Factors affecting drug absorption

1. Physiological Factors

The main considerations for the design of oral dosage forms are:

1. Extreme pH ranges in GIT. 2. The presence or absence of food.

3. Degradative enzymes in GIT. 4. Motility of GIT

5. Varying drug permeability in the different regions of the intestine.

Effect of food on gastrointestinal drug absorption

1. Delay in gastric emptying

2. Stimulation of bile flow. Bile contains bile acids, which are surfactants involved in the digestion and solubilization of fats, and also increases the solubility of fat-soluble drugs through micelle formation

3. A change in the pH of the GI tract. For some basic drugs (e.g.; cinnarizine) with limited aqueous solubility, the presence of food in the stomach stimulates hydrochloric acid secretion, which lowers the PH, causing more rapid dissolution of the drug and better absorption. Absorption of this basic drug is reduced when gastric acid secretion is reduced

4. An increase in splanchnic blood flow

5. A change in luminal metabolism of the drug substance

6. Physical or chemical interaction of the meal with the drug product

- Increased drug absorption following a meal can be due to:

a) Increased time for dissolution of poorly soluble drug.

b) Enhanced solubility due to GI secretions like bile.

c) Prolonged residence time and absorption site contact of the drug

- Delayed drug absorption by food can be due to the following reasons:

a) Delayed gastric emptying, affecting the drugs unstable in the stomach e.g. penicillin, erythromycin.

b) Preventing the transit of enteric tablets into the intestine which may be as long as 6 –8 hrs.

c) Formation of poorly soluble non absorbable complex. Tetracycline

hydrochloride absorption is reduced by milk and food that contains calcium, due to tetracycline chelation. However, significant reduction in absorption may simply be the result of reduced dissolution due to increased PH.

d) Alteration of PH. Coadministration of sodium bicarbonate raises the stomach PH and reduces tetracycline dissolution and absorption

e) Competition between food components and drugs for specialized absorption mechanisms.

f) Food can also affect the integrity of the dosage form, causing an alteration in the release rate of the drug, e.g. the bioavailability of theophylline from controlled release tablets is much more rapid when given to a subject in the fed rather than fasted state because of dosage form failures, known as dose-dumping.

Gastric emptying

The passage from stomach to small intestine, called as gastric emptying. It is the rate limiting step in absorption because the major site of drug absorption is intestine. It is advisable when:

1) Rapid onset of action is desired, e.g. Sedatives.

2) Dissolution occurs in the intestine, e.g. Enteric coated tablets.

3) Drugs not stable in GI fluids, e.g. Penicillin G.

4) Drug is best absorbed from small intestine, e.g. Vitamin B12.

- Delay in Gastric Emptying recommended when:

1) Food promotes drug dissolution and absorption, e.g. Griseofulvin.

2) Disintegration and dissolution is promoted by gastric fluids.

Large particles, including tablets and capsules, are delayed from emptying for 3 –6 hours by the presence of food in the stomach.

- Several parameters used to quantify are:

Gastric emptying rate (speed at which stomach contents empties into intestine) and Gastric emptying time (time required for gastric contents to empty into small intestine).

Factors influencing gastric emptying:

1. Volume of meal: larger the bulk of meals, longer the gastric emptying time. An initial rapid rate of emptying observed with large volume of meal and an initial lag phase in emptying of small volume of meal.
2. Composition of meal: delayed gastric emptying occur with fatty meal, and it is beneficial for the absorption of poorly soluble drugs like griseofulvin.
3. Physical state and viscosity of meal: liquid meals take less than hour to empty whereas a solid meal may take as long as 6 to 7 hours.
4. Temperature: high or low temperature of ingested fluid reduces the gastric emptying.
5. Gastro intestinal PH: retarded at low stomach PH and promoted at high PH. The inhibitory effect of various acids on emptying decreases with increase in molecular weight.
6. Drugs that retard gastric emptying include poorly soluble antacids: aluminium hydroxide, Anticholinergics: atropine, Narcotic analgesics: morphine ,Tricyclic antidepressents: imipramine.
7. Disease state: like gastroenteritis, gastric ulcer, pyloric stenosis retard gastric emptying rate.

Intestinal transit

Since small intestine is the major site for absorption of most drugs, long intestinal transit time is desirable for complete drug absorption.

