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Role of biochemicals and other factors affecting biotransformation and drug absorption

Abdul Mannan and Fatima Unnisa

Abstract
Biotransformation means chemical alteration of chemicals such as xenobiotics, nutrients, toxins and drugs in the body Biotransformation of xenobiotics can dominate toxicokinetics and the metabolites may reach higher concentrations in organisms than their parent compounds. The metabolism of a drug or toxin in a body is an example of a biotransformation Drugs can undergo one of four potential biotransformation: Active Drug to Inactive Metabolite, Active Drug to Active Metabolite, Inactive Drug to Active Metabolite, Active Drug to Toxic Metabolite Drug metabolism involves the enzymatic conversion of therapeutically important chemical species to a new molecule inside the human body. The process may result in pharmacologically active, inactive, or toxic metabolite. (Biodetoxification) presystemic metabolism occurs when an orally administered drug undergoes biotransformation into different metabolites by the biochemicals such as cyp450, hormones and the other factors such as genetic variation, nutrition exposure to environment and leads to decreases the oral bioavailability and absorption of the drugs. All the drugs given by oral route undergoes a first pass metabolism either in the gut or the liver, while some of the drugs gets destroyed before they reach into a systemic circulation. In this article we review how the various Strategies such as the SEDDS CDEPT prodrugs and other routes eventually helps in elimination of the first pass effect of orally administered drugs and enhancing the oral bioavailability of drugs.

Keywords: Biotransformation, presystemic metabolism, biochemicals, oral bioavailability

Introduction
Biotransformation has an important role in the determination of the pharmacokinetic parameters like oral bioavailability, drug-drug interaction, clearance and the half-life of the entity within the cell. It can play an important role in identifying factors underlying the problems, facilitate the optimal selection of compounds for further development, provide information on metabolites for possible improvement in drug design, and contribute to the identification of the appropriate animal species for subsequent toxicity testing
Drug metabolism may be defined as the biochemical modification of one chemical form to another, occurring usually through specialized enzymatic systems. It often involves the conversion of lipophilic chemical compounds (drugs) into highly polar derivatives that can be easily excreted from the body.
The primary site of drug metabolism is the smooth endoplasmic reticulum of the liver cell. This is because of the presence of large amounts of many varieties of enzyme the other sites include lungs, kidney, and placenta, epithelial cells of gastrointestinal tract, adrenals and skin However, these sites are involved to a limited extent in this process. The drug metabolism happening in the liver

Chemistry of drug metabolism
Drug metabolism is a chemical process, where enzymes play a crucial role in the conversion of one chemical species to another. The major family of enzymes associated with these metabolic reactions is the Cytochrome P450 family
The Cytochrome P450s play a very important role in drug metabolism as they help in the addition or unmasking of functional groups so that the Phase II enzymes act upon them. Cytochrome P450s are home- containing is enzymes present in the lipid belayed of the endoplasmic reticulum of the in hepatocytes

Drug Absorption
The oral bioavailability of numerous drugs is not only limited by poor solubility and/or poor membrane permeability as addressed by the biopharmaceutical classification system (BCS) but

also by a pre-systemic metabolism taking place to a high extent in the intestine. Enzymes responsible for metabolic reactions in the intestine include Cytochrome P450 (CYP450), transferases, peptidases and proteases
The goal of the BCS is to function as a tool for developing *in vitro* dissolution specifications for drug products that are predictive of their *in vivo* performance
According to the BCS, drug substances are classified as follows:

Class 1: High Solubility-High Permeability: Generally very well-absorbed compounds

Class 2: Low Solubility-High Permeability: Exhibit dissolution rate-limited absorption

Class 3: High Solubility-Low Permeability: Exhibit permeability rate-limited absorption

Class 4: Low Solubility-Low Permeability: Very poor oral bioavailability

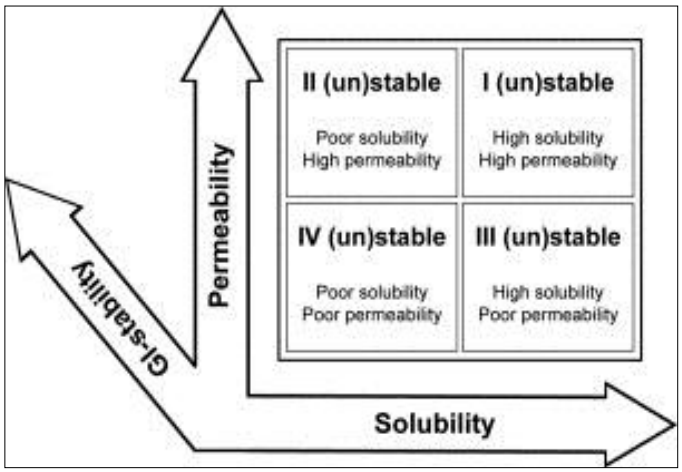


Fig 1: BCS classification of drugs based on solubility.

First Pass Effect
All the drugs given by oral route undergoes a degree of first pass metabolism either in the gut or the liver, while some of the drugs gets destroyed before they reach into a systemic circulation. It is the fraction of drug lost during the process of absorption which is generally related to the liver and gut wall. First pass metabolism may occur in the liver (for propranolol, lidocaine, chloromethiasole and GTN) or in the gut (for benzyl penicillin and insulin)
The liver metabolizes many drugs; sometimes to such an extent that only a small amount of active drug emerges from the liver to the rest of the circulatory system. This first pass through the liver thus greatly reduces the bioavailability of the drug. For drugs that undergo first-pass effects $AUC^{\infty}_{0,\ oral}$ is smaller than $AUC^{\infty}_{0,\ IV}$ and $F < 1$. Drugs such as propranolol, morphine, and nitroglycerin have F values less than 1 because these drugs undergo significant first-pass effects.

