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FACTORS AFFECTING ORAL DRUG ABSORPTION: A BIOPHARMACEUTIC PERSPECTIVE

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ABSTRACT

The oral route of administration is the most common and popular method of drug dosing, yet it presents a highly complex process for systemic delivery. This review aims to explore the multifaceted kinetics and underlying principles governing oral drug absorption. Systemic absorption from the gastrointestinal (GI) tract depends on a crucial triad of variables: the physicochemical properties of the drug (such as aqueous solubility and pK_a), the formulation or dosage form used, and the anatomical and physiological characteristics of the absorption site.[1] Key physiological processes—including GI transit time, gastric emptying, and presystemic first-pass metabolism—act as rate-limiting steps that dictate whether absorption is dissolution-rate limited or permeability limited.[2] Additionally, variables at the absorption site can cause significant interpatient and intrapatient differences in the rate and extent of absorption. Ultimately, this variability can be minimized through the proper biopharmaceutical design of dosage forms, ensuring predictable bioavailability and reliable therapeutic outcomes in clinical settings.[1]

KEYWORDS: Oral drug absorption, Biopharmaceutics, Bioavailability, Gastrointestinal transit, First-pass metabolism, Pharmacokinetics.

INTRODUCTION

The oral route of administration remains the most common and popular method for drug dosing due to its convenience, patient compliance, and manufacturing cost-effectiveness.[1] Oral dosage forms, such as solid tablets and capsules, are generally compact, stable, and

straightforward to manufacture cheaply in large quantities without the stringent need for sterilization.[2] However, unlike intravenous administration—where a drug is injected directly into the general circulation—oral delivery is an extravascular route that strictly requires the drug to be absorbed from the gastrointestinal (GI) tract before achieving systemic effects.[1]

The rate and extent of intact drug appearance in the systemic circulation depend on a complex succession of kinetic processes.[2] Consequently, drug absorption relies on three primary biopharmaceutical pillars: the physicochemical properties of the drug, the specific design of the dosage form, and the anatomy and physiology of the patient's alimentary canal. An oral dosage form must be carefully designed to account for extreme pH ranges, the presence or absence of food, degradative enzymes, and varying motility and drug permeability across different intestinal regions. Proper biopharmaceutical design is essential to minimize significant interpatient and intrapatient differences in the rate and extent of absorption, thereby providing predictable and reliable drug therapy.

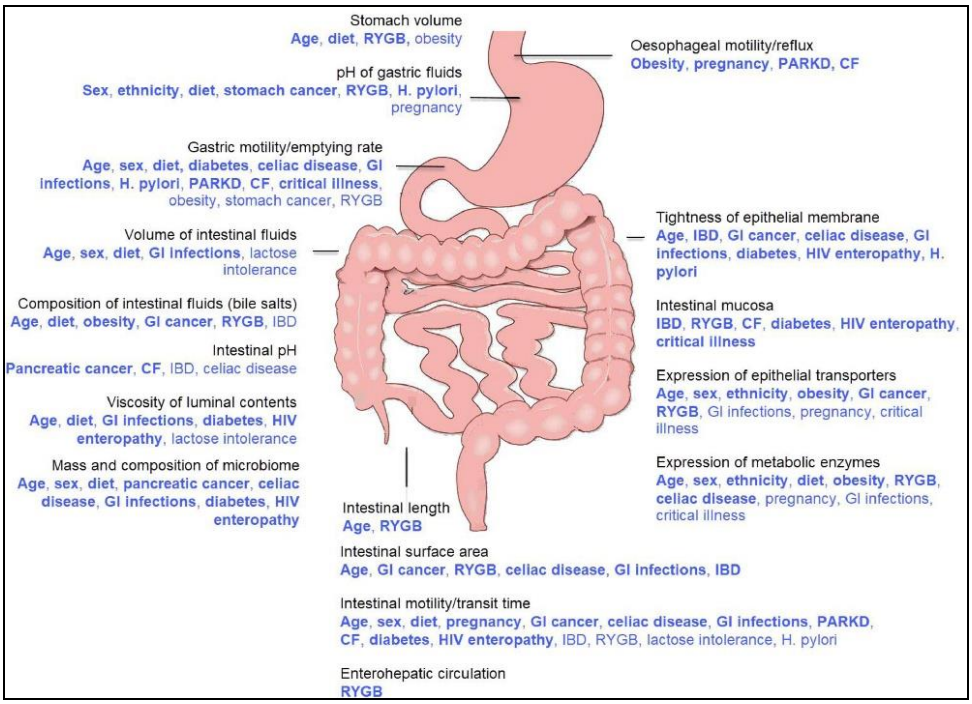

Figure 1 Overview of the main GI parameters influencing oral drug absorption (black) and the corresponding disease and non-disease related conditions that are known to alter these physiological properties (blue) [RYGB: Roux-en-Y gastric bypass; H. pylori: Helicobacter pylori; PARKD: Parkinson's disease; CF: Cystic fibrosis; CD: celiac disease; IBD: irritable bowel syndrome; HIV: human immunodeficiency virus]. (Adapted from Stillhart et al., European Journal of Pharmaceutical Sciences, 2020)[10]

