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A Literature Review of the Physicochemical, Physiological and Pharmaceutical Considerations in GIT Absorption of Drugs.

Abstract

Oral route of drug administration is the most common among all routes and hence their pharmacokinetic and pharmacodynamic factors are substantial to study. Among such factors, GIT absorption is the key factor in new drug development affecting the efficacy as well as safety of the drug. Different protocols have now been developed for the usage of in vitro also the in vivo as well as in situ methods in drug absorption determination. In this article, different mechanisms like passive diffusion, pore transport, ionic-mediated transport, endocytosis and other mechanisms involved in drug absorption will be explained. Moreover, different factors i.e. physico-chemical, pharmaceutical and physiological factors that affect drug absorption have been summarized as they play a significant role in the research studies for new drug development. Different absorption determining methods are also discussed.

Key Words: Absorption, Gastro-Intestinal Tract, Transport, Bioavailability, Drug Dissolution, Diffusion, Drug Stability

Introduction

GIT absorption has always been considered as an important factor in studying the bioavailabilty, stability, efficacy and safety of a drug formulation. All the other pharmacokinetic factors depend on this key factor. Many drugs have already failed in the past due to their absorption associated concerns. Therefore, now it is extensively studied to understand the mechanisms by which the drugs gets absorbed, factors affecting the drug absorption and the methods used for the determination of drug absorption. Passive transport is also called as down hill transport as there is no requirement of energy in its transportation like facilitated transport which is the type of carrier mediated transport. Moreover, pore transport (involved in the absorption of low molecular weight molecules), active transport (a kind of up hill transport), ionic and ion-pair transport (involved in the transport of charged molecules), endocytosis (involved in engulfing of the extracellular materials) all explain the mechanisms through which the transport of materials across the cells happen to carry out GIT absorption.

To study the factors that affect the absorptive properties of drugs in the body is vital because they have a subsequent effect on the bioavailability or the systemic availability of drugs as well as their stability. Pharmaceutical factors when changed in turn disturb the drug absorption like dissolution and disintegration time, type and nature of dosage form, pharmaceutical excipients and more. Physico-chemical type properties of a drug substance like solubility of drug, rate of dissolution, effective surface area, ionization state and lipophilicity of drugs along with other factors also show significant impact on drug absorption. Physiological factors like routes of administration, cell-membrane physiology, drug transport processes, gastro-intestinal pH and blood flow along with disease conditions and many more also affect drug absorption. Specialized methods like in-vitro, the in-vivo type as well as in-situ methods are used for the efficient determination of absorption that play a significant role in the new drug development (Billat et. Al., 2017).

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Drug and Absorption

Pharmaceutical drug or *medicine or medication means* any chemical form of a substance that is considered to be useful for the treating and curing as well as preventing or diagnosing the disease or promoting the overall well-being *whereas the phenomena of movement of drug in unchanged form, from the site where the drug is administered to the site where it shows the action or into the systemic circulation is called as Absorption.*

Solubility

Solubility can be defined as the property of a solute which can be in solid form or the liquid form or can be in the gaseous to get dissolved in a liquid, solid or gaseous solvent so that a uniform solution is formed. Solubility of a substance is basically dependent upon three factors which include the solvent used, temperature and pressure at which the solubility reaction is taking place.

Permeability

The ability of drug molecules to penetrate through a liquid is termed as Permeation. It is directly dependent upon the concentration gradient of the drug molecules as well as mass diffusivity and intrinsic permeability of the material (Brahmankar & Jaiswal, 1995).

Drug Absorption Mechanism

The drug is absorbed into GIT by 6 mechanisms which include

1) Passive type of diffusion
2) Transport through pores (Pore transport)
3) Carrier-mediated type transport which can be either
a. Facilitated diffusion
b. Active transport
4) Endocytosis
5) Electrochemical or ionic type of diffusion
6) Transport through ion-pair

Passive Diffusion

When there is the difference in the concentration of drug across the sides of the cell membrane, then the molecules of the drug get diffused into the cell membrane which is considered as Passive type of Diffusion.
Fick's first law of diffusion can be used to explain the mechanism of passive diffusion which says that the molecules of the drug flow from higher to low concentration and continue this process until the equilbrium is obtained on both sides of the cell membrane and the diffusion rate of the drug molecules have a direct relationship to the concentration gradient across the sides of the membrane.

$$\frac{dQ}{dt} = \frac{D\,A\,K_{m/w}\,(C_{GIT} - C)}{h}$$

Following are some specification of Passive Diffusion

- ✓ It is a down hill transport
- ✓ Diffusion rate is directly dependent upon the membrane surface area and is inversely proportional to the membrane. In addition to this, the rate of absorption is directly dependent upon the membrane/water partition coefficient of the drug.
- ✓ Although passive diffusion is an energy independent process but it somehow depends upon the square root of molecular size of the drugs.
- ✓ Most of the drugs have the molecular weight in between 100-400 Da and can be absorbed passively.

