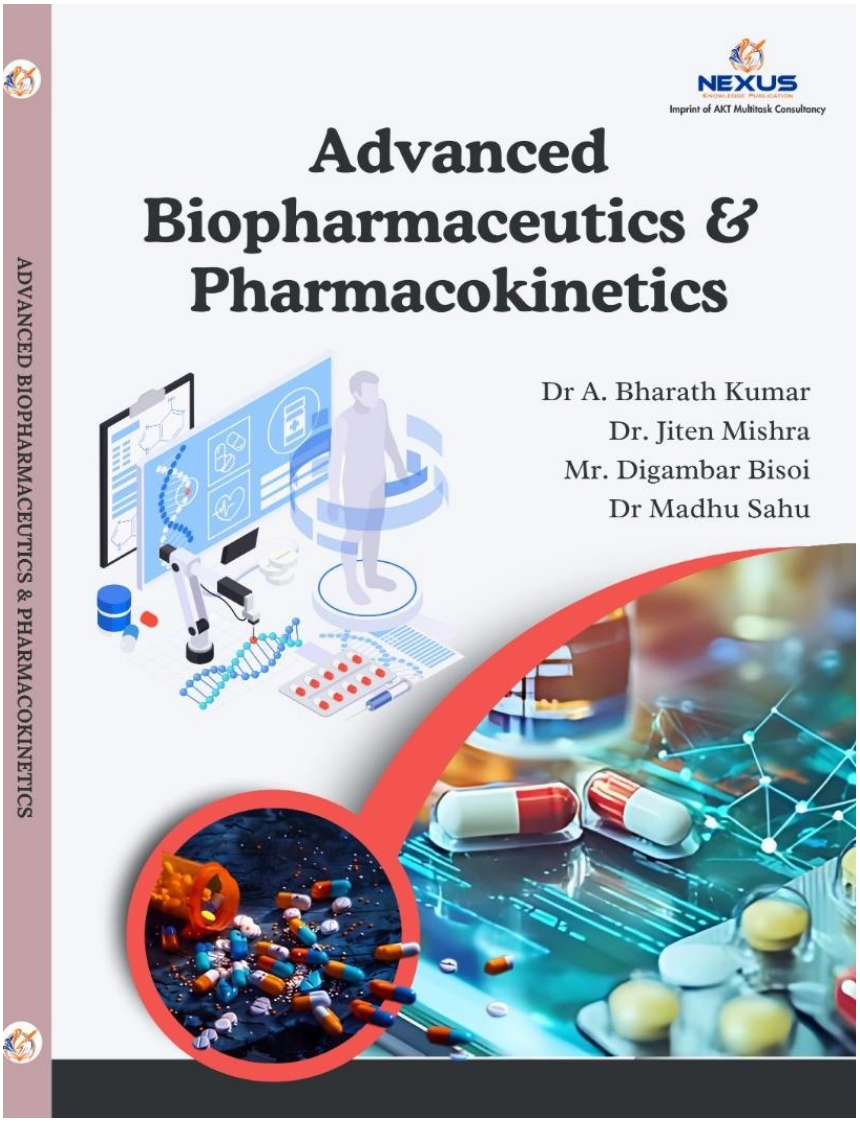
10.5281/zenedo.15960797

NEXUS KNOWLEDGE PUBLICATION

https://nknpub.com/index.php/1

ADVANCED BIOPHARMACEUTICS & PHARMACOKINETICS

ISBN Number- 978-81-985724-7-9



Published By – Nexus Knowledge Publication

(Imprint of AKT Multitask Consultancy)

Bilaspur, Chhattisgarh, India, 495006

www.aktmultitask.com

Chapter- 1

DRUG ABSORPTION FROM THE GASTROINTESTINAL TRACT

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How drugs enter our system affects their medical value and how much remains available to our system. This chapter studies how drugs move through the gastrointestinal tract as most oral medications enter through this pathway [1]. The gastrointestinal tract, with its unique structure and physiological functions, plays a vital role in the absorption of drugs into the bloodstream. The methods drugs use to pass through membranes influence how well they can enter the body so scientists need to understand these processes before creating new medication forms. Several things impact drug absorption through the GI tract including its natural condition and features plus how the body handles other medications or health problems. Drugs have better absorption when pH-partition theory shows how their environment affects their solubility. This chapter studies all the ways drugs enter the intestine while analyzing key factors and scientific principles about it.

1.1. GASTROINTESTINAL TRACT OVERVIEW

The body's gastrointestinal organs cooperate to transform food into nutrients for body use and pass waste matter from the body. Almost all oral medications enter the body by crossing the GI tract's surface.

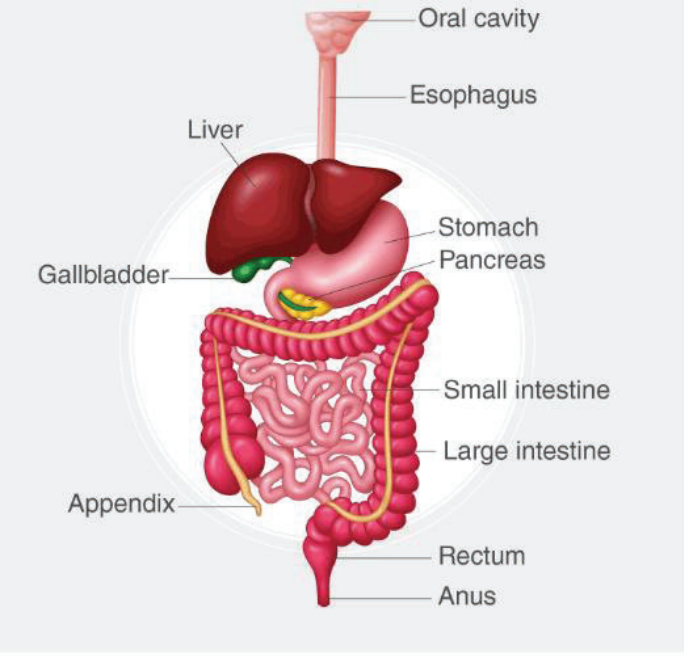

Figure 1: Gastrointestinal Tract

To explain how drugs absorb into the body you need to focus first on the basic features of the digestive system. Here we examine all important aspects of the GI tract including its internal design, natural functions, and its main absorption mechanism for drugs.