The physical absorption process entails the entry of constituents from the gut lumen into the body, representing the net result of both lumen-to-blood and blood-to-lumen transport movements. The overall rate of systemic drug absorption from a solid oral dosage form encompasses several individual rate processes, including the dissolution of the drug, GI motility, blood flow, and the transport of the drug across capillary membranes.[1] The slowest step in this sequence controls the overall appearance of the drug in the systemic circulation. For drugs with very poor aqueous solubility, dissolution in GI fluids is typically the slowest step, resulting in dissolution-rate limited bioavailability. Conversely, highly soluble drugs dissolve rapidly, making the rate at which the drug crosses the gastrointestinal membrane the rate-limiting step, a condition known as permeability limited absorption. Furthermore, absorption can be restricted by the rate of metabolism by intestinal mucosal enzymes or during the initial passage through the liver, commonly termed the first-pass effect.[2]

Various disease states and anatomical alterations can significantly disrupt these baseline physiological parameters, thereby complicating oral drug delivery (Figure 1). For example, the normal physiologic processes of the alimentary canal may be heavily affected by diet, contents of the GI tract, hormones, the visceral nervous system, specific disease states, and concomitant drugs. This review explores the fundamental anatomic and physiologic considerations of the enteral system, ranging from the mouth to the anus, with a specific focus on the small intestine and duodenum where most absorption occurs.[1] It details how transit times, physicochemical properties, and formulation characteristics intersect to govern systemic absorption and pharmacokinetic profiles.

Physiochemical factors affecting Drug absorption

How the gastrointestinal tracts handle the medication and its distribution system is crucial to the overall healthy operation of oral formulations. Oral medication delivery is influenced by a number of different parameters, and intestinal metabolism, pH, dissolution, solubility, gastric emptying time, and other characteristics are the key components of drug bioavailability. Estimating the volume of intestinal juice becomes crucial if the medication is a single dose that dissolves in the stomach.[3]

In the end, we may conclude that medication absorption is a very complicated process including physiological, physical, chemical, and formulation-related elements that ultimately aid in deciding the drug's therapeutic efficacy. Improved knowledge of the process of drug absorption and innovative drug delivery systems aid in the development of pharmaceutical

dosage forms that are safe, efficient, non-toxic, and dependable, which directly improves patient care.[4]

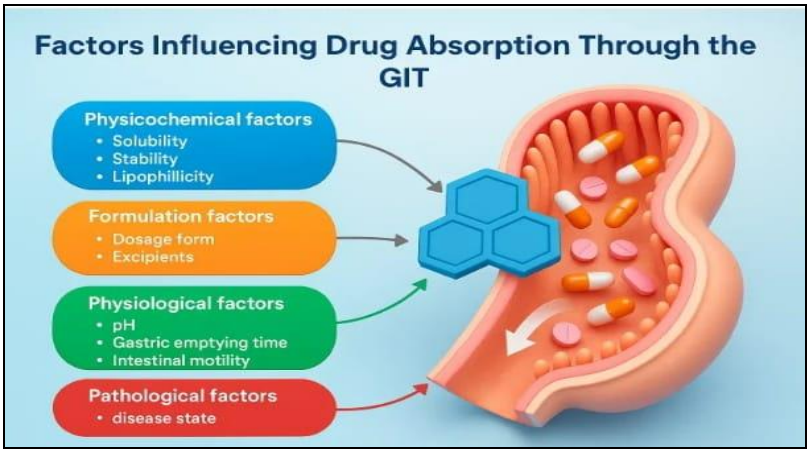

figure 2 factors influencing drug absorption through git.

The crucial factors affecting the oral drug absorption are as follow.

1. Drug solubility

Drug solubility is the ability of a drug to dissolve in a solvent and produce a homogeneous mixture. Any drug's solubility is primarily determined by the kind of solvent, temperature, and pressure. Intestinal medication absorption can be predicted with the aid of the Biopharmaceutics Classification System (BCS). Before passing through the intestinal membrane, oral medications must dissolve in the gastrointestinal tract. Since drug solubility is a rate-limiting step, more solubility will result in faster dissolution and more effective drug absorption, and vice versa.[5]

2. Dissolution rate

Medicine absorption, which affects how quickly and to what degree the supplied dose of a medicine enters the general circulation, depends on drug dissolution. The amount of time needed for the dosage form to release its drug content and subsequently for the drug to dissolve will determine the beginning of drug levels for many medications that readily pass through intestinal mucosa. The process through which a solid material dissolves is called dissolution.[6] For hydrophobic, poorly water soluble medications like spironolactone and griseofulvin, dissolution is the RDS; absorption of these medications is frequently referred to as dissolution rate-limited. If the medication has a high hydrophilicity aqueous solubility, such as neomycin or cromolyn sodium, the RDS in the absorption of such drugs is a rate of rapid dissolving. The bio membrane is penetrated. To put it another way, the absorption of

these medications is referred to as transmembrane rate or permeation rate limited. The amount of solid material that dissolves in solution per unit of time under standard parameters of temperature, pH, solvent composition, and constant solid surface area is known as the dissolution rate. The procedure is dynamic. Nonetheless, there are well-known instances of medications, like **cisapride**, that have adequate bioavailability despite their poor water solubility. This one can be attributed to two factors: First the quick rate of dissolution despite the drug's poor intrinsic solubility and second one the therapeutic dose may be so low that the GI transit time is adequate for proper dissolution and absorption. Consequently, in The dynamic process of medication dissolving is more closely associated with drug absorption and bioavailability than absolute solubility. Finally, if the dissolution rate is high then the absorption of oral drug will be greater through git and vice versa.[7]

