CHAPTER 1

INTRODUCTION
INTRODUCTION

Food has long sustained the survival needs of man. It has only been a few years since it was realised that some foods had curative properties also. The occurrence of numerous diseases has resulted in the discovery, synthesis and formulation of a large number of drugs. Over the years, it has been progressively seen that some foods have more or less curative properties and the notion of drug-food has begun to take shape (Debry, 1984). Food is one of the factors which affects the rate and pathways of metabolism of drugs. The absorption and effectiveness of a drug is influenced by food, beverages and mineral or vitamin supplements.

More recently the development of increasingly accurate and specific physiological or biochemical techniques have enabled pharmacokinetic investigators to follow up the fate of drugs in the system and to discover factors affecting their metabolism and kinetics.

A drug (GK*: pharmakon) may be defined as a substance which modifies some functions of a biological system.

Pharmacology - the study of drugs - is divisible into.

* Pharmacodynamics (GK* dynamics, power) the action upon cells (or subcellular fragments), tissues or organs

*GK = Greek
Pharmacokinetics (GK*: Kinesis, movement) the processes whereby drug concentrations at effector sites are achieved, maintained and diminished (Grundy, 1990). In a nutshell, Pharmacodynamics is what drugs do to the body and pharmacokinetics is what body does to drugs (Laurence and Bennett, 1992).

A drug interaction occurs whenever the pharmacologic action of a drug is altered by a second substance. Theoretically, this change may be related to:

1. **Pharmacokinetic interactions** - that is, differences in the plasma levels of a drug achieved with a given dose of that drug.

2. **Pharmacodynamic interactions** - that is, differences in effects produced by a given plasma level of a drug.

It has long been recognized that the intensity and duration of the pharmacological effect of a systematically acting drug are functions not only of the intrinsic activity of the drug, but also of its absorption, distribution and elimination characteristics. Also, in order to exert a required pharmacological effect, a drug must be absorbed at a rate and to an extent that will produce adequate drug concentration at the site(s) of action during a certain time period.

The term bioavailability of a drug denotes how much of the administered dose reaches the systemic circulation and hence can be distributed to the target tissues for subsequent action (Melander, 1984). In order to understand the factors affecting the bioavailability of drugs, it is necessary to understand the term 'Drug Metabolism'. The term drug metabolism in its broadest sense may be considered as the absorption, distribution, biotransformation and excretion of drugs. Majority of the drugs are given orally and en route the drug has to cross
several membranes, face numerous physiologic environments, biotransformations and finally excretion before the drug uptake by the tissues. Most orally administered drugs pass from the lumen of the gastrointestinal tract by the process of passive diffusion (Welling, 1980). Numerous factors can alter this process viz:

- Blood flow, Splanchnic Blood Flow and Gastric motility
- Particle size and formulation
- Chemical factors
- Genetic factors (Age, Sex)
- Food
- Disease and Nutritional status.

Food may directly or indirectly influence each of these steps on the bioavailability pathway. Co-administration of food or beverage may profoundly influence the absorption of oral medication by affecting drug dissolution, gastrointestinal secretions and peristalsis (Welling and Tse, 1983). The type of meal consumed, the composition of the food and its nutrients, the amount of water, the temperature of the food, the osmotic power of the meal, the nature of the food - its acidity or basicity alter drug dissolution and thus the absorption of food (Debry, 1984).

Further, the small intestine is the principle site of absorption of nutrients and it is also where most orally administered drugs enter the body. An incomplete bioavailability may occur due to degradation process like precipitation, chelation or neutralization. In order to reach the general circulation,
drugs taken orally have to pass through the wall of the gastrointestinal tract and then to the liver via the portal vein. During this passage, the drug can be altered metabolically. The drug and the metabolites thus formed, then reach the liver whose biotransformation (alterations in the chemical structure) can take place.

Drug metabolism can be divided into 2 phases:

Phase I reactions are known as 'Functionalization' reactions and these include oxidation, hydrolysis and reduction reaction. Phase II reactions are known as the 'Conjugative' reactions. There is evidence to suggest that the phase I reactions create a reactive functional group on the molecules so that it can be attacked by the Phase II enzymes.

Thus, the Phase II reactions are the true 'detoxification' pathways and give products that account for the bulk of the inactive water soluble excreted products of a drug. Phase I produces necessary derivative of the drug which then get conjugated during Phase II reactions.

