UNIT I

Drug absorption AND ITS Physicochemical properties affecting

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INTRODUCTION

FACTORS AFFECTING DRUG ABSORPTION

PHYSICOCHEMICAL FACTORS AFFECTING DRUG ABSORPTION

i. Lipid solubility and dissociation constant and pH
ii. Dissolution
iii. Particle size and Effective surface area
iv. Polymorphism and Amorphism
v. Solvates and hydrates(Pseudopolymorphism)
vi. Salt form
vii. Drug permeability and absorption
viii. Viscosity
Absorption is defined as the amount of drug that reaches the systemic circulation in an unchanged form.

Hence, the drug which is metabolized or chemically transformed at the site of application or transit is not said to be absorbed.

The main mechanisms by which absorption occurs include:

(a) Transcellular or intracellular transport

(b) Paracellular or intercellular transport

(c) Vesicular transport or endocytosis
TRANSPORT MECHANISMS

**Fig. 2.3** Illustrative comparison of transcellular, paracellular and vesicular transport mechanisms.
FACTORS AFFECTING DRUG ABSORPTION

(a) PHARMACEUTICAL FACTORS

• Physicochemical Factors

• Dosage form characteristics

(b) PATIENT RELATED FACTORS
PHYSICOCHEMICAL FACTORS AFFECTING DRUG ABSORPTION

- Lipid solubility, dissociation constant and pH
- Dissolution
- Salt form
- Particle size and Effective surface area
- Polymorphism and Amorphism
- Solvates and hydrates (Pseudopolymorphism)
- Salt form
- Drug permeability and absorption
- Viscosity
LIPID SOLUBILITY AND DISSOCIATION CONSTANT AND Ph

- More the drug in non ionized form, more is it lipid soluble and better is the absorption.

- pH-partition theory:
  
  The interrelationship of dissociation constant, lipid solubility, pH at the absorption site and absorption characteristics of various drugs throughout the GIT.

The rate of loss of drug in solution form from the absorption site is given by:

\[-\frac{DC_t}{dt} = K_a C_u\]

Where,

\(Dc_t/dt\) = rate of drug loss from absorption site

\(K_a\) = absorption rate constant

\(C_t\) = Total drug concentration

\(C_u\) = concentration of unionized drug.
The dissociation constant is expressed for both acids and bases as a pKa value:

- **FOR ACID**
  \[ \text{pH} = \text{pKa} + \log \frac{\text{conc. (ionized)}}{\text{conc. (unionized)}} \]

- **FOR BASE**
  \[ \text{pH} = \text{pKa} + \log \frac{\text{conc. (unionized)}}{\text{conc. (ionized)}} \]

- Weakly acidic drugs (eg: aspirin) dissolve faster in gastric fluids.
- Weakly basic drugs (eg: quinine) dissolve faster in intestinal fluids.
- Acidification or basification of both stomach and intestine will produce converse effects.
• Though the pH partition hypothesis simplified the concept of drug absorption, it has its own limitations

• Deviations from this theory include:

(a) presence of virtual membrane pH
(b) absorption of ionized drug
(c) GI surface area and residence time of drug
(d) presence of aqueous unstirred diffusion layer
DISSOLUTION

- A drug gets absorbed in the biological system, when it gets dissolved in the physiological fluid at the absorption site.
- The steps are as under:
  - solid dosage form (tablet or capsule)
  - disintegration (coarse particles of drug)
  - dissolution
  - drug in solution (very fine particles)
  - drug in systemic circulation
Fig. 2.15 The two rate-determining steps in the absorption of drugs from orally administered formulations
THEORIES OF DRUG DISSOLUTION

• Diffusion layer model/film theory
• Danckwert’s model/surface renewal theory
• Interfacial model/double barrier model theory
Fig. 2.16 Diffusion layer model for drug dissolution
The rate of dissolution is given by Noyes and Whitney:

\[
dc\frac{dt}{dt} = k(C_s - C_b)
\]