Materials and Methods
Agents of Biotransformation
Microsomal Biotransformation: when microbes are used Biotransformation is a process by which organic compounds are transformed from one form to another to reduce the persistence and toxicity of the chemical compounds. This process is aided by major range of microorganisms and their products such as bacteria, fungi and enzymes. Microbial biotransformation [1] or microbial biotechnology are gaining importance and extensively utilized to generate metabolites in bulk amounts with more specificity.
Microbial cells are ideal choice for biotransformation due to certain reasons like are:

I. Surface-volume ratio: Microbial biotransformation has high surface-volume ratio.

II. Growth Rate: Higher growth rate of microbial cells reduces the time of biomass transformation.

III. Metabolism Rate: Higher rate of the metabolism in microbes leads to efficient transformation of substrate.

IV. Sterility: It is easier to maintain sterile conditions

Enzymatic Biotransformation: Drug metabolizing enzymes (DME s) are a diverse group of proteins that are responsible for metabolizing a vast array of xenobiotics chemicals, including drugs, carcinogens, pesticides, pollutants, and food toxicants, as One of the major enzyme systems that determines the organism's capability of dealing with drugs and chemicals is represented by the Cytochrome P450 monooxygenases and endogenous compounds, such as steroids, prostaglandins, and bile acids.

Primary systems of first pass effect
Liver: All drug dose absorbed from the gastrointestinal tract is first delivered to the liver by the portal vein. A fraction of the drug can then be metabolized in the liver before it even reaches the systemic circulation. Therefore the oral bioavailability of the drug is reduced
Before reaching the systemic circulation such drugs must pass through the liver and are therefore exposed to enzymes in that organ which metabolize drugs and other foreign compounds. For certain drugs which are susceptible to hepatic degradation.

Example: lidocaine: A large first-pass effect is seen with oral dosing of lidocaine [2] and only 30% to 35% of an ingested dose is bioavailable. Ingestions have resulted in significant absorption, resulting in toxicity. The liver metabolizes virtually all of a lidocaine dose, with an elimination half-life in therapeutic concentrations of about 2 hours

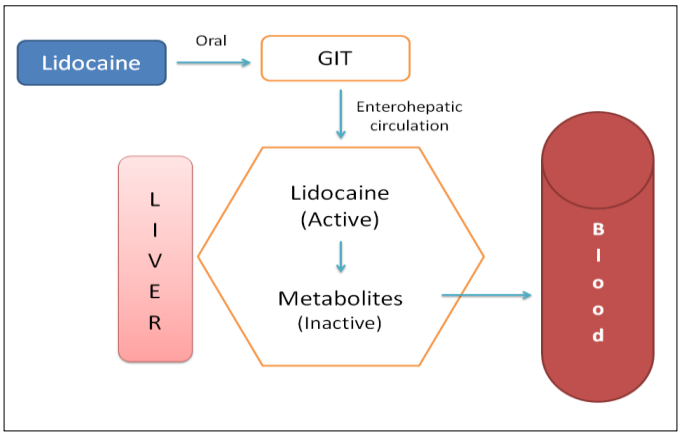


Fig 2: Lidocaine metabolism

Gut Wall: Gut bioavailability of orally administered drugs may be reduced due to presystemic elimination. The first-pass effect can occur in the gastrointestinal tract, the liver and lungs the gut wall can play an important role in the first-pass metabolism of certain drugs. Both phase I (Preconjugation) and phase II (conjugation) reactions activity of conjugation reactions in the gut may be close to that of the liver, and in some cases may exceed it. Significant drug--drug interactions have been described involving drugs undergoing sulphate conjugation.

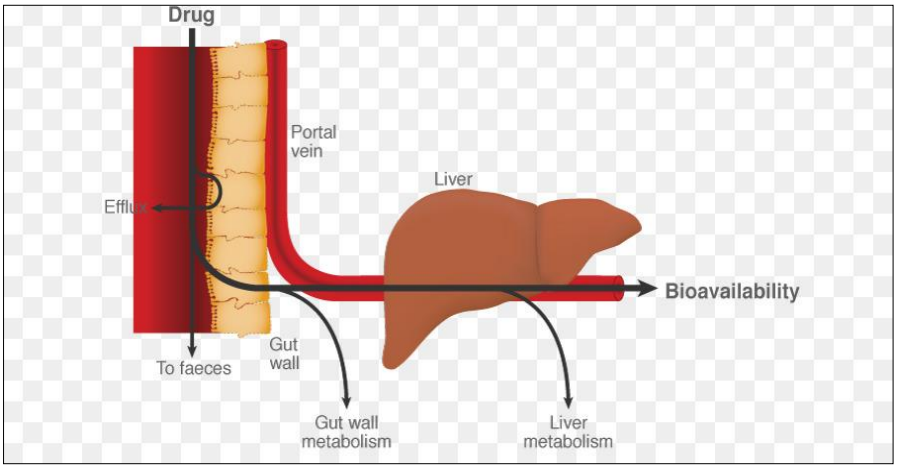


Fig 3: Bioavailability show in fig

Biochemicals involved in biotransformation

Enzymes: Enzymes are crucial to metabolism because they allow organisms to drive desirable reactions that require energy that will not occur by themselves, by coupling them to reactions that releases The chemical reactions of metabolism are organized into metabolic pathways, in which one chemical is transformed through a series of steps into another chemical, each step being facilitated by a specific enzyme energy.