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRUG</td>
<td>DERIVATIVE</td>
</tr>
<tr>
<td>Oxidation</td>
<td>Conjugation</td>
</tr>
<tr>
<td>Hydroxylation</td>
<td></td>
</tr>
<tr>
<td>Dealkylation</td>
<td></td>
</tr>
<tr>
<td>Deamination</td>
<td></td>
</tr>
</tbody>
</table>

The liver is the main organ responsible for Phase I and Phase II drug metabolism reactions. Drug localization and hence probably metabolism is dependent on many factors including physico-chemical properties of the drug.
(pka, liquid solubility and molecular weight), chemical composition of the drug and the presence of uptake mechanisms which allow the drug to be trapped. The biochemical transformation is frequently achieved by the non-specific enzymes present in the microsomes of liver cells and it is one of the chief oxidative pathways that drug molecules undergo. Hepatic drug metabolizing enzymes activate some chemically stable drugs to potent alkylating, and acylating agents. The enzyme complex, is experimentally fractionated and is prepared as 'microsomes, conventionally classified as a mixed function oxidase (Mason, 1957). This complex is comprised of cytochrome P-450, phosphatidylcholine and flavoprotein reductase and is closely invested into the structural membrane. It requires oxygen and NADPH and possess a broad substrate "specificity", since a wide variety of drugs seem to be metabolized. Apart from the gastrointestinal tract and liver, extra hepatic tissues too play an important role.

If a drug is required to act throughout the body it must get into bloodstream and other body compartments. The rate and extent of distribution of drugs in the body depend on binding of drugs to plasma proteins, the sequestration by tissues and subsequent binding to tissue components and permeability of tissue membrane. The interaction between drugs and protein molecules profoundly influence the biological activity. Plasma is a complex solution of different proteins of which albumin, alpha 1-acid glycoprotein, lipoprotein and globulins are involved in the transport of compounds, such as hormones; vitamins and drugs. While acidic drugs bind to albumin, the basic drugs bind to alpha-1-acid glycoprotein and lipoprotein. Protein binding is a means of collecting drug
molecules at sites of absorption and depositing at sites of storage, action and elimination (Krishnaswamy, 1996).

After distribution, the drug in blood is in dynamic equilibrium with that in tissues. The levels decline in blood/plasma and body simultaneously. Many drugs obey what is called first-order kinetics of elimination, i.e. a constant amount being eliminated per unit time. Kidneys are usually the primary sites of excretion of chemically unaltered drugs or water soluble polar metabolites of the parent compound (Krishnaswamy, 1996).

Thus, nutrient-drug interactions occur due to physical, chemical or physiological interactions between drugs, nutrients and human body and have a direct bearing on therapy and its outcome. The metabolic interactions between dietary constituents and drugs are varied. Unfortunately, this subject has not received the attention it deserves from either physicians or nutrition scientists; and much needs to be done in this direction.

As food commonly influences the rate of drug absorption, food drug interactions are particularly important for situations where long term dosing, say a week to about 10 days, is required. Many anti-inflammatory agents and antibiotics fall within this category. With these classes of drugs; not only are adequate drug levels required for therapeutic effect but prompt absorption may also be important to obtain rapid onset of action. Hence, for the present study, two of the most commonly used analgesic and Non-Steroidal Anti Inflammatory Drugs (NSAIDs) - Aspirin and Acetaminophen and four commonly used
Antibiotics viz. Norfloxacin, Erythromycin, Amoxicillin and Ciprofloxacin were chosen for the study.

India is a country with diversified cultures and each region having its own typical regional meal. These typical regional meals are greatly varied in their composition and nutrient content which would affect the bioavailability of the drugs quite differently depending upon their food composition. Keeping the above relevant information in mind, for the present study, seven typical regional meals of India viz. Punjabi, Gujarati, West Bengali, South Indian, Kashmiri, Rajasthani and Maharashtrian were chosen and four commonly consumed snacks viz. Samosa, Dhebra with Curd, Poha and Upma were selected to evaluate their effect on the bioavailability of the chosen drugs.

Description of each drug is as follows.

I. ANTIBIOTICS

a) Norfloxacin:

Norfloxacin is a broad spectrum antibacterial agent and belongs to the class of fluoroquinolone. The main areas of use are uncomplicated or complicated
and recurrent urinary tract infections, gonococcal infection, diarrhoeal diseases. It is effective against a wide range of gram positive and gram negative organisms. Norfloxacin binds to specific sites on the DNA molecule and thus proves bactericidal by inhibiting the vital process of reproduction. It is rapidly absorbed from gastro-intestinal tract and peak serum level attained are 1.5 to 2 mcg/ml after 1.5 hours of 400 mg dose. The plasma half life is about 4 hours. It has a low plasma binding of 14%. The drug is primarily metabolised in liver and the elimination is mainly through kidneys.

b) Ciprofloxacin

\[
\text{1-Cyclopropyl-6-Fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid}
\]

Like Norfloxacin, Ciprofloxacin is a potent, broad spectrum antibacterial agent belonging to a class of drugs called fluoroquinolones. However, it is 2 to 8 fold more potent in vitro than Norfloxacin against members of Enterobacteriaceae and S aureus.
It inhibits gram negative bacteria including E Coli, Salmonella, Plasmodium, etc. It exerts a potent bactericidal effect by inhibition of A subunit of DNA gyrase, an essential enzyme involved in DNA replication precipitating a sequence of events leading to lysis of bacteria. It also damages bacterial cell membrane.