Where,
- \(dc/dt\) = dissolution rate of the drug
- \(K\) = dissolution rate constant
- \(C_s\) = concentration of drug in stagnant layer
- \(C_b\) = concentration of drug in the bulk of the solution at time \(t\)
The Noyes Whitney Equation Was Modified By Nernst And Brunner As Follows:

\[
\frac{dc}{dt} = \frac{DAK_{w/o} (C_s - C_b)}{Vh}
\]

Where,
D= diffusion coefficient of drug.
A= surface area of dissolving solid
Kw/o= water/oil partition coefficient of drug.
V= volume of dissolution medium.
h= thickness of stagnant layer.
\((C_s - C_b)\)= conc. gradient for diffusion of drug.
DANCKWERT’S MODEL/PENETRATION OR SURFACE RENEWAL THEORY

Solid/liquid interface having concentration $C_l < C_s$

Fresh packet of solvent approaching the interface

Packet of solvent saturated with drug leaving the interface

Bulk of the solution having concentration $C_b < C_l$

Fig. 2.18 Danckwert’s model for drug dissolution
The Danckwert’s model is expressed by equation

\[ \sqrt{V} \frac{dC}{dt} = \frac{dm}{dt} = A (C_s - C_b) \sqrt{\gamma D} \]

Where,

\( m = \) mass of solid dissolved

\( \gamma = \) rate of surface renewal
The concept of this theory is explained by following equation-

\[ G = K_i (C_s - C_b) \]

Where,
- \( G \) = dissolution rate per unit area,
- \( K_i \) = effective interfacial transport constant.
• Particle size and surface area share an inverse relationship.
• Surface area can be classified as
  (1) Absolute surface area
  (2) Effective surface area
• Greater the effective surface area, better the dissolution and so the absorption.
• Absolute surface area can be converted to effective surface area by:
  (1) Use of surfactants like polysorbate 80.
  (2) Adding hydrophilic diluents like PEG, PVP etc.
POLYMORPHISM AND AMORPHISM

- Internal Structure of a Compound
  - Crystalline
  - Amorphous
    - Non Stoichiometric
      - Stoichiometric (Pseudopolymorphs)
    - Organic Solvates
    - Hydrates
  - Molecular Adducts
  - Enantiotropic
  - Monotrops
Conversion of a weakly acidic or basic drug in its salt form enhances the solubility and dissolution rate of the drug.

For salts of weak acids,

\[ [H]_d > [H]_b \]

For salts of weak bases,

\[ [H]_d < [H]_b \]

Where,

\[ [H]_d = \text{hydrogen ion conc. of diffusion layer} \]
\[ [H]_b = \text{hydrogen ion conc. of bulk layer} \]

The increase and decrease in the pH of diffusion layer by salts of weak acids and weak bases has been attributed to the buffering action of strong base cation and strong acid anion.
Fig. 2.20  Dissolution and absorption of an acidic drug administered in a salt form
Most orally administered drugs enter the systemic circulation by passive diffusion.

Three major characters that determine the permeability of the drug across the intestinal epithelium are:

(a) lipophilicity of the drug

(b) polarity

(c) molecular size
• The net effect of above three properties is given as RULE OF FIVE by Lipinski which is written as:

Molecular wt of drug $\leq 500$
Lipophilicity of drug $\leq 5$
Number of H-bond receptors $\leq 10$
Number of H-bond donors $\leq 5$

☑ If any two of these values are greater than specified limits, the oral absorption of a drug may be a significant problem.
• Viscosity and drug dissolution share an inverse relationship

• Change in viscosity may affect the drug absorption by mechanisms like:

  (1) Modification in gastric emptying rate
  
  (2) Modification in intestinal transit rate

  (3) Change in the rate of drug molecules from lumen to the absorbing membrane.
REFERENCES


- Dr. Javed Ali, Dr. Alka Ahuja, Dr. Sanjula Baboota, Dr. Roop K. Khar, Biopharmaceutics And Pharmacokinetics (Theoretical Concepts And Illustrative Practical Exercises), Treatise, absorption Of Drugs, second Edition 2008-2009, birla Publications, 6-52.