5.1.1 Structure of the Gastrointestinal Tract

Your digestive system includes all organs that run from your mouth to your anus as a single muscular passageway. It performs digestion and nutrient uptake while removing unnecessary body material through its system. The GI tract has specific organs and parts made to do their assigned jobs in the digestive process. Food undergoes vital changes and nutrients enter the body through the individual sections of the GI tract which determine how well drugs can get through the system when taken by mouth.

- **Mouth**

The food passes through our mouth first as the opening of the entire digestive process. The body starts digestion in the mouth through mechanical and chemical processes.

- **Mechanical Breakdown**: Through chewing actions, the teeth and tongue help particles of food become smaller so the stomach can process them better.
- **Chemical Breakdown**: The salivary glands produce saliva that has amylase enzymes which kickstart the carbohydrate breakdown process into simple sugar units. Saliva contains mucus substances that help keep food moving easily toward the stomach. While mouth lingual lipase loses its activity, the enzyme begins its work of digesting fats after arriving in the stomach.

The mouth not only serves as the entry point for food but also plays a role in the initial chemical digestion of carbohydrates and fats [2].

- **Esophagus**

Our esophagus function as a muscular entry passage connecting between the mouth and stomach. This organ extends 25 cm long and connects the mouth to the stomach to deliver processed food. After swallowing starts these steps take place:

- **Peristalsis**: Peristalsis refers to a series of coordinated, wave-like muscular contractions that propel food through the esophagus and into the stomach. This automatic muscle reaction happens because of the smooth esophageal muscles.
- **Lower Esophageal Sphincter (LES)**: The LES forms a valve at the stomach and esophageal connection to block stomach acids from moving backward into the esophageal tissue. The valve at the stomach-end of the esophagus protects the esophagus from the extreme stomach acid.

The esophagus is not involved in digestion but plays a key role in the transport of food.

➢ **Stomach**

The stomach functions as a cavernous muscular organ in the left side of the abdominal area. The stomach structures have multiple roles in the food processing system.

- **Reservoir**: Food stays temporarily stored in the stomach as a holding area. Food stays in the stomach through the lower esophageal sphincter before undergoing more preparation.
- **Mechanical Digestion**: The stomach muscles contract to churn and mix food with gastric juices, turning it into a semi-liquid mixture called chyme.
- **Chemical Digestion**: The stomach lining produces gastric juices which contain HCl acid and digestive enzymes. When food enters the stomach hydrochloric acid creates conditions (pH 1.5-3.5) that protects digestive enzymes and activates pepsin for protein digestion.
- **Gastric Mucosal Protection**: Gastric acid does not harm the stomach lining because mucus coats its surface to guard it. Mucus protects the stomach lining from harmful effects and stops digestive problems.

The stomach also plays an essential role in controlling the release of food into the small intestine through the pyloric sphincter, ensuring that digestion proceeds at a regulated pace.

➢ **Small Intestine**

The small intestine is the longest GI tract segment with the most important responsibility of absorbing nutrients. The small intestine works as three body sections named duodenum, jejunum, and ileum which perform special steps in food digestion.

- **Duodenum**: The small intestine starts with the duodenum which serves as the primary site for chemical digestion in the body. Through its connection with the liver and pancreas the duodenum receives digestive components to process fats before they can be digested. Along with bile the pancreas releases protease, lipase and amylase enzymes to keep digestion of fats, proteins and carbohydrates moving forward.
- **Jejunum**: The jejunum handles most digestion tasks because it functions as the main absorption site of the small intestine. The inner surface of the jejunum shows many villi structures which boost absorption capabilities of nutrients while microvilli protect them from damage. The willi in the intestine cells absorb nutrients like amino acids, sugars, fats, vitamins, and minerals into your blood.

- **Ileum**: The ileum acts as the last part of the small intestine to absorb vitamins B12 and bile acids and to take in remaining nutrients. The ileum filters out water and important salts from nutrients before transferring the residue to the large intestine.

The small intestine plays the key role in drug absorption because most oral medications enter bloodstream through epithelial cells here.

➢ **Large Intestine**

The colon functions as the main absorption organ in your body by taking water and essential minerals from leftover food parts [3]. The larger intestine holds several parts with wider shape but shorter length than the smaller intestine.

- **Cecum**: The beginning of the large intestine known as the cecum links directly to the ileum. It takes in the leftover access content from the small intestine.
- **Colon**: The colon takes in water and salt ions plus other minerals from chyme to create solid waste material. The colon contains a significant number of helpful bacteria that break down specific fibers while making gas and short-chain fatty acids.
- **Rectum and Anus**: The rectum is the final section of the large intestine where feces are stored before being expelled through the anus during defecation.

Although the large intestine absorbs less nutrients than the small intestine it helps keep the body properly hydrated and balanced for electrolyte health by removing wastes.

➢ **Accessory Organs**

In addition to the GI tract itself, several accessory organs play essential roles in digestion:

- **Liver**: The liver stands as the biggest internal organ inside the body and supports several digestive processes. It makes bile which exists in the gallbladder and goes into the duodenum to break down fats into their smaller components for digestion. The liver converts nutrients taken up from the small intestine while breaking down dangerous elements and keeps essential vitamins and minerals for later use.
- **Pancreas**: The pancreas performs both endocrine and exocrine tasks at once. The pancreatic exocrine function creates digestive enzymes including lipases, proteases, and amylases to release into the duodenum for proper food breakdown. The pancreas produces bicarbonate ions to balance stomach acid when it enters the small intestine.

