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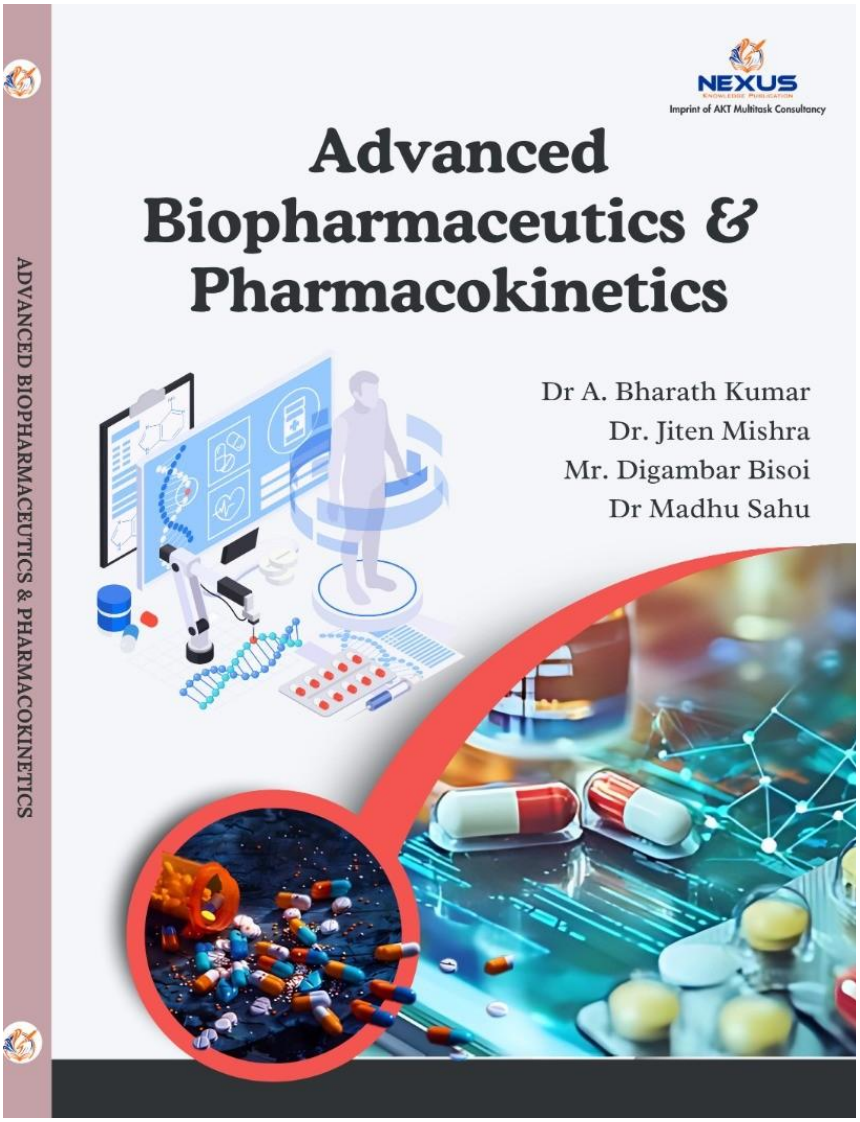

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Chapter- 3

TRANSPORT MODELS IN DRUG ABSORPTION

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Controlled understanding of drug absorption transportation rules across gastrointestinal tract tissue remains essential to forecast oral medication availability in addition to enhancing drug product development. Drug absorption relies on drug solubility and membrane permeability together with the physicochemical traits of drugs that include their charge and lipophilic nature beside the changing conditions within the gastrointestinal tract [1]. The chapter examines different transport models that clarify drug movement through intestinal epithelial cells while studying the interaction of permeability and solubility along with charge state per the pH-partition hypothesis. The text explores several gastrointestinal characteristics that affect drug absorption such as tight junction functioning and the relationship between intracellular and microclimate pH environments. A combination of physical models with physiological knowledge enables scientists to fully understand oral drug absorption which will enhance development of effective targeted oral pharmaceuticals.

3.1 PERMEABILITY-SOLUBILITY-CHARGE STATE AND PH PARTITION HYPOTHESIS

The process of drug movement through biological membranes depends on evaluating permeability as well as solubility and ionization [2]. The pH-partition hypothesis depends on drug properties together with GI tract environmental pH for determining drug absorption. The following section elaborates on these elements in their connected functions.

3.1.1 Permeability of Drug Molecules

Drugs go through permeability tests to determine their absorption rates through gastrointestinal tracts because of oral medication delivery routes. Drug permeability indicates how effectively a substance crosses membranes especially the gut wall epithelial layer to reach systemic circulation. Drug molecules need to penetrate into the lipid bilayer of intestinal epithelial cells through a process that mainly depends on their lipophilicity and molecular dimensions.

- **Passive Diffusion and Lipophilicity**

Drugs pass through tissues predominantly through passive diffusion which enables molecules to travel from high concentration areas of the intestinal lumen into low concentration blood. The drug's capacity to dissolve in lipids plays a crucial role during this process that performs without energy consumption. Drugs that belong to the lipophilic group can effortlessly become absorbed and pass through the lipid-density membranes of epithelial cells.

Non-polar molecules along with those in the moderately small size range have good passive diffusion capacity because they easily bond with the hydrophobic membrane core. The drugs obtain rapid absorption in addition to efficient uptake.