Pore transport: Pore transport a.k.a Convective transport, bulk flow or filtration is involved in the absorption of water soluble, low molecular weight and low molecular size drugs.There are some narrow channels or more simply pores that are aqueous filled present in the membrane structures through which water

soluble drugs and those drugs whose molecular size is smaller than the pore can pass easily. Examples of such molecules include water, sugars and urea. The driving force that is responsible for the transport of such molecules across the membrane is osmotic pressure or may be called as hydrostatic pressure. The rate of the drug absorption in pore transport is dependent upon the number and size of the pores in the membrane (Grassi et. Al., 2006).

$$\frac{dc}{dt} = \frac{N.R\text{^}2.A.\Delta C}{(\eta)\,(h)}$$

Where,

dc/dt = rate of absorption
N= number of pores
R= radius of pores
ΔC= concentration gradient
η= viscosity of fluid in the pores

Carrier Mediated Transport Mechanism

In this mechanism, a carrier is involved which is a constituent of cell membrane and binds with the solute molecules reversibly to form carrier solute complex which moves across the cell membrane and after reaching the other side, the complex dissociate to give solute molecules. After the delivery of solute molecules, the carries then come back to its native site to accept another solute molecule (Schanker et. Al., 2002).

Carrier mediated transport system are of 2 types.

Facilitated Diffusion

The driving force for facilitated diffusion is concentration gradient. As it is a down-hill process therefore the metabolic poisons involved in the production of energy do not abide by the process. It is involved in the absorption of Vitamin B1, B2 and B12 into the intestine as well as entry of glucose into RBC's.

An example of passive facilitated diffusion is the transport of a mixture of an intrinsic factor, a glycoprotein along with vitamin B12 across the intestinal membrane with the help of carrier system.

Active Transport

This type of transport is more important than facilitated transport.

The driving force here is against the concentration gradient simply called as uphill transport. Energy is spent in moving the molecules against the concentration gradient.

Much of the energy used to transport molecules against concentration gradient is derived by the body metabolism, the poisons derived from the metabolism can affect this transport as such transport is sensitive to such poisons.

Due to the expenditure of energy, the absorption of certain molecules gets weakened or inhibited by such transport like weakening of levodopa absorption when it is taken with protein rich meal.

The slow velocity of the active transport is resolved by using Michalies-Menten kinetics equation.

Equation:

$$\frac{dc}{dt} = \frac{[C].(dc/dt)max}{Km + [C]}$$

Where,

(dc/dt) max = maximal rate of drug absorption at high drug concentration
$[C]$= conc. of drug available for absorption
Km= affinity constant of drug for the barrier

Ionic or Electrochemical Diffusion

This charge influx the penetration of drugs.

These Molecular forms of solutes are unadorned by the membrane charge and influence faster than ionic forms (Chen, Tuo & Dong, 2016).

The influx of anions and cations is also affected by the pH.

So, at a given pH, the rate of influence may be as follows:

Unionized drug molecule > Anion > Cation.

ION pair Transport

Ion pair transport mechanism is involved in the following functions.

- In the absorption of the drugs that ionize at all pH conditions.
- To transport charged molecules due to the formation of a neutral mixture with an oppositely charged molecule.

Drugs with low values of lipid-water partition coefficient, penetrate the membrane after combining with endogenous ions and converting into neutral reversible complexes. Thus neutral complexes possess both the lipophilicity and aqueous solubility required for passive diffusion (Schanker et. Al., 1961).

Endocytosis

Endocytosis is a process by which extracellular materials are englufed by a cell by using cell membrane in order to form a vesicle or sacule containing the extracellular material. Therefore it is also termed as vesicular transport or corpuscular transport. The vesicle formed is snatched off intracellularly.

Endocytosis can be classified into 3 types namely;

A) Phagocytosis
B) Pinocytosis
C) Transcytosis

Phagocytosis

It is a type of endocytosis in which cells engulf solid materials including microbial agents. As most of the cells are capable of phagocytosis, therefore the phagocytes of the immune system, e.g. macrophages, neutrophils and mature dendritic cells really outdo in this process. In these immune cells, an important facet of innate immunity is represented by the mechanism of phagocytosis which involves containing and killing of microorganisms and processing for the presentation of antigen on cell's surface and plays a viral role to initiate the adaptive immune response.

