CHAPTER 2

REVIEW OF LITERATURE
Development of increasingly accurate and specific analytical techniques has made it possible for pharmacokinetic investigators to follow up the fate of drugs in the system and able to discover the factors affecting their kinetics and metabolism. This has brought about the relationship between physico-chemical properties of drug and its physiological disposition by the organisms, as well as its pharmacological response.

A drug (*GK: pharmakon) may be defined as a substance which modifies some function of a biological system. Every drug must be present in appropriate concentration at its site of action to produce its characteristic effect. In most cases, the time course of a drug's action simply reflects the time course of the rise and fall of its concentration at the target tissue. The amount of drug administered and the concentration attained also depend upon the extent and rate of its absorption (which is the bioavailability of a drug), distribution, binding or localization in tissues, biotransformation and excretion. Thus, this relationship between administration of a drug, the time course of its distribution and the magnitude of the concentration attained in different regions of the body forms part of drug pharmacokinetics.

*GK • Greek
PHARMACOKINETIC MECHANISMS OF DRUG INTERACTION

The behaviour of any drug within the body is governed by the following basic pharmacokinetic steps:

- **ABSORPTION** usually from the gastrointestinal tract.
- **DISTRIBUTION** mainly via the bloodstream.
- **METABOLISM** usually in liver but in some cases other organs.
- **EXCRETION** usually by kidneys but sometimes via biliary tract or other routes.

While the drug undergoes the above processes, some fraction of it reaches the receptor sites in the target organ. Now, the pharmacokinetic effect often results from conformation of drug molecule to macromolecular receptor sites, with the intensity of response proportional to drug concentration (Robinson, 1975). The pharmacokinetic processes governing drug interaction are shown in figure 1.

**Drug Transfer Across Membranes:**

The absorption, distribution, biotransformation, and excretion of a drug involves its passage across cell membranes. It is therefore essential to consider the mechanisms by which drug crosses membranes and the physiochemical properties of molecules and membranes that influence this transfer.
FIGURE 1

PHARMACOKINETIC PROCESS GOVERNING DRUG INTERACTIONS

[Diagram showing the pharmacokinetic processes involving drug absorption, site of drug binding, site of drug transformation, free drug in extracellular fluids, excretion, and specific sites of drug action.]
Important characteristics of a drug are its molecular size and shape, solubility at the site of its absorption, degree of ionization and relative lipid solubility of its ionic and nonionic forms (Benet et al., 1996). When a drug permeates a cell, it must obviously transverse the cellular plasma membranes. Other barriers to drug movement may be a single layer of cells (intestinal epithelium) or several layers of cells (skin). Despite these structural differences, the diffusion and transport of drugs across these various boundaries have many common characteristics, since drugs in general pass through cells rather than between them. The plasma membrane thus represents the common barrier

**Cell Membranes:**

The plasma membrane consists of a bilayer of amphiphatic lipids, with their hydrocarbon chains oriented inward to form a continuous hydrophobic phase and their hydrophilic heads oriented outward. Individual lipid molecules in the bilayer can move laterally, endowing the membrane with fluidity, flexibility, high electrical resistance, and relative impermeability to highly polar molecules. Membrane proteins embedded in the bilayer serve as receptors to elicit electrical or chemical signaling pathways and provide selective targets for drug actions. The membrane in addition contains pores that permit the passage of small water soluble molecules such as urea, alcohol, electrolytes, and water itself. Finally, the membrane contains channels through which substances can move after they have combined with a specific carrier.
1. **Passive Transfer:** Transfer or transport is said to be passive when the membrane need not generate energy to carry out the process
   
a. **Filtration,** as across the capillary wall, is not an important factor in limiting drug distribution.

b. **Simple diffusion:** If the rate of transfer across a membrane is proportionate to the concentration gradient, one infers that process is one of simple diffusion. A water-soluble drug of low molecular weight such as alcohol may diffuse through the aqueous pores of the membrane. Water soluble drugs of greater molecular weight either do not cross the membrane or are transported by an active process. Transfer by simple diffusion is then an important process for the distribution of lipid soluble drugs. Many drugs like ether have a lipid solubility or oil-water partition coefficient that favours their transfer regardless of the pH of the medium. However, many drugs are either weak acids or weak bases and the fraction of molecules present as the lipid soluble un-ionized form to which the cell is preferentially permeable varies depending on the drugs pKa and the pH of the system.

c. **Carrier - facilitated diffusion:** In this process, the substance to be transported combines with a carrier molecule at one membrane surface and dissociates from it at the other surface. The carrier, a protein, is specific for the transported ion and larger water soluble molecule that would not otherwise traverse the membrane. The process is still one of the diffusion and a substance cannot be moved against a concentration gradient. Exchange diffusion is a
common variation of carrier-facilitated diffusion in which the carrier combines with one substance at the outer surface to transport it inward and, having dissociated from the first substance, picks up a generally similar molecule at the inner surface and carries it to the outside.

2. **Active Transport:**

   Active transport is carrier facilitated but is able to move the substance against a chemical or electrical gradient. Performance of such work or active transport requires energy which is known, in the common examples, to be generated by the action of a variety of channels or pumps of this type. Each transports a specific chemical type - for example, sodium, organic acids - and related compounds compete for the capacity of the mechanism. Interference with the supply of energy inhibits the system noncompetitively.

**Weak Electrolytes and Influence of pH:**

Most drugs are weak acids or bases that are present in solution as both the unionized and ionized species. The unionized molecules are usually lipid soluble and can diffuse across the cell membrane. In contrast, the ionized molecules are usually unable to penetrate the lipid membrane because of their low lipid solubility.

Therefore, the transmembrane distribution of a weak electrolyte usually is determined by its pKa and the pH gradient across the membrane.
Absorption describes the rate at which a drug leaves its site of administration and the extent to which this occurs (Rang and Dale, 1987). Bioavailability is a term used to indicate the extent to which a drug reaches its site of action or a biological fluid from which the drug has access to its site of action.