3. Lipophilicity (Partition coefficient)

The capacity of a chemical substance to dissolve in fats, oils, or lipids is known as lipophilicity. The ratio of a compound's concentration between an organic phase (such octanol) and an aqueous phase is represented by the logarithm of its partition coefficient, or (at a particular pH).

$$K = \frac{Co}{Cw}$$

Where,

- K= Partition Coefficient
- $C_{o=}$ Concentration of drug in Lipophilic phase
- C_w= Concentration of drug in Hydrophilic phase
- If, K>1, then drug is Lipophilic in nature;
- K<1, then drug is Hydrophilic in nature

So more the lipophilicity of a drug, more will be the oral absorption of drug and vice versa as the drug can easily cross lipid rich GI membranes via passive diffusion.

The degree of ionisation at a specific pH is determined by a drug's pKa, and only the unionised drug—if sufficiently fat soluble—is absorbed into the systemic circulation. Consequently, If the medicine has poor lipid solubility (or low $K_{o/w}$), it will be poorly absorbed even if it is present in the unionised form. A medicine should ideally have enough lipid solubility ($K_{o/w}$) to enable the drug's partitioning in the lipoidal bio-membrane and into

the systemic circulation, as well as enough aqueous solubility to dissolve in the fluids at the absorption site. A medication must be able to dissolve in water (low lipophilicity) and partition into the lipid bilayer (high lipophilicity) in order to pass past the intestinal epithelium and have good oral bioavailability. The optimal oral absorption of a drug requires balancing between solubility and permeability.

Example

- **Diazepam** – Highly lipophilic drug- Easily can penetrate through GI membranes- Have high absorption.
- **Metformin**- Highly Hydrophilic drug – faces difficulty in penetrating through GI membranes- Have low absorption.

4. Molecular size and Structure

One important factor influencing the pharmacokinetics of medicinal medicines is the process of medication absorption. The molecule size is one of the most important parameters among the many variables affecting drug absorption. Higher permeability is typically found in molecules that are smaller and have a molecular weight of less than 500 Da. They don't need the help of transport systems to diffuse more readily through the lipid bilayer. The permeability diminishes with increasing molecule size. Large molecules have more difficulty getting past the lipid bilayer, which frequently calls for the usage of carrier proteins or alternate pathways like endocytosis. Compared to large, bulky molecules, small molecules pass through the intestinal membrane more quickly. Bigger molecules might experience restricted membrane permeability and steric hindrance.[8]

5. Degree of Ionization (pKa and pH)

By balancing solubility and permeability, the degree of ionization—which is based on the pH of the drug and the surrounding environment—determines oral absorption (Henderson-Hasselbalch equation). Ionised forms increase solubility, but un-ionized forms typically diffuse through lipid membranes. Weak bases are best absorbed in the small intestine, while weak acids are best absorbed in acidic environments like the stomach. Ionisation and Permeability: While the ionised version of a drug is typically poorly absorbed, the un-ionized form is more lipophilic and diffuses passively through biological membranes. Relationship: In situations where the environment is less than the While weak bases are mostly ionised, weak acids are usually un-ionized, which facilitates absorption. Conversely, weak bases are

mostly un-ionized when is greater than. Absorption Sites: Because of its large surface area and high permeability, the small intestine absorbs the majority of medicines, regardless of their pH-dependent ionisation. Drug Solubility: High ionisation forms are more soluble but frequently less permeable. High ionisation boosts solubility, but the non-ionized form is essential for membrane penetration, so a balance is required. Physiological Changes: The ionized/un-ionized ratio is altered by GI pH variations (such as those caused by meals or illnesses like hypochlorhydria), which affects the bioavailability of pH-dependent medications.

6. Polymorphism and Salt Formation

A crucial factor in the development of pharmaceuticals is polymorphism, or a molecule's capacity to crystallise in multiple unique crystal structures. The phenomena can have a major impact on the stability, bioavailability, and formulation of drugs. Variations in the way molecules are packed within a crystal lattice give rise to polymorphism, which results in various crystal forms with unique physicochemical characteristics. Despite having the same chemical composition, these polymorphic forms also referred to as polymorphs may show variations in solubility, dissolution rate, stability, and bioavailability. Different crystalline phases of the same molecule are called polymorphs. Higher, albeit occasionally less consistent, absorption results from metastable polymorphs because they are typically more soluble and dissolve more quickly than stable versions.

Although a more soluble polymorph increases absorption, it may be physically unstable and change into a less soluble form in the stomach or during storage, which would lessen the therapeutic effect.[9]

The main way that salt production improves oral drug absorption is by making poorly soluble acidic or basic pharmaceuticals more soluble in water and dissolving more quickly, which increases their bioavailability. Salts guarantee quicker dissolution by producing charged species that are more soluble in the GI tract, enabling the medication to reach higher concentrations for absorption.

