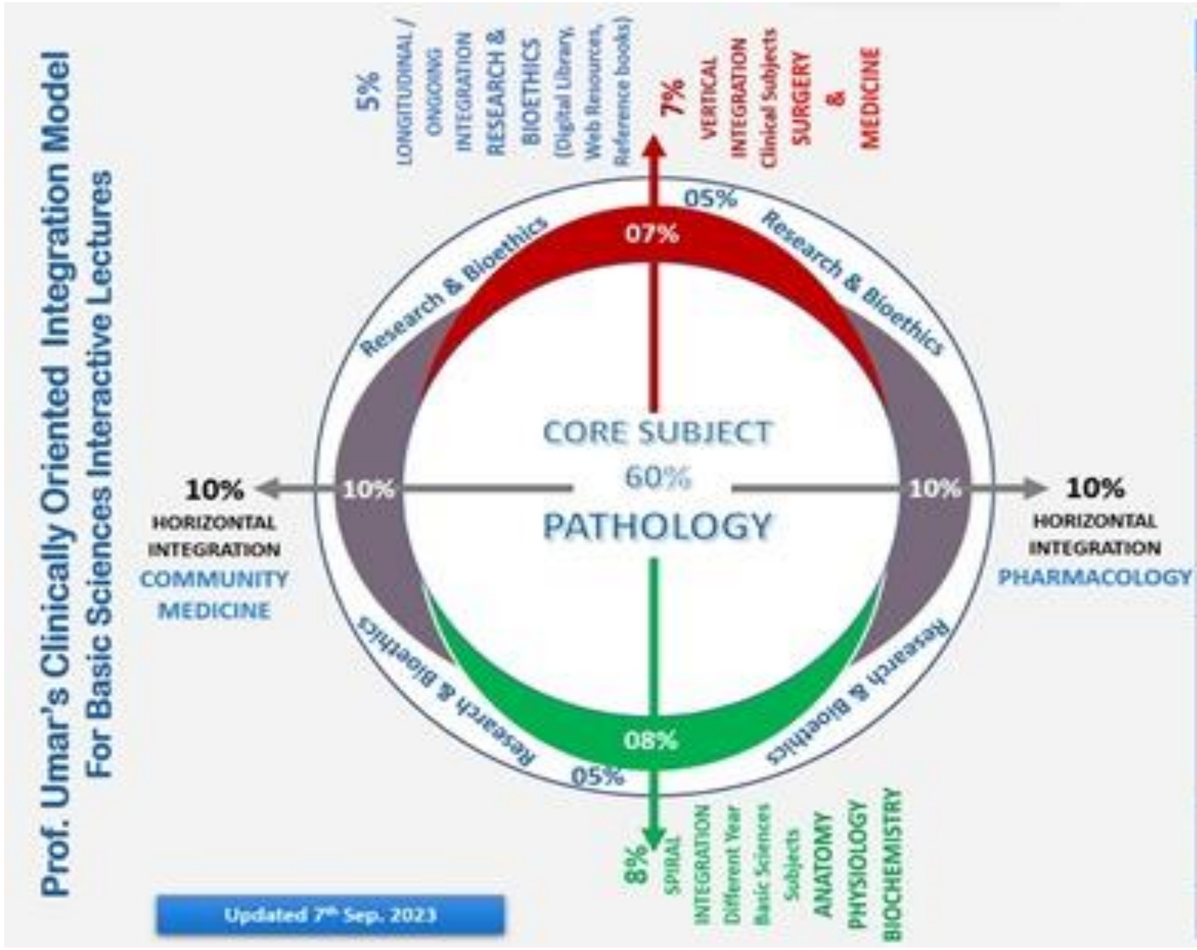
BIOAVAILABILITY

MOTO & VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

UMAR'S MODEL OF INTEGRATION



Model 3rd Year Pathology LGIS (≈30 slides)	
Core Subject – 60% (≈ 18-20 slides)	
Pathology (≈ 18-20 slides)	
Horizontal Integration – 20% (≈ 5-6 slides)	
Same Year Subjects	• Pharmacology (10%) (≈ 2-3 slides) • Community Medicine (10%) (≈ 2-3 slides)
Vertical Integration – 07% (≈ 2-3 slides)	
Clinical Subjects	• Medicine (3-5%) (≈ 1-2 slides) • Surgery (3-5%) (≈ 1-2 slides)
Spiral Integration – 08% (≈ 2-3 slides)	
Different Year Basic Sciences Subjects	• Anatomy (1-3%) (≈ 1-2 slides) • Physiology (1-3%) (≈ 1-2 slides) • Biochemistry (1-3%) (≈ 1-2 slides)
Longitudinal / Ongoing Integration – 05% (≈ 1-2 slides)	
Research & Bioethics (≈ 1-2 slides)	