Example: Cytochrome P450, Cytochrome b5, and NADPH-Cytochrome P450 reductase.

CYP450: Cytochrome P450 [3] represents a family of isozymes responsible for biotransformation of many drugs via oxidation. The enzymes are heam-containing membrane proteins, which are located in the smooth endoplasmic reticulum of several tissues. Although a majority of the isozymes are located in the liver, extra hepatic metabolism also occurs in the kidneys, skin, gastrointestinal tract, and lungs

- Drug metabolism via the Cytochrome P450 system has emerged as an important determinant in the occurrence of several drug-drug interactions
- Cytochrome P450 enzymes can be inhibited or induced by drugs, resulting in clinically significant drug-drug interactions that can cause unanticipated adverse reactions or therapeutic failures. Interactions with warfarin, antidepressants, antiepileptic drugs, and statins often involve the Cytochrome P450 enzymes
- Cytochrome P450 (CYP450) enzymes are essential for the production of cholesterol, steroids, prostacyclins, and thromboxane A_2. They also are necessary for the detoxification of foreign chemicals and the metabolism of drugs

Examples: Heytoin, sodium valproate

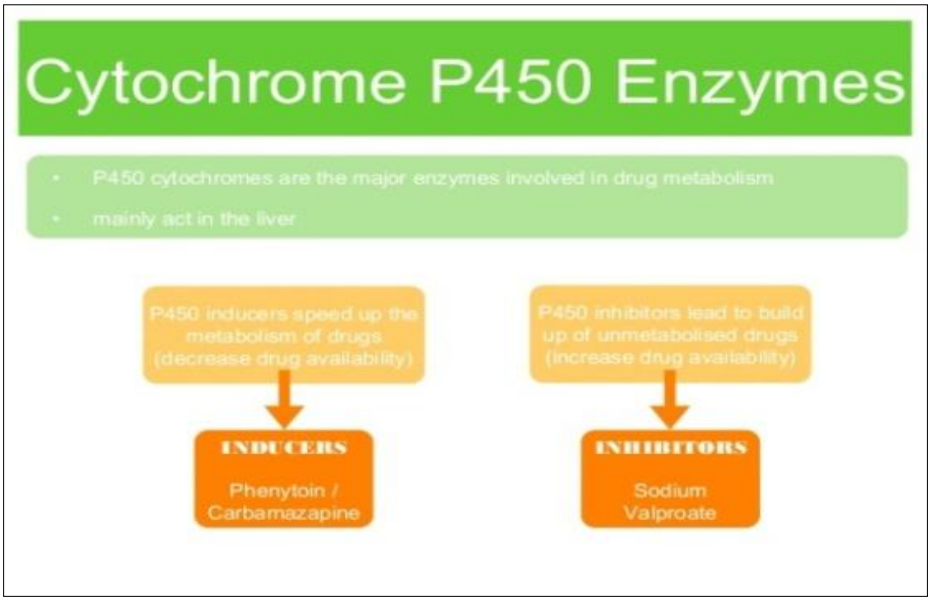


Fig 4: Phenytoin and Sodium Valproate Metabolism

CYP2D6: CYP2D6: major drug metabolizing enzyme responsible for the metabolism of 20%-25% of commonly prescribed drugs including beta blockers, antidepressants, opioids, anti-cancer, and antipsychotics; over 160 characterized polymorphisms.

- CYP2D6 [4] is a major therapeutic drug metabolizing enzyme accounting for the elimination of nearly 25% of all drugs
- If a drug is metabolized too quickly, it may decrease the drugs efficacy while if the drug is metabolized too slowly, toxicity may results.
- CYP 2D6 inhibitors showed no increase in the risk of breast cancer recurrence, but they lacked statistical power. It is better to avoidserious adverse consequences

Examples: Tamoxifen has a complex set of metabolic pathways, but CYP2D6 is primarily responsible for the production of its active metabolite. Growing evidence suggests that breast cancer patients with low CYP2D6 activity do not respond as well to tamoxifen therapy and are more likely to have cancer relapse

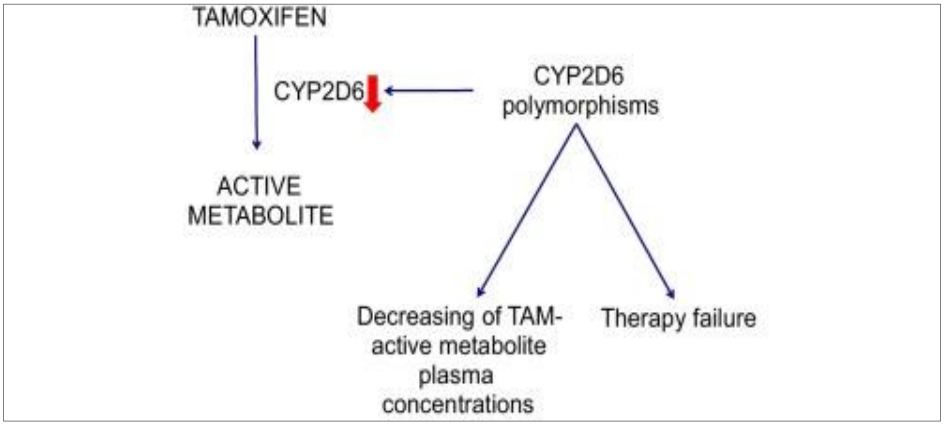


Fig 5: Tamoxifen metabolism

Microbiota Enzymes

Luminalenzymes: Luminal enzymes [5] likePeptidases: Insulin, calcitonin, teragastrin, thyrotropin releasing hormone, phenyl alanine glysine are a few of the peptidyl drugs. But the oral bioavailability of these drugs is generally poor, since they are poorly absorbed and easily degraded by proteolytic enzymes in the gastrointestinal tract.