- **Gallbladder**: The gallbladder acts as a storage device which gathers the bile generated by liver cells. The small intestine's entry of fats prompts the gallbladder to release bile into bile ducts for better fat metabolism.

➢ **Mucosal Layer of the Gastrointestinal Tract**

The entire gastrointestinal tract is lined with a mucosal layer composed of epithelial cells that serve multiple functions:

- **Protection**: The mucosal lining provides a protective barrier against digestive enzymes, stomach acid, and mechanical damage caused by the passage of food.
- **Absorption**: Specialized cells in the mucosal layer of the small intestine, such as enterocytes, actively participate in the absorption of nutrients and drugs.
- **Secretion**: The mucosal cells also secrete mucus, digestive enzymes, and bicarbonate ions to facilitate digestion and neutralize acid.

5.1.2 Physiological Functions of the Gastrointestinal Tract

The gastrointestinal tract functions as a specific system needed for proper body health and homeostasis maintenance [4]. The main roles of the GI tract focus on turning food into nutrients and transferring these nutrients and other substances to the blood. This segment explains all elements of GI tract operations by describing how it processes food into absorbable nutrients while supporting medicine intake.

➢ **Mechanical Digestion**

The physical breakdown of food into smaller sections during digestion helps create better chemical digestion. Breaking down food into smaller particles enhances its contact with digestive enzymes during digestion. Mechanical digestion happens at different sections of the gastrointestinal tract.

- **Mouth**: Our teeth start the process by breaking food into smaller parts through chewing to form a bolus. Salivary glands make enzymes in saliva that start digesting starches through amylase production.
- **Stomach**: Once eaten food reaches the stomach, digestive forces continue to break it down. Gastric digestion starts when smooth stomach muscles blend and mix food with gastric juice to form chyme. Smaller food particles emerge as the digestive system mixes food materials within the stomach.
- **Small Intestine**: The small intestine receives the chyme material while bile and pancreatic enzymes begin their breakdown process. The body releases fluids that break

fat particles apart and make them easier to absorb. Additionally, the villi and microvilli in the small intestine increase surface area for absorption.

The process of breaking down food through physical methods helps make digestion ready for chemical absorption of nutrients and enhances how well drugs enter our body through the mouth.

- **Chemical Digestion**

Through its enzymes food receives chemical conversion into basic elements that the body can easily take up. Digestive enzymes operate everywhere in the digestive organs but they work best in the stomach and small intestine sections.

- **Stomach**: The stomach makes gastric fluids from enzyme pepsin and hydrochloric acid. When your stomach acids lower pH levels pepsin starts its chemical work by splitting proteins into simpler chains. The acidic environment in the stomach makes proteins lose their shape which makes them simpler to process during digestion.
- **Small Intestine**: The small intestine processes chyme by combining the digestive enzymes released by the pancreas and liver. Pancreatic enzymes break carbohydrates into simple sugars while pancreatic lipase breaks down fats into fatty acids and glycerol together with proteases like trypsin and chymotrypsin which break down proteins into their component amino acids. Bile salts that come from the liver turn fat into tiny droplets that enzymes can reach and process.
- **Enzyme Activity**: Enzymes drive chemical digestion and their activity relies on temperature, pH conditions, and which chemical foods they process. Every enzyme works to dissolve specific kinds of molecules at their functional levels.

Body systems need Chemical digestion to transform food into basic nutrients such as amino acids, sugars, and fatty acids which can enter the bloodstream for use.

- **Absorption of Nutrients**

When food reaches its basic form it then needs to move into the bloodstream to travel through the body [5]. The small intestine serves as the primary absorption area because of its unique setup.

- **Villi and Microvilli**: The inner surface of the small intestine has finger-like villi that spread across its walls and contain microvilli on top of each villus surface. This system creates many more spaces to absorb nutrients through the gut.

- **Nutrient Absorption**: Through the cells that line villi in the digestive system nutrients of all food types reach human body. The nutrient particles move from the villi into both tiny blood vessels and lymphatic channels.
    - **Carbohydrates**: Digested carbohydrates (monosaccharides like glucose) are absorbed into the bloodstream via active transport mechanisms.
    - **Proteins**: Amino acids, the breakdown products of proteins, are absorbed into the blood through active transport proteins.
    - **Fats**: Fatty acids and monoglycerides are absorbed into the lymphatic system through specialized cells called enterocytes.
    - **Vitamins and Minerals**: Water-soluble vitamins (like vitamin C and B-vitamins) are absorbed directly into the bloodstream, while fat-soluble vitamins (like vitamins A, D, E, and K) are absorbed along with fats.

The small intestine is thus a highly efficient system for absorbing the nutrients required by the body for energy production, growth, and repair.

➢ **Drug Absorption**

Among its essential functions the gastrointestinal tract serves to absorb both nutrients and orally taken pharmaceutical agents [6]. The absorption of drugs mainly takes place within the small intestine since drug properties together with characteristics of the GI tract affect drug effectiveness. Several significant elements contribute to drug absorption according to the absorption process.

- **Solubility**: A drug requires dissolution in the aqueous environment of the GI tract before it can undergo absorption. The absorption rate of drugs poorly soluble in solution can reduce their bioavailability ultimately impacting their circulation in the body.
- **Drug Size and Lipophilicity**: Entricocytes (intestinal cells) permit better passage of small lipophilic substances (fat-soluble drugs) when compared to the slower diffusion rates of hydrophilic drugs (water-soluble molecules). Drugs that possess lipid-affinity tend to penetrate biological membranes by natural diffusion procedures.
- **Transport Mechanisms**: Intravenous drugs can be absorbed by active transport mechanisms together with endocytosis when the drugs meet one of these two requirements: they are large molecules or require specialized proteins to cross epithelial cells. Certain drugs penetrate cell membranes through transporter channels that exist on enterocyte cell membranes.