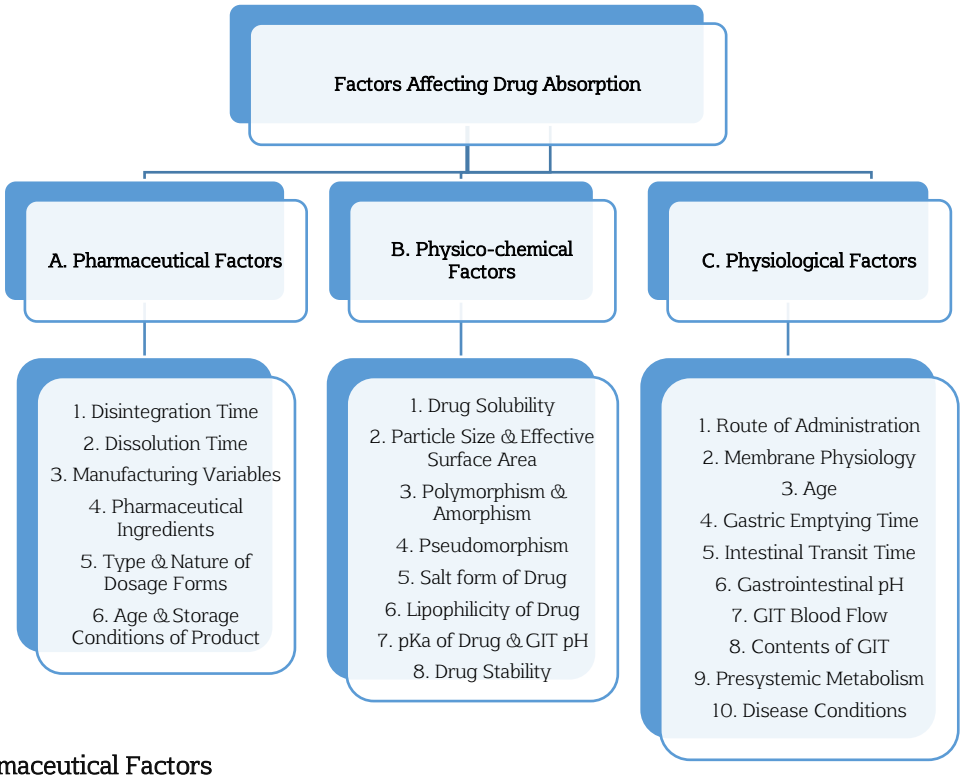
Pinocytosis

The term Pinocytosis is derived from a Greek word meaning "cell drinking". It is a process in which liquid droplets present outside the cell is engulfed by the cells. During this process, the cell surrounds the external substance to be engulfed by pinching off its cell membrane and converting the material into special membrane bound vesicle. It is generally used to engulf extracellular fluid and plays a significant role in the uptake of nutrients and absorption of oil soluble vitamins.

Transcytosis

It is the movement of macromolecular cargo in a membrane bound carrier from one side of a cell to the other. Multicellular organisms use this process to move materials selectively between two different kind of environments and not affecting the compositions of the two. Cells also have other techniques that do not involve membrane vesicle to move small ions and solutes across cellular barriers.
Paracellular transport which is the movement of ions and small molecules across adjacent cells is done by the regulation of tight junction whereas transcellular transport which is the movement of small molecules and ions through cell takes place by differential dispensation of carriers or membrane transporters on opposite sides of a cell. In short, these three processes are responsible for the success of multicellular organisms.

Factors Affecting Drug Absorption



Pharmaceutical Factors

Chemical Factors

The availability of drugs systemically and their stability can be enhanced by using variety of chemicals. e.g. derivatives of esters are stable which undergo hydrolyzation upon absorption and convert to parent product which is active. Moreover, acids and bases solubilize more efficiently in their salt form. Usually administration of soluble salts of penicillin increase the systemic circulation of the antibiotics as compared to that of the free acid. Another example is that a diffusion layer which is of high pH is formed when the dissolution of the salt of the weak acid is formed when dissolved in stomach which stimulates more dissolution just like basic drugs. But in this case, the high pH gets flooded extremely by the low pH found in stomach fluids. So, it can be concluded that the salts of basic drugs are used for the controlled dissolution instead of that of the enhanced one (Chillistone & Hardman, 2017).