**Absorption from the Gastrointestinal Tract:**

This applies to the absorption after oral administration. Small, neutral water-soluble molecules, like alcohol and water itself, are absorbed from the stomach, although the amount absorbed is limited by its rapid emptying rate. The absorption of other drugs will vary depending on the pH, which is a function of the secretory state of the stomach. Aspirin, the most commonly used drug, is a weak acid and that exists almost entirely in the non-ionized lipid soluble form at the pH of the stomach and is well absorbed from the stomach.
Factors Affecting Drug Absorption:

The various factors known to affect drug absorption are as below

a. **Disintegration and Dissolution.** The formulation of a drug product has dramatic effect on its stability and hence absorption. The major cause of difference in absorption of drug from various formulation is dissolution. Drugs administered in solid form as tablets or capsules must first disaggregate so that dissolution may occur more readily

The dissolution rate of a drug in turn is influenced by two important factors, viz,

(i) **particle size:** The greater the surface area of a drug in contact with gastrointestinal fluids the more rapid is the dissolution rate. Hence, with decrease in particles size there is an increase in the dissolution rate (Chasseaud and Taylor, 1974)

(ii) **Formulation Ingredients:** Some of the agents added to formulation which influence the absorption of drugs are fillers, binders, disintegration aids, lubricants, surfactants and suspending agents. These affect absorption either by increasing or decreasing the drug dissolution time (Chasseaud and Taylor, 1974)

b. **Gastric Emptying and Intestinal Transit**

Gastric emptying rate influences the rate of delivery of drug from the stomach to the small intestinal where most drugs are absorbed. In general, an increase in the rate of gastric emptying or in gastrointestinal motility increases
the rate of drug absorption and vice versa. However, for some drugs, such as those which are poorly soluble, erratically absorbed or metabolised in the gut the amount of the drug may increase when gastric emptying or intestinal motility is slowed.

c. Surface Area of Gastrointestinal Tract and Blood Flow. They are important determinants of the rapidity of drug absorption. The total absorptive area of small intestine, composed largely of microvilli has been calculated to be about 200 sq.mtrs. and an estimated 1 litre of blood passes through the intestinal capillaries each minute. The corresponding estimates for the stomach are only one square meter and 50 milliliters/minute respectively. Thus the drugs are rapidly absorbed from large surface areas such as the intestinal mucosa where there is also increased circulation.

DRUG DISTRIBUTION

Following absorption, drugs are rapidly distributed around the body by circulation. Drugs readily leave the vascular compartment to enter the intestinal fluid. Lipid soluble drugs pass across the entire membranous surface, and even large pores of the capillary membrane with the aid of hydrostatic pressure. Thus, distribution of a drug to a particular region of the body will be determined by the blood flow rather than by the rate of transfer across the capillary membrane.

Heart, liver, kidney, brain and other well-perfused organs receive most of the drug during the first few minutes after the absorption. Delivery of drug to muscle, most viscera skin, and fat is slower, and these tissues may require several minutes to several hours before steady state is achieved.
Drug that has accumulated in a given tissue may serve as a reservoir that prolongs drug action in that same tissue or at a distant site reached through the circulation.

**Plasma Proteins:**

Many drugs are bound to plasma proteins, mostly to plasma albumin for acidic drugs; binding to other plasma proteins generally occurs to a much smaller extent. The binding is usually reversible; covalent binding of reactive drug such as alkylating agents occurs occasionally.

The fraction of total drug in plasma that is bound is determined by the drug concentration, its affinity for the binding sites, and the number of binding sites.

Binding of a drug to plasma proteins limits its concentration in tissues and at its locus of action, since only unbound drug is in equilibrium across membranes. Binding also limits glomerular filtration of the drug, since this process does not immediately change the concentration of free drug in the plasma (water is also filtered). However, plasma protein binding does not generally limit renal tubular secretion or biotransformation, since these processes lower the free drug concentration, and this is rapidly followed by dissolution of the drug protein complex.

**Factors Affecting Drug Distribution:**

a. **Blood Flow**: The rate at which a drug reaches to different organs and tissues will depend on the blood flow to these regions.
b. **Lipid Solubility**  
Lipid solubility will affect the ability to bind to plasma proteins and to cross lipid membrane barriers. Very high lipid solubility can result in a drug initially partitioning preferentially into highly vascular lipid rich areas. Subsequently, these drugs slowly redistribute into body fat where they may remain for long periods of time.

c. **Effect of pH**: Effects of pH on the partitioning or "trapping" of drugs will not be as dramatic as those seen between stomach and plasma since the pH differences are not as great. Acidic drugs tend to accumulate where pH is higher while basic do the reverse.

d. **Capillary Permeability**: The ability of a drug to reach various tissues will depend on the permeability of the capillaries at the site in question. E.g., the capillaries in the liver are extremely permeable, while those at the blood brain barrier are at the other extreme. Hence, molecular size is the major factor affecting the permeability of water soluble drugs across capillaries.

As shown in the Figure 2, drug transfer is influenced by the size of the molecule, lipid solubility, presence of an active transport system and protein binding. With the exception of protein bound drugs, almost all commonly used drugs are able to cross readily the walls of capillary membranes (Gerald et al, 1996)

**BIO TRANSFORMATION OF DRUGS**

The lipophilic characteristics of drugs that promote their passage through biological membranes and subsequent access to their site of action hinder their elimination from the body. Renal excretion of unchanged drug plays only a
FIGURE 2
FACTORS INFLUENCING DRUG TRANSFER

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<tr>
<th>BARRIER</th>
<th>Capillary Membrane</th>
<th>Cell Membrane</th>
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<tbody>
<tr>
<td>FLUID COMPARTMENTS</td>
<td>Plasma</td>
<td>Intestinal Fluid</td>
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<td>DRUG CHARACTERISTICS</td>
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<td>Intracellular Fluid</td>
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<td>SMALL MOLECULE</td>
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<td>MECHANISM RESPONSIBLE FOR PASSAGE</td>
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<td>LIPID SOLUBLE</td>
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<td>LIPID INSOLUBLE, LARGE MOLECULE</td>
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<td>PROTEIN BOUND</td>
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modest role in the overall elimination of most therapeutic agents, since lipophilic compounds filtered through the glomerulus are largely reabsorbed through the tubular membranes. The biotransformation of drugs and other xenobiotics into more hydrophilic metabolites is therefore essential for the termination of their biological activity and the elimination of these compounds from the body. However, in some cases, metabolites with potent biological activity or toxic properties are generated. Many of the metabolic transformation reactions leading to inactive metabolites of drugs biologically active metabolites of endogenous compounds. The following discussion focuses on the biotransformation of drugs.