- **First-Pass Metabolism**: The small intestine absorbs a drug substance which then travels through portal circulation toward the liver during distribution. The drug enters the systemic circulation following potential liver metabolic processes which constitute "first-pass metabolism." The metabolism process in the portal circulation reduces the drug amount that reaches systemic circulation thereby lowering its therapeutic impact.

The delivery system of a medication together with its physical characteristics and the structure of the gastrointestinal system determine how well drugs are taken up. The conditions of gastric pH together with emptying duration and the state of being fed or unfed will influence drug absorption levels.

5.1.3 Role of the Gastrointestinal Tract in Drug Absorption

Drugs taken orally need the gastrointestinal tract to properly absorb them through the body. Once taken drugs pass through the digestive system as they endure multiple processes that strongly impact their absorption levels into bloodstream [7]. The multiple elements which determine absorption efficiency in the GI tract include solubility and permeability in addition to metabolism and transport mechanisms. A thorough comprehension of the multiple factors determines the bioavailability of a drug.

- **Solubility and Dissolution**

The absorption of drugs through the GI tract starts with dissolving the medication inside stomach and intestinal fluids before moving toward absorption. The breaking down process stands as an essential requirement because dissolved forms of drugs alone can cross through intestinal epithelium membranes to reach bloodstream circulation. The drug substance dissolves in gastric and intestinal fluids according to both chemical makeup of the drug and the pH levels present. The GI tract develops different pH conditions starting from stomach acid leading into neutral and slightly basic conditions in the small intestine. The drug's solubility traces back to the pH changes since these effects modify both drug dissolution and drug absorption potential. The absorption rates and total amounts of weak acids and bases that pass through the GI tract depend on the different pH environments at specific sites because they affect drug solubility.

The speed of the drug becoming available for absorption depends on how quickly it dissolves. The drug absorption rate suffers when drugs have poor solubility properties either resulting in delayed action or inadequate absorption levels. Drugs with rapid dissolution capabilities tend to absorb efficiently and thus enhance their bioavailability.

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- **Permeability of the Intestinal Epithelium**

The drug particles need to cross the intestinal epithelial cells (enterocytes) before entering the bloodstream after dissolving fully in fluid found within the GI tract. Drug access from the intestine to the bloodstream depends on the selectively permeable physical barrier of the intestinal epithelium. The membrane permits some substance transfer through pores depending on molecular dimensions and electrostatic characteristics and chemical makeup of molecules seeking passage [8].

Drug absorption depends heavily on the intestinal membrane permeability rates. The cell membrane allows small-size lipophilic compounds that dissolve in fats to freely pass into cells through simple diffusion. Drugs that are hydrophilic and large entities need to be transported through the membrane with specialized systems. Each part of the digestive tract displays different rates of permeability which changes according to its position within the intestine. The drug absorption capacity in the small intestine exceeds that of the stomach and large intestine because it maintains superior transport mechanisms and expansive membrane surface area.

Absorption of particular drugs through the epithelial cells depends heavily on transport proteins alongside enzymes. The epithelial cells utilize transport proteins to move drugs across their surfaces or support their passive movement through the cell membranes. Drugs need individual transport systems like P-glycoprotein to enter cells while various medications become subject to efflux processes that result in cell expulsion which reduces absorption.

- **Metabolism and First-Pass Effect**

Drugs which enter bloodstream from the GI tract pass through the hepatic portal vein during their route to systemic circulation where they meet the liver first before reaching general circulation. Many drugs must be processed by the liver during first-pass metabolism which is the central function of this organ.

The liver houses enzymes called cytochrome P450 (CYP450) enzymes that transform drugs into medically friendly water-soluble breakdown products to eliminate through urine. The drug metabolism process lessens the quantity of medication which ends up in blood circulation systems. Before an active therapeutic effect can occur a substantial amount of drugs metabolizes into inactive compounds thus decreasing their absorption into the body [9].

Evaluation of first-pass effects determines the primary design considerations for developing oral medication formulations. The use of alternate administration methods such as intravenous or sublingual becomes preferable when drugs experience extensive first-pass biotransformation because these routes minimize liver involvement to enhance drug availability. Chemical

substances exist that medical designers metabolize in liver tissue for performance optimization and the reduction of negative effects.

➢ **Transport Mechanisms of Drug Absorption**

The GI tract allows drugs to absorb through various means that rely on both drug features and gastrointestinal tract conditions. The primary mechanisms involved are:

- **Passive Diffusion**: Drug absorption through this process happens most frequently for small lipid-friendly drugs. Drugs move through passive diffusion by moving across the cell membrane between an intense concentration area inside the GI tract and a diluted concentration area in the bloodstream. The absorption occurs without energy requirements based on the drug concentration gradient and solubility properties in cell membrane lipid bilayers.
- **Active Transport**: For some drugs the absorption process across intestinal epithelium structures depends on obtaining energy. Transporter proteins, specifically sodium-dependent transporters act as mediators between drugs in the GI tract and their movement into bloodstream systems through active transport mechanisms. Drugs containing large polar molecules as well as molecules too large to pass through membranes by passive diffusion need the energy-driven mechanism of active transport for absorption.
- **Endocytosis**: The cell membrane uses endocytosis to engulf larger molecules and particles which results in drug-carrying vesicles. The method of endocytosis happens only rarely during drug absorption yet proves vital for biological drug uptake such as proteins or nanoparticles.

Drugs absorb through various factors which depend on their chemical structure together with molecular size and their interaction with the intestinal membrane. The development of optimal drug formulations requires a thorough comprehension of absorption mechanisms because it enables maximum drug absorption and therapeutic benefit.