Delayed transit time is desirable for:

- Drugs that dissolve only in intestine.
- Drugs absorbed from specific sites in the intestine.

Laxatives drugs promote the rate of intestinal transit, while anticholinergic drugs retard gastric and intestinal transit and they promote absorption of poorly soluble drugs.

Pre systemic metabolism

For a drug administration orally, the two main reasons for its decreased bioavailability are Decreased absorption and First pass metabolism

The loss of drug through biotransformation by such eliminating organs during its passage to systemic circulations called as first pass or presystemic metabolism which include the following four primary systems

a. Luminal enzymes
b. Gut wall enzymes
c. Bacterial enzymes
d. Hepatic enzymes

Effect of disease states and co-administered drugs on gastrointestinal drug absorption

A- Disease, any disease that affect (1) intestinal blood flow, (2) gastrointestinal motility, (3) changes in stomach emptying time, (4) gastric pH that affects drug solubility, (5) intestinal pH that affects the extent of ionization, (6) the permeability of the gut wall, (7) bile secretion, (8) digestive enzyme secretion, or (9) alteration of normal GI flora.

Examples include achlorhydric patients (decrease gastric pH), HIV–AIDS patients (decreased gastric transit time, diarrhea, and achlorhydria), Crohn's disease patients (thickening of the bowel wall), and congestive heart failure patients (reduced splanchnic blood flow).

B- Drugs such as anticholinergic (reduce stomach acid secretion), metoclopramide (increases intestinal peristalsis), antacids containing aluminum, calcium, or magnesium (complex with drugs such as tetracycline and ciprofloxacin), proton pump inhibitors (decrease gastric acid production), and cholestyramine (binds warfarin, thyroxine, and loperamide).

Double –Peak Phenomenon:

• Some drugs (e.g.; ranitidine, cimetidine and Dipyridamole) after oral administration produce a blood concentration curve consisting of two peaks. This phenomenon is generally observed after the administration of a single

dose to fasted patients. The rationale for this phenomenon has been attributed to variability in stomach emptying, variable intestinal motility, presence of food, enterohepatic recycling, or failure of a tablet dosage form.

• The double-peak phenomenon observed for cimetidine may be due to variability in stomach emptying and intestinal flow rates during the entire absorption process after a single dose. For a drug with high water solubility, dissolution of the drug occurs in the stomach, and partial emptying of the drug into the duodenum will result in the first absorption peak. A delay in stomach emptying results in a second absorption peak as the remainder of the dose is emptied into the duodenum.

• In contrast, ranitidine produces a double peak after both oral and parenteral (IV bolus) administration. Ranitidine is apparently concentrated in the bile within the gallbladder from the general circulation. When stimulated by food, the gallbladder contracts and bile-containing drug is released into the small intestine. The drug is then reabsorbed and recycled (enterohepatic recycling).

• Tablet integrity may also produce a double-peak phenomenon. Dipyridamole whole or crushed tablet in volunteers shows that tablet does not disintegrate or incompletely disintegrates may have delayed gastric emptying, resulting in a second absorption peak.

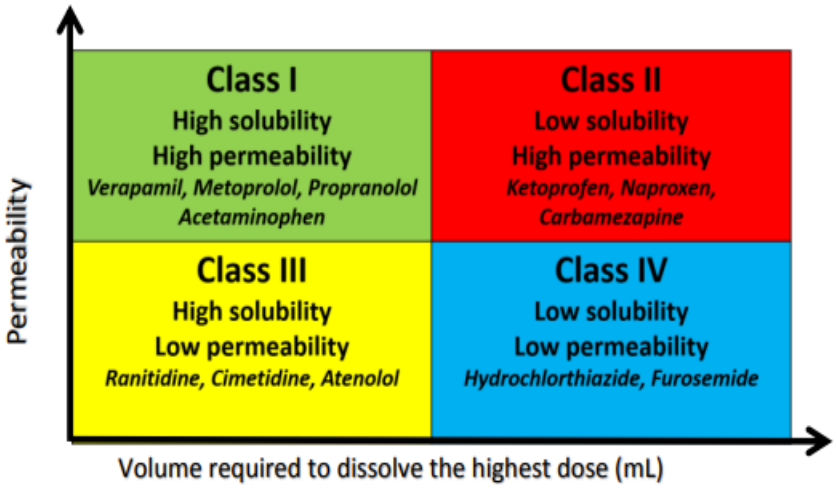
2. Biopharmaceutical Factors

For solid oral, immediate-release drug products (eg, tablets, capsules), the rate processes include:

1. Disintegration of the drug product and subsequent release of the drug,
2. Dissolution of the drug in an aqueous environment,
3. Absorption across cell membranes into the systemic circulation.