Mucosal Enzymes: As in the liver, CYP3A is the most abundant CYP subfamily expressed in the small intestine, accounting for 82% of the total intestinal CYP content33. Using immunoblotting techniques, the levels of CYP3A4 have been estimated to be 160, 120, and 70 pmol/mg of microsomal protein in the duodenum, jejunum, and ileum, respectively34. These values are comparable to the CYP3A4 content in the liver (350 pmol/mg of microsomal protein)

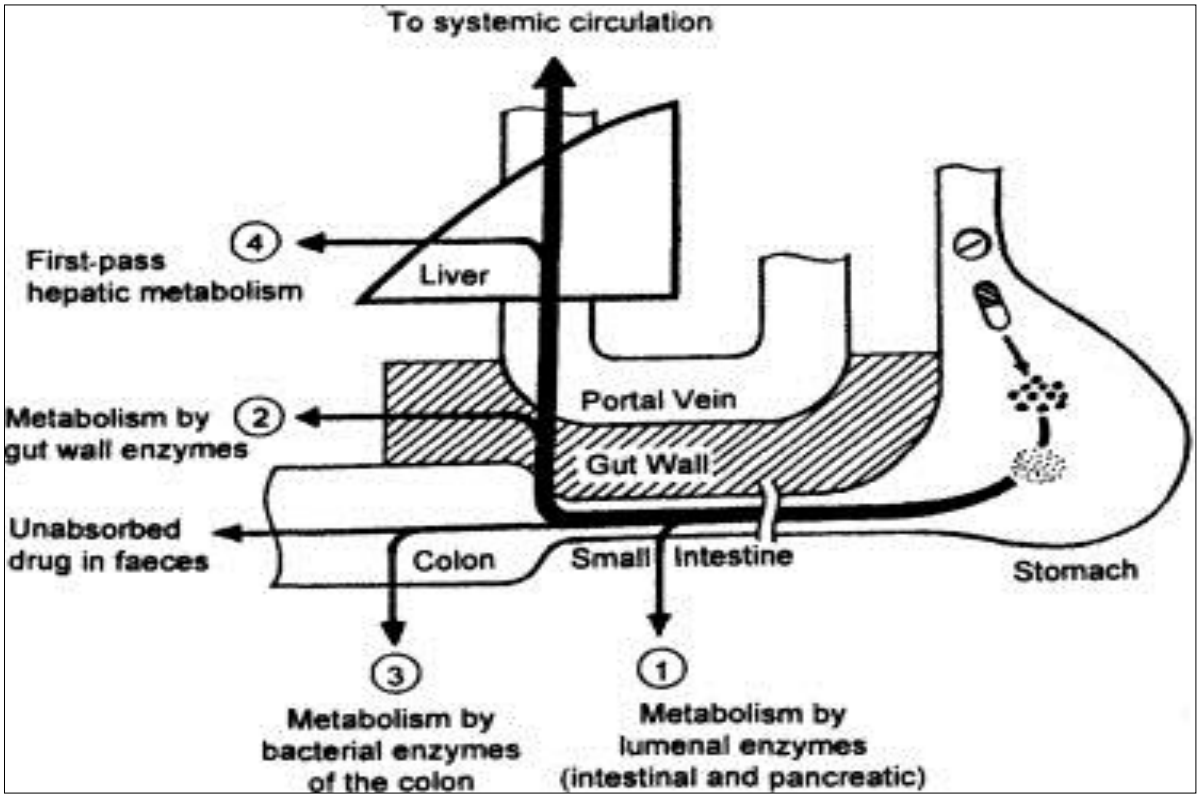


Fig 6: Microbiota metabolism

Loss of orally adminstered drug in git

Mechanism: The metabolism of the drug by microbes [6] may lower the stability of the drug, make it unsuitable for absorption, lower the bioavailability or may reduce the activity of the parent drug molecule. In addition, compounds of microbial origin can compete and interfere with absorption and metabolism of the drug molecule in the intestine. Microbial derived compounds or drug metabolites can also cause serious drug-drug interaction if they alter the pharmacokinetics and pharmacodynamics of the co-administered drugs.