1.2. MECHANISM OF DRUG ABSORPTION

Drug absorption through the gastrointestinal tract to bloodstream runs through multiple physiological procedures. A drug's absorption efficiency depends entirely on these mechanisms which adjust their effectiveness based on drug chemical properties including size along with polarity and solubility percentages[10].

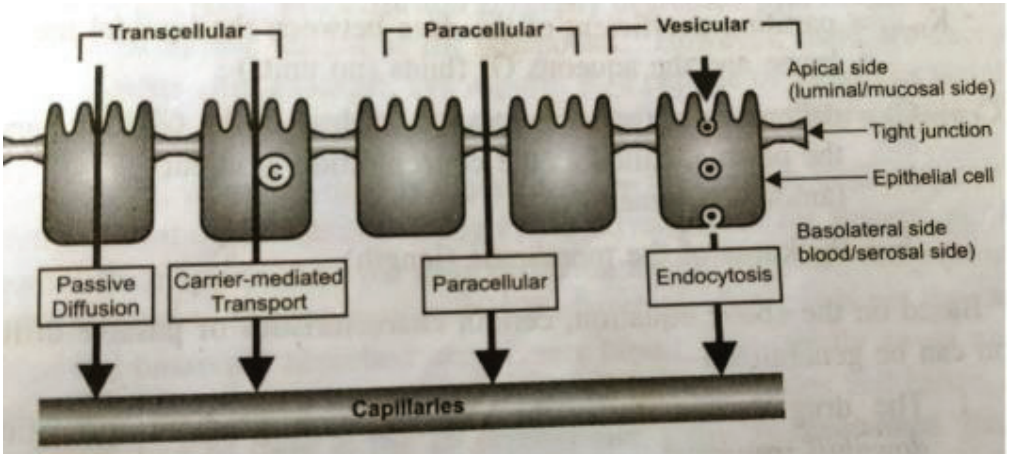

Figure 2: Mechanism of Drug Absorption

Pharmacological substances utilize three primary absorption processes for absorption: passive diffusion and active transport together with endocytosis. The knowledge of these absorption mechanisms enables better comprehension of pharmaceutical availability in combination with therapeutic treatment outcomes.

5.1.4 Passive Diffusion

The gastrointestinal (GI) tract absorption of drugs to bloodstream occurs through passive diffusion which stands as a fundamental and widely seen absorption mechanism. Passive diffusion operates as an efficient fundamental drug absorption process because it works independently from energy requirements[11]. During passive diffusion a drug moves because of the concentration gradient where the drug moves from high to low concentration areas until equilibrium is achieved.

- **Mechanism of Passive Diffusion**

The drug substance reaches the GI tract lumen after ingestion where stomach and small intestine conditions and fluids affect its position. The drug requires passing through the epithelial cells lining the digestive tract before blood absorption can happen. The passive diffusion process depends solely on the different drug concentrations found between the GI lumen and blood as the drug moves from its initial location to the blood. The drug molecules move through the epithelial membrane because of their concentration difference which allows them to penetrate the bloodstream. Donating drugs into the bloodstream through passive diffusion happens without requiring energy expenditures and stands as the principal mechanism for allowing diverse drugs to pass through from the GI lumen to blood circulation. The effective rate of passive diffusion depends mainly on how well the drug dissolves within the lipid membrane bilayer structure. Most of the intestinal membrane functions as a

phospholipid bilayer with hydrophobic characteristics. The barrier made of lipids permits the passage of drugs which dissolve well in fat. The ability of lipophilic drugs to penetrate intestinal cells for bloodstream entry remains higher compared to hydrophilic substances that cannot efficiently traverse lipid barriers. Drugs that are fat-soluble have superior membrane diffusion ability compared to hydrophilic drugs.

- **Factors Influencing Passive Diffusion**

Several elements modify both the speed and efficiency of passive diffusion. The main factor determining absorption speed through passive diffusion depends on the drug concentration difference between GI tract tissue and blood tissue. The amount of concentration difference between blood and GI tract determines how quickly the drug substance will diffuse through the membrane. Right after ingestion diffusion rate reaches its maximum because the drug concentration in the GI tract lumen is higher than blood concentration. The drug absorption reduces lumen concentration levels which causes diffusion to reduce its speed since equilibrium nears.

Passive diffusion flow depends heavily on the drug molecule dimensions along with their polar or nonpolar characteristics. Complex molecules cause greater barriers to diffusion since smaller molecules can easily move through the bilayer membrane structures. The movement of nonpolar substances occurs more efficiently when compared to movement of polar substances. The drug can penetrate the lipid membrane better through its interaction with the membrane due to its nonpolar structure. Measuring through the lipid layer becomes more difficult for polar molecules because they face obstacles to transport which decreases their passive diffusion absorption rates.

- **Role of pH in Passive Diffusion**

Drugs move into the bloodstream by passive diffusion as the acidity in GI tract envelopes serves as a vital parameter for absorption[12]. Numerous drugs along with weak acids and weak bases demonstrate incomplete ionization throughout different pH ranges. Drugs in different ionization forms exhibit different membrane diffability because they show varying degrees of lipophilicity.

Strong acids stay in non-ionized form within acidic conditions such as the stomach environment. Drugs located in non-ionized form become more compatible with lipids which allows them to diffuse immediately through cellular lipid membranes of intestinal cells. Weak acids located in the alkaline environment of the small intestine become more hydrophilic because they ionize which reduces their ability to pass the lipid membrane. Weak bases follow

a similar pattern by ionizing when in acidic solutions while staying non-ionized in basic solutions.

Drugs become more soluble in membranes after pH changes in the GI tract affect their degree of ionization. Weak base and weak acid drugs demonstrate unique absorption rates throughout the parts of the gastrointestinal tract. Designing oral drug formulations requires knowledge of GI tract pH values because these understanding creates better oral drug formulations.