- **Limitations of Excessive Lipophilicity**

High lipophilicity does not provide benefits at all occasions. Drugs that have a balanced level of lipophilicity can easily cross through membranes but drugs which have too much lipophilicity may present certain complications. Insufficient exit from the membrane becomes difficult because the drugs become trapped in the bilayer structure. The drug transfer through membranes becomes impeded because of its morphological structure which results in reduced bioavailability [3]. The absorption process suffers because highly lipophilic compounds cannot properly dissolve in aqueous GI fluids before their initial transformation into absorbable molecules.

- **Hydrophilic Drugs and Alternative Pathways**

Hydrophilic drugs experience difficulties in membrane permeability because their polarity creates chemical incompatibility with the non-polar lipid bilayer. Lipid membranes find it energetically challenging to accept hydrophilic molecules through passive diffusion because hydrophilic drugs tend to be large or charged and polar in nature [4].

Transport systems based on carriers serve as a method to address such limitations. These include:

- **Facilitated diffusion**, where drugs hitch a ride through the membrane via specific protein channels.
- **Active transport**, where drugs are moved against their concentration gradient using energy.
- **Endocytosis**, The cell membrane engulfs large molecules or nanoparticles which results in their vesicular internalization.

Specific transport proteins enable absorption of nutrients along with drug analogs resembling them even though they have poor lipid solubility properties.

- **Permeability and Drug Design**

Knowledge of permeability enables pharmaceutical scientists to create improved drug compounds which lead to improved absorption. Prodrug design as well as nanoparticle carriers and permeation enhancers are applicable methods which enhance the bioavailability of drugs

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with limited permeability through modifications to drug lipophilicity and transport characteristics.

- **Solubility and its Influence on Absorption**

A substance requires solution status for absorption to take place. For GI fluid absorption to occur a drug must dissolve to a certain extent. Solubility constitutes the fundamental necessity for drug absorption. A high level of drug permeability alone is insufficient for absorption if the drug has poor solubility properties. The Biopharmaceutics Classification System (BCS) uses solubility and permeability equilibrium to create four drug categories.

3.1.2 Charge State and Drug Ionization

Drugs achieve their absorption and distribution potential and membrane permeability status through their charge state condition[5]. Two key elements determine the charge state of drugs: the pKa of the drug as well as the pH value of surrounding conditions. The extent which a drug exists in either its ionized charged state or its non-ionized uncharged state results from these two factors working in combination.

- **Ionization: A Dynamic Equilibrium**

Drugs existing as weak acids or bases demonstrate two forms which depend on solution pH. Thus they become either non-ionized or ionized substances [6]. A drug exists in two equal quantities between ionized and non-ionized states when the solution reaches its pKa value. The Henderson-Hasselbalch equation defines the correlation between solution pH and drug pKa value.

For Weak Acid,

$$pH = pKa + \log(\frac{A^-}{HA})$$

For Strong Acid,

$$pH = pKa + \log(\frac{B}{BH^+})$$

This equation helps to predict the ratio of ionized to non-ionized drug at a given pH.

➢ **Membrane Permeability and Lipophilicity**

Lipophilic drugs in their non-ionized state pass through intestinal epithelial membrane lipid bilayer due to their fat-solubility properties during passive diffusion. Non-ionized molecules move across systemic circulation with higher ease.

The lipid membranes present in the body become less permeable to hydrophilic molecules which are ionized drug molecules [7]. The charged nature of these molecules makes them stay in gastrointestinal lumen liquid or plasma solution while needed transport systems enable their biological membrane penetration.

➢ **Site-Specific Absorption in the GI Tract**

The pH of the gastrointestinal tract varies significantly along its length, affecting the ionization and thus the absorption site of drugs:

- Stomach (pH 1–3): Favors the non-ionized form of weak acids (e.g., aspirin), promoting their absorption.
- Small intestine (pH 5–8): Favors the non-ionized form of weak bases (e.g., diazepam), enhancing their absorption.

Weak acids show better absorption in the stomach compared to weak bases which get better absorption within the intestine.

➢ **Practical Implications for Drug Formulation and Delivery**

Understanding the charge state is crucial for:

- **Drug design:** Molecules can be modified to adjust their pKa and improve absorption characteristics.
- **Formulation development:** Enteric coatings or pH-sensitive delivery systems can protect drugs from premature ionization or degradation.
- **Targeted delivery:** By exploiting local pH variations, drugs can be directed to specific regions of the GI tract.

➢ **Challenges and Limitations**

Despite its importance, relying solely on pKa and pH to predict drug absorption can be limiting because:

- Other factors like intestinal motility, presence of food, and interaction with enzymes or bile salts also affect absorption.

- Some ionized drugs may still be absorbed via active transport mechanisms if suitable carriers are present.

3.1.3 The pH Partition Hypothesis

The pharmaceutical sciences employ the pH partition hypothesis to explain drug ionization correlations with membrane permeation particularly within gastrointestinal environments [8]. The theory provides essential knowledge about how drug characteristics and stomach-intestinal pH concentrations affect absorption rates inside the GI tract.

