INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

A Comprehensive Study on Factors Influencing Drug Absorption

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ARTICLE INFO

Published: 13 May 2026
Keywords:
Pharmacokinetics, Drug Absorption, First-Pass Metabolism, Bioavailability, Compartment Models.
DOI:
10.5281/zenodo.20155328

ABSTRACT

Pharmacokinetics is a term that refers to a series of processes that govern how a body reacts to a given drug. There are four main pharmacokinetic parameters, namely, absorption, distribution, metabolism, and excretion. Drug absorption is a process by which a drug crosses a cell membrane. It is a diffusion-dependent process. The rate of drug absorption depends on the dosage form of a drug, route of administration, molecular weight of a drug, concentration gradient of a drug, protein binding, and lipid solubility of a drug. First-pass metabolism is a major factor in reducing the bioavailability of a drug when it is given by a particular route, i.e., oral route. Compartment models are used to predict a pharmacokinetic process of drug distribution. A multi-compartment model is used to understand how a drug is distributed. These models are used for a controlled infusion of a drug to maintain a certain concentration of anesthesia in the body, i.e., at a certain effect site, as specified by a user.

INTRODUCTION

The definition of the absorption process is “the transportation of unmetabolized drug from the site of administration to the circulatory system”.The major aspect of the absorption process is the transport of the drug across the cell membranes, which may take place in different ways depending on the structure of the drug. The cell membrane in the human body separates the intra- and extracellular environment. The cell membrane is made up of phospholipid molecules whose hydrophobic head groups face the outside, whereas the hydrophobic lipophilic chains/tails face the inside.The cell membrane consists of many ion channels, receptors, G-proteins, and enzymes. The cell membrane structure is such that it is in equilibrium. In order for substances to cross the cell membrane, various processes are required depending on the nature of the substances. In general, it has been observed that the lipophilic substances, such as oxygen, carbon dioxide, and steroids, are able to cross the cell membrane using the concentration gradient or pressure gradient through the hydrophobic region of the cell membrane. The hydrophobic region in the cell

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

membrane acts as a barrier for the diffusion of water and hydrophilic substances such as glucose and ions. The topic describes the various ways by which drugs are able to cross the cell membrane.

Bioavailability

Bioavailability is "the fraction of the administered dose of drug that reaches the systemic circulation in its unchanged (intact) form".7 It thus determines the dosage needed for a drug in a particular route of administration. The bioavailability of a drug administered through the intravenous route is 100%. Absolute bioavailability may be determined by comparing the plasma concentrations of the test dose and the plasma concentration of the drug administered through the intravenous route. This may be determined by constructing a graph that plots the concentrations against the time of administration; the ratio of the areas under the curve for the extravascular and the intravenous routes of administration will determine the bioavailability of the drug.

Factors Influencing Bioavailability

Physicochemical properties of the drug: The solubility and permeability of the drug are very important in the absorption process. Drugs with low solubility or low permeability through the cell membranes are not easily absorbed. Drugs in a solid form, for instance, have to dissolve in the body in order to be absorbed. The rate at which they dissolve in the body can affect their bioavailability.

Gastrointestinal factors: These factors include the pH of the stomach, gastric emptying time, and the presence of food in the stomach. For example, certain medications that are acid-base sensitive may be poorly absorbed in an acidic environment, and certain medications that require activation by enzymes may be influenced by the level of enzyme activity in the gastrointestinal tract . Diseases or conditions that may be affecting the gastrointestinal system, such as Crohn's disease or celiac disease, may influence drug bioavailability.

Drug formulation: The physical state of the drug is also a factor that influences the rate of dissolution and absorption of a drug. For instance, some drugs are formulated in a manner that allows for controlled release or extended release, which helps to increase their bioavailability by ensuring that they are absorbed by the body for a relatively longer time . However, some poorly formulated drugs may not be able to dissolve well in the body, which may subsequently reduce their bioavailability.

Food and drug interactions: The interaction between food or other drugs in the gastrointestinal tract could influence the absorption of the drug. Some drugs could be absorbed in the presence of food, whereas the effectiveness of some drugs could be reduced in the presence of food. In addition, some drugs could interact with one another, which could influence the absorption, metabolism, and excretion of the drugs, thereby affecting their bioavailability.

Bioavailability and therapeutic efficacy: Bioavailability is a critical factor that determines the therapeutic efficacy of a drug. A drug that has high bioavailability can deliver itself to the target site in sufficient concentrations to exert a therapeutic effect, while a drug that has low bioavailability may require higher doses or more frequent dosing regimens to exert a similar therapeutic effect . The relationship between bioavailability and therapeutic efficacy is particularly critical in managing chronic conditions that require a continuous therapeutic effect. In managing drugs that have low bioavailability, different pharmaceutical formulations can be used to improve their

bioavailability and efficacy. For example, nanotechnology can be used to improve the efficacy of a drug that has low bioavailability. Nanotechnology can be used to design drug delivery systems that can protect a drug from first-pass metabolism or improve its solubility and permeability . On the other hand, a drug that has high bioavailability does not require any formulation to improve its efficacy and may need to be monitored to prevent toxicity caused by high concentrations in the bloodstream.

Pharmacokinetic modeling and bioavailability: Pharmacokinetic models can be employed for the prediction of bioavailability for a drug and its concentration-time profile in the body. These models can be effectively employed for deciding upon an appropriate dosing schedule for drugs, taking into account various parameters such as rates of absorption, distribution, and clearance. The bioavailability data from various clinical trials for drugs can be incorporated into these models for arriving at an estimate for the required dose and frequency for administration, in order to ensure effective drug concentration in the body with minimal adverse effects and toxicity. Pharmacokinetic models for drugs with low bioavailability upon oral administration can be effectively employed for arriving at an appropriate decision regarding alternative routes for administration. These models can be employed for assessing various drug formulations for arriving at an appropriate method for drug administration.