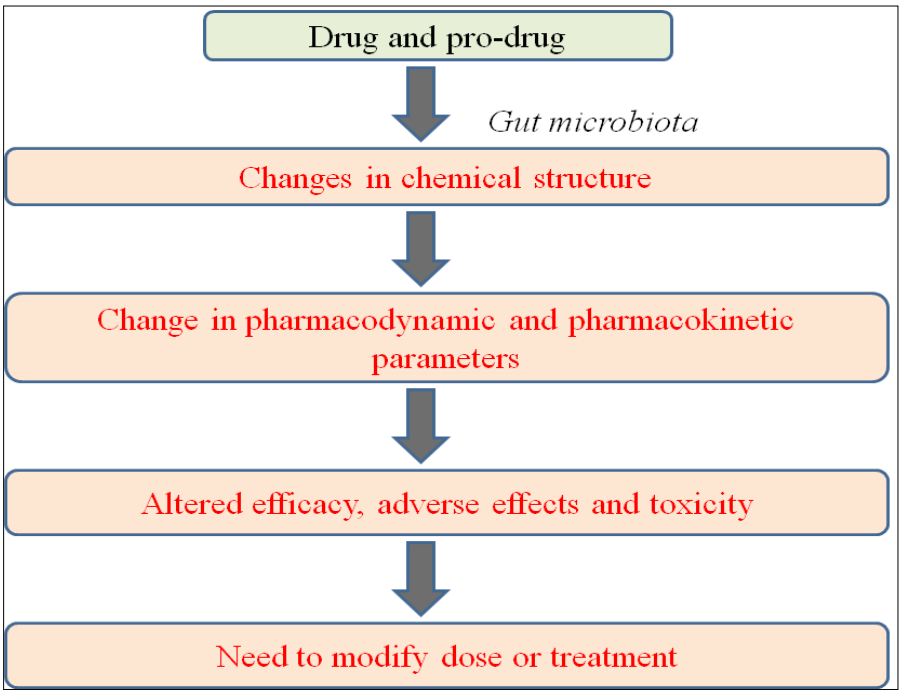


Fig 7: Sequence of GIT metabolism

Other Factors

Genetic Variability: Genetic polymorphisms have been identified for many drug-metabolizing enzymes, including the Cytochrome P450 (CYP450) enzymes. This gives rise to distinct population phenotypes of persons who have metabolism capabilities ranging from extremely poor to extremely fast.

Example: TheCYP2C9 [7] enzyme is involved in the metabolism of many common drugs such as glipizide (Glucotrol), tolbutamide; losartan, phenytoin. The phenotypes CYP2C9*2 and CYP2C9*3 are the two most common variations and are associated with reduced enzymatic activity. CYP2C9 is the principal enzyme responsible for the metabolism of S-warfarin. Persons who are CYP2C9 poor metabolizers have reduced S-warfarin clearance.

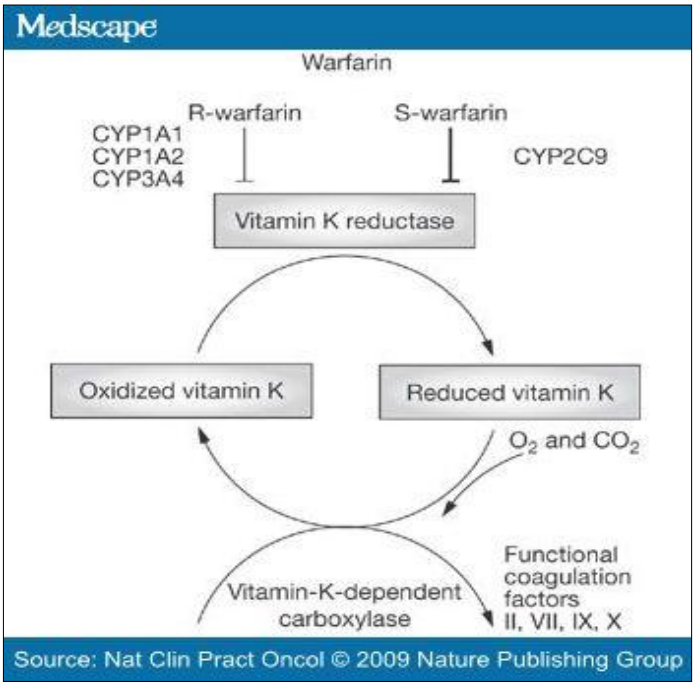


Fig 8: S-warfarin metabolism

Age: Age plays a very important role. Extreme age groups (very young and very old) behave almost the same. Drug metabolizing enzyme develops early but their capacity is low. Thus the rate of metabolism is infants is very low. Care should be taken in administering drugs in younger patients. True development of enzyme occurs in one to two months.

- Chloramphenicol (antimicrobial drug) when administered in infant, does not have great efficacy. Toxic effects in the form of grey baby syndrome might occur. The baby may be cyanosed, hypothermic, and flaccid and grey in color. Shock and even death might occur if toxic levels get accumulated.
- Diazepam (sedative hypnotic) may result in floppy baby syndrome in which flaccidity of the baby is seen

Smoking: Cigarette smoking induces the activity of human Cytochrome P450 (CYP) 1A2 and 2B6. These enzymes metabolize several clinically important drugs, including clozapine, olanzapine and methadone.

- Decreased CYP1A2 activity after smoking cessation increases the risk of adverse drug reactions, with reports of increased toxicity from clozapine and olanzapine.
- Cigarette smoking induces the metabolism of clozapine and olanzapineresulting in lower plasma concentrations. The daily consumption of 7–12 cigarettes is probably sufficient to cause the maximum induction of clozapine and olanzapine metabolism [8].

Alternative routes to avoid first pass effect

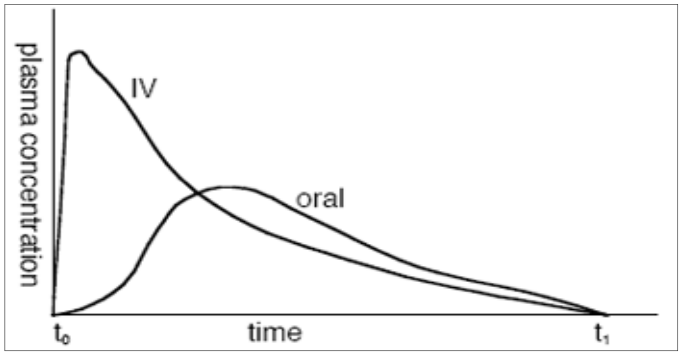
Parenteral adminstration

Parenteral administration refers to any routes of administration that do not involve drug absorption via the GI tract (*par* = around, *enteral* = gastrointestinal), including the IV, intramuscular (IM), subcutaneous (SC or SQ), and transdermal routes. Choosing a parenteral route over the oral route include drugs with low oral bioavailability

Intravenous Route: The intravenous route has a number of advantages. Drug is delivered immediately upon the completion of a response requirement and since delivery is into a vein, there is a rapid onset of drug effects.