5.1.5 Active Transport

Through active transport drugs can enter intestinal epithelial cells despite higher drug concentrations outside cells with the help of cellular energy sources[13]. The transport method needs energy since passive diffusion does not require any energy to move molecules from higher concentration areas to lower concentration areas. The cell's major source of energy called ATP supplies the power for active transportation. The cellular transporters with ATP-generated power operate through the cell membrane to push drug substances across the concentration gradient barrier.

- **Mechanism of Active Transport**

The key characteristic of active transport enables substance entry into the body regardless of the drug concentration levels inside the cell being higher than outside concentrations. A drug or nutrient becomes accessible for bloodstream transport through active transport even when its concentration levels inside intestinal epithelial cells exceed the lumen concentration barriers. Active transport functions as the main method for molecule uptake when the substances exceed typical size limits or have high polarity or charged elements because these molecules cannot enter the lipid cell membrane layer by regular diffusion.

The cell membrane houses dedicated transporter proteins that constitute active transport mechanisms. The "gatekeeper" function of these proteins enables them to let through specific molecules one by one. Transport proteins do selective filtering of molecules based on their substance features and dimensional characteristics and electrical charge properties. The specific character of these transporters allows the body to acquire necessary nutrients like amino acids along with glucose and specific vitamins but maintain exclusion of undesirable substances.

- **Transporter Families Involved in Active Transport**

The gastrointestinal tract utilizes two main transporter families called SLC transporters and ABC transporters for the execution of active transport operations.

1. **Solute Carrier (SLC) Transporters**: The SLC class comprises extensive transport systems which carry multiple substances including amino acids, glucose, organic acids together with different drugs. All SLC transports operate through symport either by moving substances in parallel directions or through antiport by carrying them in reverse directions. One type of SLC transporter known as sodium-dependent glucose transporter (SGLT1) permits small intestine glucose absorption by utilizing sodium gradients across the membrane. The transport process uses sodium gradient present in the cell membrane to draw glucose molecules into epithelial cells.
2. **ATP-Binding Cassette (ABC) Transporters**: Substrate elimination through cells occurs mainly through the outward transport functions of ABC transporters which remove drugs among other substrates. The cell membrane moiety moves through transporter action using the energy released from ATP hydrolysis. P-glycoprotein (P-gp) represents one of the most recognized ABC transporters that participates in moving various drugs and xenobiotics outward while decreasing drug absorption throughout the GI tract as well as aiding cancer drug resistance mechanisms. ABC transporters maintain minimal importance for absorption compared to the major function of SLC transporters.

- **Role of Active Transport in Drug Absorption**

The absorption process depends heavily on active transport because drugs with poor solubility and oversized molecules require this method for entry. Most drugs including polar function-bearing compounds and molecules larger than the size limit for cell membrane diffusion require active transport systems to absorb them within the GI tract. Some drugs, including peptides and biologics and antiviral medications require specific examples to pass the GI tract[14].

The absorption of peptide-based drugs and biologic substances depends on particular transporters to function properly. Some peptide transporters located in the intestinal epithelium play a role in absorbing peptide drugs. Specialized transport systems help large biologic medications including insulin and growth hormones to cross the intestinal barrier since they cannot diffuse through the membrane.

- **Saturation and Capacity Limitations**

The effectiveness of active transport methods faces limitations when used as a transport solution. The primary limitation of active transport systems occurs because of saturation. The transporters possess a defined operating threshold that reaches its maximum as drug levels increase. The absorption rate of the drug remains constant when drug concentrations reach the

maximum processing limit of the transporters. Beyond a specific threshold of drug dosage saturation occurs which produces a curve relationship between medication dose and absorption rates thus additional dosage increases do not correspond to better absorption. High drug doses affect bioavailability negatively for compounds that depend heavily on active transport for absorption because such compounds reach limitations in transporter capacity.

The saturation phenomenon serves as an essential concept for drug development which becomes particularly vital while designing oral drug forms. Drugs requiring active transport for absorption need precise dosage adjustments to overcome transporter saturation since this will maximize drug availability yet prevent absorption inefficiencies.

- **Clinical Implications and Drug Design**

Inactive transport mechanisms and drug absorption have essential ramifications in drug manufacturing and design development. Scientists develop two different strategies to work around membrane penetration requirements because polar and large drugs such as biologic therapies or peptides do not absorb easily across membranes. Research shows that nanotechnology improves the transport of drugs relying on active transport by utilizing nanoparticles and delivery vehicles that cross epithelial barriers efficiently.

Learning about active transport provides critical information for assessing the interactions between medicinal drugs (DDIs). The activity of specific transporters either experiences inhibition by certain drugs or becomes activated by others thus impacting the absorption and efflux capabilities of alternative drugs. The absorption of drugs typically handled by P-glycoprotein (P-gp) becomes enhanced by inhibitor medications which results in hazardous drug levels. Knowledge of active transport mechanisms in drug absorption allows healthcare professionals to enhance drug treatment plan effectiveness and reduce security risks.

5.1.6 Endocytosis

Endocytosis serves as an important drug absorption system which specialized in absorption of larger drug molecules and nanoparticles together with biologic drugs including proteins and monoclonal antibodies and some vaccines. Cell membranes use endocytosis to engulf drugs as a unique entry method that separates from passive diffusion along with active transport[15]. The cell membrane creates vesicles through endocytosis to encompass drugs while conducting internalization processes. Drug molecules can reach absorption through endocytosis even if they do not easily penetrate cell membrane bilayers thus providing an important transport pathway for biologic and other large molecules.

➢ Types of Endocytosis

Both drug absorption mechanisms through endocytosis operate as phagocytosis and pinocytosis. Endocytosis contains two cellular ingestion processes yet these methods vary because of their distinct substance properties and size characteristics.