➢ **Concept of Ionization and Absorption**

Drug molecules are typically either weak acids or weak bases, and their degree of ionization in solution depends on:

- The pKa of the drug (the pH at which 50% of the drug exists in its ionized form)
- The pH of the environment

Drug molecules need to be non-ionized at their basic state to enable passive diffusion across cell membrane lipid bilayers according to the pH partition theory. The charged form of a drug remains water soluble but becomes non-lipid permeable because of its inability to penetrate cell membranes.

➢ **Regional pH Variations in the GI Tract**

The GI tract exhibits significant pH differences along its length:

- The stomach has an acidic environment with a pH of ~1 to 3.
- The duodenum has a pH around 5 to 6.
- The small intestine and colon range from pH 6 to 8.

Drug ionization status at different regions across the GI tract depends on the variations which determine optimal absorption sites.

➢ **Absorption of Weakly Acidic Drugs**

Weak acids (e.g., aspirin) tend to be non-ionized in acidic conditions, such as those found in the stomach. In their non-ionized form, these drugs can:

- Diffuse readily through the lipid membranes of gastric epithelial cells
- Be absorbed effectively in the stomach and upper small intestine

However, as the pH rises in the intestine, weak acids become more ionized, reducing their permeability and thus their absorption from these regions.

➢ **Absorption of Weakly Basic Drugs**

Codeine along with diazepam exhibit weak basic properties that result in poor absorption levels when present in stomach acid. The alkaline condition in the bowel causes these drugs to transition to a non-ionized state that enables the absorption to occur.

- Penetrate the intestinal mucosa more efficiently
- Be absorbed primarily in the small intestine

The better absorption of basic drugs takes place through intestinal release rather than stomach release because of this occurrence.

➢ **Clinical and Pharmaceutical Implications**

Understanding the pH partition hypothesis helps in:

- **Designing drug formulations**: Enteric coatings function to protect drugs that would dissolve in stomach acid so these medicines reach the intestinal tract where absorption occurs better.
- **Predicting drug–drug and drug–food interactions**: Drugs taken with antacids and proton-pump inhibitors may experience altered absorption because the medication solubility and ionization state changes due to elevated gastric pH.
- **Personalizing medication regimens**: The decision to administer this medication depends on patient gastric pH levels particularly when patients have hypochlorhydria or gastric surgical procedures.

3.1.4 Interrelationship of the Three Factors

The ability of orally given drugs to be absorbed relies on three fundamental properties such as permeability as well as solubility alongside the drug's ionic nature. The three factors determine the effectiveness with which a drug can traverse the gastrointestinal barrier to achieve systemic circulation. Both drug development success and therapeutic effectiveness require complete analysis of this relationship between permeability and solubility along with drug ionization state.

➢ **Permeability vs. Solubility: A Delicate Balance**

The optimization of drug properties through permeability and solubility produces opposing effects in drug development. A drug that quickly dissolves in GI fluids produces beneficial concentration conditions across the epithelial membrane. The drug faces challenges with membrane passage because excessive hydrophilicity makes diffusion through lipid enclosing

membranes difficult. A permeable drug tends to be lipid in nature yet when solubility is low its dissolution rate in GIT fluids restricts the amount reaching the absorption phase.

Managing the equilibrium becomes essential when treating drugs belonging to BCS Class II and IV since both dissolving along with permeating capabilities are minimal. Formulation scientists need to develop unique strategies to improve both properties when these drug attributes exhibit an interconnected response.

- **Influence of Charge State and pH Environment**

Drugs exist in absorption-affine forms depending on their ionization state that results from intrinsic pKa and local environmental pH values. The non-ionized state of a drug possesses better membrane permeability because it manifests lipophilic properties which enable passive diffusion. The natural environment of water acts as an effective barrier that restricts the movement of drug molecules which exist in ionized forms.

For instance:

- A weakly acidic drug is better absorbed in the acidic environment of the stomach, where it remains predominantly non-ionized.
- A weakly basic drug shows better absorption in the alkaline environment of the small intestine, where its ionization is reduced.

Thus, regional pH variations along the GI tract can strongly influence where and how well a drug is absorbed.

- **Formulation Strategies to Enhance Absorption**

Local absorption capabilities of drugs become more effective when pharmaceutical scientists understand how these factors interact with each other. Strategies include:

- Salt formation to enhance solubility without sacrificing permeability.
- Use of pH modifiers or buffer systems in formulations to maintain a local environment favorable to drug ionization and solubility.
- Nanoparticle and lipid-based delivery systems to improve both dissolution and membrane penetration.
- Prodrug approaches, where a chemically modified drug form is more soluble or better absorbed and then converted into the active drug in the body.

Scientists use customized approaches to enhance drug absorption quantities at the site of entrance into the body which leads to better bioavailability levels.

- **Predictive Modeling and Drug Development**

In silico tools and mathematical models have become essential for modern drug development because they predict drug absorption potential through simulations of permeability and solubility and ionization interactions. The computational models serve to estimate drug oral absorption rates before significant development stages thus preventing resource waste. Therapeutic outcomes become more consistent while drug responses among patients decrease when scientists can well understand and control these three properties.

3.2 PROPERTIES OF THE GASTROINTESTINAL TRACT (GIT)

Food along with drugs together with the GIT perform active roles by controlling the drug dissolution process and related drug metabolic transformations and absorption steps. Drugs move from the lumen to systemic circulation with different rates of effectiveness which results from various physiological, biochemical and structural properties of the gastrointestinal tract. Effective oral drug delivery systems require thorough understanding of the substantial property variations between different parts of the tract.

