FACTOR AFFECTING DRUG ABSORPTION

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Definition:

The process of movement of unchanged drug from the site of administration to systemic circulation.

or

There always exist a correlation between the plasma concentration of a drug & the therapeutic response & thus, absorption can also be defined as the process of movement of unchanged drug from the site of administration to the site of measurement. i.e., plasma
CELL MEMBRANE

- Also called the plasma membrane, plasmalemma or phospholipid bilayer.
- The plasma membrane is a flexible yet sturdy barrier that surrounds & contains the cytoplasm of a cell.

- Cell membrane mainly consists of:
  1. Lipid bilayer-
     - phospholipid
     - Cholesterol
     - Glycolipids.
  2. Proteins-
     - Integral membrane proteins
     - Lipid anchored proteins
     - Peripheral Proteins
MOVEMENT OF SUBSTANCE ACROSS CELL MEMBRANE
FACTORS AFFECTING DRUG ABSORPTION

PATIENT RELATED FACTORS
- PHYSIOLOGICAL FACTOR
- CLINICAL FACTOR

PHARMACEUTICAL FACTOR
- Physico-chemical factors
- Formulation factors
PATIENT RELATED FACTORS

PHYSIOLOGICAL FACTORS

A) MEMBRANE PHYSIOLOGY
   i) Membrane Structure
   ii) Transport Process

B) GASTRO-INTESTINAL PHYSIOLOGY
   i) Characteristics of GI Physiology
   ii) GI Motility and emptying
   iii) Blood flow through GIT
   iv) Influence of food
   v) Intestinal transit time
   vi) Pre-systemic metabolism by various enzymes.
MEMBRANE PHYSIOLOGY

- MEMBRANE STRUCTURE

- TRANSPORT PROCESS
  1. PASSIVE DIFFUSION
  2. PORE TRANSPORT
  3. FACILITATED DIFFUSION
  4. ACTIVE TRANSPORT
  5. PINOCYTOSIS
ILLUSTRATION OF DIFFERENT TRANSPORT PROCESS

Passive  Facilitated  Active
1. PASSIVE DIFFUSION

- Major process for absorption of more than 90% of drugs
- Diffusion follows Fick’s law:
  - The drug molecules diffuse from a region of higher concentration to a region of lower concentration till equilibrium is attained.
  - Rate of diffusion is directly proportional to the concentration gradient across the membrane.
- Factors affecting Passive diffusion:
  - Diffusion coefficient of the drug
    - Related to lipid solubility and molecular wt.
  - Thickness and surface area of the membrane
  - Size of the molecule
2. PORE TRANSPORT

- It involves the passage of ions through Aq. Pores (4-40 Å)
- Low molecular weight molecules (less than 100 Daltons) eg- urea, water, sugar are absorbed. Also imp. In renal excretion, removal of drug from CSF and entry of drugs into liver.
3. FACILITATED DIFFUSION

- Carrier mediated transport (downhill transport)
- Faster than passive diffusion
- No energy expenditure is involved
- Not inhibited by metabolic poisons

- Important in transport of Polar molecules and charged ions that dissolve in water but they cannot diffuse freely across cell membranes due to the hydrophobic nature of the phospholipids.

Eg.
1. entry of glucose into RBCs
2. intestinal absorption vitamin B1, B2
3. transport of amino acids thru permeases
4. ACTIVE TRANSPORT

- Carrier mediated transport (uphill transport)
  - Energy is required in the work done by the carrier
  - Inhibited by metabolic poisons

- Endogenous substances that are transported actively include sodium, potassium, calcium, iron, glucose, amino acids and vitamins like niacin, pyridoxin.

- Drugs having structural similarity to such agents are absorbed actively
  - Eg. 1. Pyrimidine transport system – absorption of 5 FU and 5 BU
  - 2. L-amino acid transport system – absorption of methyldopa and levodopa
ACTIVE TRANSPORT
5. PINOCYTOSIS

Pinocytosis ("cell-drinking")

- Uptake of fluid solute.

- A form of endocytosis in which small particles are brought into the cell in the form of small vesicles which subsequently fuse with lysosomes to hydrolyze, or to break down, the particles.

- This process requires energy in the form of (ATP).

- Polio vaccine and large protein molecules are absorbed by pinocytosis.
PINOCYTOYSIS
(B) GASTROINTESTINAL PHYSIOLOGY

Diagram of GIT
GASTRIC EMITYING AD MOTILITY

- Gastric emptying is the passage from stomach to small intestine.

- Rapid gastric emptying time is required when drug is absorbed from the distal part of intestine.

- Delayed gastric emptying time is required when drug is absorbed from proximal part of the intestine.

- It is faster in case of solution and suspension than solid dosage form.
<table>
<thead>
<tr>
<th>Type of Meal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty food</td>
<td>Decrease</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics (e.g. atropine), Narcotic (e.g. morphine, alfentanil), Analgesic (e.g. aspirin)</td>
<td>Decrease</td>
</tr>
<tr>
<td>Metoclopramide, Domperidone, Erythromycin, Bethanchol</td>
<td>Increase</td>
</tr>
</tbody>
</table>
ii) GI MOTILITY

- GI motility tends to move the drug through the alimentary canal so that the drug may not stay at the absorption site.

  e.g. cathartic drug increase gastric motility & decrease drug absorption of another drug.
A potential rate limiting step:

<table>
<thead>
<tr>
<th>DRUGS</th>
<th>BLOOD FLOW EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOR HIGHLY LIPID SOLUBLE DRUGS</td>
<td>MORE</td>
</tr>
<tr>
<td>FOR HYDROPHILIC DRUG</td>
<td>LESS</td>
</tr>
</tbody>
</table>
Intestinal Blood flow (ml/min/gram of tissue)

Absorption rate (n mole/min/gm of tissue)

- Tritiated water
- Methanol
- Urea
- Erythritol
- Ribitol
iv) Effect of Food

- Food can affect absorption by Altering,
  - Stomach pH
  - Affect Gastric emptying
  - Forms complex with the drug.
(V) INTESTINAL TRANSIT TIME

Since, intestine is the major site of absorption of most of the drugs, Long intestinal transit time is desirable for the complete absorption of drugs.