PRELECTURE ASSESSMENT

When a drug is administered by the intravenous route then an absolute bioavailability will be

A. 0
B. 1
C. 2
D. 3
E. 4

Bioavailability is expressed by formula

A. AUC IV / AUC oral
B. AUC ora1 X AUC IV
C. AUC ora1 / AUC IV
D. AUC oral/AUC oral
E. AUC IV/AUC IV

PRELECTURE ASSESSMENT

Which of the following is the pharmacodynamics method of studying bioavailability?

A. Acute pharmacologic response
B. Plasma-level time studies
C. Urinary excretion studies
D. Stool excretion studies
E. Dose response curve

Two drugs, A and B, have the same mechanism of action. Drug A in a dose of 5mg produces the same magnitude of drug B in a dose of 500mg.

A. Drug B is less efficacious than drug B
B. Drug A is 100 times more potent than drug B
C. Toxicity of drug A is less than that of drug B
D. Drug A is a better drug if maximal efficacy is required
E. Drug A has a shorter duration of action

PRELECTURE ASSESSMENT

The relative amount of an administered dose that reaches the general circulation and the rate at which this occurs:

A. Biological Equivalence
B. Bioavailability
C. Biopharmaceutics
D. Bioequivalency
E. Therapeutic equivalence

Invasive measurement of drug concentration includes

A. Hair
B. Urine
C. Saliva
D. Blood
E. Nail

PRELECTURE ASSESSMENT

Bioavailability of an intravenous drug is always 100% by definition because:

A. Bioavailability measures the amount of substance that reaches the bloodstream.
B. Absolute bioavailability is 50%, for any drug taken intravenously
C. Absolute bioavailability is a much more important measure than relative bioavailability
D. Intravenous administration gets the drug into your bloodstream the fastest.
E. Intravenous administration bypasses first pass metabolism

What would be the order of greater or lesser bioavailability of the dosage forms?

A.Intravenous > rectal > oral > topical
B.Intravenous > oral > rectal > topical
C.Intravenous > topical > rectal > oral
D. Oral > intravenous > rectal > topical
E. Topical> intravenous> oral> rectal

PRELECTURE ASSESSMENT

Which of the following is not an important parameter of plasma level time studies?

A. Cmax
B. Tmax
C. Area under the plasma level-time curve
D. Steady state level
E. Cmin

Which of the following drugs has a high extraction ratio?

A. Diazepam
B. Theophylline
C. Phenytoin
D. Warfarin
E. Propranolol

LEARNING OBJECTIVES

At the end of the academic sessions, students of 3rd Year MBBS will be able to :

01. Define bioavailability

02. Express it mathematically and graphically

03. Describe the clinical significance of bioavailability

04. Define first pass metabolism

05. Recognize the effect of first pass metabolism on bioavailability of drugs

06. Discuss the factors affecting bioavailability of drugs

07. Differentiate between chemical equivalence, bioequivalence & therapeutic equivalence

BIOAVAILABILITY

Fraction of the active drug contained in any dosage form that reaches its site of action or reaches the biological medium that represents its accessibility to the site of action after administration through any route