3.2.1 Surface Area and Mucosal Architecture

Molecular Absorption Effectiveness in Drugs Depends on Both the Git Surface Area and The Mucosal Architecture of It [9]. Among all GIT regions the small intestine plays the greatest role in drug absorption because it contains advanced structural features alongside its extensive surface area. The specific structure is essential for driving drug molecules to efficiently contact the intestinal epithelium which leads to enhanced absorption.

- **Villi and Microvilli: Increasing Surface Area**

The small intestine contains villi that divide its inner surface into finger-shaped extensions which stick into the lumen. The intestinal surface area becomes larger through this villous structure which enhances contact between the intestinal contents and intestinal epithelial cells. Each epithelial cell on a villus displays microvilli along with its surface. The microvilli create the brush border structure that results in surface area enhancement of several hundred times.

The combined villi and microvilli surface structures make an efficient structure for absorption because they provide extensive surface area which enables the intake of nutrients drugs and other substances [10]. More area exposure facilitates many drug molecules to interact with the absorptive cells while providing enhanced drug absorption efficiency. The brush border enzymes which reside on the microvilli surfaces break down peptides and disaccharides along with other large molecules while assisting in their absorption process.

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- **Role of Mucus Layer in Drug Absorption**

The mucosal structure contains an important element which is the mucus layer that operates above the villi and microvilli surfaces. A mucus secretion from intestinal lining goblet cells fulfills various roles regarding drug absorption functions. Drug diffusion towards epithelial cells slows down because of the physical barrier impact but at the same time the hydrophilic nature helps maintain drug molecules in close proximity to the absorption surface.

The intestinal lining wears a viscous gel-like mucus that offers dual functions to help reduce friction inside the digestive tract while defending the epithelium from gastric acid and stomach enzymes. The GIT mucus exhibits dynamic characteristics that change based on both the GIT segment location and active physiological conditions (whether the person is fasting or ingested food present). Mucus serves as a supportive factor in drug absorption because it helps maintain drug proximity to the mucosal surface to increase absorption potential on a long-term basis even though it creates initial challenges for drug diffusion.

- **Balancing Permeability and Protection**

The specialized structure of small intestine mucosa maintains equilibrium between enabling drug absorption and defending against unwanted substances. The extensive surface area of villi and microvilli helps drug molecules contact each other more effectively although it needs to be evaluated with the tightening junctions between cells which maintain permeability barriers. Most drug molecules must use epithelial cells to pass through rather than passing between cells due to the tight junctions (transcellular absorption).

Drugs encounter the epithelial cells for uptake better due to the ability of the mucus layer to trap them near absorption sites although it slows down their movement. Drugs absorb optimally through the body when the combination of surface area and structural organization functions with mucus protection to effectively deliver medications into bloodstream circulation.

- **Influence of Mucosal Architecture on Drug Formulation**

The features of gastrointestinal tissue produce vital effects on how drugs are formulated. The pharmaceutical industry designs drug formulations to maximize their solubility together with dissolution properties because this improves absorption into the intestinal mucosa. The use of enteric-coated formulations protects drugs in stomach acid since they release medication specifically at optimal absorption sites within different regions of the intestine. Drugs need a proper formulation to match the physical features of the intestinal surface in order to achieve maximum bioavailability when absorbed through the mouth.

3.2.2 Epithelial Cell Layer and Transport Barriers

A protective layer of epithelial cells in the gastrointestinal tract functions as the main obstruction to drug passage into bloodstream circulation. The protective barrier which covers the body defends from dangerous substances yet creates difficulties for therapeutic agents to pass through. Drugs and other substances can pass through the intestinal lining with control through the tight cell alignment of GIT epithelial cells.

- **Tight Junctions and Paracellular Transport**

The GIT epithelial cells maintain their connection with tight junctions which function as specialized proteins to control intercellular molecule movement known as paracellular transport. Among the functions of tight junctions exists their fundamental role to limit the movement of large or charged molecules through the epithelial boundary. The small intestine has junctions that provide limited permeability to small solutes including water and ions through the paracellular route [11]. The necessary lipophilicity and small molecular dimensions that drugs need to overcome tight junctions exist only for nonpolar uncharged molecules to diffuse through easily between cells. Most drugs need to cross cells during absorption which requires their passage through epithelial cells to take place.

- **Transcellular Transport and Drug Properties**

First the transcellular pathway operates when drugs permeate through epithelial cell membranes utilizing the lipid bilayer as they pass through. The drug's capability to dissolve in lipids combined with its ionization state shapes how well it crosses the epithelial cell membrane during this process. Drugs which are fat-loving substances permeate transcellular pathways because their hydrophobic nature allows them to pass through cell membrane barriers. Hydrophilic particles along with those bearing charge need dedicated transfer methods in order to move across membranes [12].

The majority of drugs that need to absorb through the small intestine function well as non-ionized substances or have minimal ionization at typical intestine pH levels. The solubility decrease in lipid membranes causes ionized molecules to avoid crossing the cell membrane. Drug formulation strategies intend to readjust surroundings pH values or transform medication structures to boost the non-ionized drug compounds which improve absorption.