**Phase I and Phase II Biotransformation:**

Drug biotransformation reactions are classified as either Phase I functionalization reactions or Phase II biosynthetic reactions. Phase I reactions introduce or expose a functional group on the parent compound. Phase I reactions generally result in the loss of pharmacological activity. Prodrugs are pharmacologically inactive compounds designed to maximize the amount of the active drug that reaches its site of action. Inactive prodrugs are converted rapidly to biologically active metabolites, often by the hydrolysis of an ester or amide linkage. If not rapidly excreted into the urine, the products of Phase I reactions can then react with endogenous compounds to form a highly water soluble conjugate.

Phase II conjugation reactions lead to the formation of a covalent linkage between a functional group or the parent compound with glucuronic acid, sulfate,
glutathione, amino acids or acetate. These highly polar conjugates are generally inactive and excreted rapidly in the urine and faeces.

**Site of Biotransformation:**

The metabolic conversion of drugs generally is enzymatic in nature. The enzyme systems involved in the biotransformation of drugs are localized in the liver, although every tissue has some metabolic activity. Other organs with significant metabolic capacity include the kidneys, gastrointestinal tract, skin and lungs. Following non-parenteral administration of a drug, a significant portion of the dose may be metabolically inactivated in either the liver or intestine before it reaches the systemic circulation. This "**first pass metabolism**" significantly limits the oral availability of highly metabolized drugs. Within a given cell, most drug metabolizing activity is found in endoplasmic reticulum and the cytosol, although drug biotransformation also can occur in the mitochondria, nuclear envelope and plasma membrane. Upon homogenization and differential centrifugation of tissues, the endoplasmic reticulum breaks up and fragments of the membrane form microvesicles, referred to as microsomes. The drug-metabolizing enzymes in the endoplasmic reticulum therefore often are classified as microsomal enzymes. The enzyme systems involved in phase I reactions are located primarily in the endoplasmic reticulum, while the phase II conjugation enzyme systems are mainly cytosolic. Often drugs biotransformed through phase I reaction in the endoplasmic reticulum are conjugated in the cytosolic fraction of the same cell.
Cytochrome P450 Mono-oxygenase System:

The cytochrome P450 enzyme family is the major catalyst of drug biotransformation reactions. Since its origin more than 3.5 billion years ago, the cytochrome P450 gene family has diversified to accommodate the metabolism of a growing number of environmental chemicals, food toxins and drugs. The resulting superfamily of enzymes catalyzes a wide variety of oxidative and reductive reactions and has activity towards a chemically diverse group of substrates. Cytochrome P450 enzymes are heme-containing membrane proteins localized in the smooth endoplasmic reticulum of numerous tissues. These heme-proteins are in close association with a second membrane protein, NADPH-Cytochrome P450 reductase, in a ratio of about ten cytochrome P450 molecules per one reductase. The flavoprotein reductase contains equimolecular amounts of flavin mononucleotide and flavin adenine dinucleotide and is the source of one or both of the electrons required for the oxidation reaction. The interaction between the cytochrome P450 and reductase proteins is facilitated by the lipid bilayer in which they are embedded.

Oxidative Reactions:

They are catalyzed by the microsomal monoxygenase system which require cytochrome P450 hemoprotein, NADPH-Cytochrome P450 reductase, NADPH, and molecular oxygen.

As a result of the relatively low substrate specificity among the cytochrome P450 proteins, two or more individual enzymes often catalyze a given biotransformation reaction. CYP3A4 is involved in the biotransformation of a
majority of all drugs and is expressed at significant levels extrahepatically. It is now recognized that extensive metabolism by CYP3A4 in the gastrointestinal tract is a significant factor contributing to the poor bioavailability of many drugs.

**Conjugation Reactions:**

The hallmark of phase II conjugation reactions is their requirement for energy. Glucuronidation is quantitatively the most important conjugation reaction, uridine diphosphate glucuronosyltransferases (UDP) catalyze the transfer of an activated glucuronic acid.

**TERMINATION OF DRUG ACTION**

The processes that terminate drug action determine the duration of effect of a drug.

**Elimination by the Kidneys:**

Drugs and their metabolites or conjugates appear in the urine as a result of two processes:

1. They appear in the glomerular filtrate.
2. An additional fraction is then secreted or reabsorbed through the renal tubular cell. The reabsorptive process is also an example of passive diffusion. The more lipid-soluble the material, the greater the degree of reabsorption. The more the water soluble the material, the greater the fraction that remains in the urine. The excretion of the unmetabolized, lipid soluble drug can be altered by
acidification or alkalinization of the urine. For example, intoxication with salicylates or barbiturates (both weak acids) is treated by maintaining a high volume of alkaline urine. The weak acids then exist largely in the salt form or the ionized water soluble form, and reabsorption is greatly decreased.

The renal tubulae is also able to actively transport or secrete organic anions and cations through separate channels.

**FACTORS AFFECTING DRUG METABOLISM**

The most important variables relating to drug metabolism that are of clinical significance have been summarized below.

1. **Individual Differences**

   Individual differences in metabolic rate depend on the nature of the drug itself. Thus, within the same population, steady state plasma levels may reflect a 30-fold variation in metabolism of one drug and only a 2-fold variation in the metabolism of another. Genetic factors that influence enzyme levels account for some of these differences. Environmental factors also contribute to individual variations in drug metabolism. Cigarette smokers metabolize some drugs more rapidly than non-smokers because of enzyme induction. Industrial workers exposed to some pesticides metabolize certain drugs more rapidly than non-exposed individuals.

2. **Age and Sex Differences**

   Increased susceptibility to the pharmacologic or toxic activity of drugs has been reported in very young and old patients as compared to young adults.
Although this may reflect differences in absorption, distribution, and elimination, differences in drug metabolism cannot be ruled out. Drugs are metabolized at reduced rates during the pre-pubertal period and senescence. A lower metabolism could be due to reduced activity of metabolic enzymes or reduced availability of essential endogenous factors.

Sex dependent variations in drug metabolism have been well documented in rats but not in other rodents. Young adult male rats metabolize drugs much faster than mature female rats or pre-pubertal male rats. These differences in drug metabolism have been clearly associated with endogenic hormones.