Disintegration time

Faster the disintegration time, faster would be the absorption. So, it is essential to have lower disintegration time. The tablet disintegration time is proportional to the

- Binder quantity
- Compression force

In case of in vitro disintegration testing, the drug particles don't dissolve with no possibility of absorption and ultimately no assurance pf bioavailability can be given.

Dissolution time

It is the mass transfer from solid to the liquid state in which solid particles get solubilized in a specified solvent. This factor is very essential as it has the potential of disturbing the absorption of drugs.

Variables during Manufacturing

Compression force:

The compression force is very important before preparing any preparation because when it is increased, a more hard tablet with less wettability is produced having an extensive disintegration time. On the other hand, when it is considerably increased, the large drug components get broken into smaller ones increasing the surface area and reducing the disintegration time.

Granulation method

The granulation method has an effect on dissolution rate. Greater the granules of the tablet are present, greater would be the rate of dissolution. There is a method known as wet granulation method that produces tablet having the ability to dissolve rapidly as compared to that of the other granulating methods. But it does have certain limitations like crytsal bridge formation etc. So, new methods like agglomerative phase of communition are used having enhanced crushing and enhanced dissolution rate due to the formation of larger surface area.

Nature and the type of dosage forms

All the preparations of drugs are made in such a way that they look attractive and are stable and in a condition to use them appropriately. The drug preparations categorized in the assceding order of the rat of dissolution as given below:

Solutions

They are considered as ideals of bioavailability as they do not have to disintegrate first and then dissolve and absorb. They have only a single process of dissolution and absorption. Hence they have excellent absorption properties as conpared to other dosage forms like solid dosage forms. Their examples include elixirs, syrups and emulsions etc.

Solid Solutions

Solid solution is the solution in which the drug gets trapped into the solid form of the solution or the monomolecular type of dispersion is present in the medium which is water soluble. Solid solution is also an important method while studying the absorption of the drug. E.g. Griseofulvin.

Suspension

In the case of suspension, the particles of the drug are uniformly distributed throught the medium and possess greater surface area. The absorption does not depend on the emptying rate of the stomach as the constituents of the drug diffuse greatly between small intestine and the stomach. In case of liquid dosage forms, the practical advantages are very few but Adjusting patient's dose is easy as compared to other solid dosage forms. The disadvantages are also to be mentioned that their handling is bulky which is difficult and also possess low stability.

Tablets and the Capsules

Capsules dissolve at once. When the shell breaks, it gets dissolved rapidly. On the other hand, the tablets dissolve in a series of steps. First, they are broken down into grains then to primary particles. When particles become smaller and smaller, the rate of dissolution increases. That's why the disintegration of the tablet is considered as an expected criterion in the type of absorption known as in vivo absorption.

Pharmaceutical Ingredients/ Excipients

When the number of excipients are increased in a dosage form, the formulation becomes much complex and hence complicate the bioavailability and absorption. Some of the examples include thiamine and tetracycline, riboflavin, phenytoin etc. (Horter & Dressman, 2001).

The oral activity of the phenytoin is increased when calcium sulphate is replaced to lactose and the proportion of magnesium silicate is increased in the formulation. Moreover, when the Fuller's clay is present in the

formulation, the bioavailability of riboflavin and thiamine gets decreased. On the usage of calcium phosphate, the absorption of the tetracycline from the capsules gets decreased due to complexity. Now, due to the extensive testing of the dosage forms, such interactions are less likely to occur.

Vehicle

The absorption rate of any formulation depends on the factor that whether the particular vehicle is miscible with a specified biological fluid or not. The two conditions can arise most prominent being the rapid absorption of vehicles that are miscible with the biological fluids but on the other hand rapid absorption does occur when the vehicle is immiscible that is said to occur when the vehicle gets splitted from its oil phase to aqueous phase.

Diluents

Hydrophilic coat around hydrophobic drug particles is formed by hydrophilic diluents and stimulate the absorption as well as dissolution of drugs that are poorly water soluble or hydrophobic drugs.

Granulating Agents and the Binders

When hydrophilic binders are used in the formulation, they are the source of imparting the properties of hydrophilicity to the surface of hydrophobic agents of the formulation so that they can be dissolved better e.g. gelatin, PVP etc. But if the amount of binder is increased beyond a certain level, it causes the tablet to become hard and ultimately decreases the dissolution and as well as disintegration of the tablet formulation.