- **Phagocytosis:** The process of cell eating is performed mainly by neutrophils and macrophages which serve as larger cells for this purpose. During phagocytosis large particles including pathogens or debris get engulfed by the cell body. The immune response relies on phagocytosis yet this process proves unimportant for drug absorption since it engages primarily with bigger particle sizes.
- **Pinocytosis:** You can distinguish pinocytosis from the other method through its wider meaning as "cell drinking." The process has heightened significance in drug absorption primarily when dealing with biologic drugs. Through pinocytosis the cell membrane creates a small vesicle that encloses extracellular fluid and drug molecules for their cellular entry. Through pinocytosis the cell can absorb therapeutic proteins as well as oligonucleotides and nanoparticles and smaller molecules of all kinds.

➢ Mechanism of Endocytosis in Drug Absorption

Cell membranes begin endorsement of drugs and drug delivery systems such as nanoparticles as the initial contact occurs. A drug will form a vesicle after the cellular membrane creates a pocket which encloses the drug. The vesicle penetrates the cytoplasm before discharging its drug content inside the cellular space for future transport processes. Cells enable drug entry through specific receptors located on their surface which bind with the drug molecules or drug delivery structures. The drug enters specific organelles inside the cell such as the lysosome after its internalization or it is released into the bloodstream for systemic delivery.

Drugs that either have a large size or heavy electrostatic charge require endocytosis as a vital pathway to gain entry across the cell membrane since passive diffusion and active transport methods remain ineffective. Therapeutic macromolecules such as monoclonal antibodies, proteins and peptides use endocytosis for cellular entry before treating diseases including cancer and autoimmune disorders. Through endocytosis medication uptake becomes possible even though the drugs exceed the cell membrane size requirements or carry significant electrical charges.

- **Influence of Drug Characteristics on Endocytosis**

Multiple elements shape the endocytosis drug uptake efficiency since drug or drug delivery system dimensions affect this process alongside their physical structure and electrostatic properties. Therefore to improve endocytosis drug scientists use nanoparticles because these small delivery systems enhance cellular internalization through their surface features. Drugs can reach specific cells or tissues through drug delivery systems that employ modifications on nanoparticles to have either ligand or coatings which recognize particular receptors on the target cells.

Surface modifications enhance the tendency of nanoparticles to enter cells through receptor-mediated endocytosis as these processes represent focused types of pinocytosis. The surface charges of drugs and delivery platforms determine the speed at which cells will engulf these components. Cell membranes with a negative electric charge become more accessible to positively charged nanoparticles that lead to easy internalization. The uptake rate of particles depends on their surface characteristics as well as their size because smaller and optimally designed particles are more effective at being absorbed.

- **Applications of Endocytosis in Drug Delivery**

Drug delivery through endocytosis maintains an essential position for transporting biological drugs. Therapeutic proteins along with monoclonal antibodies and oligonucleotides are unable to naturally pass through cell membranes due to their large size and polar characteristics. The drugs are endocytosed to access target cells where they execute their therapeutic capabilities.

Liposomes alongside nanoparticles represent significant applications of endocytosis in pharmacological drug delivery methods. Liposomes represent spherical structures made from lipid bilayer membranes which enable drug encapsulation for improved endocytotic drug absorption and biochemical protection. Polymeric nanoparticles can be engineered to transport drugs through receptor-mediated endocytosis which allows precise delivery of drugs to their intended site of operation[16].

The whole process of vaccine development depends on endocytosis mechanisms. The immunological response to vaccines depends heavily on nanoparticle structures as well as virus-like particles which imitate pathogen appearance. Endocytosis process by cells leads to the uptake of these particles while their subsequent analysis produces immunological responses.

- **Challenges and Limitations**

The cellular drug uptake system of endocytosis acts effectively but it shows specific restrictions. The cellular capability for performing endocytosis presents a limitation because it is unavailable to every cell type and the uptake efficiency differs between capable cells. Drugs and drug delivery systems experience reduced uptake efficiency and quick breakdown patterns within the cell that diminishes their therapeutic benefits.

Nanoparticles need precise size and surface optimizations to achieve maximum internalization inside biological cells. Drugs and drug delivery systems with an improper size or surface charge fail to penetrate cell membranes properly but drugs with sizes that are too small get cleared from the body without being able to work.

5.1.7 Facilitated Diffusion

The cell membrane utilizes specific carrier proteins through facilitated diffusion to conduct passive drug transport across its pathways. Examples of passive diffusion do not need carrier proteins because passive diffusion functions only with concentration differences yet facilitated diffusion needs membrane carrier proteins to transport substances across membranes. The functional process continues to be energy-independent while using drug concentration gradients as the driving force.

Through facilitated diffusion the body can absorb medications that cannot cross membranes through passive diffusion easily. A set of designated facilitated diffusion transporters enable the absorption of glucose and particular amino acids within the GI tract. The drug absorption process may utilize the facilitated diffusion mechanism when the drug features characteristics resembling those of glucose or amino acids.

1.3.FACTORS AFFECTING DRUG ABSORPTION

Drug uptake through the gastrointestinal tract presents numerous physiological as well as anatomical along with biochemical and physicochemical aspects that affect the absorption process. The ability to understand these influencing factors leads to better optimization of oral drug availability since it defines how much drug substance enters blood circulation and how quickly the process happens[17]. The absorption factors can be divided between physical elements of body systems and structural elements and elements caused by diseases alongside drug interactions.

5.1.8 Physiological and Anatomical Factors

Drug absorption depends significantly on gastrointestinal pH since the stomach acid differs from the rest of the GI tract. The stomach keeps its pH at levels of 1 to 3 for maintaining acidic conditions that impact how drugs dissolve and remain stable. The rising intestinal pH during the small intestines assists in breaking down weakly basic medications. The pH variation causes drug ionization changes and impacts drug permeability across intestinal mucosa according to the pH-partition theory.