Example**: Ibuprofen lysine** and **diclofenac sodium** have enhanced bioavailability through salt formation.

Table 1: Physiochemical factors affecting Drug absorption. [10]_ [6]

Physiochemical factors	Description & its impact on Absorption
Drug solubility & Dissolution rate	The main factor is the dissolution rate. For a medicine to be absorbed, it must be in solution; low solubility (less than 1% w/v) frequently restricts absorption.
Particle size & Surface area	Area the dissolving rate is accelerated and absorption is generally improved by the increased effective surface area of smaller particles.
Lipophilicity (Partition Coefficient)	The highly lipophilic drug has greater extent of absorption as they easily penetrates through GI membranes.
Ionization state (pH & pKa)	Lipid-soluble drugs can only pass across membranes in their un-ionized form. The pH-partition concept links absorption to both local pH and drug pKa.
Polymorphism & Amorphism	The solubilities of various crystal forms, or polymorphs, vary. Compared to crystalline forms, amorphous forms are typically more soluble and better absorbed.
Salt Form	Weak acid or basic salt versions typically dissolve more quickly and are more soluble in water than their parent medication.
Hydrates vs Solvates	Since water molecules in the crystal lattice can decrease solubility, anhydrous forms (also known as solvates) frequently dissolve more quickly and are better absorbed than hydrates.
Drug Stability	Drugs must remain stable in the gastrointestinal tract because the amount that can be absorbed is decreased when they are broken down by enzymes or stomach acid.
Molecular size & weight	Biological membranes are more easily penetrated by smaller molecules (usually less than 500 Daltons) than by larger ones.

Types of Dosage Form

Solid Dosage Form

Because of their obvious consistency and straightforward large-scale production, these same dry powder shapes are actually the most commonly used active ingredient. Its oral dosage forms influence patient populations, but this is more due to their own cost in the context of industrial production, such as the pharmaceutical industry. Therefore, it is particularly crucial to try to take solid oral dosage forms safely and effectively. This same solid oral dosage type is determined by important factors, such as the patient's reported attempts to accurately take tablets or capsules (FDA 2009). Even in situations where there is no need for an oropharyngeal motion disorder, the same productive gullet passing as well as the travel time

following all oral dosage forms shape necessary and essential upon that body posture when trying to swallow duration.

Advantages and Disadvantages: More accurate than other dosage forms; easier to handle; no need for preservation; costly machines that are difficult for children and patients to swallow while they sleep.[11]

Liquid Dosage Form

Highly water-soluble shapes have been paired with preparations that appear to be disintegrated, particularly liquid or used as drugs. Benefits: relief similar to giving. beginning of the action. flexibility in relation to dosage. improved the quality of the food. comparatively uniform medication.

Disadvantages: Relief from production Consistent state issues Instead of capacity, transport Accurate medication administration Short shelf life.[12]

Semi-Solid Dosage

Semi-solid formulations such as ointments, creams, pastes, and gels are widely used for localized drug delivery to the skin and mucosal surfaces, primarily targeting the epidermis. These formulations are generally non-dehydrating, easy to apply, and provide a smooth finish while remaining at the site of application. Ointments are typically greasy, inert, and occlusive preparations, whereas creams are viscoelastic emulsions with good patient acceptability. Pastes contain a high proportion of insoluble solids dispersed in an ointment base, offering protective action. Gels are semi-solid systems consisting of colloidal dispersions or microemulsions, suitable for delivering both hydrophilic and hydrophobic drugs.

These dosage forms offer several advantages, including improved drug solubility, enhanced patient compliance, avoidance of first-pass metabolism, rapid onset of action, and reduced systemic side effects. However, they also present limitations such as difficulty in dose uniformity, challenges in accurate application, potential for skin irritation or hypersensitivity, and susceptibility to environmental conditions like temperature and humidity, which may affect stability and drug release.[13]

Gaseous Dosage Form

Gaseous pharmaceutical formulations include aerosols, vapors, and inhalable substances such as water vapor and hydrocarbons, designed for rapid and targeted drug delivery, particularly

to the respiratory system. These systems deliver drugs in the form of fine particles or vapor, enabling direct absorption through the respiratory epithelium while bypassing the gastrointestinal tract, resulting in a rapid onset of action. They are widely used in the management of respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD), as well as in anaesthesia and allergy treatment.

Gaseous dosage forms can be classified into aerosols, vaporized agents, and intranasal delivery systems. Aerosols utilize pressurized containers to deliver a metered dose of medication, while volatile anaesthetics are administered as vapors. Intranasal sprays generate fine mists for local or systemic drug delivery through the nasal cavity.