The slowest step in a series of kinetic processes is called the rate-limiting (determining) step (RDS) , so the dissolution is RDS for lipophilic drugs , while permeation is RDS for hydrophilic drugs.

THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)



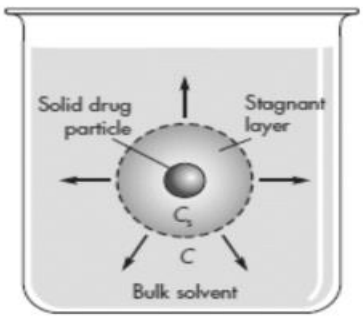
Dissolution and Solubility

The rate at which drugs with poor aqueous solubility dissolve from an intact or disintegrated solid dosage form in the gastrointestinal tract often controls the rate of systemic absorption of the drug. Thus, dissolution tests may be used to predict bioavailability.

Noyes–Whitney equation

$dC/dt = DA/h$ (Cs – C)

Where dC/dt = rate of drug dissolution at time t, D = diffusion rate constant, A = surface area of the particle, Cs = concentration of drug (equal to solubility of drug) in the stagnant layer, C = concentration of drug in the bulk solvent, and h = thickness of the stagnant layer



In addition to these factors, the temperature of the medium and the agitation rate also affect the rate of drug dissolution. An increase in temperature will increase the kinetic energy of the molecules and increase the diffusion constant, D. Moreover, an increase in agitation of the solvent medium will

reduce the thickness, h, of the stagnant layer, allowing for more rapid drug dissolution. In addition, the viscosity of the dissolution medium affects D, food increases the viscosity of the medium and therefore increases D.

Factors affecting drug dissolution of a solid oral dosage form include

(1) The physical and chemical nature of the active drug substance. (2) The nature of the excipients, such as the use of surfactant (3) The method of manufacture, such as milling (decrease in particle size). (4) The dissolution test conditions, temperature and agitation

Physicochemical properties of the drug

A. Solubility, pH, and Drug Absorption

The solubility–pH profile is a plot of the solubility of the drug at various physiologic pH values. A basic drug is more soluble in an acidic medium, forming a soluble salt. Conversely, an acid drug is more soluble in the intestine, forming a soluble salt in the more alkaline pH environment found there. Solubility may be improved with the addition of an acidic or basic excipient.

B. Stability, pH, and Drug Absorption

The stability–pH profile is a plot of the reaction rate constant for drug degradation versus pH. For example, the stability of ciprofloxacin decreases with the increase in the pH of the medium

Pharmaceutical approaches for the enhancement of drug stability For example, erythromycin has a pH-dependent stability profile. The knowledge of erythromycin stability subsequently led to the preparation of a less water-soluble erythromycin salt that is more stable in the stomach. The dissolution rate of erythromycin drug substance powder, without excipients, varied from 100% dissolved in 1 hour for the water-soluble version to less than 40% dissolved in 1 hour for the less water-soluble version. The slow-dissolving erythromycin drug substance also resulted in slow-dissolving drug products formulated with the modified drug.

C. Particle Size and Drug Absorption

Dissolution takes place at the surface of the solute (drug), and thus, the greater the effective surface area (area of solid surface exposed to dissolution medium) , the better the water saturation, and the more rapid the rate of drug dissolution. Griseofulvin, nitrofurantoin, and digoxin are drugs with low aqueous solubility (BCS II); reduction of the particle size by milling to a micronized form has improved the oral absorption of these drugs. In these cases, so-called nanosizing, or producing even smaller drug substance particles, may be beneficial.

D. Polymorphs, solvates, and amorphous solids

- Polymorphism: The ability of solid material to exist in more than one crystalline form is called polymorphism. Polymorphs characterized by

1. They are chemically identical but they are different in the crystalline structure in the solid state.
2. They have different melting points, solubility, hygroscopicity, density, hardness, and compression characteristics.
3. They have different stabilities and may spontaneously convert from the metastable (less stable) form to the stable form.