**FOOD AND DRUG ABSORPTION**

Orally administered drugs are absorbed from the gastrointestinal tract into the systemic circulation to exert their pharmacologic effect. When drugs and nutrients are taken concurrently the biological availability of either or each one may be affected by the other. The type and size of a meal may have marked effect on nature of drug nutrient interactions. The possible physiological interactions due to presence of food may affect drug absorption have been summarized below:

1. **Stomach Emptying Rate**

   The predominant effect of food ingestion is that of inhibition of stomach emptying rate due to feed back mechanisms from osmoreceptors, acid receptors, and fat and fatty acid receptors situated in the proximal small intestine (Hunt and Knox, 1968). This occurs particularly with high fat meals but also with high
protein and high carbohydrate meals (Bachrach, 1959). The prolonged residence of drug in the acidic environment of stomach is likely to delay dissolution of basic molecules. Although some acidic and neutral compounds are absorbed directly from stomach, the optimal site for absorption is in the small intestine and delayed stomach emptying is likely to cause a delay in drug absorption. Increased residence time in the stomach may also cause a reduction in overall absorption efficiency of drugs which are either acid labile or are sensitive to action of gastric enzymes (Toothaker and Welling, 1980).

Large fluid volumes on the other hand, tend to accelerate stomach emptying and therefore reduce the time interval between drug ingestion and presentation of compound to the optimal absorption surface of proximal small intestine. Despite the possible reduction in drug concentration gradient between the mucosal and serosal surfaces of gastrointestinal membrane due to dilution, a number of studies have shown that large intestine volume tend to increase drug absorption efficiency (Ferguson, 1962, Borowitz et al, 1971). Apart from the advantage of promoting dissolution of poorly soluble drugs, large fluid volume may also increase drug absorption due to mucosal to serosal solvent flux.

2. Intestinal Motility

Food stimulates intestinal motility and this may increase drug absorption rates due to increased dissolution and greater accessibility of drug molecules to the intestinal epithelium. Absorption may be impaired, however, owing to reduced intestinal residence time (Welling and Tse, 1983).
3. Acid Secretion

Ingestion of food increases the gastric secretion of hydrochloric acid which may increase the degradation and dissolution of basic drug and decrease that of acidic drugs. Conversely, it may increase the absorption of acidic drugs and decrease the absorption of basic drugs because of changes in percentage of ionized compound. However, much of the influence of altered gastric pH due to increased acid secretion is probably masked by the buffering effect of food components (Toothaker and Welling, 1980).

4. Bile Secretion

Ingestion of food increases secretion of bile which may accelerate the dissolution of poorly soluble compounds. However, drug absorption may be impeded by increased bile flow due to bile salt drug complexation (Toothaker and Welling, 1980).

5. Enzyme Secretion

Ingestion of food increases the secretion of many gastric enzymes which may affect drug dissolution and degradation (Toothaker and Welling, 1980).

6. Splanchnic Blood Flow

Ingested food may affect splanchnic blood flow, but the degree and direction of change may vary with the type of food (Olanoff et al, 1986). A high protein meal has been shown to cause a 35% increase in splanchnic blood flow, whereas a liquid glucose meal show a 8% decrease.

The effect of food on the various gastro-intestinal processes described above are depicted in Figure 3.
Figure 3: Principal Determinants of Drug Absorption from the Gastrointestinal Tract

1. Dissolution
2. Gastrointestinal Motility
3. Mucosal Uptake
4. Mucosal Losses
5. Circulatory Systems
DIRECT EFFECT OF FOOD ON DRUG ABSORPTION

In addition to the indirect effects on gastrointestinal physiology, food may also affect drug absorption directly. Food may act as a physical barrier inhibiting drug dissolution and preventing access to the mucosal surface of the gastrointestinal tract. Specific ions or other substances in food may cause reduced drug absorption. For drugs that are actively absorbed, a direct competition for active carriers may occur between protein fragments and drug molecules, giving rise to decreased drug systemic availability (Welling, 1996).

Hence, food has variable and complex effects on drug metabolism. The following section presents the inter-relationship between various dietary factors, which can be grouped into macronutrients and micronutrients with respect to their effects on drug metabolism.

Drug - Macronutrients Interactions:

Lipids:

Dietary fat consists of complex organic compounds and includes lipid substances such as triacylglycerols (>90% of total dietary fat), phospholipids, sterols, hydrocarbons and waxes. The ingestion of dietary fat results in formation of an oil or emulsion phase that improves solubility and thus absorption of lipid soluble drugs. A fatty meal also initiates a sequence of biochemical and physiological events, any one or combination of which may affect drug absorption, viz. secretion of gastric fluids, secretion of bile and various lipases.
emulsification and enzymatic hydrolysis of esterified lipids and solubilization of lypolytic products within bile salt miscelles (Castro, 1991). It has been suggested that the effect of dietary fat depends strongly on route of drug absorption, either portal route, or lymphatic. For the lymphatic route, dietary fat enhances absorption of presumably dissolved drug, whereas for the portal route, dietary fat enhances absorption of poorly lipophilic drugs by improving dissolution (Zhi et al., 1995).

Cyclosporine, a cyclic polypeptide immuno-suppressant agent has a high degree of lipophilicity and binding to lipoprotein and is absorbed predominantly in small intestine (Drewe et al., 1992). The effect of low fat and high fat meals on cyclosporine pharmacokinetics in healthy volunteers was studied and it was found that high fat meals not only increased the bioavailability but also increased its clearance and volume of distribution (Gupta et al., 1990). Stimulation of bile flow which accompanies dietary fat consumption, may be the contributing factor to the improved solubility and subsequent increased absorption of cyclosporine (Lindholm et al., 1990). This is consistent with the lymphatic route of absorption for cyclosporine (Takada et al., 1988).

A comprehensive study examining the factors responsible for food induced alteration in absorption of atovaquone (an antiprotozoal agent), which is highly lipophilic compound and practically insoluble in water, showed an increase in its absorption following food ingestion. The influence of dietary fat on atovaquone absorption was seen when the drug was administered during fasting with plain toast alone, with a medium fat equivalent meal (28g butter on toast).
and with a high fat equivalent meal (56g butter on toast) The mean area under curve (AUC) values showed an increase of 3.0 and 3.9 fold respectively for medium and high fat meals, compared with the fasting state where toast alone had no significant effect on atovaquone absorption. Buttered toast given 45 minutes before drug ingestion could have enhanced bile release and the formation of micelles and thus improved drug solubility (Rolan et al, 1994).