Delayed intestinal transit is desirable for
-- Drugs that dissolve only in intestine (enteric coated)
-- Drugs absorbed from specific sites in the intestine.
(vi) **PRE SYSTEMIC METABOLISM**

For drugs administered orally, two main reasons for its decreases bio-availability are

- Decreased absorption
- Pre-systemic metabolism / First-pass effect.
Metabolism

By gut wall enzymes

First pass Hepatic Metabolism

Metabolism by lumenal enzymes

Way to colon

Gut wall

Portal vein

Liver

To site of measurement

Metabolism by bacterial enzymes of the colon

Un-absorbed drug in faeces
vii) AGE

In children & Infants  Gastric pH is high, membrane permeability & BBB permeability is high, protein binding is less therefore it imparts drug absorption.

- while in Elderly patient there is altered gastric emptying, decrease intestinal surface area, decrease gastric blood flow & higher incidence of achlorhydria so it imparts drug absorption.
CLINICAL FACTORS

A) DISEASES
B) SURGERY
C) INFECTIONS
D) INTERACTIONS
i) *Gastric diseases*: – ACHLORHYDRIA

Achlorhydria affects Aspirin absorption by increasing gastric emptying time & increasing stomach pH.

ii) *Intestinal diseases* like celiac disease, chrons disease.

iii) *Cardio-vascular diseases*

Several changes associated with congestive cardiac failure influence the bio-availability of the drug viz., edema of the intestine, decreases blood flow to GIT, etc.

iv) *Hepatic diseases*

Disorders such as hepatic cirrhosis influence bio-availability mainly of drugs that undergo considerable first-pass hepatic metabolism e.g. Propranolol
### INTERACIONS

1. **Food–Drug Interactions**

2. **Drug–Drug Interactions**
   - **PHYSICO-CHEMICAL**
     - Adsorption, Complexation
     - E.g. Antacids, Heavy Metals
   - **PHYSIOLOGICAL**
     - Decrease GI transit,
     - Increase Gastric emptying
     - E.g. Metoclopramide

3. **Drug–GI contents interactions**
   - Interaction with mucin, enzymes and bile salts influence drug absorption.
   - E.g. Bile salts
     - Increase absorption of – Vitamins (Solution)
     - Decrease absorption of – Neomycin and Kanamycin (Insoluble complex)
PHARMACEUTICAL FACTORS

- Physico-chemical factors
- Formulation factors
PHYSICO CHEMICAL FACTORS

A) pH-PARTITION HYPOTHESIS
B) DRUG SOLUBILITY AND DISSOLUTION RATE
C) PARTICLE SIZE AND EFFECTIVE SURFACE AREA
D) POLYMORPHISM AND AMORPHISM
E) PSEUDO-POLYMORPHISM
F) SALT FORM OF THE DRUG
1) pH–partition Hypothesis

**Simplest principle:**

- **Unionised Drug:** Higher Absorption
- **Ionised Drug:** Low Absorption
**High Absorption**
- Weak Acid (Pentobarbital & aspirin)
- Weak Base (Theophylline, caffeine, codeine)

**Low absorption**
- Strong Acid (Disodium cromoglycate)
- Strong Base (Guanethidine)
D) POLYMORPHISM AND AMORPHISM

POLYMORPHISM

When substance exists in different crystalline forms, it is polymorphism.

Plot of Cp Vs Time for three formulations of Chloramphenicol Palmitate
(E) **AMORPHISM**

These drugs can exist with no internal crystal structure.

Such drug represents the highest energy state and can be considered as super cooled liquids and thus have greater solubility.

E.g. Novobiocin

Thus, the order of Dissolution & hence Absorption for different solid dosage forms is amorphous > meta-stable > stable.
Salt of weak acid and weak bases have much higher aqueous solubility than the free acid or base.

Therefore, if the drug can be given as a salt, the solubility can be increased and the dissolution thus can be improved.

**Fig 1. It shows the dissolution Profile of various salts**
FORMULATION FACTORS

A) DISINTEGRATION TIME (Tablets/Capsules)
B) MANUFACTURING VARIABLES
C) PHARMACEUTIC INGREDIENTS (Excipients, Adjuvants)
D) NATURE AND TYPE OF DOSAGE FORM
E) PRODUCT AGE AND STORAGE CONDITIONS
A) DISINTEGRATION TIME

Rapid disintegration is important to have a rapid absorption, so lower Disintegration time is required.

In-vivo disintegration gives no means of guarantee of drug bio-availability, because if the disintegrated drug particles do not dissolve, then the dissolution is not possible.
- Biopharmaceutics and pharmacokinetics. P L Madan, no 1st edn.
- Applied Biopharmaceutics and pharmacokinetics. Leon Shargel and Andrew Yu, 4th edn.
- Biopharmaceutics and clinical pharmacokinetics. By Milo Gibaldi, 4th edn.