First Pass Metabolism

First pass metabolism is the metabolic process of a drug before it is absorbed into the systemic circulation. When the drug is given orally, the first pass metabolism occurs in the wall of the bowel and the lumen of the bowel, or the hepatocytes. If the first pass metabolism of the drug is high, the difference between the doses of the drug given through the extravascular routes and the dose of the drug given intravenously is more. In the lumen of the bowel, the drug is metabolized by digestive enzymes that can break molecular bonds. In the lumen of the bowel, ‘phase 1’ metabolic changes occur in the bacteria. Oxidation, reduction, and hydrolysis occur in the intestinal lumen. In the intestinal wall, there are many enzymes and drug transporters involved in the first pass metabolism of the drug. For example, the enzyme monoamine oxidase and the enzyme CYP3A4 are located in the intestinal wall. In the intestinal wall cells, there is a drug transporter called p-glycoprotein that transports the drug back into the lumen of the bowel after it is transported into the cell of the intestinal wall. The liver receives a high blood volume from the gastrointestinal tract via the portal tone. The liver is the point for the maturity of the first pass metabolism in the body. The metabolism of the medicines occurs by the enzymes in the liver before the medicines enter the general rotation. This process can be accelerated by the administration of medicines which induce the CYP450 enzyme system, therefore adding the quantum of the haemoprotein. also, the metabolism in the liver can be dropped by the CYP450 enzyme impediments, which are amiodarone.

The first pass metabolism in the liver is directly commensurable to the hepatic birth rate of the medicine. Hepatic birth rate(HER) is defined as ‘ the bit of the medicine entering the liver in the blood which is irreversibly uprooted in one pass through the liver’. If the hepatic enzymes are effective in the metabolism of the medicine, the first pass metabolism is high. GTN, propofol, propranolol, and lidocaine have high hepatic birth rates. The quantum of free medicine in the rotation, the natural concurrence of the substance in the liver.

Absorption from the Gut

The cheapest and easiest route of administering medication is oral administration. When this route is used, the drug is absorbed via the mucosa. However, there are various factors that affect the amount of drug that reaches the circulation. This route has the poorest bioavailability of any route because it has the highest metabolism rate. Firstly, the nature of the drug is vital in determining how easily it can be absorbed from the gut when ingested. A higher dose of the drug will produce a greater gradient for diffusion and a greater rate of absorption. In addition, lipophilic and smaller molecules can be absorbed better than larger hydrophobic molecules. The formulation of the drug can also be altered to favor better absorption. Modified-release formulations can be used to sustain the drug in the bloodstream at therapeutic concentrations. This is done by slowly dissolving the drug using a polymer of varying thickness to control the amount of drug that is absorbed. The stomach lining produces 2 litres of gastric fluid daily, including hydrochloric acid at a pH of 0.8, secreted by the parietal cells in the stomach lining. Hence, the pH of the stomach is highly acidic in nature. As described in the latter part of the article, the proportion of the drug that is in the unionized form in the stomach will be more, and the unionized form of the drug will be absorbed more by the cell membrane. So, it is expected that the absorption of the drug in the stomach would be more in the case of an acidic drug. However, the presence of a thick mucus layer and a smaller surface area in the stomach, in comparison to the small intestine, also affects the rate of absorption in the stomach. For the absorption of the drug in the stomach, the drug should be a small molecule, weakly acidic, and highly concentrated, such as aspirin, furosemide, phenytoin, and theophylline. The ionized form of the drug exists in the stomach in the case of a basic drug, so the absorption of the drug in the stomach would be less. The properties of the gastrointestinal system can also influence how well this drug is absorbed into the system. Gastric stasis is a common occurrence in critical patients and can increase the time taken for a drug to be adequately concentrated in the system by slowing down the rate at which this drug is absorbed. Enteral nutrition, nicotine, levodopa, and hyperglycaemia can all slow down gastric emptying. A slower intestinal transit time will also mean a slower rate of absorption since this will mean that the rate at which this drug is delivered to the surface of the small intestine is reduced. However, since this drug is being exposed to this surface for a longer time, this will increase the rate of absorption. There are many factors that influence intestinal motility. These factors include pain, diabetes, metabolic disorders, and medications. In most instances, transit time through the small intestine is between 5 and 10 hours; however, most of this drug is absorbed in the first hour in this region. The large gastrointestinal surface area is important in order to be able to utilize oral medications effectively. The small intestine is only 7m long, but it has a

large surface area of more than 250m2 due to the presence of valvulae coniventes, villi, and microvilli. Diseases like coeliac disease and short gut syndrome can cause a large reduction in the small intestine's surface area. Critically ill patients may experience a reduction in the amount of blood flow to the gastrointestinal tract, as blood flow is shunted away from this area in hypotension and shock states, and inotropes and vasopressors, used in these conditions, cause a shunting of blood flow to more "vital" areas. This can cause a reduction in the amount of absorption of almost all orally ingested medication. Ischaemia can cause a loss of microvilli on the brush borders, thus affecting plasma concentrations of drugs. Lastly, within the gastrointestinal tract, drugs have the potential to interact with other substances. They may potentially be able to form a complex that is unable to be absorbed. For example, activated charcoal is used in a therapeutic manner in poisoning cases due to its large surface area, capable of absorbing a variety of substances.

Absorption from Inhalational Administered Drugs

The particle size of the drug plays an important role in determining the effect of the drug. When the drug is inhaled, the drug needs to reach the alveoli to be absorbed into the circulation. This can only happen if the particle size of the drug droplet is less than 1 micron in diameter. This can be achieved by using a nebulizer to administer the drug. When the drug reaches the alveoli, it is rapidly absorbed by diffusion due to its large surface area, which is 70 square meters. Larger particle sizes have a localized effect in the respiratory tract.

Intramuscular route

The bioavailability for an intramuscular drug is almost similar to an intravenous drug; however, the rate of onset is greatly determined by regional blood flow. A good example is the use of muscles with good blood flow, such as the deltoid muscles, to avoid delayed onset and insufficient plasma concentration. Inaccurate intramuscular injections can cause unintentional intravenous injections, abscesses, and hematoma; thus, careful selection is required.