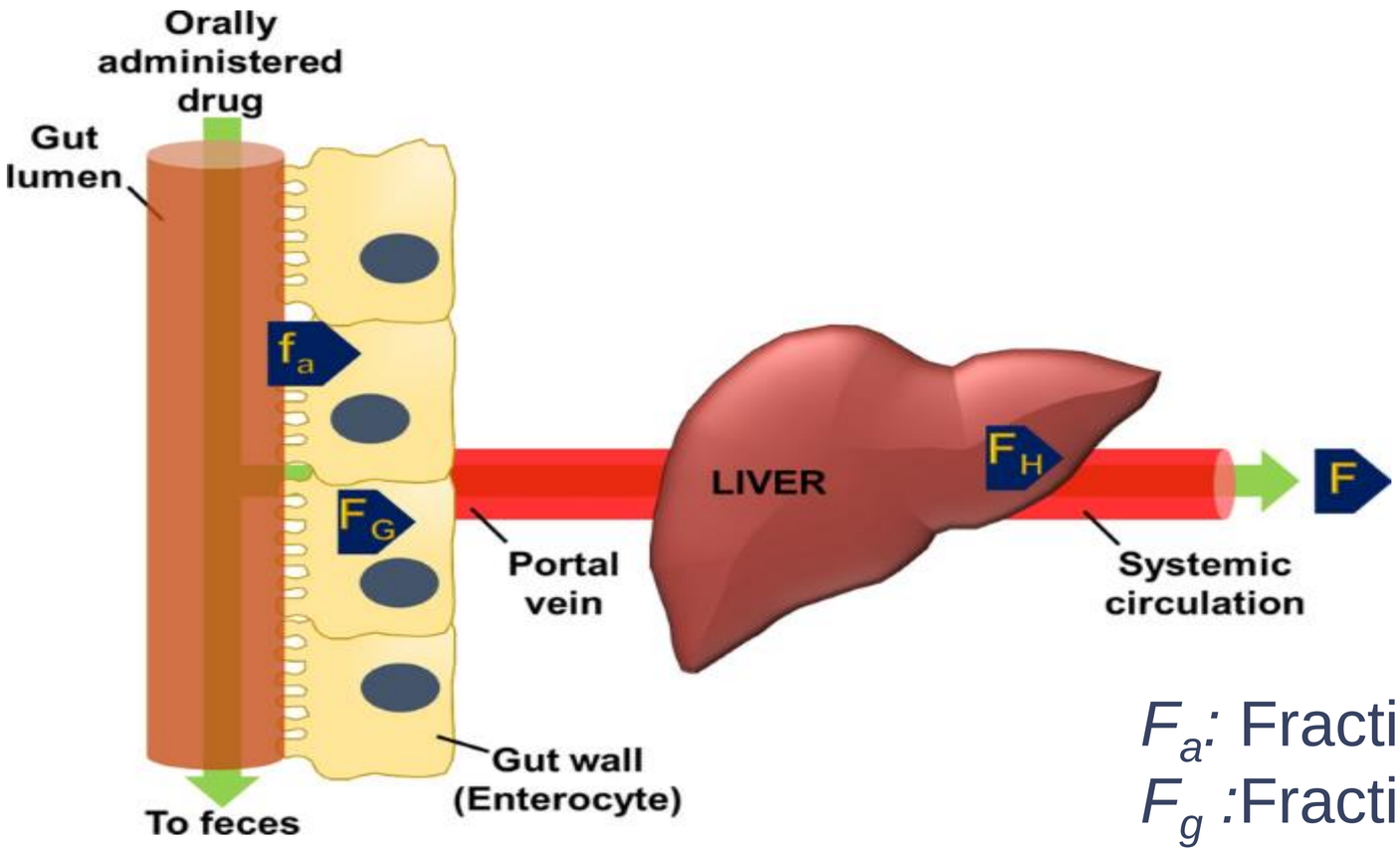
Fraction of unchanged drug reaching the systemic circulation following administration by any route

BIOAVAILABILITY

$$F = \frac{\text{Quantity of drug reaching systemic circulation}}{\text{Quantity of drug administered}}$$

- For IV route = 100 %
- For non IV route = < 100 %

BIOAVAILABILITY



$$F = F_a \cdot F_g \cdot F_h$$

F_a: Fraction absorbed from gut lumen
F_g :Fraction escaping intestinal metabolism
F_h: Fraction escaping hepatic metabolism

BIOAVAILABILITY

Since the body is exposed only to the dose that is absorbed:

Effective dose of a drug = bioavailability x the dose administered

Effective dose of a drug = *F* · dose administered

Thus, if 100 mg of a drug is administered and if $F = 0.8$,
Effective dose = $0.8 \times 100 = 80$ mg