These systems offer several advantages, including rapid therapeutic response, targeted drug delivery to the lungs, reduced systemic side effects, and improved patient compliance. However, they also have limitations such as formulation complexity, dependence on specialized delivery devices, challenges in dose uniformity, and potential environmental concerns related to propellants.[14]

Role of Excipients

Drug bioavailability can change as a result of substances that either increase or decrease cytochrome P450 activity. Numerous studies have been conducted on novel materials as drug delivery vehicles, such as vesicles, block copolymer micelles, degradable polymer particles, dendrimers, polymer prodrugs, and lipid nanoparticles; however, the impact of the excipients used is frequently overlooked. For example, propylene glycol-containing liquid cetaminophen is less toxic than solid preparations without propylene glycol. Acetaminophen is the primary cause of acute hepatic failure in both Europe and the US.[15] [16] Reductive metabolism through CYP2E1 is the cause of its toxicity.[17] Propylene glycol, a solubilizing agent, is used in the liquid formulation of acetaminophen to dissolve the medication in aqueous solution.[18] A single-blinded cross-over study was carried out using 15 healthy adult volunteers to compare the metabolism of solid and liquid acetaminophen 15 mg/kg dose by CYP2E1 because children consume liquid formulation and are less susceptible to its toxicity. Consequently, the metabolites' measured AUCs were 16% lower than those of the solid formulation. Propylene glycol exhibits a protective effect in liquid formulation because it is a competitive antagonist to CYP2E1[17] Inhibiting the CYP450 enzymes found in cellular microsomes is one way excipients can change how drugs are metabolized.[18]

Particle Size and Surface Area

Crystal size and its distribution (CSD), also known as particle size distribution (PSD), can have a significant impact on the physicochemical and biopharmaceutical characteristics of biologically active substances. Nearly 80% of new, promising molecules with biological activity are thought to be rejected during the research and development process because of their low water solubility, which is closely linked to the drug's bioavailability and release, according to the most recent scientific reports. Therefore, increasing the crystal surface and decreasing the crystal size can improve the API solubility parameters, particularly for ingredients in classes II and IV of the Biopharmaceutical Classification System.

Powder flowability, bulk density, hygroscopicity, compatibility, porosity, and blend uniformity are all greatly impacted by particle size. The efficacy and shelf life of the medication are impacted by these factors at every stage of tablet production, including compression, coating, granulation, and mixing. The final step of the tableting process is not the only one where particle size matters. The producer of the active pharmaceutical ingredient is also affected by the PSD control. It establishes the effectiveness of production processes like filtration and drying as well as the performance of crystalline material. Additionally, it has an impact on the stability of the material while it is being stored.[19]

Many pharmaceutical drug products are formulated and manufactured using bulk powders and particles. Designing common solid dosage formulations made of powder, like tablets and capsules, requires an understanding of the powder properties of both active pharmaceutical ingredients (APIs) and inactive ingredients (excipients). However, submicron- or nano-sized particle dispersions have been employed as drug carriers in nano-medical drug delivery systems (DDS) in clinical settings.[20] Particle size and surface characteristics are important factors that may need to be considered when designing drug carriers for delivery to cells and organs. Using nanoparticles to address unmet medical needs and patient-oriented/user-friendly formulations, such as orally disintegrated (OD) tablets based on particle design technology, researchers have developed emerging nanomedicines in the past or present (the focus of this article is on powders and particles).[21, 22, 23] Additionally, in order to attain and guarantee high-quality control and effective manufacturing, the pharmaceutical quality-by-design (QbD) concept and continuous manufacturing of pharmaceutical drug products have drawn increasing attention in the field of drug production.[24, 25, 26]

Manufacturing Processes

Conventional formulations, however, are not tailored for individual patients with diverse backgrounds because they are designed for large numbers of patients based on the "one-size-fits-all" principle. The US government introduced the Precision Medicine Initiative (PMI) in 2015, and this idea is what will propel the use of personalized medications in future health care systems.[17] Patients can now receive cutting-edge medical care that combines individual dosages with the most recent genomics-based diagnostic techniques thanks to research and development based on the PMI concept. In order to develop PMI and achieve personalized medicine, it will be crucial to establish formulation design and on-demand manufacturing that can flexibly apply dosage forms, dose, and DDS characteristics, such as drug-release patterns that are optimal for individual patients. In the future, every hospital and pharmacy might have fully automated pharmaceutical manufacturing equipment installed, allowing medical personnel—such as pharmacists with engineering backgrounds—to offer patients customized products.

Drug release mechanism

Mechanisms of Drug Release from Various Dosage Forms Drug Administration via Parenteral Route Among the various dosage forms, parenteral dosage forms are the most common, followed by aerosols and nasal dosage forms. Diffusion and dissolution-controlled processes are the mechanisms underlying drug release. Excipient types, amounts, manufacturing processes, dosage form geometry, routes of administration, pharmacokinetics, and physico-dynamics all play a major role in drug release mechanisms.

Drug deposition in the respiratory tract occurs through multiple mechanisms, including inertial impaction, sedimentation, diffusion, interception, and electrostatic attraction. Larger or high-velocity particles tend to deposit in upper airways due to inertia, while smaller particles (0.5–3 μm) settle in bronchioles and alveoli via sedimentation. Diffusion becomes significant for very fine particles and increases with longer residence time, such as during breath-holding. Particle charge and morphology also influence deposition patterns, with particles <5 μm showing enhanced lung penetration. In nasal delivery, deposition is largely governed by particle size, airflow, and nasal anatomy, with impaction being predominant, followed by mucociliary clearance.