Transdermal Administration

Transdermal immersion is a non-invasive way of introducing a medicine into the system through the skin's face. Skin has colorful layers conforming of the epidermis, dermis, and hypodermis. The remotest subcaste of the skin is the epidermis and consists of the stratum corneum. The lipid subcaste of the stratum corneum only allows lipid-answerable substances to be absorbed. still, damage to the epidermis, similar as becks and scrapes, can affect in briskly and unselective immersion of substances. The advantages of transdermal administration of specifics include the avoidance of first- pass metabolism and the easy administration of the medicine to the case.

Issues of Concern

Regardless of where it is absorbed, it has to penetrate the cell membrane to reach the general circulation. The drug can penetrate by simple diffusion and membrane transport. The major route by which drugs are absorbed is by simple diffusion. The principle behind this is based on Fick's law of diffusion, in which the drug molecule diffuses from an area of high concentration to an area of lower concentration until equilibrium is achieved. The diffusion can be aqueous or lipid. Aqueous diffusion takes place in an aqueous compartment in the body, such as interstitial space, or through aqueous pores in the vessel endothelium. Drugs attached to albumin or large plasma proteins cannot diffuse through aqueous

pores. Lipid diffusion takes place in the lipid compartment in the body. It is therefore considered to be the most important factor in drug permeability because there is an increased number of lipid barriers between body compartments. The lipid aqueous partition coefficient for the drug is used to measure how quickly it is able to diffuse from one compartment to another.

Another mechanism of absorption is through a carrier-mediated membrane transport. There are many specialized carrier-mediated membrane transport systems in the body that are used for transporting ions and nutrients, especially in the intestine. These systems include active and facilitated diffusion. Active diffusion is a very important, energy-requiring system that is used in the GI tract for the excretion of many drugs, as well as in the kidney and biliary system. This method is used for the absorption of those lipid-insoluble drugs that resemble endogenous physiological metabolites, such as 5-fluorouracil, from the GI tract. As opposed to passive diffusion, in active diffusion, it is possible for a drug to move from areas of lower concentration to areas of higher concentration.

With active diffusion, the carrier binds with the drug to form a complex, which then helps in the transport of the drug through the membrane. The complex then dissociates on the other side. The carrier molecule can be very specific to the drug molecule. Drugs with similar structures can compete with each other at the absorption sites. Since only a few carrier molecules are present, the sites on the carrier can get saturated if the concentration of the drug is very high. After that, any increase in the dose will not increase the concentration of the drug. Some transporters can facilitate the absorption of the drug, but transporters like P-glycoprotein can very efficiently prevent the absorption of the drug. P-glycoprotein, also known as MDR1, is an energy-requiring efflux transporter, which helps in the secretion of the drug back to the lumen, thereby preventing its absorption.

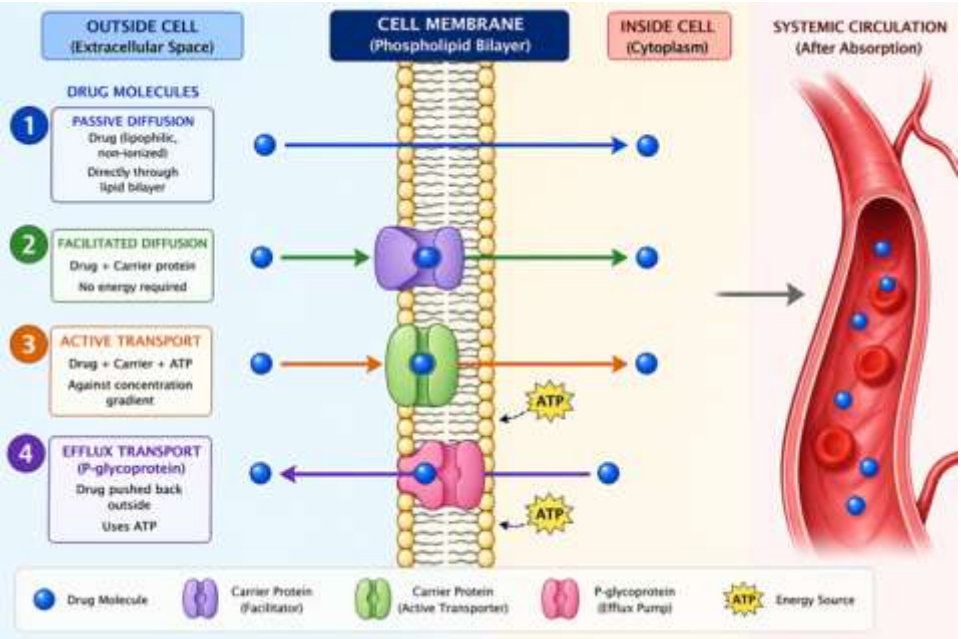
The drug-specific factors that influence drug absorption include physicochemical and pharmaceutical factors. One of the physicochemical factors is solubility, including the role of pH and pKa, where most of the drugs are weak acids or bases in solutions in both their ionized and non-ionized forms. These ionized forms of the drug are hydrophilic and cannot cross the cell membrane. However, the non-ionized forms of the drug seem to be lipophilic, thus easily crossing the cell membrane by simple diffusion. The distribution of weak electrolytes in cells is influenced by the pH gradient in the cell membrane and the pKa of the drug. Weakly acidic drugs can be easily absorbed in an acidic environment, such as in the stomach. However, weakly basic drugs are not absorbed until they are in a higher pH environment, such as in the small intestine.

Other physicochemical factors like particle size and surface area, rate of dissolution, amorphism, polymorphism, and type of dosage form will also influence the rate of drug absorption. The rate of dissolution is defined as the quantity of a given solid that is dissolved at a given time at standard pH conditions and solvent composition and temperature and constant surface area. For example, cisapride is a gastroprokinetic drug that has poor aqueous solubility. However, it has good oral bioavailability since it has a good rate of dissolution in GI fluids. Particle size is inversely proportional to the rate of dissolution. For example, if a drug has a small particle size, this will increase the rate of dissolution. Micronization of a drug will increase its rate of dissolution and solubility. For example, digoxin has 100%

bioavailability in micronized tablet form. In addition, the structure of a drug can be crystalline or amorphous.