Lipids are also required by drug metabolizing enzymes as membrane components, and possibly for specific interactions Anything that affects the amount or fatty acid composition of hepatic microsomal phosphatidyl-choline, can affect the capacity of liver to metabolize drugs. Increase in phosphatidylcholine or unsaturated fatty acid content of phosphotidylcholine tends to increase drug metabolism (Gibson and Skett, 1986)

**Protein:**

Protein intake has a marked influence on normal development of drug metabolizing enzymes and thus on oxidative drug metabolizing capacity. A study undertaken to examine the influence of change in dietary carbohydrate and protein content on the oxidation of antipyrine and theophylline in normal human volunteers whose usual normal home diets were changed to low carbohydrate and high protein diets showed a 35% - 40% decrease in plasma half life of antipyrine and theophylline (suggesting faster metabolism of drug), while a change from low carbohydrate - high protein diet to high carbohydrate - low
protein diet resulted in 50%-60% increase in half-life of the two drugs (Kappas et al, 1976)

**Carbohydrate.**

It seems to have few effects on drug metabolism. In experimental animals, a high carbohydrate diet has been associated with a decrease liver mono-oxygenase activities (Janson and Schenkman, 1975) and prolonging of barbiturate-induced sleeping time (Strother et al, 1971)

**Drug-Micronutrient Interactions:**

The micronutrients viz. vitamins and minerals also have an effect on drug metabolism

**Vitamins:**

Vitamins form an essential part of diet and changes in the vitamin levels are known to cause changes in drug metabolising capacity.

Vitamin A deficiency is related with reduced cytochrome P-450 levels, thus causing decrease in drug metabolism.

Niacin deficiency is also known to cause alteration in drug metabolizing capacity. Niacin is a precursor of co-enzymes like NADPH which is the electron donor for oxidative drug metabolism and NAD, which is required for glucuronidation.

Riboflavin is an essential part of flavoprotein NADPH - Cytochrome P-450 reductase which is itself a component of mixed function oxidase system. Thus, a
deficiency of riboflavin would be expected to reduce NADPH-Cytochrome P-450 reductase content and thus decrease drug metabolizing capacity. In contrast to this, certain reports indicate that riboflavin deficiency can also enhance drug metabolizing capacity. It is suggested that the disappearance of a flavin like inhibitor caused the increase in cytochrome P-450 oxidase metabolism. (Gibson and Skett, 1986)

Thiamine is not directly involved in drug metabolism but is essential for carbohydrate metabolism. Despite the apparent lack of connection to drug metabolism, thiamine does affect the capacity of the liver to metabolize drugs. Thiamine deficiency has shown to increase the metabolism of aniline and reduce hexo-barbitone metabolism. The effect of thiamine is related to changes in the macrosomal cytochrome (P-450) and NADPH cytochrome P-450 reductase levels (Gibson and Skett, 1986).

Vitamin C deficient animals showed reduced levels of cytochrome P-450 and there is evidence to suggest that vitamin C is involved in the biosynthesis of haem and thus directly in the synthesis of microsomal cytochromes.

Vitamin E is required for haem synthesis notably for the function of the enzyme δ - aminolaevulinic acid dehydratase. The activity of microsomal cytochrome P-450 has been found to decrease during Vitamin E deficiency.

Minerals

Minerals are needed in the diet for maintenance of good health. Those which have been shown to affect drug metabolism include iron, calcium, potassium, magnesium, zinc, copper, selenium and iodine.
The effect of a magnesia and alumina antacid suspension on the absorption of clorazepate dipotassium was studied. The results revealed that there was a trend of initially slower absorption of clorazepate dipotassium.

Thus, as can be seen, many macro and micronutrients in deficiency or in excess can have noticeable effects on drug metabolism. The summary of the effects of the macro and micronutrients on drug metabolism have been depicted in Figure 4.

**ANTIBIOTICS**

One of the most profound developments in the history of modern medicine has been the discovery of antibiotics. Antibiotics are substances produced by various species of micro-organisms (bacteria, fungi, actinomycetes) that support the growth of other micro-organisms and eventually may destroy them. Some antibiotics are new products of microbes such as sulfonamides and quinolones (Meyers et al, 1968).

**Classification of Antibiotics**

Historically the most common classification has been based on chemical structure and proposed mechanism of action as follows:

1. Agents that inhibit synthesis of bacterial cell walls; these include the penicillins, cephalosporins, etc.
A SUMMARY OF THE EFFECTS OF MACRO AND MICRONUTRIENTS ON DRUG METABOLISM

KEY

(+): An increase in drug metabolism
(-): A decrease in drug metabolism
(?): No change

FIGURE 4

PROTEIN

CARBOHYDRATE(?)

CALCIUM(+)

MAGNESIUM(+)

COPPER

ZINC (+)

SELENIUM (?)

DRUG METABOLISM

IRON(-)

IODINE (-)

FAT

VITAMIN A(+)

VITAMIN B1(+/-)

NIACIN (?)

VITAMIN C (+)

VITAMIN E (+)
2 Agents that act directly on the cell membrane of the micro-organism, affecting permeability and leading to leakage of intracellular compounds: these include polymyxin, colistimethate etc.

3 Agents that affect the function of 30S or 50S ribosomes subunits to cause a reversible inhibition of protein synthesis, these bacteriostatic drugs include chloramphenicol, the tetracyclines, erythromycin and clindamycin

4 Agents that bind to the 30S ribosomal subunit and alter protein synthesis, which eventually leads to cell death; these include aminoglycosides.

5. Agents that affect nucleic acid metabolism, such as the rifamycin (e.g. rifampcin) which inhibit DNA-dependent RNA polymerase and the quinolones, which inhibit gyrase, e.g. Norfloxacin and Ciprofloxacin.

Erythromycin:

Erythromycin was isolated from a strain of streptomyces erythreus (McGuire et al, 1952) and it belongs to a group of antibiotics known as the ‘Macrolides’ which have in common a macrocyclic lactone ring. Erythromycin has a 14-membered lactone ring. These antibiotics are all weak bases, only slightly soluble in water.

Erythromycin base is very bitter, insoluble in water and inactivated by acid. To prevent inactivation by gastric secretions, erythromycin base has been manufactured in various acid resistant forms, such as enteric-coated tablets and granules.
Sensitive Organisms

(a) Gram positive aerobic bacteria: Erythromycin is normally highly active against organisms such as Streptococcus pyogenes, strep pneumoniae etc.

(b) Gram positive anaerobic bacteria: It is active against Eubacterium, Lactobacillus etc.

(c) Gram-negative bacteria: Erythromycin is active against Neisseria meningitides, Haemophilus influenzae etc.

Organisms such as Mycoplasma pneumoniae, Chlamydia trachomatis etc. are also sensitive to Erythromycin.

Mode of Administration and Dosage:

Erythromycin is usually administered by the oral route. This is destroyed by acid in the stomach, so that tablets are manufactured with an acid-resistant coating, which subsequently dissolve in duodenum. Erythromycin is widely distributed in tissues and is concentrated in the liver and spleen. It persists in the tissues for longer periods than in the serum.