Example: Chloramphenicol has several crystal forms, and when given orally as a suspension, the drug concentration in the body was found to be dependent on the percent of B -polymorph in the suspension. The B form is more soluble and better absorbed.

- Solvates (Pseudopolymorphs): Pharmaceutical synthesis includes purification and crystallization; residual solvent can be trapped in the crystalline structure. This results to solvate formation. The residual solvent could be water, and therefore called hydrate.

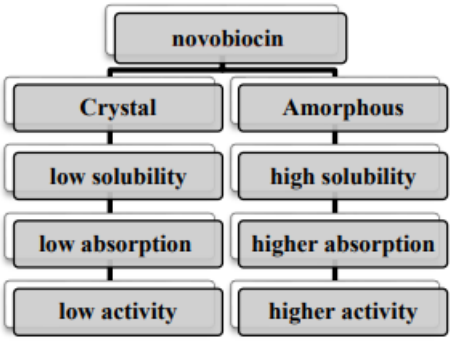
Drugs that are formed by removing the solvent from the solvate or hydrate are called desolvated or anhydrous, respectively.

Examples: 1. Erythromycin hydrates have quite different solubility compared to the anhydrous form of the drug. 2. Ampicillin trihydrate was reported to be

less absorbed than the anhydrous form of ampicillin.

Note: anhydrous form of drug has higher aqueous solubility that dissolve at a faster rate and have more bioavailability than their monohydrate & trihydrate forms due to effect of hydrogen bonding.

- Amorphous solids: They can be considered as supercooled liquids in which the molecules are arranged in a random manner as in the liquid state. Amorphous form (a substance that lacks a crystalline structure) have greater aqueous solubility than the crystaline forms because the energy required to transfer a molecule from the structurally rigid crystal lattice is greater than that required for non-crystalline solid. eg: amorphous form of novobiocin is 10 times more soluble than crystalline form.



Other Physicochemical Properties for Consideration in Drug Product Design	
Hygroscopicity	Moisture absorption may affect the physical structure as well as stability of the product
Partition coefficient (**log *P***)	May give some indication of the relative affinity of the drug for oil and water. A drug that has high affinity for oil may have poor release and dissolution from the drug product.
Impurity profile	The presence of impurities may depend upon the synthetic route for the active drug and subsequent purification. Impurities need to be "qualified" or tested for safety. Changes in the synthetic method may change the impurity profile
Chirality	The presence of chirality may show that the isomers have differences in pharmacodynamic activity.

Disintegration time

Rapid disintegration is important to have a rapid absorption so lower disintegration time is required. The disintegration time of tablet is directly proportional to the amount of binder and the compression force.

Manufacturing variables

A) Method of granulation: Wet granulation yields a tablet that dissolves faster than those made by other granulating methods. But wet granulation has several limitations like formation of Crystal Bridge or chemical degradation.

B) Compression force: Higher compression force yields a tablet with greater hardness and reduced wettability & hence have a long disintegration time, but on other hand higher compression force cause crushing of drug particles into smaller ones with higher effective surface area which is decrease in disintegration time. So effect of compression force should be thoroughly studied on each formulation.