Buccal and sublingual drug delivery primarily involve passive diffusion through paracellular and transcellular pathways, influenced by drug lipophilicity, molecular weight, and solubility;

however, limited surface area necessitates high drug potency. Oral absorption depends on drug physicochemical properties such as dissolution rate, ionization, and molecular size, as well as physiological and formulation factors, with most absorption occurring in the small intestine. In transdermal delivery, drugs must effectively penetrate the skin barrier to achieve systemic effects, typically requiring high potency and low dose due to limited permeability.[27,28]

Biopharmaceutics classification system

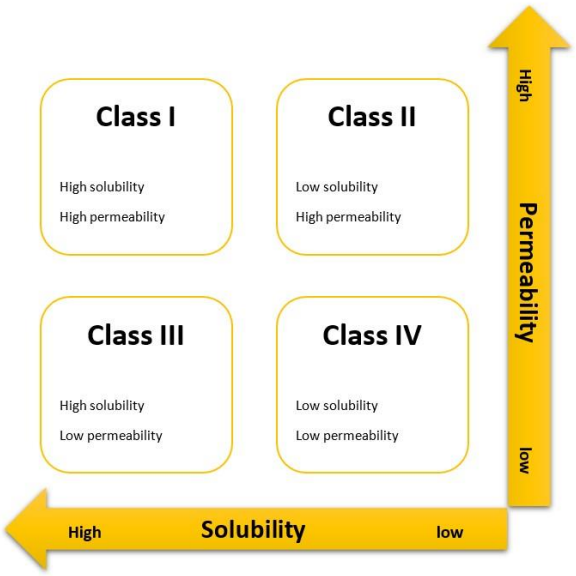

***Figure 3 BCS Division.*[29]**

BCS divides medications into four categories according to their permeability and solubility:

- **Class I medications:** High permeability and solubility indicating that the body can absorb them with ease.
- **Class II medications:** High permeability but low solubility indicating that their solubility limits their absorption instead of permeability.
- **Class III medications:** Low permeability but high solubility indicating that their absorption is constrained by permeability.
- **Class IV medications:** Low permeability and solubility causing the body to absorb them poorly.[30]

BCS's Significance in Drug Development

Researchers design drugs with the aid of the BCS classification.

formulations that are not based on trial-and-error experiments but rather on scientific principles. Regulatory organizations like the

- BCS guidelines are used by the FDA (2000) for
- Approval of New Drug Applications (NDAs)
- New Drug Application Abbreviated (ANDA) approvals
- Post-approval manufacturing and scale-up.[31]

Crucial Elements That Impact Drug Absorption

The three rate-limiting steps are explained by the BCS framework in absorption of drugs

- Drug discharge from the dosage form
- Gastrointestinal (GI) tract dissolution
- Infiltration into the liver via the GI membrane circulation.[32]

Physiological factors affecting Oral Drug Absorption

The mechanism that underlie how a drug is handled by human body are known as pharmacokinetics. The four components of pharmacokinetics are excretion, metabolism, distribution and absorption. Diffusion plays major role in drug absorption, which entails the drug passing through a cell membrane. The drug's preparation, administration route, molecular size, concentration gradient, degree of protein binding and lipid solubility of all affects the drug absorption rate. When drugs are administered orally, for example, their bioavailability may be decreased by first pass metabolism.[33] One of the most important factors in a successful drug product design is the drug's systemic absorption from the site of application. The effectiveness of drug delivery and its therapeutic effect at the intended site depend heavily on the absorption site.

Drug molecules are absorbed into the systemic circulation through a variety of diffusion pathways, including facilitated and carrier-mediated transportation. However, the human cell membrane's physiology typically acts as a barrier to these drug molecules' absorptions and prevents them from entering. Mucosa and nonmucosal barriers are the two categories into which physiological barriers are divided.[34]

Factors affecting the oral drug absorption as follow

1. Gastrointestinal pH

Drug absorption in humans is known to be impacted by gastrointestinal conditions. The absorption of oral medications is frequently significantly impacted by food consumption and gastric emptying, according to numerous studies. It has been demonstrated that the fraction of the dose absorbed (Fa) of a medication is strongly influenced by the pH of gastrointestinal fluid. In healthy volunteers, the pH of gastric fluid is normally acidic (between 1 and 2), but in human subjects with gastric anacidity or hypoacidity or those receiving antacid treatment, it is considerably changed. The pH of gastric fluid has been shown to have a significant impact on the systemic exposure of poorly water-soluble medications like albendazole, dipyridamole, and ketoconazole. Due to their fundamental physicochemical characteristics, these medications dissolve more readily in the stomach in acidic environments, which causes the drugs to become supersaturated in the intestinal fluid. As a result, the stomach's acidic environment affects the absorption of basic medications that are poorly soluble in water.[35]