Mode of Action:

Erythromycin interferes with bacterial protein synthesis at the ribosomes. This drug, similar to other macrolide antibiotics, becomes bound to the 50S subunit of the ribosome (Goldman et al, 1990). It was suggested that it may interfere with the 'translocation reaction' which is catalysed by an enzyme, translocase (Cundliffe and McQuillen, 1967). During this reaction the growing...
peptide chain with its t-RNA moves from the 'acceptor site' to the 'donor site' and by competing for this site of attachment, prevents translocation of the peptide chain from the acceptor to the donor site. More recently it has been suggested that erythromycin stimulates dissociation of peptidyl-tRNA from the ribosomes during the elongation phase, leading to inhibition of protein synthesis (Mazzeri et al, 1993)

Symptoms such as nausea, vomiting and diarrhea are fairly frequently encountered with oral erythromycin, but these are occasionally severe

**Interaction of Erythromycin with Diet:**

In a study conducted on infants and children when milk was concomitantly given with erythromycin ethyl succinate, the absorption of the drug was enhanced (Mc Cracken et al., 1978)

In a single dose study conducted on 37 patients to determine the effect of a standard breakfast on the absorption of erythromycin estolate capsule the absorption of the drug was found to be enhanced as compared to fasting (Bechtol et al, 1979).

Welling and co-workers in 1979 studied the influence of food intake in ten healthy subjects on the absorption of Erythromycin stearate and estolate. Increased absorption occurred with the estolate in the presence of food, whereas the absorption of stearate was found to be reduced.

Co-administration of orange juice with erythromycin did not alter the absorption of the antibiotic (Del-Valle et al, 1989)
The effect of antacid administration on erythromycin pharmacokinetics was studied in eight healthy volunteers (aged 18-40 years) Analysis of mean values for time to peak concentration, peak serum concentration and total area under the curve revealed no significant difference between the absorption of the drug when taken alone and with 30 ml of antacid (Yamrenduwang et al, 1989).

However, no effect of food was found in a randomized crossover study on the absorption of erythromycin citrate (Jarvinen et al, 1992)

Erythromycin has been shown to increase gastric emptying (Landry et al, 1995; Keshavarzian and Isaac, 1993)

Hence, different studies conducted to evaluate the bioavailability of Erythromycin when different food items were given, reveal varied results.

Norfloxacin:

Norfloxacin was synthesized at the Kyrin Central Research Laboratory in Japan (Ito et al, 1980). It is a fluorinated quinolone carboxylic acid derivative.

Sensitive Organisms:

(a) Gram Negative Bacteria. The activity of norfloxacin against Gram-negative bacilli is similar to, or less than, that of Ciprofloxacin. Most Enterobacteriaceae are sensitive to Norfloxacin including Escherichia coli, the Enterobacter, Salmonella, Shigella etc.

(b) Gram-positive Bacteria: It is less active against Staphylococcus aureus, staph epidermidis than Ciprofloxacin (Neu and Labthavikul, 1982; Murray et al, 1993)
Mode of Administration and Dosage.

Norfloxacin is available only in oral preparation. The recommended adult dosage is 400 mg twice daily. After oral administration, 30-40% of the norfloxacin dose is rapidly absorbed and peak serum levels occur in one to two hours (Stein, 1987). Overall, norfloxacin is absorbed slightly slower than ciprofloxacin (Wise et al, 1986). Norfloxacin is only about 14% protein bound and is highly lipid soluble.

Norfloxacin is widely distributed in the many tissues, achieving concentrations slightly less than, or similar to, those obtained with Ciprofloxacin (Norrby, 1983).

Mode of Action.

It is similar to that of Ciprofloxacin. Norfloxacin has excellent activity against virtually all bacterial urinary pathogens (Greenwood and Laverick, 1983).

Interaction of Norfloxacin With Diet

Studies conducted by Sulkowska and Staroscik (1989) and Issopoulos (1989) have shown that foods rich in iron may reduce the bioavailability of Nalidixic acid and Norfloxacin.

Milk, yogurt and dairy products delay and also reduce the absorption of Norfloxacin (Issopoulos, 1989, Kivisto, 1992 and Lehito, 1995).
Norfloxacin was found to form unabsorbable complexes with iron, magnesium and aluminium ions when pharmacokinetics of oral Norfloxacin was observed in the healthy volunteers given the above preparations. When Norfloxacin was administered with calcium carbonate, its bioavailability reduced by 47% (Okhamafe et al, 1991).

A balanced crossover study of the effects of antacids (liquid containing aluminum hydroxide and magnesium hydroxide) on the absorption of oral Norfloxacin was conducted in 12 healthy male subjects revealed that bioavailability of Norfloxacin was reduced (Nix et al, 1990)

**Ciprofloxacin:**

Ciprofloxacin is a fluoroquinolone which was developed by Bayer Pharmaceuticals for both oral and parenteral use. It is one of the second generation of quinolones including Norfloxacin and others which have substantially enhanced antibacterial activity compared with nalidixic acid. Although developed after Norfloxacin, the successful widespread clinical experience with Ciprofloxacin has resulted in many clinicians regarding it as the classic fluoroquinolone, against which other later generation quinolones are to be compared. It has a good penetration into human cells, thereby providing activity against intracellular pathogens. In general, Ciprofloxacin has 2 to 4 fold greater antimicrobial potency than Norfloxacin.
Sensitive Organisms:

1. Gram-negative organisms: Ciprofloxacin has excellent activity against Escherichia coli, Enterobacter, Klebsiella etc.

2. Gram-positive bacteria: Staphylococcus aureus and staphylococcus epidermidis are susceptible to ciprofloxacin.

Ciprofloxacin, similar to various fluoroquinolones has reasonable activity against Mycobacteria.

Mode of Administration and Dosage:

The usual adult oral dose of ciprofloxacin ranges from 250mg to 750mg twice-daily, depending upon type and severity of infection. For infections such as mild to moderate lower respiratory tract, skin and soft tissue and bone and joint infections, 500mg twice daily is generally appropriate.

Ciprofloxacin is generally 60-70% absorbed from the gut, mostly from the duodenum and jejunum. It is primarily (50-75%) excreted unchanged by the kidneys in healthy volunteers.