Mechanism

Drugs delivered through the intravenous route [9] circulate directly to the brain, with onset occurring within 20 to 40 seconds. Infusions provide for controlled and constant plasma profiles and maximum infusion volumes. The fast dilution of injected solutions in the blood stream allows for a greater tolerance of the drug product components of blood components.



Graph showing bioavailability of oral vs. IV DRUGS

Enteral Routes

Sublingual: sublingual routes than by oral routes because the sublingual [10] route avoids first-pass metabolism by the liverthe drug avoids destruction by gastric juices or complexation with food

Mechanism

The drugs absorbed from the gut travel first to the liver via the portal vein. Drugs absorbed through the intestine may, thus, reach systemic circulation at a concentration significantly below the initial dose. drug to be delivered sublingually, the drug should dissolve rapidly, produce desired therapeutic effects with small amounts ofdrug, and be tasteless. Examples of commonly prescribed sublingual tablets include nitroglycerin, loratadine, mirtazapine, and rizatriptan

Glyceryl trinitrate (or nitroglycerin) undergoes extensive hepatic presystemic metabolism when given orally, and is therefore usually given by the sublingual route, by which it is well absorbed and rapidly taken up into the circulation

Nhalation Route: The inhaled route [11] of administration is widely accepted as being the optimal way of giving drugs such as corticosteroids and 32 agonists for the treatment of patients with airflow obstruction. It is possible with the inhaled route to deliver relatively small doses of drug to produce high local concentrations in the airway, and at the same time minimize absorption into the systemic circulation and avoids the first pass metabolism.

Mechanism: Systemic bioavailability of inhaled drugs may arise from absorption from the gastrointestinal tract or the lung. The systemic bioavailability from gut and lung vascular beds will, in turn, be determined by the respective first-pass metabolism prior to absorption. Furthermore, systemic absorption across the mucosal barrier will also depend on the relative lipid solubility of the drug being delivered.

Examples: beclamethasone; dipropionate

Strategies to avoid presytemic metabolism

Prodrugs: Prodrugs are pharmacologically inactive medications that have to be converted to an active form through chemical reactions, such as hydrolysis or phosphorylation

- The idea of prodrugs in cancer therapy is to reduce unintended side effects by designing compounds that interact with specific targets. The majority of antineoplastic[12] drugs are metabolized by CYPs
- Prodrugs are irreversible derivatives of drug molecules that undergo an enzymatic and/or chemical transformation *in vivo* to release the active parent drug, which can then exert the desired pharmacological effect

Steps in Prodrugs Design

- ¾ Identification of drug delivery problem ¾ Identification of desired physicochemical properties
- ¾ Selection of transport moiety which will giveprodrugs desired transport properties be readily cleaved in the desired biological compartment

Applications of prodrugs

Prodrugs to improve Stability

Many drugs are unstable and may either breakdown on prolonged storage or are degraded rapidly on administration.

Several drugs may decompose in GIT when used orally. Although enteric coatings may be used, it is also possible to utilize prodrugs design

- Overcome this problem. An antineoplatic drug Azacytidine hydrolyses readily in acidic pH, but the bisulfateprodrugs of it is more stable.

Prodrugs to improve absorption

- Ampicillin a wide spectrum antibiotic is readily absorbed orally as the inactive prodrugs, Pivampicillin, Bacampicillin and Talampicillin which are then converted by enzymatic hydrolysis to Ampicillin.

Prodrugs to Improve Membrane Transport

- Dopamine used for the treatment of Parkinsonison's disease can be improved by administering its prodrugs 3, 4-dihydroxy phenyl alanine (Levodopa). Prodrugs for Prolonged duration of action.
- Nordazepam, a sedative drug loses activity quickly due to metabolism and excretion. A prodrugs Diazepam improves the retention characteristics, due to the presence of N-methyl group

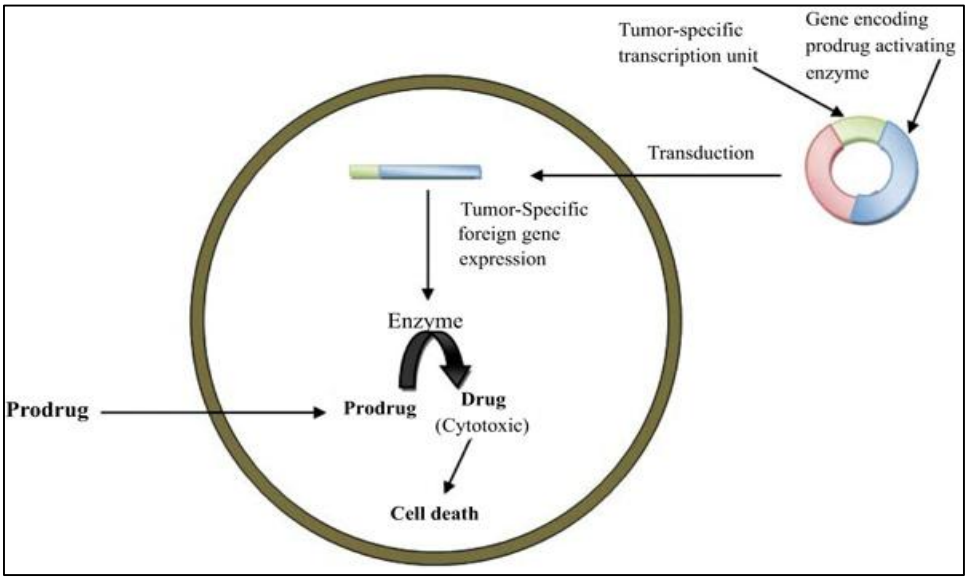


Fig 9: Prodrugs in cancer treatment

Co-adminstration with another drugs: If a drug has a high first-pass hepatic metabolism, one can expect a marked increase in its plasma concentration if it is co-administered with another drug which inhibits its metabolism.