DETERMINATION OF BIOAVAILABILITY

- Measure area under the curve (AUC) between blood concentration & time.

$$\text{Bioavailability (F)} = \frac{\text{AUC Oral}}{\text{AUC Injected I/V}} \times 100$$

- Bioavailability expressed as *F* is measured on a continuous range from 0 to 1 ($0 < F < 1$) but can be represented as a percentage between 0 and 100 %

DETERMINANTS OF BIOAVAILABILITY

A. Physiochemical properties of drug

B. Biological factors affecting extent of absorption from GIT

C. Quality control in manufacturing and formulation

D. First pass metabolism / effect

E. Route of drug administration

DETERMINANTS OF BIOAVAILABILITY

A. Physiochemical properties of the drug

- Particle size
- Molecular size
- Lipid aqueous solubility coefficient
- Physical form
- Chemical form
- Degree of ionization
- Dosage form
- Formulation excipients

DETERMINANTS OF BIOAVAILABILITY

B. Biological factors affecting extent of absorption from GIT

- Area of absorptive surface
- Vascularity
- pH
- Presence of other substances (e-g food and drugs)
- GI motility
- Functional integrity of absorptive surface (diseases)
- Presence of reverse efflux pumps (P-gp)

DETERMINANTS OF BIOAVAILABILITY

C. Quality control in manufacturing and formulation

- Compression pressure
- Moisture content
- Polymorphism
- Disintegration content

DETERMINANTS OF BIOAVAILABILITY

Depending upon the quality control to related drugs may be:

- **Pharmaceutical equivalent**
  Drug products that contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration.

- **Bioequivalent**
  Pharmaceutical equivalents that display comparable bioavailability when studied under similar experimental conditions.

- **Therapeutic equivalent**
  Drug products that are pharmaceutical equivalents and are expected to produce the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling

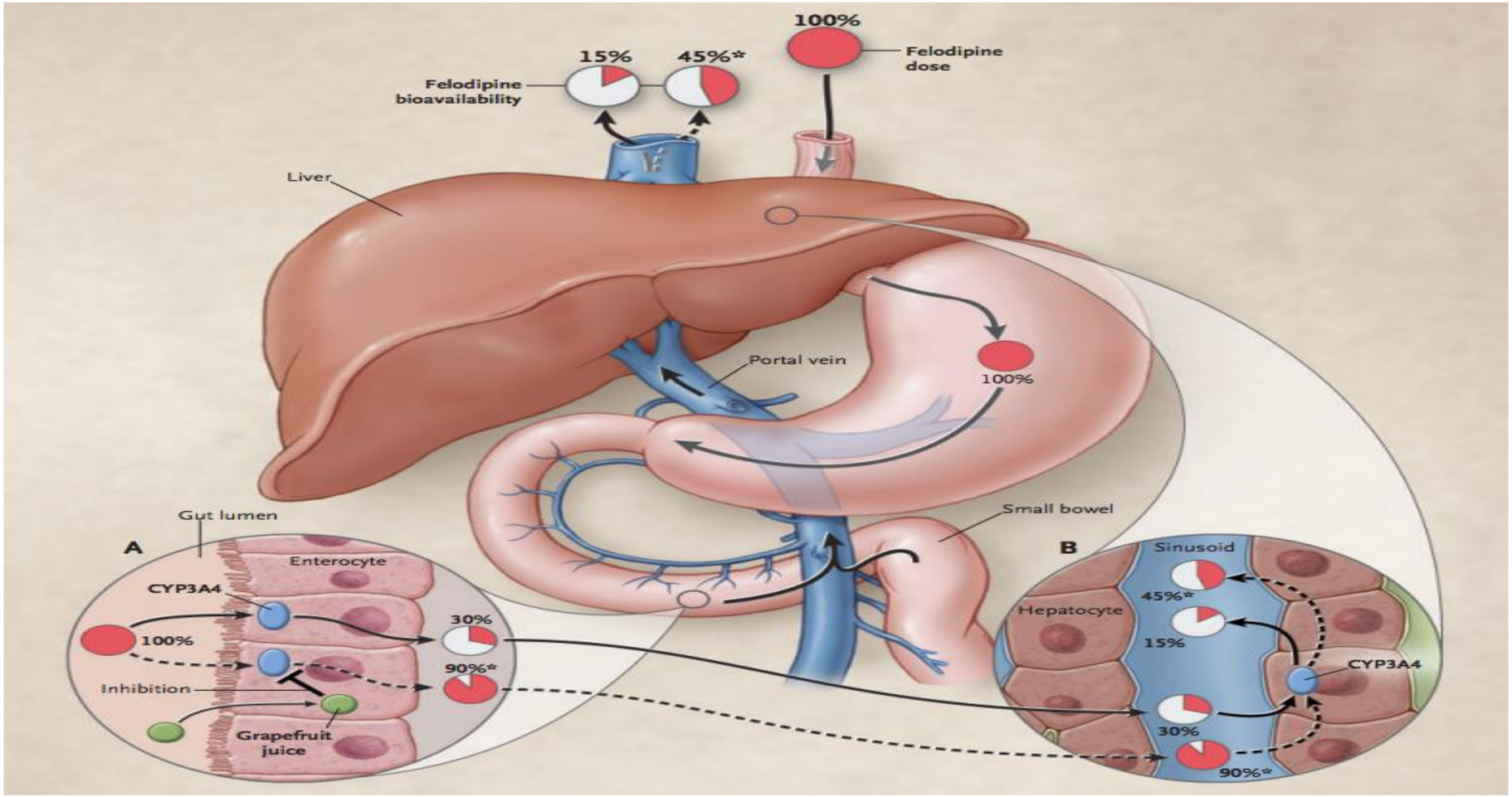
DETERMINANTS OF BIOAVAILABILITY

D. First pass metabolism (pre-systemic metabolism)

- It is the metabolism / inactivation of drug before it reaches systemic circulation.