Polymorph is a term where the solid has more than one crystalline form. In other words, the polymorphs may have different physical properties such as solubility, hardness, and melting point. For instance, chloramphenicol palmitate has three polymorphic forms: A, B, and C. Of the three forms, B is found to have the best absorption and bioavailability. In the case of pharmaceutical variables, the presence of different excipients may increase or decrease the absorption rate of the drug. Excipients are the inactive ingredients of the drug. In the case of the drug's dosage forms, there are various forms in which the drug can be administered. In each of the forms, the absorption rate is different based on various factors such as the nature of the dosage form and the site of administration. In the case of orally ingested dosage forms, the solution has the best absorption rate. In the case of drug expiration and storage conditions, they are the other pharmaceutical variables.

Patient-specific factors influencing drug absorption (physiological factors) include age, gastric emptying time, intestinal transit time, disease condition, blood flow at the site of absorption, presystemic metabolism, and GI content. As the person gets older, various physiological changes occur in the body. This may result in reduced absorption of the drug. In general, the absorption of the drug in the intestine is more significant than in any other region of the GI tract because of the large surface area of the mucosal lining of the intestine. In the duodenum, the mucosal lining has the fastest rate of drug absorption because of the presence of structures such as villi and microvilli. However, the number of such structures is small in the other parts of the GI tract. Drugs can be absorbed in the GI tract at a different rate. Before the drug is absorbed into the bloodstream following oral administration, the drug may undergo metabolism in the walls of the GI tract and the liver. For instance, the rate of absorption of levodopa is reduced in the presence of food containing protein, and the absorption of albendazole is increased in the presence of lipid-containing food.



Clinical Significance

The benefit and toxicity of a drug are related to its plasma concentration. Bioavailability is critical in maintaining the plasma concentration of a drug within the therapeutic range. Bioavailability of a drug is directly dependent on the rate and extent of drug absorption at the site of administration. Thus, factors that influence drug absorption, including routes of administration, directly influence the bioavailability of that drug. When a drug has optimal physicochemical properties for absorption under normal physiological conditions, the rate and extent of drug absorption are directly influenced by the route of administration of that drug.

Generally, the order of bioavailability of the various routes of administration, ranked in order from highest to lowest, is parenteral, rectal, oral, and topical. Drugs given intravenously (IV) have 100% bioavailability because the process of absorption is bypassed by the drug being able to enter the systemic circulation directly. IV drugs are usually given in cases where the rapid onset of the response is needed, such as in emergency cases. Other cases where IV drugs are needed are in unconscious patients, in patients where the GI tract is not functioning, in cases where the oral dosage form is not available to avoid the first-pass effect on the liver, and in cases where tissue penetration is needed but not feasible by the oral route.

While it is true that the bioavailability of orally administered drugs is a complex and variable issue depending on factors affecting the absorption process, it is more convenient for many patients. It is the most commonly used route of administration for all drugs. Bioavailability and pharmacokinetic studies are conducted to determine a dosage regimen for a new drug candidate to ensure that it is therapeutically effective and safe, to find new formulations of existing drugs, to compare the bioavailability of a drug in different forms or of a similar form of a drug from a different manufacturer, and to monitor the quality of a drug product in the early stages of marketing by determining physicochemical and physiological factors affecting absorption.

Absolute bioavailability is a test in which the bioavailability of a drug given orally is compared to that of a drug given intravenously. Bioavailability is used to assess the characteristics of drug absorption when a drug is given orally. Comparative bioavailability, or relative bioavailability, is a test in which the bioavailability of a drug given orally is compared to that of a standard oral preparation of that drug. It is also known as relative bioavailability. Unlike absolute bioavailability, relative bioavailability is used to assess the characteristics of drug absorption of different formulations. Bioequivalence studies are conducted in order to distinguish between two drug products that contain the same active ingredients. It is helpful in comparing a brand drug and a generic drug.

The absorption and bioavailability of the drug are significant factors in pharmacokinetics. They impact the efficacy as well as the safety of the drug. In addition, the onset, potency, as well as the time course, are sometimes influenced by the absorption as well as the bioavailability. There are many factors which impact the absorption as well as the bioavailability of the drugs. Some factors are specific to the drug, whereas some factors are specific to the patient. The bioavailability as well as the pharmacokinetics studies are carried out to optimize the use of the drug by maintaining the drug concentration in the therapeutic range.

Factors affecting drug absorption

A) Chemical Methods

Several possible chemical approaches can be considered to make drugs more stable and available systemically. One option would involve synthesis of esters of acids and bases. Esters will hydrolyze to the respective acid/base forms once they enter the circulation. Both acids and bases become more stable and soluble if converted to salts. In general, injection of soluble salts of penicillin results in higher levels of antibiotics in the bloodstream compared to the free acid. Upon dissolution of salt of weak acid in stomach, a diffusion layer with relatively high pH will be formed, thus allowing for easier dissolution. This reasoning may be applied to basic drugs as well. Nevertheless, extremely low pH of stomach fluid neutralizes this effect. o Therefore, salts of basic drugs are used mostly for handling and solubility reasons.

B) Physicochemical Properties of Drugs

1. Drug Solubility & Dissolution Rate –

Absorption processes of drugs administered orally involve, .Dissolution rate ,.Diffusion of drug molecules through the biological membrane. Dissolution is rate limiting Diffusion is rate limiting process in case of lipophillic process in case of hydrophillic drugs. drugs. Examples include, Griseofulvin Neomycin. The prerequisite for the absorption of drugs requires the drug to be present in aqueous solution, which is dependent on its solubility & dissolution rate in an aqueous medium.

2. Particle Size and Effective Surface Area –

Finer the particle size (with micronization), the larger the effective surface area, greater the contact between solid surface and aqueous solvent, faster the dissolution rate, and higher the efficiency of absorption . e.g. drugs with poor aqueous solubility and nonhydrophilic in nature such as Griseofulvin and chloramphenicol where dissolution is rate limiting step. Many poorly soluble drugs have undergone particle size reduction to improve their absorption, these include bishydroxycoumarin, digoxin, griseofulvin, nitrofurantoin, and tolbutamide. Drug in particle form Drug in solution form Drug in blood stream.