Disintegrants

They are generally of hydrophobic nature. If less amount of disintegrants are used, they decrease the bioavailability.

Lubricants

They are also generally of hydrophobic nature. They inhibit diffusion of water around the tablet into the tablet and subsequently decrease the dissolution as well as disintegration of the tablet.

Suspending Agents

They are also known as viscosity imparting agents to the formulation. They are solid drug particles that are stabilized and hence has an effect on the drug absorption. Example include Na CMC. Viscosity imparters also function as an obstacle of diffusion i.e. it slows the diffusion of drugs to to the outside and hence increase the emptying time of the stomach.

Colorants

Water soluble dyes with low concentration inhibit the dissolution rate of certain drugs most prominently the crystalline ones. This is because of the reason that the molecules of dye are absorbed into the faces of crystals to inhibit drug dissolution. A prominent example of this is the inhibition of the sulfathiazole by the colorant brilliant blue.

Age of drug Products and their Storage Conditions

The aging of the drug as well as the conditions in which the product is stored has an effect on the bioavailability and stability of the formulation. E.g. when drug gets precipitated in the solution. Suspension particle size and tablet hardness are also adversely affected by the above factors.

Physio-Chemical Factors

Physicochemical Properties of Drug Substances

There are 7 major physicochemical factors that effect the drug absorption through GIT which include;

1. Drug solubility & dissolution rate
2. Particles size & effective surface area

3. Polymorphism & amorphism
4. Solvates & hydrates
5. Salt form of drug
6. Ionization state
7.Drug pKa & lipophilicity & GI pH ---pH partition hypothesis

Solubility and Dissolution rate of Drug

The rate of retention of orally regulated medications is dependent upon disintegration rate and dissolvability of drug and rate of saturation of medication through the cell layer.

Particle Size and Effective Surface Area

Smaller the size of the molecule, greater is the compelling surface zone, leading to increased contact between the surface of solute and solvent causing an increase in disintegration rate, thereby, leading to an increment in ingestion proficiency,

For example, a number of drugs are poorly water soluble e.g. Griseofulvin, Chloramphenicol, Digoxin, Tolbutamide etc, the disintegration rate of these drugs is restricted. Therefore, the particle size of these drugs is decresed making them adequately aqueous soluble nonhydophobic medications.

Polymorphism and Amorphism

The existence of a substance in more than one crystalline forms is known as Polymorphism. The polymorphs have different physical properties like solvency and disintegration rate. On the other hand, Amorphism can be defined as existence of a drug or substance with no internal crystal structure.

Metastable state

- Less stable
- Highest energy state
- Lowest melting point
- Higher aqueous solubility
- Better bioavailability and absorption

Stable state

- Lowest energy
- Highest melting point
- Low aqueous solubility
- Limited dissolution rate

Crystalline form

- Low solubility
- Slower dissolution
- Insignificant absorption

Amorphous form

- High solubility
- Fast dissolution
- Easily absorbed

Solvates/Hydrates

Water is the most widely recognized solvate. Due to the presence of water molecules in gem structure, the ability of the gem to draw in water to initiate the disintegration process is lost and hydrated/ solvated precious

stones will in general break up more gradually than anhydrous structure.

Salt form of drug

At a particular pH, the solvency of medication is consistent regardless of whether the medication is acidic/ essential or its salt. Considering the medication's salt type, it is the Ph of the dissemination layer which is demon and not the ph of the main part of the arrangement. For example, salt of frail corrosive which causes an expansion in the ph of dissemination layer which increases disintegration and solubility of a feeble corrosive and retention will be quick undoubtedly. An increase in solvent salt type medication may lead to poor drug absorption e.g., Sodium salt of phenobarbitone and tablet of salt of phenobarbitone expand, it didn't disintegrate in efficient manner causing poor assimilation (Rouge, Buri & Doelker, 1996).

Disintegration profile of different salts. Here Graph A shows that most elevated dissolvability is shown by Potassium salt whereas Graph B represents the disintegration profile of different penicillin salts.