- First pass effect depends upon the anatomical site from which absorption takes place & it ↓ Bioavailability .

DETERMINANTS OF BIOAVAILABILITY

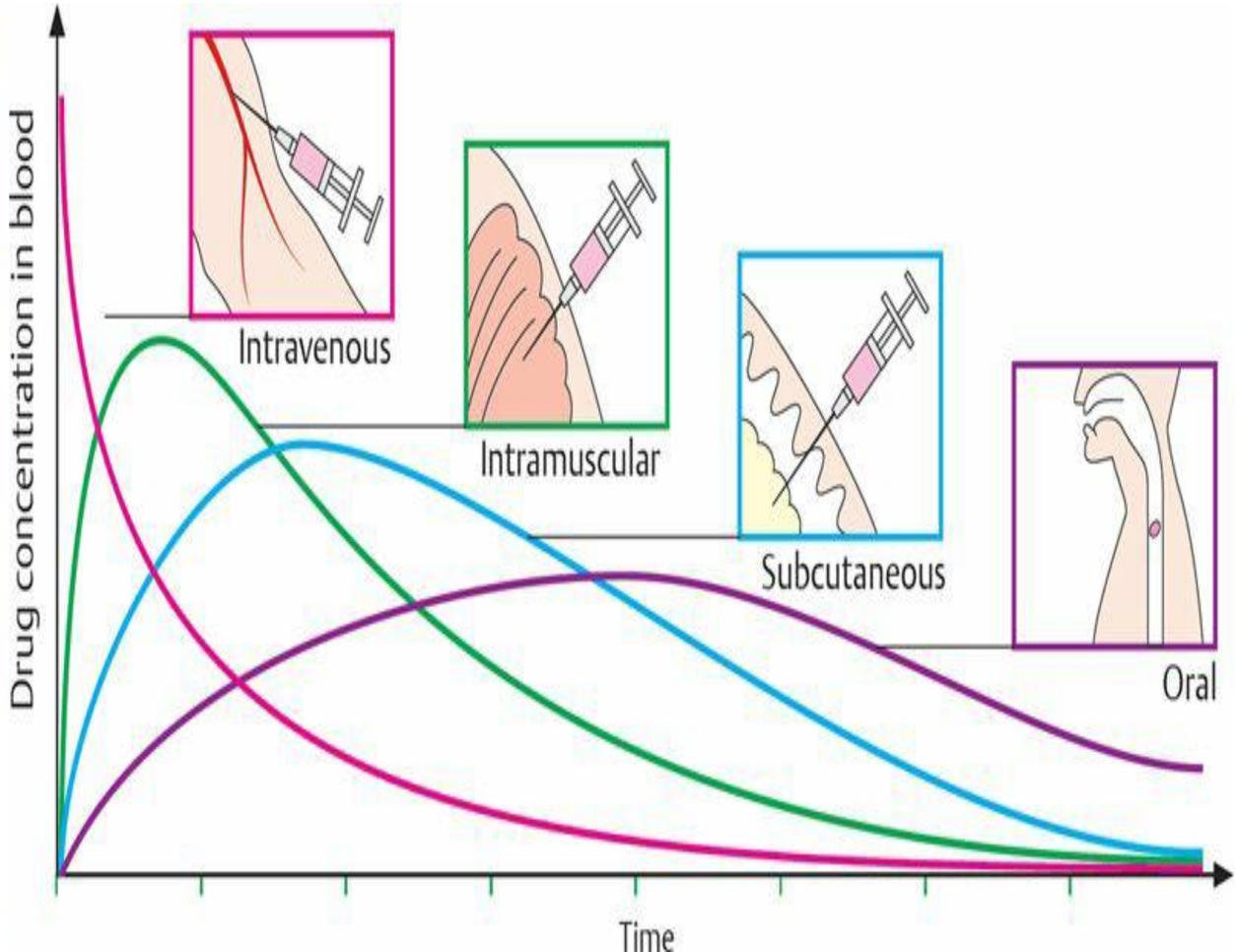
D. First pass metabolism (pre-systemic metabolism)