3. Polymorphism and amorphism

When sub exist in different crystalline forms i.e., in polymorphic form, then different forms are Several compounds crystallize in various molecular configurations known as polymorphs. Such polymorphs differ in their physical characteristics, including dissolving rates and solubility.Eg: the vitamin riboflavin can occur in multiple polymorphic states, each with an aqueous solubility 20 times greater than that of the others.Some polymorphs lack crystal structure and hence are called amorphs. These exhibit physical properties distinct from those of the crystalline polymorphs.The absorption of oral medications is regulated by their dissolving rates.Amorphs are more easily dissolved compared to the crystalline forms since there is no need for energy to destroy the crystal lattices. Hence, amorphs are more desirable than crystalline forms, and certain drugs like hydrocortisone and prednisolone are sold in amorphic form. Eg: Novobiocin

4. Solvates/hydrates-

During their formation, the crystals of drugs can contain one or more molecules of a solvent to become solvates. Water is the most common type of solvent used for forming a solvate. The presence of water molecules within a crystalline structure limits the ability of the crystal to attract water molecules from the surrounding environment to cause dissolving of the crystal, thus hydrated crystals take time to dissolve than anhydrous

crystals. Important differences in the dissolution rates have been documented between hydrated and anhydrous forms of ampicillin, caffeine, theophylline, glutethimide and mercaptopurine. However, clinical importance of these differences is yet to be determined although it may be minimal. Solvates are much more soluble than their corresponding nonsolvates e.g. chloroform solvates of Griseofulvin and n-pentanol solvate of fludrocortisone.

5. Salt form of drug –

The solubility of any drug (whether basic/acidic or their salts) at a particular pH is constant. In case of considering salt form of drug, then pH of diffusion layer should be considered and not the pH of bulk solution.Example of salt of weak acid which increases the pH of diffusion layer, it will promote the dissolution of weak acid drugs and also leads to rapid absorption.Conversely in case of salts of weak base drug, the pH of diffusion layer decreases and the absorption of such drugs is promoted. Another technique used for improving absorption of certain drugs involves the formation of in situ salt formation (i.e., increase the pH of immediate environment of the drug by incorporating buffer). E.g. aspirin and penicillin o Sometimes highly soluble salt form of drug might have poor absorption rate. E.g. Sodium salt of phenobarbitone and phenobarbitone, tablets of sodium salt of phenobarbitone swells, it does not dissolve rapidly and hence the poor absorption of the drug. Various salts of dissolution profile, where A) has high solubility profile of Potassium B) dissolution profile of various penicillin salts.

6. Ionization State-

The unionized state of the medicine is important for unresistant prolixity through the membrane and, thus, essential for immersion. The ionized state of the medicine is important for solubility.

7. GI pH-partition theory-

Under the pH-partition theory, absorption of medicinal drugs having molecular weights above 100 through the passage across the biomembrane primarily through passive diffusion is regulated by Drug pKa. The lipid solubility of the unionized drug , the pH at the point of absorption. The drug concentration in its unionized and ionized forms depends upon the pKa value of the drug and the pH of the medium during absorption. This can be determined using the following Henderson-Hasselbach equation:

For acidic drugs :

pH= pKa + log [ionized form]/ [unionized form]

For basic drugs:

pH=pKa + log [unionized form]/ [ionized form]

C) Formulation factors

1) Disintegration time-

Low disintegration time is needed because rapid disintegration ensures rapid dissolution. The D.T. of the tablet is now directly related to the amount of binder. Compression pressure- it should be noted that the disintegration test in vitro cannot ensure good pharmaceutical B.A., as dissolution will not take place without first disintegrating the drug particles.

2) Manufacturing variables –

a) Granulation method- the tablets are produced using the wet granulation method are faster to dissolve compared to tablets produced through other methods. Nevertheless, there are several disadvantages associated with the wet granulation method, such as chemical decomposition or formation of crystal bridges. In addition, another

advanced method known as APOC (agglomerate phase of communition) involves comminution of the drug until self-agglomeration takes place and yields granules with a greater surface area. Consequently, the tablets made from such grains dissolve more rapidly.

b) Compression force- the tablets having high compression forces have relatively long D.T., due to hardness, as well as being difficult to wick. This is mainly because high compression forces reduce drug particles to smaller sizes with an increased surface area.

3) Nature and type of dosage form-

Drug formulations are designed to provide an attractive, stable, and convenient method to use products. Conventional dosage forms may be broadly characterized in order of decreasing dissolution rate as solutions, solid solutions, suspensions, capsules and tablets, coated capsules and tablets, and controlled release formulations.

A. **Solutions-** Aqueous solutions, syrups, elixirs, and emulsions do not present a dissolution problem and generally result in fast and often complete absorption as compared to solid dosage forms. Due to their generally good systemic availability, solutions are frequently used as bioavailability standards against which other dosage forms are compared.

B. **Solid solutions-** The solid solution is a formulation in which drug is trapped as a solid solution or monomolecular dispersion in a water-soluble matrix. Although the solid solution is an attractive approach to increase drug absorption, only one drug, griseofulvin, is currently marketed in this form.

C. **Suspensions-** A drug in suspension form is solid but is highly divided with large surface areas. This is because the drug particles can easily diffuse from the stomach to the small intestine irrespective of stomach emptying rates. Dosage adjustment according to the requirement of patients is relatively easy using liquid formulations such as suspensions as compared to solid dosage forms. But there are some disadvantages of liquid dosage forms too, such as bulkiness and inconvenience to handle.

D. **Capsules and Tablets-** There is a difference between the two solid dosage forms in the sense that the material in capsules is not so affected as in compressed tablets. As soon as the capsule dissolves, its material disperses very rapidly. The capsule material, even though it is water soluble, sometimes interferes with the drug dissolution process. It does so by reacting with the drug. Disintegration of tablets takes place in two stages – into granules and into primary particles. As the particle size reduces, the rate of dissolution becomes higher owing to increased surface area. The disintegration of tablet was once considered enough to determine drug absorption.