- **Variability in Tight Junctions Across Different Regions of the GIT**

The drug absorption process is affected by the varying permeability capabilities of the epithelial layer which differ between GIT segments. The colon shows tighter cell contacts between

epithelial cells together with a smaller absorption area when compared to the small intestine. Drugs face additional impediments for absorption because of the thick mucosal layer within the colon's structure. The colon operates as a limited drug absorption site due to its lower efficiency compared to the general drug absorption levels across the small intestine [13].

The small intestine stands as the main drug absorption location since it possesses maximal surface area which becomes possible through villi and microvilli structures. The drug absorption process in the intestine benefits from these structures because they significantly expand the total contact area which the drugs have with intestinal epithelial cells. The potassium permeability within small intestine tight junctions remains more open compared to colonic tight junctions thus ensuring better drug absorption through cells.

- **Significance for Drug Formulation**

The development of oral drug formulations heavily depends on knowing how epithelial cells function and transport mechanisms work. The absorption effectiveness of drugs which move through cells by passive diffusion depends directly on their lipophilicity level and their pH-dependent ionization state. New drug formulations that preferentially increase permeability contain added substances which both enhance drug solubility and help it move across the epithelial membrane [14].

The dimensions together with electric charge characteristics of drugs influence the creation of delivery methods that enhance drug absorption levels. Exploring active transport mechanisms together with nanoparticle formulation should be considered when drugs demonstrate poor ability to penetrate the epithelial layer.

3.2.3 Gastrointestinal pH Gradient

The gastrointestinal system shows pH variations throughout its length because these conditions strongly affect the way drugs get absorbed through oral intake. The pH conditions transition from strongly acidic stomach levels toward less acid and basic conditions within the intestinal region. Drugs absorb and become bioavailable in the GIT based on site-specific pH because it influences their permeability together with solubility and ionization state.

- **Stomach (pH 1–3)**

Gastric acid that consists mainly of hydrochloric acid (HCl) leads to a pH range between 1 to 3 within the stomach environment [15]. The acidic stomach environment supports various tasks including food breakdown through hydrochloric acid action and digestive enzyme’s function and nutrient and medication absorption.

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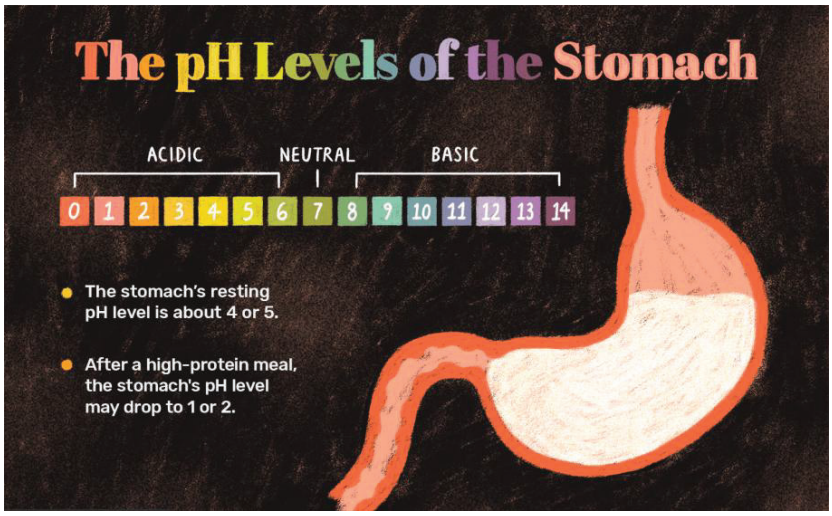

Figure 1: pH of Stomach

Weak acidic drugs absorb better within stomach tissues because acidic conditions lead them to stay in their uncharged state. Such drugs easily penetrate cell membranes because their non-ionized state makes them lipophilic substances that dissolve in fat. The stomach easily absorbs aspirin (a weak acid) because its ionization reacts to pH changes [16].

- **Duodenum (pH 5–6.5)**

The first intestinal segment called duodenum exists in a pH range between 5 to 6.5 which represents primarily neutral conditions. The pancreatic bicarbonate joins gastric acid in the small intestine to produce this pH value. The slightly acidic duodenal environment supports complete function of enzymes responsible for digesting carbohydrates and proteins as well as fats.

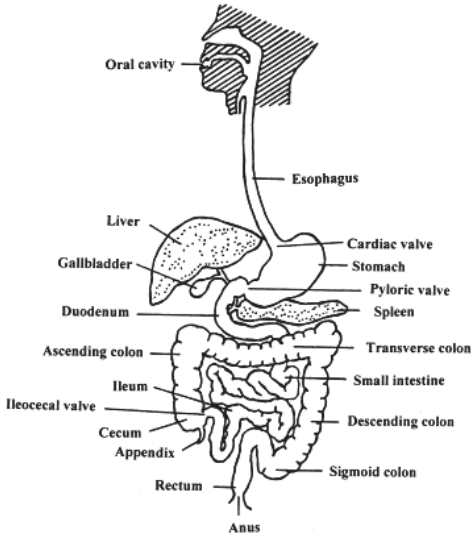

Figure 2: Duodenum pH

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Most weak base substances reach maximum absorption potential when the pH matches this environment. The non-ionized weak bases become more soluble as well as better able to passively diffuse across intestinal epithelial cells under this mildly acidic to neutral environment. Drugs that enter the bloodstream through oral administration absorb mainly in the duodenum because this area provides maximum surface area combined with elevated blood flow and acidic to neutral pH suitable for absorbing both weak acids and weak bases.