Ionization state

Ionized state of drug is important for dissolvability whereas unionized state is important for ingestion along with inactive dispersion through layer.

pKa and lipophilicity of drug and Gstrointestinal pH --- pH partition hypothesis:

pH – partition theory states that in case of drugs with molecular weight greater than 100 Dalton and drugs that move across the cell membrane by the process of passive diffusion, the absorption is dependent upon;

pKa value of drug
pH of absorption site
Lipid miscibility of unionized drug

pKa of drug

Measure of medication that exist in unionized structure and in ionized structure is an element of pKa of medication and pH of the liquid at the assimilation site and it very well may be controlled by Henderson-hesselbach condition: -

$$pH = pKa + \log \frac{ionized\ form}{unionized\ form} \quad \text{For, acidic type of drugs}$$

$$pH = pKa + \log \frac{unionized\ form}{ionized\ form} \quad \text{For, basic type of drugs}$$

Lipophilicity and Medication Absorbance

For ideal absorbance, a medication must have adequate aqueous solubility in order to disintegrate in liquids at the site of assimilation and solvency of lipid should be high enough to encourage the transport of the drug in lipid biomembrane (Lozoya-Agullo et. Al., 2017).

$$Ko/w = \frac{Distribution\ of\ drug\ in\ organic\ phase\ (octanol)}{Distribution\ of\ drug\ in\ aq.phase}$$

As Ko/w lipid solubility i.e. an increase in partition coefficient is equal to the increase in percentage of drug absorbed.

Physiological Factors

Routes of Administration

Physical features of drug, absorption speed of drug, requirement to bypass hepatic metabolism and to attain high concentrations at certain site, are used to determine routes of administration. It has great effect on absorption (Shargel, Wu-Pong & Yu, 2005).

Table 1. Absorption through different routes of Administration

Oral Route	➢ Drug taken orally ➢ Absorption occur through entire GIT length

Buccal or Sublingual Route	➢ Drug placed inside mouth or beneath tongue ➢ Fast absorption prevent by-pass effect **e.g.** nitroglycerin
Inhalation	➢ Inhalation & absorption of drug occur through lungs ➢ Fast absorption ➢ Prevent by-pass effect
Intra-Nasal	➢ Drug administered into nasal cavity ➢ Absorption occur at nasal membrane ➢ Local or systemic effects e.g. oxytocin, vasopressin
Rectal	➢ Slow absorption as compared to oral ➢ Prevent by-pass effect e.g. lidocaine, ergotamine, metoclopramide
Intra-venous	➢ Drug administered into venous circulation ➢ Fast absorption ➢ 100% bioavailability
Intra-Muscular	➢ Drug administered into muscles ➢ Rapid absorption than subcutaneous but slower than intravenous
Subcutaneous	➢ Absorption occur in subcutaneous tissue

Cell-Membrane Physiology

Nature & Structure of Cell Membrane

- Drug should cross cell membrane to reach systemic circulation
- Drug's permeability into systemic circulation at site of absorption is dependent on;
- Structure of molecule & properties of drug
- Biochemical & physical properties of cell membrane
- lipid soluble drugs permeate readily than polar drugs
- proteins help in permeation of polar and ionized molecules.

Drug Transport Processes

- Passive diffusion
- Pore transport
- Carrier-mediated transport
- Facilitated diffusion
- Active transport
- Ionic diffusion
- Ion-pair transport
- Endocytosis

Age

Table 2. Association of Age with the Drug Absorption

Infants & Adults	➢ In infants, high gastric pH, low Intestinal surface area & GIT blood flow lead to change in absorption state as compared to adults.
Elders	➢ Alteration in gastric emptying ➢ Reduced intestinal surface area & low Gastrointestinal blood flow ➢ Excessive achlorhydria ➢ Reduced absorption of drug

Gastric Emptying Time

Table 3. Factors Affecting Gastric Emptying time

Factors	Effect on Gastric emptying
Volume	The initial rate of gastric emptying is directly dependent upon the starting volume and after this initial period, the rate of gastric emptying is inversely related to the original volume.
Type of meal	Gastric emptying rate is inversely dependent upon the concentration of carbohydrate, lipids and proteins in the meals.
Osmotic pressure	Gastric emptying rate is inversely related to the concentration of salts and electrolytes.
Physical state of stomach contents	Rapid gastric emptying is observed in case of solutions and suspensions having small particle size.
Body position	Gastric emptying rate is decreased in patients lying on the left side.
Viscosity	Rate of gastric emptying is directly proportional to viscosity of solutions.
Emotional conditions	Gastric contractions and emptying is increased during stressful and aggressive emotional conditions whereas depression decreases gastric contractions and emptying.
Disease conditions	Diabetic patients and patients suffering from local pyloric lesions and hypothyroidism exhibit reduced gastric emptying rate whereas in case of hyperthyroidism gastric emptying rate is increased.
Drugs	Gastric emptying is decreased by Anticholinergics and Narcotic analgesics

- Gastric motility and activity of the pyloric sphincter affects the time required for stomach substances to pass through duodenum. For drugs that are better absorbed from distal part of small intestine, fast gastric emptying time is required whereas for drugs that are best absorbed from proximal part of small intestine, delayed gastric time is favorable.
- It's a 1st order process. Numerous factors used to measure are following;
- Gastric Emptying Rate: speed with which gastric contents empty into small intestine.
- Gastric Emptying Time: time needed by gastric contents to leave the stomach and enter into small intestine.
- Gastric Emptying Half-Life: time needed by half of gastric content to leave the stomach and enter into the intestine (Hurst et. Al., 2007).