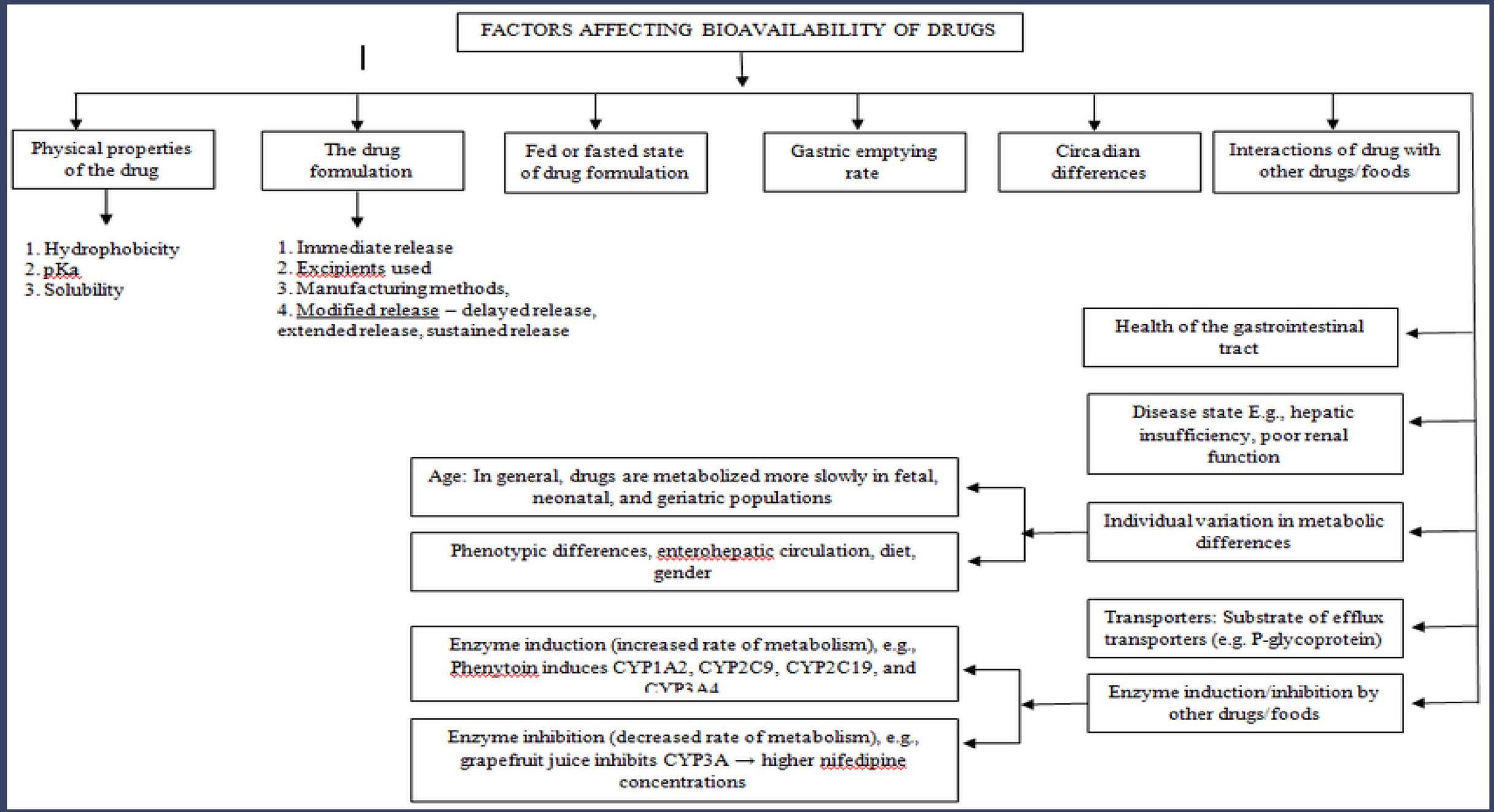


DETERMINANTS OF BIOAVAILABILITY

E. Route of drug administration

Route	Biovailability (%)	Characteristics
Intravenous (IV)	100 (by definition)	Most rapid onset
Intramuscular (IM)	75 to ≤100	Large volumes often feasible; may be painful
Subcutaneous (SC)	75 to ≤100	Smaller volumes than IM; may be painful
Oral (PO)	5 to <100	Most convenient; first-pass effect may be important
Rectal (PR)	30 to <100	Less first-pass effect than oral
Inhalation	5 to <100	Often very rapid onset
Transdermal	80 to ≤100	Usually very slow absorption; used for lack of first-pass effect; prolonged duration of action




FACTORS AFFECTING BIOAVAILABILITY OF DRUGS
Physical properties of the drug
The drug formulation
Fed or fasted state of drug formulation
Gastric emptying rate
Circadian differences
Interactions of drug with other drugs/foods
1. Hydrophobicity
2. pKa
3. Solubility
1. Immediate release
2. Excipients used
3. Manufacturing methods,
4. Modified release – delayed release, extended release, sustained release
Health of the gastrointestinal tract
Disease state E.g., hepatic insufficiency, poor renal function
Age: In general, drugs are metabolized more slowly in fetal, neonatal, and geriatric populations
Phenotypic differences, enterohepatic circulation, diet, gender
Individual variation in metabolic differences
Transporters: Substrate of efflux transporters (e.g. P-glycoprotein)
Enzyme induction (increased rate of metabolism), e.g., Phenytoin induces CYP1A2, CYP2C9, CYP2C19, and CYP3A4
Enzyme inhibition (decreased rate of metabolism), e.g., grapefruit juice inhibits CYP3A → higher nifedipine concentrations
Enzyme induction/inhibition by other drugs/foods

PATHOLOGICAL STATES

- **<u>Diseases with high BA:</u>**
  In severe hepatic cirrhosis / portal systemic shunts, the dose of the drugs should be ↓ otherwise toxicity due to increased bio-availability

❖High extraction ratio

❖Extensive first pass metabolism

ENHANCEMENT OF BIOAVAILABILITY

- **High Oral Doses:**
- Verapamil & Lidocaine have high hepatic extraction ratio & F < 40%.
  High oral doses of verapamil may be given but Lidocaine has metabolites toxic to CNS, so given I/V.