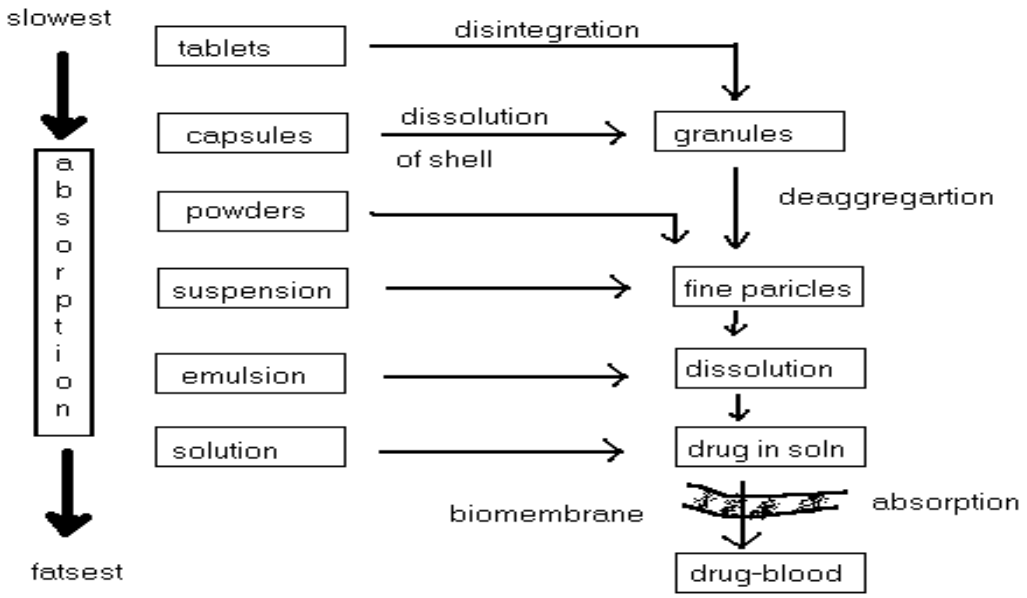
Formulation approach to enhance the absorption of each BCS

BCS	Absorption rate control	Formulation approaches for oral administration
Class 1	Gastric emptying	Can easily be formulated as tablets or capsules
Class 2	Dissolution	Particle size reduction (e.g., formation of microparticles or nanoparticles), solid dispersions, salt formation, addition of surfactants, self-emulsifying systems, liquid capsules, complexation
Class 3	Permeability	Addition of permeation enhancers, efflux inhibitors
Class 4	Dissolution and Permeability	Combination of Class II and III approaches

3. Formulation Factors

Nature and type of dosage form

As a general rule, the bioavailability of a drug from various dosage forms decrease in the following order: Solutions > Emulsions> Suspensions > Capsules >Tablets > Coated Tablets > Enteric coated Tablets > Sustained release Products



The advantages of using excipients on drug product performance

1. Improve the manufacturability of the dosage form.
2. Stabilize the drug against degradation.
3. Decrease gastric irritation.
4. Control the rate of drug absorption from the absorption site.
5. Increase drug bioavailability.

The mechanisms by which excipients affect the drug dissolution kinetics

1. Altering the medium in which the drug is dissolving

 Suspending agents can increase the viscosity of the drug vehicle and thereby diminish the rate of drug dissolution from suspensions.

 Tablet lubricants, such as magnesium stearate, may repel water and reduce dissolution when used in large quantities

 Coatings, particularly shellac, will crosslink upon aging and decrease the

dissolution rate.

 Surfactants: low concentrations of surfactants decrease the surface tension and increase the rate of drug dissolution, whereas higher surfactant concentrations tend to form micelles with the drug and thus decrease the dissolution rate.

 Disintegtants: decrease in amount of disintegrants significantly lowers bioavailability.

 Colorants: Even a low concentration of water soluble dye can have an inhibitory effect on dissolution rate of several crystalline drugs. The dye molecules get absorbed onto the crystal faces and inhibit the drug dissolution. e.g: Brilliant blue retards dissolution of sulfathiazole.

 Some excipients, such as sodium bicarbonate, may change the pH of the medium surrounding the active drug substance.

Example: Aspirin, a weak acid when formulated with sodium bicarbonate, will form a water-soluble salt in an alkaline medium, in which the drug rapidly dissolves.

2. Directly in interaction with the drug to form a water-soluble or water-insoluble complex. For example, if tetracycline is formulated with calcium carbonate, an insoluble complex of calcium tetracycline is formed that has a slow rate of dissolution and poor absorption.

Effect of excipients on the pharmacokinetic parameters of oral drug products

Excipients	**Example**	k_a	t_{max}	**AUC**
Disintegrants	Avicel, Explotab	↑	↓	↑/–
Lubricants	Talc, hydrogenated vegetable oil	↓	↑	↓/–
Coating agent	Hydroxypropylmethyl cellulose	–	–	–
Enteric coat	Cellulose acetate phthalate	↓	↑	↓/–
Sustained-release agents	• Methylcellulose, ethylcellulose • Castorwax, Carbowax (waxy agents) • Veegum, Keltrol (gum/viscous)	↓	↑	↓/–