Intestinal Transit Time

- Main site for absorption of maximum drugs
- Affected by different factors like: food, diseases, drugs etc.
- Delayed intestinal transit is required for;
- Sustained release drugs
- Enteric coated tablets
- Some B vitamins
- Laxatives

Table 4. Transit time of different parts of Intestine

Intestinal Region	Transit Time
Duodenum	5 mins
Jejunum	2 hours
Ileum	3-6 hours
Caecum	0.5-1 hour
Colon	hours

Gastro-Intestinal pH

GIT Blood Flow

GIT blood flow plays main part in absorption by continuously keeping concentration gradient through epithelial membrane. Absorption of lipid soluble molecules greatly depend upon blood flow whereas in case of polar molecules, absorption doesn't depend upon blood flow (Koenigsknecht et. Al., 2017).

Contents of GIT

Table 5. Interactions of different drugs with GIT contents (food-drug interactions)

Delayed	Reduced	Increased	Unaffected
Aspirin	Penicillin	Griseofulvin	Methyldopa
Paracetamol	Erythromycin	Nitrofurantoin	Propylthiouracil
Diclofenac	Ethanol	Diazepam	Sulfasomidine
Nitrofurantoin	Tetracycline	Actively absorbed vitamins	
Dioxin	Levodopa		

Fluid Volume

Great fluid volumes, result in enhanced dissolution, fast gastric emptying & greater absorption. **E.g.** erythromycin.

Interactions between drug and normal GIT components

Certain enzymes, mucin and bile salts are normal GIT constituents that affect absorption of drug. GI mucosa is lined by Mucin which is a defensive mucopolysaccharide, it interacts with quaternary ammonium compounds and streptomycin and hinder their absorption (Siepmann, Siepmann & Florence, 2016).

Pre-Systemic Metabolism

Pre-systemic metabolism or First pass effect is defined as the phenomenon in which concentration of drug is decreased due to metabolism by eliminating organs before entering the systemic circulation (Lin & Wong, 2017).

Pre-systemic drug metabolism is disturbed by four main systems;

Table 6. Distribution of Pre-Systemic Metabolism by four Systems

Luminal Enzymes	Gut Wall Enzymes	Bacterial Enzymes	Hepatic Enzymes
Major enzyme present in gastric juice is pepsin Lipases, amylases & proteases secreted from pancreas into small intestine in reaction to food ingestion	Mucosal enzymes, existing in stomach, colon & intestine Alcohol dehydrogenase enzyme deactivates ethanol	Existing in colon Also secret enzyme responsible for range of reactions	Numerous drugs go through 1st pass metabolism
Pepsins & proteases cause protein & peptide drug's degradation	e.g. sulfation of ethinyl estradiol & isoprenaline	e.g. sulphasalazine	e.g. isoprenaline, propranolol, diltiazem

Disease Conditions

Table 7. Effect of Disease Conditions on the Absorption of the Drugs

Diarrhea	Reduced absorption as of lessened contact time
Malbsorptive Syndrome	Reduced absorption
Aclohydria	Weak-base drugs stay undissolved in stomach as of inadequate acid e.g. dapsone
HIV/AIDS	Enhanced gastric transit time, diarrhea

Cardio-Vascular Disease	Intestinal edema, reduced blood flow & gastric emptying time, change in pH, secretions & microbial flora
Crohn's Disease	Decreased absorption due to low surface area
Celiac Disease	Enhanced stomach emptying rate & absorptivity of small intestine

Methods of Determination of Different Dosage Forms

1. In vivo method
2. In situ method
3. In vitro method

In Vivo Method

1. Direct method
2. Indirect method

Direct Method

In this method the drug level is going to be determined in urine and our blood and it should be as a function of time

Indirect Method

We are applying the indirect method when the measurement of the drug is not possible directly or it is impossible to determine.