Drug absorption depends to a large degree on the speed at which food content moves through the gastrointestinal tract. Drug absorption receives direct influence from stomach emptying speed into the small intestine since the majority of drug absorption occurs in this segment where its vast surface area meets robust blood circulation. Long residence in an acidic stomach environment could trigger drug breakdown or hinder drug reaching its absorption region. Drugs that require dissolving in the stomach will experience decreased absorption when gastric emptying occurs too quickly.

The GI tract surfaces along with its circulatory system play essential functions in this process. The human small intestine has villi together with microvilli that increase its absorption surface area more than the stomach or colon do. The splanchnic blood supply efficiently drains absorbed drugs from the absorption site so that a profitable concentration gradient stays established for additional diffusion. A reduction in blood circulation caused by shock or heart failure or vasoconstriction will result in substantial drug absorption difficulties.

The GI tract absorption of drugs undergoes various changes when food exists inside the system. Food-based substances create delays in stomach emptying times and affect stomach pH levels and bile production and also physically bind drug components to calcium or fat molecules. The drug absorption may receive either beneficial or detrimental effects based on its unique properties.

5.1.9 Disease and Drug Interactions

Multiple gastrointestinal diseases change how drugs absorb into the body. Crohn's disease and celiac disease and short bowel syndrome together decrease absorption area which blocks the entry of nutrients and drugs into the body. The metabolic transformation of drugs absorbed in the bloodstream changes when liver function becomes compromised which affects drug bioavailability due to first-pass metabolism alteration.

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Drug-drug interactions must be evaluated among all essential considerations. Several medications disrupt other drugs' absorption because they modify gastric acid levels while altering gastrointestinal motor functions as well as sharing transport mechanisms. When individuals take antacids they boost stomach acidity and this affects the absorption of weakly acidic medicines yet the antibiotic tetracycline interacts with antacids containing calcium or magnesium to form insoluble compounds that lowers the amount of antibiotic absorbed into the body.

Drugs absorption rates together with their bioavailability levels change because of enzyme effects such as induction and inhibition. The administration of rifampin leads enzymes in drug metabolism to become active which results in decreased plasma levels of drugs currently being taken together. Grapefruit juice components demonstrate the ability to boost drug availability when used as enzyme inhibitors through their mechanism of lowering pre-systemic metabolic breakdown in intestinal walls and liver tissue.

1.4. PH-PARTITION THEORY OF DRUG ABSORPTION

The pH-partition theory of drug absorption functions as a vital bio pharmacological principle which demonstrates how absolute ionization affects membrane penetration of drugs[18].

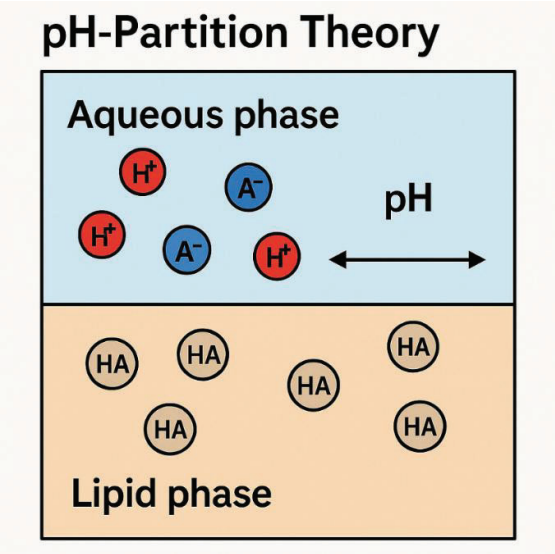

Figure 3: pH Partition Theory

Drug absorption through cellular membranes depends on uncharged drug molecules because they possess enough lipid-solubility to penetrate these lipid-rich membranes of the GI tract. The charged ions show higher water solubility which makes them less capable of permeating cell membranes. The balance of drug ionization relies on pH environmental levels and drug pKa which determines the GI tract absorption position and intensity.

5.1.10 The Concept of pH-Partition Theory

The pH-partition theory relies on the Henderson-Hasselbalch equation to connect drug pKa to solution pH and calculate ionized to non-ionized form proportions. A weak acid maintains its non-ionized form as the main species at pH levels found in stomach environments yet a weak base stay in its non-ionized state within the alkaline conditions of the small intestine.

The acidic pH of stomach tissue prefers the non-ionized form over the ionized form of aspirin and phenobarbital which leads to their primary absorption in this stomach section. Weak basic drug substances such as diazepam and codeine absorb better in the small intestine because its higher pH environment promotes their non-ionized forms[19].

Drugs tend to show better absorption in the small intestine rather than the stomach because its extended surface area and longer transit time and superior perfusion rate prevail over any unfavourable ionization conditions.

5.1.11 Influence of pKa and Environmental pH

A drug's ionization status depends on the distance between the drug pKa value and the pH level of its surroundings. When an agent has a pKa value of 4.5 it remains primarily uncharged in stomach solutions (pH ~1.5–3.5) but becomes mostly ionized in the small intestinal environment (pH ~6–7.4). Every drug formulation scientist and pharmacist understand pKa to anticipate where drugs show optimal absorption in the GI tract enabling them to optimize dosage forms.

Drug design together with delivery system optimization benefits from the pH-partition theory to enhance drug absorption. Enteric-coated tablets protect acid-sensitive drugs from dissolving in stomach acids by releasing them into the composition of the small intestine which has a higher pH.

5.1.12 Exceptions and Limitations

The pH-partition theory serves as an important conceptual framework yet faces certain boundaries and cases within which it is not applicable. Some drugs pass through specialized transporters which absorb their ionized form in combination with amino acids and peptides as well as vitamins. Surfactants together with lipid-based delivery techniques serve as formulation methods which enhance absorption of ionized pharmaceutical compounds[20].

Its main disadvantage derives from the assumption of passive diffusion as the sole absorption mechanism because other processes such as active transport and endocytosis can become vital for poorly permeable drugs or large molecular compounds.

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