- **Avoidance of hepatic first pass metabolism:**
  - Alternate routes of administration:
    Sublingual, transdermal, e.g. Nitroglycerine
    Injections e.g. Lidocaine
  - Co-administration with other drugs:
  - Administration as prodrugs

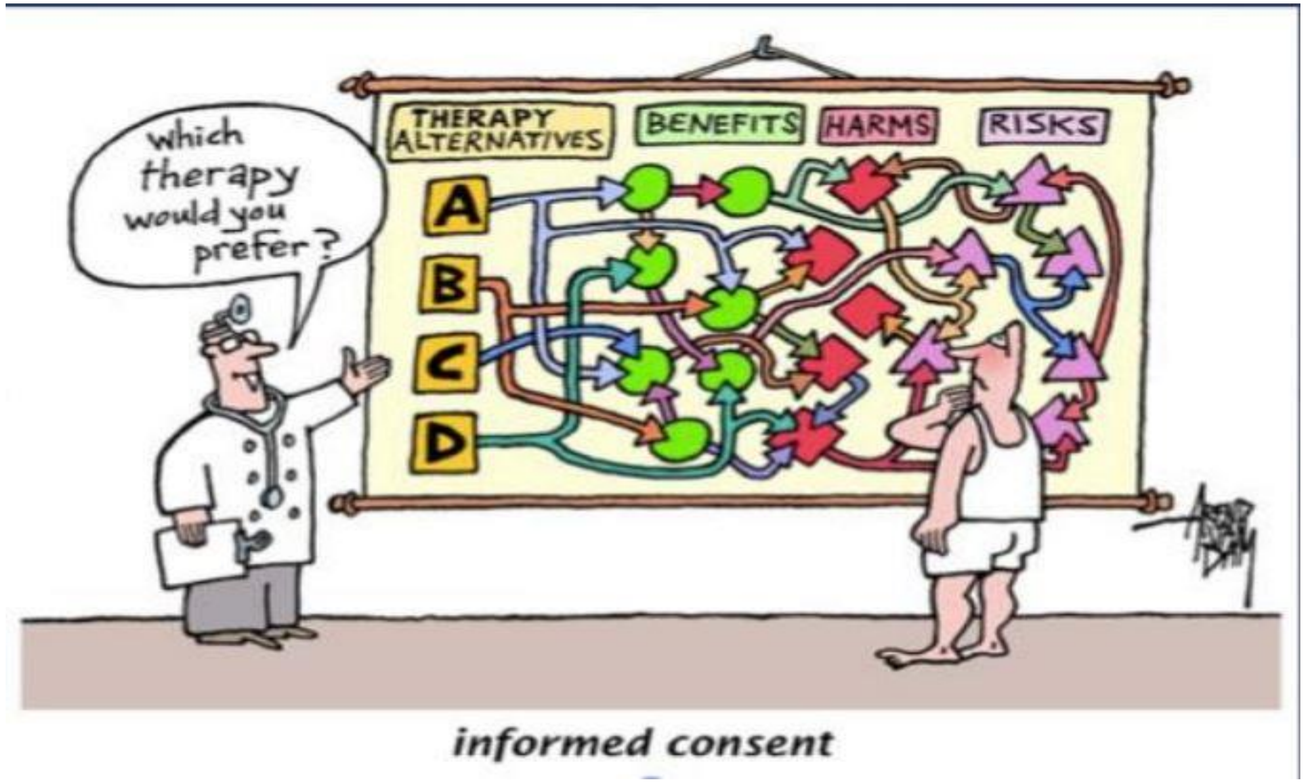
SIGNIFICANCE OF BIOAVAILABILITY

- **Change in F may lead to under medication or over medication**
  - Under medication –**Therapeutic failure**
    Life saving drugs
  - Over medication – **Toxicity**
    Low therapeutic index (cardiac glycosides)
  - **Substitution of therapeutically equivalent drug formulations with each other**
  - **Prevention of misuse of drugs (pentazocine + nalaxone)**

RESEARCH

- Eisenmann, E.D., Talebi, Z., Sparreboom, A. and Baker, S.D., 2022. Boosting the oral bioavailability of anticancer drugs through intentional drug–drug interactions. *Basic & clinical pharmacology & toxicology*, *130*, pp.23-35.

BIOETHICS



“Informed consent is rooted in the fundamental recognition—reflected in the legal presumption of competency—that adults are entitled to accept or reject health care interventions on the basis of their own personal values and in furtherance of their own personal goals.”

ARTIFICIAL INTELLIGENCE

Tyagi S, Pathak A, Rao NR, Nehra S, Asthana A, Sharma V, Katyal G, Bhardwaj A, Sharma L, Prakash S. AI-assisted Formulation Design for Improved Drug Delivery and Bioavailability. Pakistan Heart Journal. 2023;56(3):1-4.