Distribution of the Drug in the Body:

Similar to all fluoroquinolones, Ciprofloxacin penetrates well into tissues, with a large volume of distribution which far exceeds the extracellular volume (Karabalut and Drusano, 1993). Marked concentration of Ciprofloxacin in human neutrophils with good intracellular antibiotic activity is also observed (Garcia et al., 1992).
Fluoroquinolones, including Ciprofloxacin, make ideal agents for the treatment of urinary tract sepsis. They are suitable for treatment of skin and soft tissue infections. Respiratory tract infections are also very effectively cured by fluoroquinolones.

Mode of Action:

Fluoroquinolones such as Ciprofloxacin are similar to nalidixic acid in their mode of action. Both Gyrase A and Gyrase B are targets for fluoroquinolones in which they bind with the DNA gyrase-DNA complex, rather than to DNA gyrase alone. Disrupting DNA gyrase function results in decreased introduction of negative supercoils in DNA and therefore an increase in subsequent DNA damage.

Nausea, vomiting, diarrhea, fever and abdominal discomfort have been reported in 2-15% patients treated with Ciprofloxacin. These are generally transient and mild, but are more common with higher dose.

Interaction of Ciprofloxacin With Diet

Kara in 1991 showed that the bioavailability of Ciprofloxacin was decreased with co-ingestion of iron-containing foods by the formation of Ciprofloxacin ferric ion complex.

Other Antacids were also observed to have a negative relation with Ciprofloxacin. Formation of a chelate complex between magnesium, calcium or aluminium cations was observed (Roush and Dupuis, 1991).
However, contrary to the above findings, Lomastro in 1993 observed that administration of calcium carbonate two hours before Ciprofloxacin consumption does not significantly alter the bioavailability of Ciprofloxacin.

Another randomized crossover study conducted by Newonen and co-workers in 1990 also depicts a similar trend. Effects of milk and yogurt on the bioavailability of ciprofloxacin was observed in 7 healthy subjects who received an oral dose of 500 mg Ciprofloxacin hydrochloride with 300 ml water, milk or yogurt. Plasma drug levels were significantly lower during the milk and yogurt phases from 0.5-10 hours. At 0.5 hour the concentration was reduced 70% by milk and 92% by yogurt. Bioavailability was reduced by 30-36% by milk and yogurt (Newonen et al, 1991).

**Amoxycillin:**

Ampicillin has been modified chemically in various ways in an attempt to produce an improved compound. Eight such modifications have been available. Amoxycillin, empicillin and cyclocillin have intrinsic antibacterial activity, but other five antibiotics are hydrolysed in the body to ampicillin after administration. Amoxycillin has advantages over ampicillin and probably will gradually replace it, at least for oral administration. It was developed by Beechem Research Laboratories (Sutherland et al, 1972), its main advantage over Ampicillin is its better absorption from the gastrointestinal tract.
Sensitive Organisms:

Amoxicillin is about twice as active as ampicillin against Enterococcus faecalis and Salmonella, but 2-fold less active against Shigella (Neu, 1974). Amoxicillin is inactive against all bacteria which have developed either intrinsic resistance or resistance due to beta-lactamase production to penicillin G or ampicillin.

Mode of Administration and Dosage

The usual dosage of this drug is 250-500 mg, given 6- or 8-hourly. Amoxicillin is well absorbed after oral administration (Verbist, 1976). About 58-68% of an orally administered dose of Amoxicillin is exerted in the urine in an unchanged active form, during the first six hours. Protein binding of Amoxicillin is about 17% (Sutherland et al, 1972). Amoxicillin has been used to treat urinary tract infection (Sabto, 1973). For the treatment of chronic bronchial infections amoxicillin has been regarded as superior to ampicillin as it penetrates into bronchial secretions to a greater extent. It has also been used to treat typhoid fever.

Interaction of Amoxicillin With Diet:

Various studies have documented that bioavailability of Amoxicillin is better in fasting state as compared to the fed state (Welling et al, 1977). Lutz and co-workers in 1987 conducted a study to evaluate the effect of different levels of dietary fibre on the bioavailability of Amoxicillin in healthy
volunteers. It was observed that bioavailability of Amoxicillin was higher with diet containing lower fibre content.

**NON-STERoidal ANTI INFLAMMATORY DRUGS**

**Aspirin**

Among ancient folk remedies for pain and fever, extracts of the barks, leaves or fruits of a number of trees had a high reputation. It is now known that many of these herbal remedies owed their effectiveness to their contained salicylates. Aspirin made its appearance in 1899. The salicylates, particularly Aspirin remain one of the most widely used group of drugs but inspite of their long history it is only very recently that their mode of action has become established.

Aspirin is a simple organic acid, which is also known as Acetyl Salicylic Acid (ASA).

The salicylate are active when taken by mouth and they are readily absorbed from the gastrointestinal tract. Although absorption is favoured by the low pH, salicylates are more readily absorbed from the small intestine than from the stomach and anything that accelerates gastric emptying promotes their absorption. This is a simple consequence of the fact that the surface available for absorption is so much greater in the small intestine than in the stomach that it overweights the disadvantage of the unfavourable pH. It will be seen that much of the salicylate is conjugated with glycine or with glucuronic acid but in alkaline
urine the proportion excreted as free salicylate is much higher than that indicated. It can reach 85 per cent of the administered dose.

Aspirin is hydrolysed by esterases in tissues yielding salicylate. However, most of it seems to be hydrolyzed in liver. Approximately 25% of salicylate is oxidized, some is conjugated to glucuronic or sulphuric acid before excretion. It's action is related to the primary action of its inhibition of arachidonate cyclooxygenase and thus inhibition of production of prostaglandins and thromboxanes. During hydrolysis the acetyl group is removed, a process that has half life of 15 minutes.

Because of the liver's limited capacity to metabolize salicylates, the drug's plasma half life varies between about 3 and 30 hours depending on the amount that has been ingested. With doses in the therapeutic range constant blood levels can be maintained by doses spaced at intervals of 4 to 6 hours.

Aspirin is used for the relief of pain and inflammation associated with the rheumatic diseases and gout but in addition it is widely employed by the layman for the treatment of minor family ills, ordinary headaches, muscle pains and mild fevers respond very well to the drug and little harm attends its use in the moderation observed by most people. Aspirin is not without value in relieving the pain of more serious conditions and the physician should always consider the possibility of using it in preference to the stronger analgesics.

