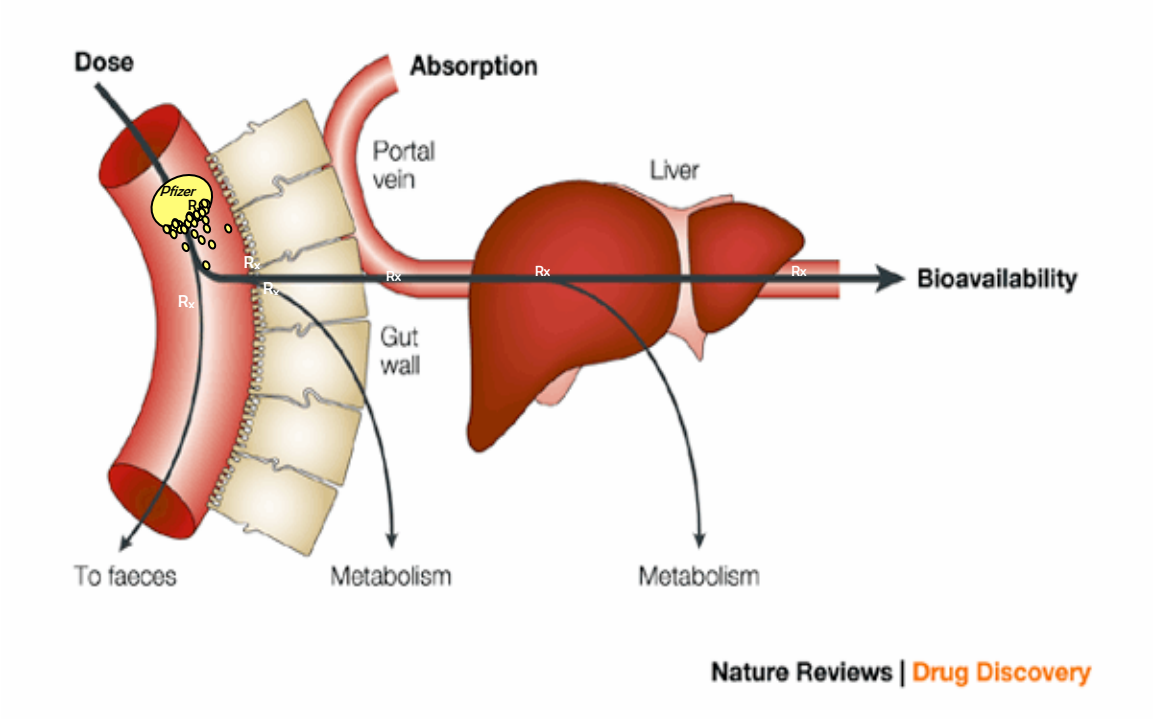

Is Poor Bioavailability in Early drug Discovery a Problem and If So, How Can We Solve It?

Presented by: Ayman El-Kattan, B.Pharm., Ph.D.

1. **Introduction**
    1.1. Overview on drug discovery and development
        1.1.1. Chronology of the drug discovery and development
        1.1.2. Challenges of drug discovery and development
        1.1.3. Role of drug discovery in reducing NME attrition
2. **Pharmacokinetics**
    2.1. Pharmacokinetics definition
        2.1.1. First order and zero order kinetics
        2.1.2. Non-compartmental and compartmental analysis
        2.1.3. Area under the curve (AUC)
        2.1.4. Cmax and Tmax
        2.1.5. Absorption Rate Constant (Ka)
        2.1.6. Volume of distribution (Vd)
        2.1.7. Clearance (CL)
        2.1.8. Half life ($T_{1/2}$)
3. **ADME**
    3.1. Oral absorption
        3.1.1. Factors affecting oral absorption
            3.1.1.1. GIT surface area
            3.1.1.2. GIT pH
            3.1.1.3. Absorption window
            3.1.1.4. Gastric emptying and intestinal motility
    3.2. Distribution
        3.2.1. Perfusion vs. permeability rate limited
        3.2.2. physicochemical and physiologic factors influencing drug distribution
    3.3. Metabolism
        3.3.1. Phase I and II reaction
    3.4. Excretion
        3.4.1. Routes of excretion
        3.4.2. Renal excretion
        3.4.3. Biliary excretion
        3.4.4. Enterohepatic circulation
4. **Oral bioavailability**
    4.1. Oral bioavailability definition
    4.2. Oral bioavailability calculation
    4.3. Parameters affecting oral bioavailability
        4.3.1. Absorption impact on oral bioavailability

4.3.1.1. The process of drug absorption

4.3.1.2. Approaches on structural modification to alter drug solubility

4.3.1.2.1. Drug pKa

4.3.1.2.2. Drug ionization

4.3.1.2.3. Drug lipophilicty

4.3.1.2.4. Drug hydrogen bonding

4.3.1.2.5. Out of plane substitution

4.3.1.2.6. Prodrug

4.3.1.3. Approaches to increase drug dissolution/solubility

4.3.1.3.1. Particle size and its impact on drug dissolution

4.3.1.3.2. The use of nanoparticle in overcoming poor dissolution

4.3.1.3.3. Amorphous drug

4.3.1.3.4. pH and salt interplay

4.3.1.3.5. Polymorphism

4.3.1.3.6. Drug complexation

4.3.1.4. Approaches on structural modification to alter drug permeability

4.3.1.4.1. pH partition theory

4.3.1.4.2. pKa and drug permeability

4.3.1.5. Impact of p-glycoprotein on oral bioavailability

4.3.1.6. Impact of BCRP on oral bioavailability

4.3.2. Impact of first pass on oral bioavailability

4.3.2.1. First pass definition

4.3.2.2. Impact of species differences on drug hepatic elimination and oral bioavailability

4.3.2.3. Intestinal metabolism and its impact on first pass and oral bioavailability

4.3.2.4. Approaches to overcome first pass effect

4.3.2.4.1. Impact of drug lipophilicty on first pass

4.3.2.4.2. Impact of polar groups introduction on first pass

4.3.2.4.3. Overcoming metabolically labile groups

5. <u>Approaches to assess poor oral bioavailability issues</u>

5.1. In Silico, In Vitro and In Situ approaches

5.1.1. In silico evaluation and data modeling

5.1.2. Thermodynamic and kinetic solubility determination

5.1.3. Dissolution evaluation

5.1.4. Caco-2 cell line

5.1.5. In situ rat intestinal perfusion

5.2. In Vivo approaches

5.2.1. AUC comparison between oral and intravenous administration

5.2.2. Mass balance

5.2.3. Clearance method

5.2.4. Dose proportionality studies

5.3. Approaches to assess the pharmacodynamic activity of NME with poor oral bioavailability

5.3.1. Intraperitoneal (IP) dosing

5.3.2. Subcutaneous (SC) dosing

5.3.3. Challenges with IP and SC dosing

6. Group Problem Solving-Case Studies in Oral Bioavailability and Pharmacokinetics

6.1. Case Studies

6.2. Dissecting some case studies for specific problems encountered by attendees

7. Questions and Answers