Example

1. When administered alone, lopinavir has insufficient bioavailability (25%) however, like several HIV protease inhibitors, its blood levels are greatly increased by low doses of ritonavir, a potent inhibitor of Cytochrome P450.
2. The absolute oral bioavailability of docetaxel is 8% +/- 6% which was increased to 90% +/- 44% when co administered with cyclosporine

Lymphatic Circulation: Recent advancement to improve bioavailability is the utilization of lymphatic circulation upon the oral delivery as it circumvents the hepatic first pass effect. The drugs with higher lipophilicity, poor solubility and poor oral bioavailability serve as the potential candidate for lymphatic targeting.

Mechanism: The drugs could be effectively transported through the intestinal lymphatics via thoracic lymph duct to the systemic circulation, joining at the junction of the jugular and the left subclavian vein. This avoids presystemic hepatic metabolism and thus enhances the concentration of orally administered drugs in the systemic circulation.

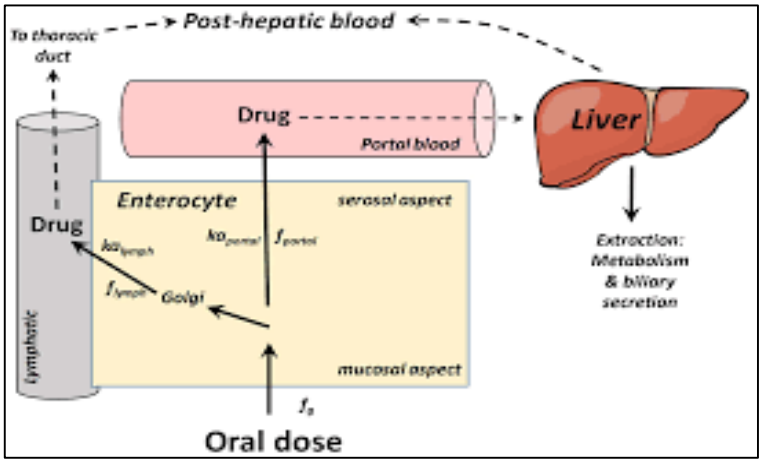


Fig 10: Lymphatic circulation in elimination of first pass effect

Nano-Phytomedicines: One of the big impediments of oral administration of phytomedicine is their lack of stability in the gastrointestinal tract. The surface-modified micro or nano phytomedicine can be used as an efficient strategy to circumvent this problem. The poly (lactic-co-glycolic) acid (PLGA) microspheres with chitosan and PEGylated PLGA-based nano particles were used to modify the properties of formulation.

Example

Quercetin [13] has exhibited a wide range of beneficial biological activities including antioxidant, radical scavenging, anti-inflammatory, anti-atherosclerotic, anti-tumors and anti-viral effects.

Quercetin has been shown to increase bioavailability, blood levels and efficacy of a number of drugs including diltiazem, digoxin, and diltiazem is metabolized by CYP3A4 both in the liver and small intestine. The absorption of diltiazem in the intestinal mucosa was inhibited by P-glycoprotein efflux pump.

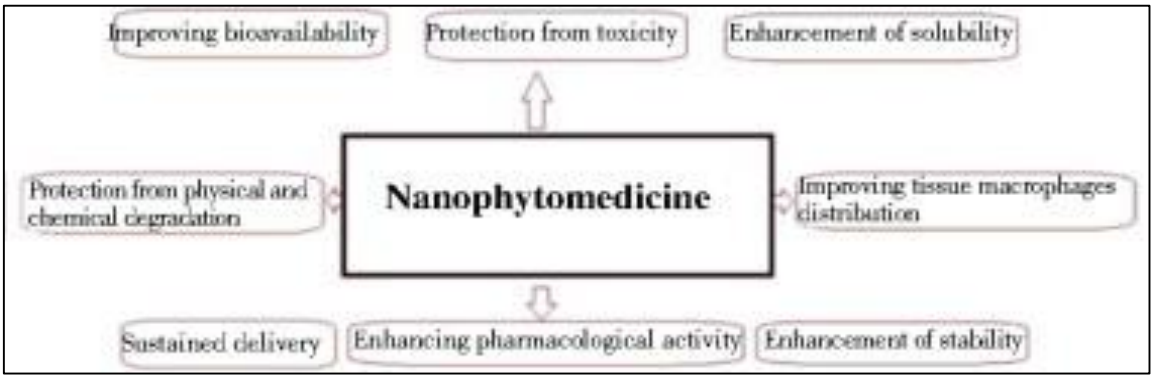


Fig 11: application of nano phytomedicine

Self emulsifying drug delivery systems (Sedds)

The efficiency of the oral absorption of a drug compound from the self-emulsifying formulation depends on many formulation-related parameters, such as surfactant concentration, surfactant Hydrophilic Lipophilic Balance (HLB), oil/surfactant ratio and droplet size, all of which determine the self-emulsification ability.