As a general principle, the availability of drug from different types of dosage forms decreases in the following order

Solutions > Emulsions > Suspensions > Capsules > Tablets > Coated tablets > Enteric Coateds Tablets > Sustained release products

4. Pharmaceutical Excipients: -

The greater the number of excipients in a dosage form, the more complex it becomes & consequently more difficult to get adequate absorption and bioavailability. Modification of excipient from calcium sulphate to lactose and

increase of magnesium silicate will increase oral effectiveness of phenytoin.Availability of thiamine and riboflavin is decreased by the use of Fuller's earth. Absorption of tetracycline is decreased when used with calcium phosphate because of formation of complexes.Most of these interactions have been seen long back and not very likely to occur now in today's stringent evaluation of newly formulated drugs.

a) Vehicle

Rate of absorption- depends upon miscibility with biological fluid.Miscible vehicles (aqueous or water miscible vehicles)- rapid absorption such as propylene glycol.Immiscible vehicles- rate of absorption depends upon partition coefficient from oily vehicle to aqueous body fluid.

b) Diluent

Hydrophilic diluents – forms hydrophilic layer around hydrophobic drug particles thus promotes dissolution and absorption of poorly soluble hydrophobic drug.

c) Binders and granulating agent-

Hydrophilic binders- gives the granules' surface hydrophilic properties leading to better dissolution of poorly wettable drugs. E.g., starch, gelatin, PVP.Use of excessive amounts of binders leads to harder tablets which will lower the rate of dissolution and disintegration.

d) Disintegrants-

Usually, disintegrants are hydrophilic in nature. Reduction in the use of disintegrants would significantly reduce B.A.

e) Lubricants-

Commonly hydrophobic in nature; hence they prevent water from penetrating the tablet and thus affect disintegration.

f) Suspension agents/ viscosity agents-

Stabilizes the suspension and thus affects drug absorption. Also, macromolecular gums form complexes that cannot be absorbed by the body, e.g. Na CMC. Viscosity increasing agents; create a physical barrier against diffusion of drugs from their dosage forms and inhibit GI transit of the drug.

g) Surfactants-

May either increase or retard drug absorption by interacting with the drug or membranes or both. Surfactants have been known to enhance drug absorption mostly in animals. Poly oxyethylene ethers were able to enhance gastric or rectal absorption of lincomycin, penicillin, cephalosporins, and fosfomycin in rats and rabbits. In humans, orally administered polyoxyethylene-20-oleyl ether caused low and inconsistent absorption of insulin. Generally, unionic surfactants exert negligible influence on membrane structure while cationic surfactants have been found to cause reversible cell damage and destruction of goblet cells. Physiological surfactants (bile salts) enhance absorption – e.g., Griseofulvin, steroids. The surfactant decreases absorption by forming an unabsorbable complex with drug above -CMC

h) Bile salts-

Bile consists of conjugated cholic and chenodeoxycholic acids that act as emulsifiers for dietary lipids, causing fat emulsification, lipolysis, and solubilization of lipids by micellar transport across the unstirred layer of the intestinal mucosa. Their ability to increase lipid absorption has made

them candidates as absorption enhancers, with mixed results. Insulin absorption can be enhanced by bile salts, both in animal models and in human studies.

i) Colorants-

Even small amounts of water-soluble dyes reduce the dissolution rates of crystalline drugs. Dye molecules adhere to the crystal surface and inhibit the dissolution process. E.g., Brilliant blue reduces sulfathiazole dissolution.

5. Product age and storage conditions –

Product aging and poor storage conditions negatively impact B.A.. E.g.– Precipitation of drug in solution reduces dissolution rate, change in particle size of suspension and hardening of tablet and absorption.

D) Patient- related factors

1) Membrane Physiology

A) Nature of membrane of the cell- Fluid Mosaic Model- It describes how polar molecules diffuse through cells. In this model, the cell membrane comprises globular proteins in a fluid lipid bilayer.The proteins act as channels that allow specific polar molecules and ions to selectively cross the lipid layer.Inferences from studies of capillary membrane transport suggested two types of pores, one of 10 nm, and another between 50 to 70 nm () in the cell membrane. These channels enable water and soluble substances such as ions and urea to pass through the membrane.

B) Transport Processes

- **Passive Diffusion-** The lipophilic drug either passes through the cell or bypasses it. For a low-molecular weight drug that is also lipophilic, the lipid cell membrane does not hinder drug passage. Passive diffusion is when molecules move from regions of high to low concentrations through the natural process. It is called passive because no extra energy is required in this case.

- **Carrier-Mediated Transport-** If a lipophilic drug passes through the cell or circumvents it, it theoretically does so. For example, when the drug is both lipophilic and low in molecular weight, then its diffusion and absorption will not be hindered by the lipid cell membrane. Drugs or other substances may diffuse or undergo a carrier-mediated transfer through the epithelium lining the intestinal wall. There exist various carrier-mediated transport mechanisms in the body, especially in the intestines, where they facilitatethe absorption of ions and nutrients that the body needs.

- **Active Transport-** It is a carrier-mediated process of transmembrane movement involved in drug gastrointestinal absorption, as well as drug secretion by kidney and bile. There are a number of water-soluble drugs that bear structural resemblance to some natural physiologic metabolites, like 5-fluorouracil. These drugs undergo active transport during absorption in the gut. Active transport is marked by drug transfer against a concentration gradient, that is the transfer of drugs from areas where the drug concentration is low to areas where it is high. This is a process that requires a source of energy. Besides, the transfer of drugs requires a specific carrier in order to form a carrier-drug complex.

- **Vesicular Transport-** Exocytosis can be described as the movement of a protein, such as insulin, from insulin-secreting pancreatic cells to the extracellular environment. First,

the insulin molecules are enclosed within the intracellular vesicle, which fuses with the plasma membrane to release them into the extracellular environment.

- **Pore (Convective) Transport-** The small-sized molecules (urea, water, and sugars), which move through the cell membrane quickly, act as if there were channels and pores within the membranes. Even though these channels have not yet been directly observed, the pore model is used to explain the process of excretion and distribution of drugs in the kidneys and their absorption by the liver, respectively.