- **Ileum and Colon (pH 7–8)**

The ileum as well as the colon maintain an alkaline condition that spans between pH 7 and 8. Further bicarbonate secretion and coating of the intestine with alkaline mucus protects the intestinal lining against the way too acidic stomach material and controls acidity. Weak acids absorb less efficiently during drug transmission through cell membranes when present in alkaline solutions because alkalinity promotes their ionization making them less lipophilic and more difficult to cross the membranes [17].

Weak bases show better intestinal absorption behavior during the alkaline condition of ileum and colon because they remain non-ionized at these pH levels thus improving their ability to cross intestinal epithelial barriers. The colon provides an environment with longer transit time that helps drugs with slower absorption properties to fully dissolve before they can enter the circulation.

- **Influence on Drug Absorption**

Drug solubility and absorption are largely determined by drug ionization status under the influence of GIT pH gradients across this organ. Drugs present themselves as both ionized and non-ionized forms under the pH-partition theory which determines drug absorption depending on the pH environment. The cellular membrane allows the lipophilic non-ionized drug form to pass through whereas an ionized drug form remains mostly water-soluble providing difficulty when crossing lipid membranes.

- Weak acids: Weak acids remain unchanged in stomach acid solutions because of which they absorb better during the process. After the drug reaches the intestines which have higher alkalinity the drug becomes more ionized thus making it less absorbable.
- Weak bases: Within an acidic stomach environment weak bases become ionized which reduces their ability to absorb in this area. The process of absorption increases for weak bases in the basic conditions found within the duodenum, ileum and colon.

This interplay between pH, drug ionization, and membrane permeability dictates the efficiency of absorption at various sites in the GIT.

3.2.4 Gastrointestinal Transit Time

Drugs traverse through different areas of the digestive system known as gastrointestinal transit time from when they enter the body until when they become absorbed. Drug absorption relies on the transit time because this timeframe decides how long drugs spend in GIT sections which affects both their dissolution and bloodstream absorption rates [18]. Physical and chemical properties of drugs together with person-related physiological factors influence the duration drugs spend traveling through gastrointestinal compartments. Designing effective oral drug delivery systems requires an understanding of transit time while drug bioavailability predictions heavily depend on the evaluation of this factor.

- **Stomach Transit Time and Food Intake**

The transit period in the stomach displays high variability since stomach emptying occurs based on food consumption amounts meal content makeup and natural metabolic processes. Individuals who have not eaten show faster stomach emptying along with shorter drug residence within the stomach. Both stomach content digestion and mixing processes activate when a person consumes food yet this activation forces delays for both stomach-digesting substances and medications to advance toward the small intestine. Medications that contain fat specifically reduce gastric emptying speed but liquids decrease this process.

The changing duration drugs spend in the stomach affects medications that need fast dissolution or drugs with pH sensitivity such as those requiring acid conditions to dissolve. The duration of drug exposure to stomach acid is crucial for drugs which need small intestine absorption because their release from the stomach determines their ability to dissolve properly. The potential absorption of the drugs can decrease when their movement into the intestine occurs before complete dissolution occurs.

- **Small Intestine Transit Time**

Food consumption does not affect the typical three-to-four-hour transit time that occurs during the small intestine process. The main site for drug absorption exists because this timeframe maintains stable absorption conditions. The extensive surface area of the small intestine occurs because of villi and microvilli structures which function to maximize nutrient and drug absorption.

The majority of orally taken medications absorbs at this section of the GIT thanks to its perfect blending of moderately neutral pH along with permeable membranes and extensive drug interaction surfaces. Drugs have sufficient time in the small intestine to penetrate both epithelial cells and bloodstream due to its stable transit duration. The absorption process remains subject to variation when drug solubility meets with the pH microenvironment and drug physicochemical properties and the absorption ability is affected.

- **Colon Transit Time and Its Implications**

The period of time substances stay in the colon greatly exceeds both stomach and small intestine transit periods because it extends from twelve to forty-eight hours based on individual physiology. Many pharmaceutical drugs experience enhanced absorption through the colon because of its long stay duration that allows for the dissolution of drugs with slow absorption rates. Drugs that need controlled-release definitions obtain improved absorption because of better exposure to the intestinal fluids throughout the prolonged duration. These medical situations benefit from drug releases that gradually occur during extended periods to sustain constant drug blood levels.

Nevertheless, the extended colon transit period helps medicine that needs delayed release but it creates difficulties during drug consumption. A smaller surface area in the colon hinders absorption because it reduces the available area for drug interaction. The tight junctions between epithelial cells in the colon present reduced permeability to both polar drug molecules and larger drug molecules thus affecting their absorption levels negatively. Conditions inside the colon tend to be alkaline which does not favor proper drug absorption for all medications.

- **Impact on Drug Formulation**

Professional understanding of gastrointestinal transit time becomes essential for pharmaceutical engineers who should create formulations which exhibit desired release properties. The measured duration of gastrointestinal transit within the colon drives the development of drug formulations that use this time for controlled substance delivery. Two examples of controlled-release medicine designs include enteric-coated tablets and extended-release capsules that slowly dispense their therapeutic components to extend drug absorption periods. Pharmaceutical preparations with extended therapeutic profiles work best for medicines such as pain medications and hypertension medications and certain antibiotic drugs.

