oral, transdermal  | Diarrhea, nausea, indigestion, abdominal pain, dizziness and rash |
| 2         | Atorvastatin      | Oral               | Nose inflammation, joint pain, diarrhea, pain in extremity, urinary tract infection, indigestion, nausea, muscle and bone pain, muscle spasms, sleeplessness |
| 3         | Losartan          | Oral               | Swelling, abdominal pain, chest pain, nausea, headache, inflammation of pharynx, diarrhea, indigestion, muscle pain, sleeplessness, cough and sinus disorder |
| 4         | Naproxen Sodium   | Oral               | Nausea, constipation, diarrhea, indigestion and mouth ulcer, convulsions. Skink- itching, skin eruptions, increased sweating and bruising. Liver-Jaundice and abnormal liver function tests [74]. |
| 5         | Rapamycin         | Oral, intravenous  | Thrombocytopenia and hyperlipidaemia |
| 6         | Piroxicam         | Oral               | Heartburn, nausea, ulcers. Blood - Anemia and increased bleeding time. Central Nervous System - Dizziness and headache. Skin – Itching and rash. ENT - Ringing in the ear. Genitourinary - Abnormal kidney function. |
| 7         | Cyclobenzaprine   | Oral               | Drowsiness, headache, dizziness, blurred vision, nausea, abnormal taste, palpitations, tremor, dry throat, pimples, attention disturbances, sleeplessness, fatigue, constipation and indigestion. |
| 8         | Pentoxifylline    | Oral               | Heart - Chest pain, abnormal heart rhythm, palpitations and flushing. Gastrointestinal - Abdominal discomfort. Central Nervous System - Agitation, nervousness, dizziness, drowsiness, headache, sleeplessness, tremor and blurred vision. |
| 9         | Darbepoetin Alfa  | Intravenous, Sub-Cutaneous | Local - Injection site pain. Body As A Whole - Swelling in the extremities, fatigue, fever, death, fluid retention, influenza-like symptoms, and weakness and bleeding. |
| 10        | Ofloxacin         | Oral, Eye Drops    | Nausea, headache, sleeplessness, genital itching in women, dizziness, vaginal inflammation, diarrhea and vomiting. |
| 11        | Emtricitabine      | Oral               | Headache, diarrhoea, fatigue, pains, weakness, increased cough, and nose inflammation. |
| 12        | Artesunate        | Oral, Intravenous, Intramuscular | Temporary and reversible anemia, slow heart rate, rash and fever. |
| 13        | Metloquine        | Oral               | Dizziness, muscle pain, nausea, fever, headache, vomiting, chills, diarrhea, skin rash, abdominal pain, fatigue, loss of appetite and ringing in the ear. |
| 14        | Doxycycline       | Oral               | Inflammation and difficulty in swallowing. Skin-Rash and Blood Urea Nitrogen. Hypersensitivity-Hives, swelling, shock and redness of the skin. |
| 15        | Erythromycin      | Oral               | Nausea, vomiting, abdominal pain, diarrhea and loss of appetite. |
| 16        | Azithromycin      | Oral               | Skin- Itching, severe allergic reactions and smell sensation. Respiratory- Increased cough, inflammation of pharynx, pleural effusion and rhiinitis. |
| 17        | Melatonin         | Oral               | Drowsiness, change in sleep pattern and headache |
| 18        | Desvenlafaxine    | Oral               | Nausea, dizziness, sleeplessness, excessive sweating, constipation, drowsiness, decreased appetite, anxiety and specific male sexual function disorders. |
| 19        | Imatinib Mesylate | Oral               | Heart-Compression of the heart, skin, redness of the skin and flushing. Eye and ENT- Eye edema, inflammation of conjunctiva, dry eye |
| 20        | Digoxin           | Oral               | Toxicity levels should be monitored in patients to avoid renal toxicity |

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