- **Ion-Pair Formation-** Strong electrolytes are highly charged drugs (e.g., quaternary nitrogens) with extremely high pKa values. The strong electrolyte drugs remain charged at any physiologic pH levels and, thus, do not cross membranes readily. When an oppositely charged ion is attached to the ionized drug, they form an ion pair that has a net zero charge. The net charge allows easier diffusion of the drug complex. For example, the formation of ion pairs to facilitate drug absorption has been demonstrated propranolol, a basic drug that forms an ion pair with oleic acid, and quinine, which forms ion pair with hexylsalicylate.

2) Gastro-intestinal Physiology

A) Gastric-emptying Rate- From an anatomical point of view, a swallowed medication quickly enters the stomach.In the end, the content of the stomach goes into the small intestine. Since the duodenum has the largest absorptive surface for drugs in the GI tract, any delay in the gastric emptying time of the drug before reaching the duodenum will increase the onset time of the drug. For example, a drug such as penicillin which is unstable in an acidic medium and is decomposed by it if stomach emptying is delayed. Or other drugs like aspirin that irritate the gastric lining due to contact. The rate of gastric emptying is faster in the case of solutions and suspensions than solids or non-dispersible forms of dosage. There are various factors that affect the rate of gastric emptying: -

a. Meal volume

b. Content of the meal

c. Physical nature of the meal

d. Temperature of the meal

e. Gastric pH

f. Electrolytes and osmotic pressure of the meal

g. Posture of the body

h. State of emotion

i. Diseased state.

B) Intestinal Motility - Normal peristalsis mixes the contents in the duodenum, ensuring that the drug particlesare brought into close contact with the mucosal cells of the intestines.The drug needs to spend sufficient time in the absorption site to ensure maximum absorption. However, when there is increased intestinal motility, such as in diarrhea, there is reduced residence time for the drug, and hence less chance for proper drug absorption.

C) Drug stability in GIT-

The process of metabolism or enzymatic/chemical hydrolysis may limit the absorption of the drug; thereby affecting the B.A. of the drug. Degradation in the stomach by the acid medium. Normally applies to drugs taken orally.

(D) Intestinal Transit Time: -

For the complete absorption of drugs from enteric coated formulations and drugs from specific areas in the intestines, a long intestinal transit time is required.Peristalsis promotes the absorption of drugs through the increased contact between the drug and the intestinal mucosa, as well as enhanced dissolution, particularly of drugs with poor solubility. Factors affecting include diet, illness and drugs. For example, metoclopramide will promote intestinal transit and, hence absorption of easily soluble drugs whereas anticholinergic drugs will retard intestinal transit promoting absorption of poorly soluble drugs.

E) Blood flow to GIT:

As soon as the medication is absorbed by the small intestine, it is transported by the mesenteric vessels to the hepatic portal vein and into the liver before entering into the systemic circulation. The reduction in blood flow to the mesenteric area due to any reason like congestive heart failure will slow down the process of elimination of the drug from the GIT, leading to slower absorption of the drug.The blood flow to the GIT is high as it is richly supplied with the capillaries Hence, it helps in maintaining the condition of sink and concentration gradient for drug absorption, as it removes the drug quickly from the site of action. In case of highly permeable drugs or drugs that get absorbed through pores, the perfusion of GIT is rate limiting. In contrast, if the drugs are poorly permeable, then GI perfusion is not an important factor.

F) Effects of food-

The presence of food in the GI tract may influence the bioavailability of a drug from an oral drug product ( ). Foods contain amino acids, fatty acids, and many other nutrients that might influence the pH in the gut and the solubility of drugs. Effects of food cannot always be predicted and may have important clinical implications. The following are some ways food may influence the bioavailability of a drug from a drug product ( ):

- Gastric emptying time delay
- Bile flow stimulation
- Change in the pH of the GI tract
- Increase in splanchnic blood flow
- Luminal metabolism alteration of the drug substance
- Physical/chemical interaction between the meal and the drug product/drug substance

Some antibiotics, including penicillin and tetracycline, are absorbed less in the presence of food. In contrast, lipid-soluble drugs like griseofulvin and metazalone are absorbed better in the presence of a high-fat diet. Propranolol plasma levels are higher in the presence of food compared to fasting. This could be due to interaction with food constituents.

3) Age

The infants have a high gastric pH value, and low intestinal surface and blood flow in the gut which means that there is an alteration in drug absorption compared to adult. The elderly have causes of poor drug absorption in gastric emptying, decrease in intestinal surface and blood flow in the gut, achlorhydria and bacterial overgrowth.

- **Clinical Factors**

1) Diseases-

The patient suffering from Parkinson's disease experiences difficulty swallowing andseverely

decreased gastrointestinal motility. The case report indicates that the patient suffered from the inability to manage the disease with the regular intake of the oral levodopa medication due to its insufficient absorption. However, levodopa infusion with the j-tube ensured the patient's condition control. Individuals who take tricyclic antidepressants (imipramine, amitriptyline, nortriptyline), and antipsychotic agents (phenothiazines) may face the problem of the decreased gastrointestinal motility and intestinal obstructions. Drug absorption delays, particularly with the slow-release formulation, might occur in the patients with the above-said diseases.

Achlorhydric individuals experience insufficient stomach acid secretion; gastric HCl plays a critical role in dissolving insoluble free base. Weak-base drugs that cannot create soluble salts stay insoluble in the stomach without the presence of hydrochloric acid and are, thus, not absorbed. The preparation of salt-based formulations is impossible because the free base separates easily from its salt due to weak basicity.

Additionally, dapsone, itraconazole, and ketoconazole drugs can experience poor absorption in patients with achlorhydria. The patients with the acid reflux syndrome undergo treatment with the proton pump inhibitors, including omeprazole, turning the stomach achlorhydric. Orange juice, colas, or other acidic beverages that enhance absorption of those drugs that need an acidic environment to get absorbed.