It is well absorbed on oral administration and serum concentrations in the range of 1-4 mg/L are obtained after oral administration of 250 to 500 mg of ciprofloxacin. The oral bioavailability is about 70%. Urinary excretion accounts for elimination of 40 to 50% of an oral dose. Protein binding varies but range upward from about 20%. It is used to treat respiratory tract infections, urinary tract infections, gastrointestinal infections etc.

c) Erythromycin

(Erythronolide A)
Erythromycin is a lipophilic drug produced by the growth of a strain of Saccharopolyspore erythraea and is a mixture of macrolide antibiotic consisting largely of erythromycin A. It is used as an alternative to penicillin in infections due to gram positive cocci, especially streptococci. It interferes with bacterial protein synthesis by binding to 50 S subunit of ribosomes. Activity of erythromycin increases with increase in pH up to about pH 8.5. Peak plasma erythromycin concentration of about 0.5 to 1.0 µg per ml are achieved within 4 hours of doses of 250 and 500 mg of the base respectively. The plasma half life is about 1.2 to 4 hours.

Erythromycin binds chemically to α acid glycoprotein in plasma and to a minor extent to albumin. Erythromycin is excreted in high concentration in the bile and upto 5% of an oral dose appears in the urine.

Erythromycin base is incompletely but adequately absorbed from the upper part of the small intestine. It diffuses readily into intracellular fluids.

d) Amoxicillin
Amoxycillin is an amino penicillin. It is very active against Enterococcus faecalis and Salmonella. It is rapidly and completely absorbed when given by mouth. About 20% is bound to plasma proteins in the circulation and plasma half life of 1-1.5 hours has been reported. It is widely distributed at varying concentrations in body tissues and fluids. It is metabolized to a limited extent to penicilloic acid which is excreted in urine.

About 60% of an oral amoxycillin is excreted unchanged in the urine in 6 hours by glomerular filtration and tubular secretion. Urinary concentration above 300 mg/ml has been reported after a dose of 250 mg. It is used in bone and joint infections, bronchitis, gastro-enteritis, typhoid and urinary tract infections.

II. NON STEROIDAL ANTI INFLAMMATORY DRUGS (NSAIDS)

a) Aspirin

Aspirin is a simple organic acid, which is also known as Acetyl Salicylic Acid (ASA). Since it is a weak acid it is largely unionized in the acid environment of the stomach and thus its absorption is facilitated. 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. Its action is related to the primary action of its inhibition of arachidonate cyclo-oxygenase 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. It falls in the category of analgesic, antireheumatic, antipyretic and antithrombotic drugs.

b) Acetaminophen

\[
\begin{align*}
\text{NH COCH}_3 \\
\text{OH}
\end{align*}
\]

Acetaminophen has more of antipyretic action than anti-inflammatory. It is given orally and is well absorbed and peak plasma concentration is reached within 30-60 minutes. Its saturated aqueous solution has a pH of 6 at 25°C. It has a half life of 2 hour and is well absorbed from the alimentary tract and is inactivated in liver principally by conjugation as glucuronide and sulphate.

Thus keeping in view the relevant information, the study was planned to evaluate the effect of seven typical regional meals viz North Indian (Punjabi), Gujarati, South Indian, West Bengali, Maharastnan, Kashmiri, Rajasthani and four commonly consumed snacks namely, Dhebra with Curd, Poha, Upma and
Samosa on the bioavailability of four Antibiotics and two Non-Steroidal Anti-Inflammatory Drugs (NSAIDS). The specific objectives of the study were:

(1) To study the urinary recovery rates of Norfloxacin, Erythromycin, Ciprofloxacin, Amoxicillin, Salicylic acid and 4-p-aminophenol when consumed orally in fasting state as compared with the seven typical regional meals of India and four commonly consumed snacks for a period of six hours.

(2) To compare the effect of the seven typical regional meals of India and four snacks on the urinary recovery rates of the selected drugs for a period of six hours.