The absorption speed of specific drugs determines which dissolution approach should be selected between rapid and sustained mechanisms. Liquid dosage forms along with oral

solutions facilitate faster drug absorption because they avoid dissolution requirements in the stomach.

3.2.5 Enzymatic and Microbial Activity

The GIT contains high enzyme concentrations with proteases and lipases as the main digestion enzymes operating in stomach and small intestine compartments. Drugs containing peptides and proteins become vulnerable to breakdown by digestive enzymes that exist in the GIT before their absorption takes place. The dense microbial populations in the colon act to metabolize both drugs and their excipients although this process leads to either better drug performance or reduced effectiveness.

Knowledge about enzyme and microbial response helps create oral drug delivery systems for biologics combined with degradable drugs.

3.2.6 Blood Flow and Lymphatic Access

Drugs are better absorbed when the tissues under the intestinal epithelium possess well-developed blood vessels. Drugs absorbed by the body quickly enter portal blood circulation which leads to liver metabolism before reaching the systemic circulation. Lipophilic medications can use the lymphatic system to avoid liver detoxification on their way to systemic circulation [19].

Absorption pathway selection depends upon drug dimensions along with oil/water affinity together with drug composition while knowledge about local bloodstream and lymphatic penetration systems helps predict systemic drug exposure.

3.3 MICROCLIMATE AND INTRACELLULAR PH

Drug absorption in the gastrointestinal (GI) tract relies on two crucial factors which include the microclimate together with the intracellular pH. The drug's absorption efficiency depends on these two factors which control its dissolution process and makes it more soluble and enables better permeability throughout GI mucosa. The term "microclimate" defines the drug molecule surroundings in the GI tract while intracellular pH measures the pH conditions inside the enterocytes of the small intestine lining [20].

3.3.1 Microclimate in the Gastrointestinal Tract

Several elements affect the continuously changing microenvironment within both stomach and small intestine tissues including mucosal lining secretions together with ingested food items

and normal bodily conditions. The mucosal layer functions both as a protective shield of the GI epithelium cells and assists in maintaining drug environment pH values.

The acidic microclimate of the stomach forms because of gastric secretions particularly hydrochloric acid (HCl) that maintains neutral conditions between 1.5 and 3.5. The acidic quality of this environment enables the breakdown as well as dissolution of various drugs. Weak acid drugs become less soluble in acidic low pH stomach solutions because their ionization increases but remain vulnerable to absorption difficulties until reaching neutral intestinal conditions.

The microclimate environment of the small intestine maintains an alkaline state when pH levels fall within the range of 5.5 to 7.5. A pH range from neutral to slightly basic functions well for drug absorption especially for weak base medications because weak bases dissolve better at alkaline conditions. Bile salts together with digestive enzymes affect the small intestine's microclimate because they help break down fats for improved drug absorption.

The intestinal microclimate determines drug solubility along with its absorption rate through its three main components: the mucus layer structure alongside pH levels combined with digestive enzyme and bile salt presence. Drug developers need to examine this microclimate during their formulation designs.

3.3.2 Intracellular pH and Its Role in Drug Absorption

The absorption of drugs depends on enterocytes' intracellular pH levels which are measured between 7.0 and 7.4. Intracellularties of these cells exist at a pH level spanning from 7.0 through 7.4 due to their alkaline nature. The drug’s solubility alongside its ionizing state depends on pH levels in a manner that affects how the drug crosses the membrane using passive diffusion paths together with alternative transport systems.

The pH level of the surrounding environment determines to a great extent how many drugs become ionized. The majority of weak acids remain non-ionized forms within acidic solutions but change into ionized forms when exposed to basic solutions. Drugs that stay unionized in the small intestine possess improved absorption because unionized molecules show better membrane permeability. Drug absorption becomes limited when medication demonstrates high ionization levels within this environment because such molecules struggle to penetrate enterocyte lipid membranes.

The pH conditions in the cell space affect the operation of both membrane transport proteins and several drug uptake pathways. The activity levels of P-glycoproteins and solute carriers

(SLCs) transport proteins adjust based on pH conditions which determines how well they transfer drugs throughout the bloodstream. The disease status along with inflammatory conditions combined with drug interactions can modify intracellular pH which subsequently affects the transport system efficiency leading to changes in drug absorption.

3.3.3 Microclimate and Intracellular pH Interactions in Drug Absorption

Medical absorbance depends on multiple complex interactions between drug microenvironments and cell interior pH conditions. The drug's ability to dissolve in the GI tract depends strictly on the mucosal pH values. The dissolution of drugs that act as weak acids or bases will vary based on the surrounding pH values. The drug solubility together with its ionization state can change when it moves from stomach into small intestine because of pH variations which affects the amount of drug ready for bloodstream absorption.

The drug's solubility along with its transport efficiency becomes affected by cellular pH after it enters the enterocyte. The intracellular conditions of the small intestine enable drug substances with poor absorption in the stomach to transfer more efficiently through ionization-dependent transport mechanisms. The intracellular pH affects transporter and enzyme interactions within the enterocyte because different transporters exhibit pH-dependent activities.

Drugs requiring active transport will experience better absorption rates when the intracellular pH matches the optimum condition for transporter functionality. Drug absorption becomes less effective when the intestinal pH changes because of conditions such as acid reflux or inflammation in the body.