HIV/AIDS patients may suffer from various gastrointestinal (GI) disturbances like increased gastric transit time, diarrhea, and achlorhydria. Both the rapid gastric transit time and diarrhea can affect the absorption of orally taken medication. Achlorhydria will only affect the absorption of certain drugs that depend on acid levels for their absorption. Indinavir, for instance, needs an acidic medium for absorption. This drug has a very narrow therapeutic window. The right serum concentration is thus required for it to work efficiently.

Patients suffering from congestive heart failure (CHF) with persistent edema will experience reduced splanchnic blood flow leading to formation of edema in the wall of the intestines. Moreover, the intestinal motility will be slowed down. The poor blood supply and poor intestinal motility cause a reduction in drug absorption. Furosemide (Lasix), a common loop diuretic, is absorbed variably and inefficiently by CHF patients, taking too long before its effects set in.

Crohn's disease affects the small intestine and the large intestines.The disease has the following accompanying signs: areas of bowel wall thickening, proliferation of anaerobic bacteria, and, in addition, bowel obstruction and deterioration. Impact on drug absorption is unpredictable; however, impaired absorption of drugs can possibly take place due to decreased surface area and thickened gut wall for diffusion.

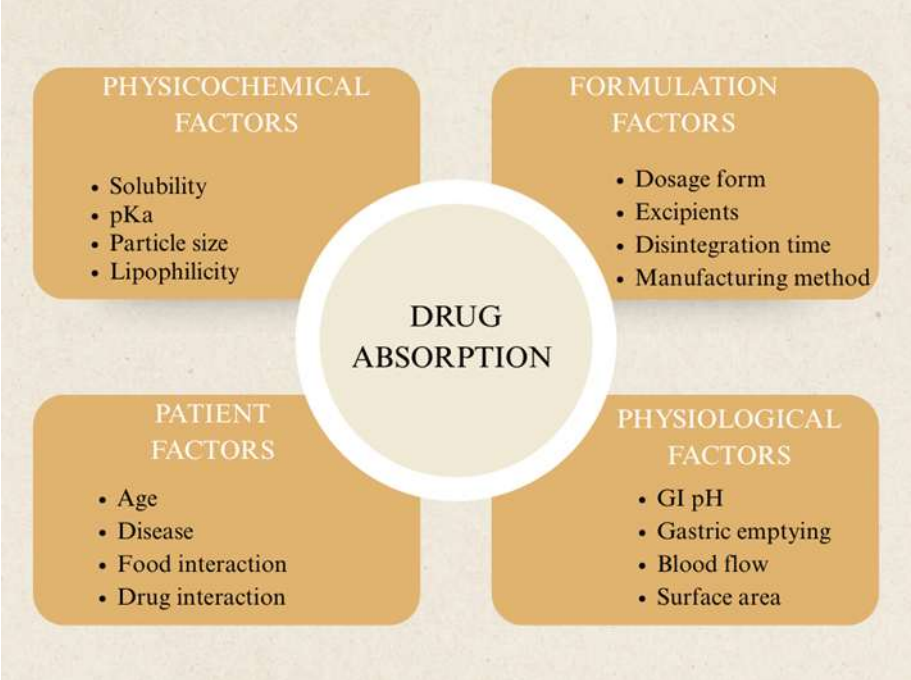
2) Drugs

Anticholinergics usually decrease the secretion of gastric acid. Propantheline bromide is an anticholinergic agent that slows down stomach emptying and small intestine motility. Antidepressants of tricyclic type and phenothiazines are anticholinergic and result in peristaltic slowdown within GI tract. Slowdown of stomach emptying causes delays in drug absorption. Metoclopramide stimulates stomach contraction, relaxation of the pyloric sphincter, and increase in intestinal peristalsis. This leads to shorter absorption period and lower peak levels. Thus, absorption of drugs from tablets will be slower due to metoclopramide but faster due to the anticholinergics, e.g. Propantheline bromide.

Antacids should not be given in combination with cimetidine, since the antacid preparations may reduce the absorption of the drug. The aluminum-, calcium-, and magnesium-containing antacids form complexes with drugs such as tetracycline, ciprofloxacin, and indinavir; hence, there is reduced absorption of drugs. To avoid this interaction, antacids should be given 2 hours prior to or 6 hours after drug intake. It was stated that the use of proton pump inhibitors like omeprazole makes the stomach achlorhydric.

Cholestyramine is a non-absorbable ion exchange resin for hyperlipemia. Cholestyramine binds warfarin, thyroxine, and loperamide, similarly to activated charcoal; thus, it lowers the absorption of drugs.

Calcium absorption in the duodenum is an active process that is facilitated by vitamin D. Fourfold increase in calcium absorption occurs in vitamin D deficiency states. There is a calcium binding protein that increases following vitamin D administration and binds calcium in the cell of the intestine and moves it out from the cellular base into the blood circulation.



CONCLUSION

In summary, absorption is a dynamic and multifactorial process that is regulated by many parameters such as physiological, physicochemical, and environmental factors. Such variables as pH, surface area, blood flow, solubility, formulation, and interaction with food affect significantly the extent and rate of absorption and play a significant role in increasing the efficiency of the drug. Therefore, a deeper understanding of absorption determinants can be valuable for developing more efficient drugs, reducing interindividual variability in absorption and minimizing the risks associated with drug exposure. In this case, biopharmaceutics will enable predicting drug behavior and designing drug products that have optimal pharmacological effects on patients.drug absorption is an important principle of biopharmaceutics, which connects the physicochemical characteristics of drugs with their biological behavior. Solubility, permeability, drug

ionization based on pH value, dosage form design, and digestive physiology determine the speed and degree of drug absorption as well as its bioavailability. Using the Biopharmaceutics Classification System (BCS), all of these factors can be predicted in order to optimize drug delivery. Consequently, biopharmaceutics is very important for designing drug delivery systems and ensuring bioequivalence of products.

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HOW TO CITE: Ifat Shaikh, Nisha Choudhary, Kedar Lonare, Dhanraj Kande, Anisha Nagar, A Comprehensive Study on Factors Influencing Drug Absorption, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 5, 2973-2991. https://doi.org/10.5281/zenodo.20155328