In Situ Method

It simulates the in vivo conditions for drug absorption and rare based on dispersion of a part or segment of gastrointestinal tract by drug solution and identification of amount of drug which is perfuse through it.

In Vitro Method

In vitro procedure is caring out externally or out of the body and is used to determine the permeation of drug by using a live animal tissues.

In vitro models have been identified and introduced to evaluate the factors that interfere in the absorption procedure and anticipate the rate and extent of absorption of drug (Youhanna & Lauschke, 2021).

So here, the intestine of lower experimental animals like rats, guinea pigs, rabbits are used for the study.

The different in Vitro methods are

Physicochemical methods

1. Partition coefficient
2. Artificial membranes
3. Chromatographic retention indices
4. Brush border membrane vesicles (BBMV)
5. Isolated intestinal cells
6. Tissue techniques
7. Diffusion cell method
8. Cell culture techniques

Partition Coefficient

Partition coefficient between two phases which are oil and water phase, log P, is one of the simplest properties of a drug molecule that can be identified and determined. Lipophilicity of a molecule and amount or extent of drug that will cross the biological membrane can be measured by using partition coefficient eg. Octanol is selected as an oil phase as it has same properties to biological membranes.

Artificial Membrane

Artificial membranes are very helpful in studying passive membrane permeability as they are reproducible and are suitable for high throughput screening. In this method, PAMPA model is used.

Parallel Artificial Membrane Permeability Assay (PAMPA)

PAMPA is a technique which determines or identifies the permeability of materials from a donor compartment. The artificial membrane is like a phospholipids membranes supported by filter substances or materials. It is preparing by pipetting a solution of lipids in an inert and pure organic solvent on a supporting filter material that is placed on 96-well microstate plate.

Chromatographic Retention Indices

Immobilized artificial membranes chromatography along with physicochemical parameters is used for evaluation or identification of passive intestinal absorption.

IMA packing are prepared by covalently immobilizing monolayer of membrane phospholipids to silica materials and particles.

Brush Border Membrane Vesicles

Brush border is the other name of microvillus covered area of simple caboodle epithelium and simple columnar epithelial cells, which are existed in small intestines.

Using Isolated Intestinal Cells

Here the small intestine is perused with enzyme solutions that spread the cells and then after that cells are treated with chelating material of enzymes.

Tissue Techniques

- Everted small intestinal sac technique
- Everted sac modification
- Circulation techniques
- Everted intestinal ring or slice technique

Diffusion Cell Method

In this technique minute segments of small intestine are mounting among two glass chambers full of with buffer at 37C.

Cell Culture Techniques

Cell culture is the composite procedure by which cells are developed below restricted environment, usually exterior to their natural background.

Conclusion

Drug absorption is the most important factor in studying the oral route of administration. It has the direct impact on the safety and efficacy of the drug and hence the deciding factor that whether the drug is stable in this route in its specific form or not. It is considered as the key pharmacokinetic factor in new drug development. For this reason, its extensive study is essential. There are various types of mechanisms through which the drugs are absorbed. Passive diffusion and pore transport are the types of down hill transport without any energy expenditure and useful for the transfer of small molecules. Carrier mediated transport including facilitated transport and active transport requires carriers for the drug transport in which active transport is the up hill type transport. Moreover, ionic diffusion and ion-pair type transport involves ionization and transport of ions. Endocytosis involves engulfing materials including phagocytosis and pinocytosis. On the other hand, transcytosis involves the transport of macromolecular burden across the cells. Factors that affect the drug absorption are vital to study for the stability as well as systemic availability of drugs. Majorly three types of factors affect drug absorption significantly i.e. pharmaceutical factors, physiological factors and physico-

chemical factors. Pharmaceutical factors include chemical factors, drug dissolution and disintegration time, manufacturing variables, nature of dosage form, pharmaceutical excipients and age and the storage conditions of drug products. Drug solubility, its dissolution rate, ionization state of the drug, polymorphism, solvates, drug lipophilicity and pKa are all studied under physicochemical factors affecting the drug. Physiological factors involve route of administration, cell-membrane physiology, drug transport processes, GIT pH and blood flow, pre-systemic metabolism, drug interactions with normal contents of GIT and disease conditions. Different methods have been evolved for the exact determination of absorption like in-vivo, in-vitro and in-situ methods. In-vivo involves absorption studies inside the living organism whereas in-vitro involves such studies outside the organism. In in situ studies, there is no isolation of any specific gene or a protein from the main tissue. Hence, all such information is necessary for the effective absorption studies.

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