ORAL DRUG ABSORPTION

The oral route of administration is the most common and popular route of drug dosing.

Considerations for the design of oral dosage forms

1. Extreme pH ranges (**Figure 7**).
2. The presence or absence of food.
3. Degradative enzymes.
4. Varying drug permeability in the different regions of the intestine.

Motility of the gastrointestinal tract.

Anatomic and physiologic considerations in the GIT

The major physiologic processes that occur in the GI system are **secretion, digestion, and absorption.**

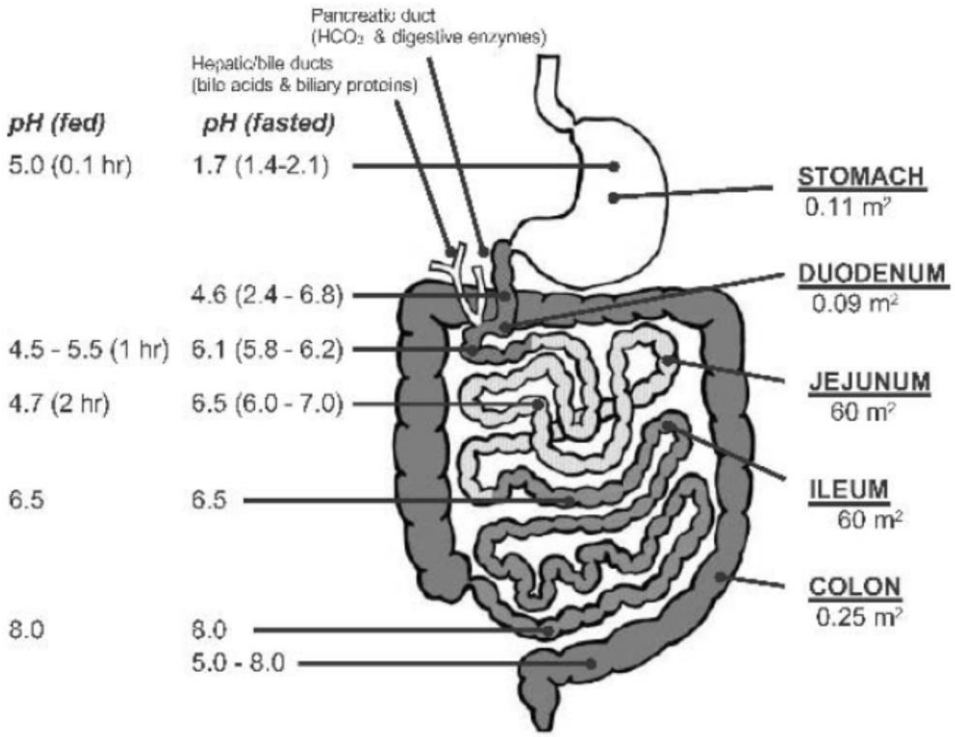


Figure 7. Schematic representation of the main parts of the gastrointestinal tract (GIT) showing the differences in pH and surface areas at each part.

Factors affecting the normal physiology of the gastrointestinal tract (GIT)

1. Diet (high-fat meal increases the intestinal transit time such as decreasing gastric emptying, the absorption of hydrophilic drugs decreases with food as it the case with penicillin and tetracycline while the absorption of lipid-soluble drugs increases with high-fat food such as griseofulvin and metaxalone).

2. Contents of GIT, such as bile salts.

3. Hormones, such as gastrin and CCK.

4. The visceral nervous system (controls contractile, secretory, and endocrine functions of GIT).

5. 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 (thickening of the bowel wall), and congestive heart failure (CHF) patients (reduced splanchnic blood flow).

6. 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).

Effect of Food on Gastrointestinal Drug Absorption

1. Delay in gastric emptying
2. Stimulation of bile flow
3. A change in the pH of the GI tract
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 or drug substance