BIBLIOGRAPHY

1. Duan, Y., Dhar, A., Patel, C., Khimani, M., Neogi, S., Sharma, P., ... & Vekariya, R. L. (2020). A brief review on solid lipid nanoparticles: Part and parcel of contemporary drug delivery systems. *RSC advances*, *10*(45), 26777-26791.
2. Dwivedi, V. P., Bhattacharya, D., Singh, M., Bhaskar, A., Kumar, S., Fatima, S., Sobia, P., Van Kaer, L., & Das, G. (2019). Allicin enhances antimicrobial activity of macrophages during *Mycobacterium tuberculosis* infection. *Journal of Ethnopharmacology, 243*, 111634.
3. El-Khateeb, E., Burkhill, S., Murby, S., Amirat, H., Rostami-Hodjegan, A., & Ahmad, A. (2021). Physiological-based pharmacokinetic modeling trends in pharmaceutical drug development over the last 20-years; in-depth analysis of applications, organizations, and platforms. *Biopharmaceutics & Drug Disposition*, *42*(4), 107-117.
4. Emami, F., Vatanara, A., Park, E. J., & Na, D. H. (2018). Drying technologies for the stability and bioavailability of biopharmaceuticals. *Pharmaceutics*, *10*(3), 131.
5. Evers, A., Clénet, D., & Pfeiffer-Marek, S. (2022). Long-term stability prediction for developability assessment of biopharmaceutics using advanced kinetic modeling. *Pharmaceutics*, *14*(2), 375.
6. Fahimirad, S., & Hatami, M. (2019). Nanocarrier-based antimicrobial phytochemicals. In *Advances in Phytonanotechnology* (pp. 299–314). Elsevier.
7. Fan, B., Mellinghoff, I. K., Wen, P. Y., Lowery, M. A., Goyal, L., Tap, W. D., ... & Dai, D. (2020). Clinical pharmacokinetics and pharmacodynamics of ivosidenib, an oral, targeted inhibitor of mutant IDH1, in patients with advanced solid tumors. *Investigational New Drugs*, *38*, 433-444.
8. Farah, F. H., & Farah, F. H. (2019). Nanocarriers as delivery systems for therapeutics agents. *International Journal of Pharmaceutical Sciences and Research*, *10*, 3487-3507.
9. Fink, C., Sun, D., Wagner, K., Schneider, M., Bauer, H., Dolgos, H., ... & Peters, S. A. (2020). Evaluating the role of solubility in oral absorption of poorly water-soluble drugs using physiologically-based pharmacokinetic modeling. *Clinical Pharmacology & Therapeutics*, *107*(3), 650-661.

10. Fleming, D., & Rumbaugh, K. (2018). The consequences of biofilm dispersal on the host. *Scientific Reports, 8*, 10738.

11. Fraterrigo Garofalo, S., Tommasi, T., & Fino, D. (2020). A short review of green extraction technologies for rice bran oil. *Biomass Conversion and Biorefinery.*

12. Frijlink, H., Lagarce, F., Touw, D., & Woerdenbag, H. (2023). Biopharmaceutics. In *Practical pharmaceutics: an international guideline for the preparation, care and use of medicinal products* (pp. 67-91). Cham: Springer International Publishing.

13. Gajewska, M., Blumenstein, L., Kourentas, A., Mueller-Zsigmondy, M., Lorenzo, S., Sinn, A., ... & Heimbach, T. (2020). Physiologically based pharmacokinetic modeling of oral absorption, pH, and food effect in healthy volunteers to drive alpelisib formulation selection. *The AAPS journal*, *22*, 1-13.

14. García, M. A., Bolger, M. B., Suarez-Sharp, S., & Langguth, P. (2022). Predicting pharmacokinetics of multisource acyclovir oral products through physiologically based biopharmaceutics modeling. *Journal of Pharmaceutical Sciences*, *111*(1), 262-273.

15. Ghosh, S., Ray, A., & Pramanik, N. (2020). Self-assembly of surfactants: An overview on general aspects of amphiphiles. *Biophysical Chemistry, 265*, 106429.

16. Górniak, I., Bartoszewski, R., & Króliczewski, J. (2019). Comprehensive review of antimicrobial activities of plant flavonoids. *Phytochemistry Reviews, 18*(1), 241–272.

17. Gray, V. A., Mann, J. C., Barker, R., & Pepin, X. J. (2020). The case for physiologically based biopharmaceutics modelling (PBBM): what do dissolution scientists need to know. development, 12, 14.

18. Guidance, F. D. A. (2020). The use of physiologically based pharmacokinetic analyses—biopharmaceutics applications for oral drug product development, manufacturing changes, and controls. *Center for Drug Evaluation and Research (CDER)*.

19. Guimarães, M., Statelova, M., Holm, R., Reppas, C., Symilllides, M., Vertzoni, M., & Fotaki, N. (2019). Biopharmaceutical considerations in paediatrics with a view to the evaluation of orally administered drug products–a PEARRL review. Journal of Pharmacy and Pharmacology, 71(4), 603-642.

20. Gukasyan, H. J., Hailu, S., Karami, T. K., & Graham, R. (2019). Ocular biopharmaceutics: impact of modeling and simulation on topical ophthalmic formulation development. *Drug Discovery Today*, *24*(8), 1587-1597.