- SEDDS [14] improve the oral bioavailability of Poorly soluble drugs by enhancing the solubility and maintaining the drug in a dissolved state, in small droplets of oil, during its transit through the gastrointestinal tract. The improvement of the oral bioavailability has been attributed to dissolution increase of drug, larger surface area provided by the fine emulsion droplets, improved diffusion across the unstirred aqueous layer, and increased mucosal permeability due to high content of surfactants and also by the long chain oil that promotes lipoprotein synthesis with subsequent lymphatic absorption

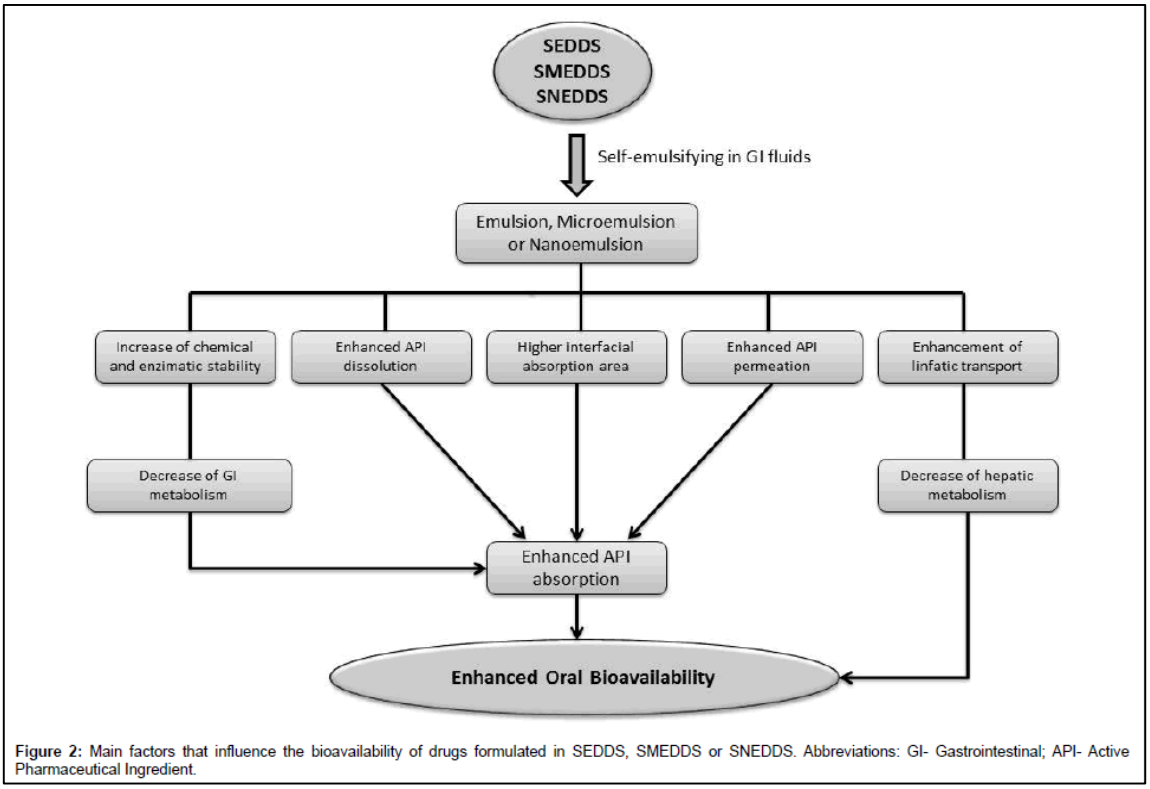


Fig 12: SEDDS enhancing oral bioavailability

Anti metabolites: These are the chemical substances that interact with the biological process that is normal of regular metabolites that are biochemicals. They are present in mostly all happenings and that is because of the functional similarity with the substrates that are physiological and hence known as competitive inhibitors of enzymes. They consist of cytotoxic anticancerous drugs through with suppressing DNA and RNA chemical process and antifolates examples are hydroxyl urea and pyrimidine and purine analog. The main use of it is for division of cells

Conclusion: Biotransformation has an important role in the determination of the pharmacokinetic parameters like oral bioavailability, drug-drug interaction, clearance and the half-life of the entity within the cell. It can play an important role in identifying factors underlying the problems; facilitate the optimal selection of compounds for further development All the drugs given by oral route undergoes a first pass metabolism either in the gut or the liver, while some of the drugs gets destroyed before they reach into a systemic circulation. Enzymes are crucial to metabolism because they allow organisms to drive desirable reactions. One of the major enzyme systems that determine the organism's capability of dealing with drugs and chemicals is represented by the Cytochrome family, endogenous compounds, such as steroids, prostaglandins, and bile acids and other factors such as the genetic, dose level. First pass metabolism can be avoided by the parenteral and enteral routes and the use of the nanotechnology and different approaches such as prodrugs, CDEPT therapy, p-glycoprotein inhibitors, SEDDS by use of these strategies as well as the different routes the bioavailability of oral Drugs can be increased and presystemic metabolism can be reduced& ultimately increases the bioavailability.

Acknowledgement
By the grace and generous blessings of God Almighty, I attribute the successful completion of seminar work on a research study on 'Role of Biochemicals and Other Factors Affecting Biotransformation and Drug Absorption.
I respect and a heartfelt gratitude to my guide ABDUL MANNAN Mpahrm, Ph.D (Dept. of pharmaceutics) for providing a continuous assistance, support and guidance in completing my seminar topic by providing all the necessary information for developing a good system. I consider this opportunity to express my deep sense of gratitude and repect to my parents who always believe in my thoughts, and supported me in completion of seminar work. I am grateful to Prof. Dr. ABDUL AZEEZ Mpharm, PGDMIR, PCCRM, Ph.D. honorable principal of DECCAN SCHOOL PHARMACY for providing the facilities to do this work for his constant support and encouragement.

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