2. Gastric emptying time

Because the absorption from the stomach is typically very small due to the stomach's very small effective surface area and the 1-1.5 mm thick mucus layer covering the mucosal surface, gastric emptying may be the rate-limiting step in the absorption of high permeability-high solubility drugs classified as Class I in the Biopharmaceutics Classification System. Gastric emptying during a fast is known to regulate the oral administration of acetaminophen as a liquid solution. According to Lipka et al., the rate and degree of celiprolol absorption in dogs were determined by fasted-state gastric motility. Tmax for a number of drugs after oral administration in the fasted state in rats has been reported to be delayed due to the retardation of GI transit, particularly that of gastric emptying. Variability in gastric emptying has been linked to the increased variability in cimetidine's plasma concentration-time curves. A common illustration of plasma profile variability is the emergence of double peaks in plasma concentration-time curves, which has been seen with a number of medications. To explain these findings, a number of theories have been put forth, including region-dependent variation in absorption, enterohepatic recirculation, variable gastric emptying and intestinal transit rates and intestinal bacterial reconversion of biliary metabolite.[36] One of the primary factors influencing oral drug bioavailability and gastrointestinal drug absorption is gastric emptying rate. Almost nothing will be absorbed if the stomach does not empty. Due to the

small bowel's relatively large surface area, even medications that are completely dissociated there and undissociated in stomach acid are still primarily absorbed there.[37]

3. Intestinal Motility

By regulating a drug's residence time in the GI tract, gastrointestinal (GI) motility is a physiological factor that influences oral drug absorption. This article describes the creation of the pulsatile emptying transit (PET) model, an oral drug absorption model that accounts for changes in GI motility brought on by the migrating motor complex (MMC). Pharmacokinetic models can estimate drug plasma concentration-time profiles using the absorption rate that the PET model produces as an input. It was simulated how changes in GI motility affected the drug plasma concentration-time profiles of high permeability and high solubility (BCS Class I) drugs. Simulations revealed that when medications with an effective permeability greater than 0.04 cm/min and a high dissolution rate (85% of the dose dissolves within 15 minutes) are dosed during phase III of the MMC, increases in the maximum plasma concentration (Cmax) greater than 10% may occur. The appearance of double peaks in oral ranitidine plasma concentration-time curves has been explained in a number of ways.

Dosage time in relation to the MMC, dissolution rate, effective permeability in the duodenum and ileum, and intravenous pharmacokinetic parameters (k12, k21, kout, Vd) were all subjected to parameter sensitivity analysis using a discontinuous PET model with a 2-compartment pharmacokinetic model. According to simulations, individual variations in these parameter values are responsible for the range of shapes for ranitidine plasma concentration-time profiles with double peaks. Furthermore, simulations revealed that the absence and presence of double peaks in oral ranitidine plasma concentration-time profiles can be explained by the dosing time in relation to the MMC combined with discontinuous absorption sites along the small intestine.[38]

4. Blood Flow to GIT

Intestinal blood flow influences intestinal absorption through a variety of mechanisms and interacts with it on multiple levels. Since there is currently no suitable method for measuring blood flow to the absorptive site, it is challenging to determine the exact relationships. O2 must be transported through the blood to maintain carrier-mediated transcellular transport in order for some nutrients to be absorbed. Tissue hydrostatic and colloid osmotic pressure, as well as epithelial and interstitial space conductance, can be affected by both changes in absorption and altered capillary pressure, which may or may not coexist with altered blood

flow due to myogenic autoregulation. For a constant driving force, these latter can then alter the passive ultrafiltration rate.

The rate at which absorbed substances are washed out can also be affected by changes in blood flow. Water absorption may be aided by countercurrent exchange in the villous vasculature, which can also buffer the rate at which certain substances are absorbed. Both independently and in combination, regulatory substances like hormones and neurotransmitters can impact blood flow and absorption. Changes in blood flow may alter the effects of agents that induce active intestinal secretion. The rate at which absorbed substances are washed out can also be affected by changes in blood flow. Water absorption may be aided by countercurrent exchange in the villous vasculature, which can also buffer the rate at which certain substances are absorbed. Both independently and in combination, regulatory substances like hormones and neurotransmitters can impact blood flow and absorption. Changes in blood flow may alter the effects of agents that induce active intestinal secretion.[39]

5. Surface area of intestine

The presence of several digestive enzymes, including lipase and peptidase, as well as the exocrine secretions of zymogen, including trypsinogen, chymotrypsinogen, and procarboxypeptidase, which are released from the pancreas and biliary system, may contribute to the improved absorption of oral medications in the small intestine. The villi and microvilli, which increase the intestinal surface area by 30-600 times, also aid in the absorption of the drug molecules. However, the absorption of some medications is restricted by the presence of barriers like mucous, tight junctions, efflux transporters, and enzymes. Due to its large surface area of about 400 m2, the small intestine is the primary location for drug absorption. Goblet cells, which line the microvilli, are primarily responsible for secreting the glycoproteins that make up the small intestine's mucosal lining. Proteins, nucleic acids, mucins, and electrolytes make up the mucous, a rigid layer that primarily functions as a buffer by controlling the pH at six along the apical surface, forming an acidic mantel that lines the small intestine. The glycocalyx borders the apical surface of this mucus, which covers the intestinal lumen's epithelial cells. An unstirred water layer (UWL) with a thickness of about 100 μm is formed by both the glycocalyx and the mucosal layer, which divides the bulk fluid phase of the small intestine lumen from the brush border of the

enterocytes. Lipophilic medications have trouble passing through the UWL to reach the brush border membrane, where absorption can occur, because of their poor aqueous solubility.[40]