It falls in the category of analgesic, antirheumatic, antipyretic and antithrombotic drug.
Interaction of Aspirin With Diet

A striking interference by meal in the absorption of Aspirin was reported in a study where ten normal subjects were given 1.5g of calcium. Six subjects had taken the dose in fasting state while four of them had meal shortly before the intake of drug. The mean serum salicylate levels obtained one hour following the dose were significantly reduced from 12.1 mg% in fasting subjects to 5.9 mg% in non-fasting subjects (Spiers and Malonel, 1967).

In another study serum salicylate levels obtained up to 20 minutes following 650 mg dose of commercial Aspirin in non-fasting subjects were approximately one-half of those in fasting subjects. It was estimated by the authors that the absorption half-life was more than doubled by the non-fasting condition (Wood, 1967).

In order to see the effect of food and fluid volumes on Aspirin absorption, a study was conducted on healthy volunteers by measuring plasma levels of both acetyl salicylic acid and salicylate (Koch et al, 1978). Subjects received two tablets of Aspirin with 25 or 250 ml of water while fasting or following standard carbohydrate, fat or protein meals. Peak acetyl salicylic acid levels were found to be 40-50% reduced by food and the rate of absorption was also significantly reduced. Plasma acetyl salicylic acid levels were decreased somewhat by the reduced water volume in fasting subjects, although not to the same extent as in non-fasting treatments. While circulating levels of salicylic acid were found to follow similar trends to those of acetyl salicylic acid, difference in plasma profile between treatments for this metabolite were not statistically significant.
Food may have variable effect on drugs absorption depending not only on the compound but also on the formulation. Enteric-coated products have been frequently associated with poor or erratic bioavailability. A study was conducted to compare the effect of food on the absorption efficiency of drug from enteric coated acetyl Salicylic acid and from a formulation of enteric coated acetyl salicylic acid granules contained in capsules (Bogentoft et al, 1978). The subjects received the dosage form either while fasting or immediately following a standard breakfast. The plasma salicylic acid levels from the two formulations were similar under fasting condition, however, while food appeared not to influence absorption from granules, the salicylic acid levels from tablets were both decreased and delayed in non-fasting individuals.

Acetaminophen:

Acetaminophen is an analgesic, antipyretic and is as effective as Aspirin. It is used to treat headache, mild to moderate myalgia, arthralgia chronic pain of cancer, postpartum pain, post operative pains, fever. It is the preferred alternative to Aspirin for patients who cannot tolerate the latter, those with a coagulation disorder (e.g. hemophilia) or individuals with a history of peptic ulcer.

It is rapidly and almost completely absorbed from the gastro-intestinal tract following oral administration. It is given orally and is well absorbed and peak plasma concentration is reached within 30 to 60 minutes. Its saturated aqueous solution has a pH of 6 at 25 °C. It has a half life of two hours. Significant serum protein binding does not occur with therapeutic doses. It is metabolized in the
liver, largely to glucuronide and sulphate conjugates and eliminated in the urine. A minor fraction is metabolized to hydroxylates and deacetylated derivatives.

**Interaction of Acetaminophen With Diet**

Jaffe and co-workers in 1971 reported a delayed absorption of Acetaminophen due to high carbohydrate meals, while high protein, high lipid or balanced meals had little effect. The apparent inhibition of Acetaminophen by carbohydrate test meals was thought to be due to a possible interaction with pectin. Pectin acts as an adsorbent and protectant in the gastrointestinal tract and may delay absorption by adsorption, complexation on increase in viscosity of gastrointestinal contents.

In order to see the effect of food on Acetaminophen absorption in young and elderly subjects a study was performed wherein subjects received 650 mg of the drug (Divole et al, 1982). The results showed that food slowed the rate of absorption and there was no significant difference in the peak.

Hence, it can be observed from various studies that there is a differential response of the drugs with various nutrients.

**DRUG DISPOSITION IN MALNUTRITION**

Drug oxidation in Protein Energy Malnutrition (PEM) syndromes such as Kwashiorkar and Marasmus in children and oedema in adults have been found to be impaired and therefore clearance of drugs from the body is reduced. Antipyrine, phenylbutazone and theophylline can accumulate in severe forms of malnutrition. On the other hand, in mild and moderate forms of adult malnutrition,
metabolism is enhanced in the liver and the steady state levels of drugs are
reduced due to faster elimination from the body (Krishnaswamy, 1996).

Drug conjugations in malnourished children are impaired. Clearance of
drugs such as chloramphenicol, paracetamol, sulfadiazine and isoniazid is
reduced and therefore the steady state concentrations build up in moderate or
severe states of malnutrition. In adults, however, conjugation including that of
steroidal contraceptives is not impaired. Thus, the drug oxidations and
conjugations appear to be related to the severity and the age at which the dietary
deficiency occurs (Krishnaswamy, 1996).

Thus, the conceivable alterations produced in malnutrition would influence
various bioprocesses involved in drug metabolism which in turn may be so
altered that drug therapy may became either ineffective or hazardous if dosage
continues to be calculated on fixed parameters such as body weight or age. The
various pathophysiological changes in malnutrition likely to alter drug metabolism
and disposition have been summarized in Table 1.

Thus, the above mentioned studies clearly indicate the potential influence
of food on drug bioavailability and clinical efficacy of oral medication and
emphasizes the importance of food and drug interactions. The magnitude of
change in drug bioavailability depends not only on the composition but also on
relative content of food ingested concomitantly with it.

Keeping the relative information in mind the present study was planned to
study the effect of snacks and regional meals of India on the bioavailability of
Antibiotics and Non Steroidal Anti Inflammatory Drugs.
<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Pathophysiological Changes</th>
<th>Likely Alterations in Drug Metabolism And Disposition</th>
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<tr>
<td></td>
<td>Alteration in gastric intestinal and pancreatic function.</td>
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<tr>
<td>2</td>
<td>Body Composition</td>
<td>Drug binding, Distribution volume, Drug reception binding, Tissue uptake and retention, elimination.</td>
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<td></td>
<td>Alterations in protein / fat synthesis and turnover, plasma protein and tissue proteins and alteration in body water distribution</td>
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<td>3.</td>
<td>Kidney</td>
<td>Renal clearance,</td>
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<td>Renal plasma flow, glomerular filtration rate and tubular function.</td>
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<td>4.</td>
<td>Cardiac Muscle</td>
<td>Organ blood flow (hepatic, renal and other tissues), Tissue perfusion.</td>
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<td>Cardiac output, blood volume and circulation time.</td>
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<td>5</td>
<td>Hormonal and Metabolic</td>
<td>Binding, Distribution, Biotransformation, Receptors</td>
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