6. Effect of Food

Food changes the rate at which the stomach empties, the pH of the stomach, the flow of bile, the flow of hepatic and splanchnic blood, and the physical interaction with the medication that causes problems with the rate and degree of absorption. When choosing the dosage and formulation type, one must take potential food-drug interactions into account. A drug's effect can be significantly altered by the presence of food. This can result in either unexpected side effects from the drug's rapid absorption or a less therapeutic effect than anticipated due to the drug's lower absorption. While levothyroxine and ciprofloxacin were found to be 40–50% less bioavailable after meals, commonly used medications such as propranolol and ketoconazole demonstrated improved absorption in the presence of food. As a result, many regulatory bodies are now requesting data regarding the dissolution and absorption of drugs caused by food, taking into account the impact of food on the drug's bioavailability. To address the issue of drug-food interactions, researchers have recently taken the initiative and created a variety of dosage forms. In addition to methods to increase drug bioavailability, the current review emphasizes food interactions.[41]

7. Age and Disease Conditions: -

More recent reports have not confirmed these findings in healthy subjects, despite earlier studies reporting significant apparent age-related effects such as reduced gastric acid secretion and gastric emptying, reduced splanchnic blood flow, and absorptive capacity of the small intestine, likely due to the effects of disease states. Results from pharmacokinetic research on how aging affects drug absorption have been inconsistent. The absorption of vitamin B12, iron, and calcium through active transport mechanisms is decreased, while the absorption of levodopa is increased. However, some studies have not demonstrated significant age-related differences in absorption rates for various drugs.[42] Pre-term and term neonates, infants, children, and adolescents are just a few of the subpopulations that make up the diverse "special" pediatric population. Recent reviews have examined how age affects drug absorption in children (Guimaraes et al., 2019; Johnson et al., 2018) and neonates (Neal-Kluever et al., 2019; Somani et al., 2016). Children's drug absorption differs from that of adults in both rate and extent, with neonates showing the biggest differences (Batchelor et al., 2014). The dose adjustment made for the population adds to the challenges of extrapolating

oral absorption data from adult data into pediatric populations. For a long time, the standard method for adjusting dosages was based on the patient's weight or body surface area, without taking into account the pediatric intestine's overall absorptive capacity or age-related changes in the intestine's oral drug absorption processes. The GI tract experiences a number of morphological and functional changes as people age, which lead to a general decline in body function. Therefore, in the elderly population—who frequently experience polypharmacy—effective drug absorption may be compromised by the complex deterioration of normal GI parameters. There is little evidence of the effects of advanced age on GI physiological factors, such as GI transit, pH, expression of membrane transporters and metabolizing enzymes, permeability, and the microbiome (Khan and Roberts, 2018). However, research has shown slight variations when compared to healthy adults (Brogna et al., 1999; Carréon, 2017; Fakhoury et al., 2005; Holt, 2018; Russell et al., 1993). Drug absorption and dietary habits that are common in the elderly population have a significant interaction. inflammatory bowel disease (IBD). are collectively referred to as primarily the colon and small intestine, Inflammatory conditions affecting the GI tract, ulcerative colitis (UC) and Crohn's disease (CD). Numerous intestinal and extra-intestinal characteristics are linked to both. ulcerative colitis (UC) and Crohn's disease (CD). Numerous intestinal and extra-intestinal characteristics are linked to both. As a chronic transmural inflammation, CD can impact any part of the GI tract from the mouth to the anus as well as the entire thickness of the bowel wall. Inflamed segments and so-called "skip areas" of healthy tissue typically make up the discontinuous inflammation pattern. CD is a chronic transmural inflammation, meaning that it can affect the entire thickness of the bowel wall as well as any segment of the GI tract from mouth to anus. The distal ileum is the most common initial location of CD, and the earliest mucosal lesions frequently appear over Peyer's patches. Inflamed segments and so-called "skip areas" of healthy tissue typically make up the discontinuous inflammation pattern. The distal ileum is where CD typically starts, and Peyer's patches are frequently where the first mucosal lesions appear.[43]

CONCLUSION

Oral drug absorption is a complicated, multifaceted process that is controlled by the interaction of gastrointestinal physiology, formulation design, and the drug's physicochemical characteristics. Drug permeability and bioavailability are greatly influenced by important variables such solubility, dissolution rate, lipophilicity, and ionisation. Variability in absorption is further influenced by physiological factors such as GI pH, stomach emptying,

intestinal motility, and first-pass metabolism. A scientific foundation for comprehending and forecasting various absorption behaviours is offered by the Biopharmaceutics Classification System (BCS). Absorption obstacles can be overcome with the use of appropriate formulation techniques, such as excipient selection and particle size optimisation. In the end, developing safe, efficient, and dependable oral drug delivery systems with predictable therapeutic results is made possible by a comprehensive understanding of these variables.

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