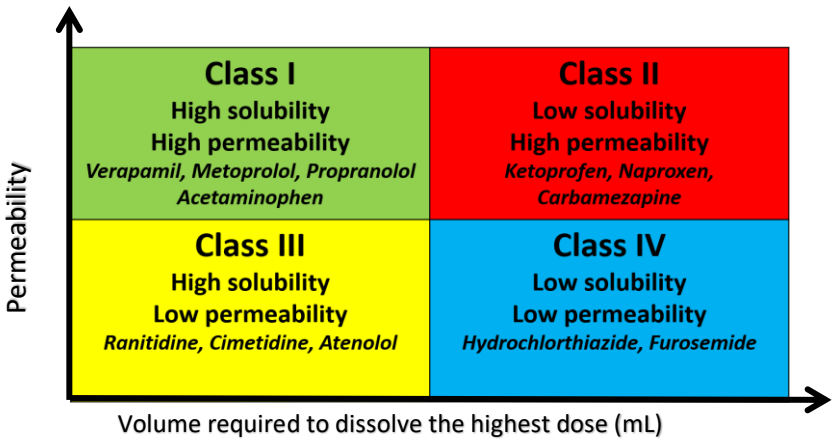
Rate-limiting Steps in Oral Drug Absorption

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, and
3. **Absorption** across cell membranes into the systemic circulation.

The slowest step in a series of kinetic processes is called the ***rate-limiting step***

THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)



1. Disintegration

For immediate-release, solid oral dosage forms, the drug product must disintegrate into small particles and release the drug.

To monitor uniform tablet disintegration, the *United States Pharmacopeia* (USP) has established an official disintegration test (**Figure 8**).

Solid drug products exempted from disintegration tests include troches (lozenges), tablets that are intended to be chewed, and drug products intended for sustained release or prolonged or repeat action as well as liquid-filled soft gelatin capsules.

Complete disintegration is defined by the USP-NF (National Formulary) as "that state in which any residues of the tablet remaining on the screen of the test apparatus in the soft mass have no palpably firm core.

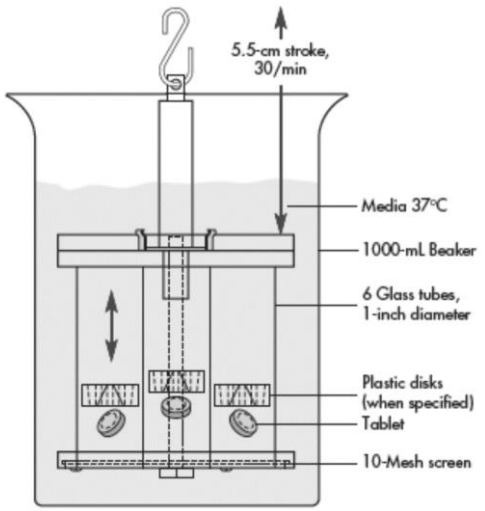


Figure 8. USP disintegration testing apparatus.

Recommended timing of the disintegration test

1. **For immediate-release preparation**, place 1 dosage unit in each of the six tubes of the basket, operate the system using water as the immersion fluid, maintained at 37 ± 2º C, carry out the test for 20 minutes for capsules, 30 minutes for plain tablets, and 60 minutes for coated tablets and pills.
2. **For enteric coated preparations** perform the following two tests, **(a)** the test with 1st fluid (pH 1.2) for disintegration, carry out the test for 120 minutes according to the procedure described in immediate release preparations test, (b) perform the test with the 2nd fluid for disintegration test (pH 6.8) according to the procedure described in immediate-release preparations, carry out the test with new dosage units for 60 minutes. Tablets should not disintegrate in the 1st fluid but only in the 2nd fluid.

2. 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 and may be used to discriminate formulation factors that affect drug bioavailability.

Dissolution is the process by which a solid drug substance becomes dissolved in a solvent over time.

Solubility is the mass of solute that dissolves in a specific mass or volume of solvent at a given temperature (eg, 1 g of NaCl dissolves in 2.786 mL of water at 25°C).

Noyes–Whitney equation

$$\frac{dC}{dt} = \frac{DA}{h}(C_s - C)$$

dC/*dt* = rate of drug dissolution at time *t*,
D = diffusion rate constant,
A = surface area of the particle,
*C*s = 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

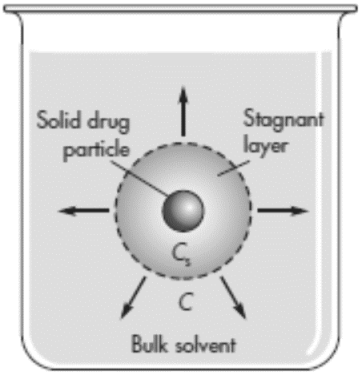


Figure ٩ . Representation of dissolution process.

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, temp 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 (**Figure 9**).

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.

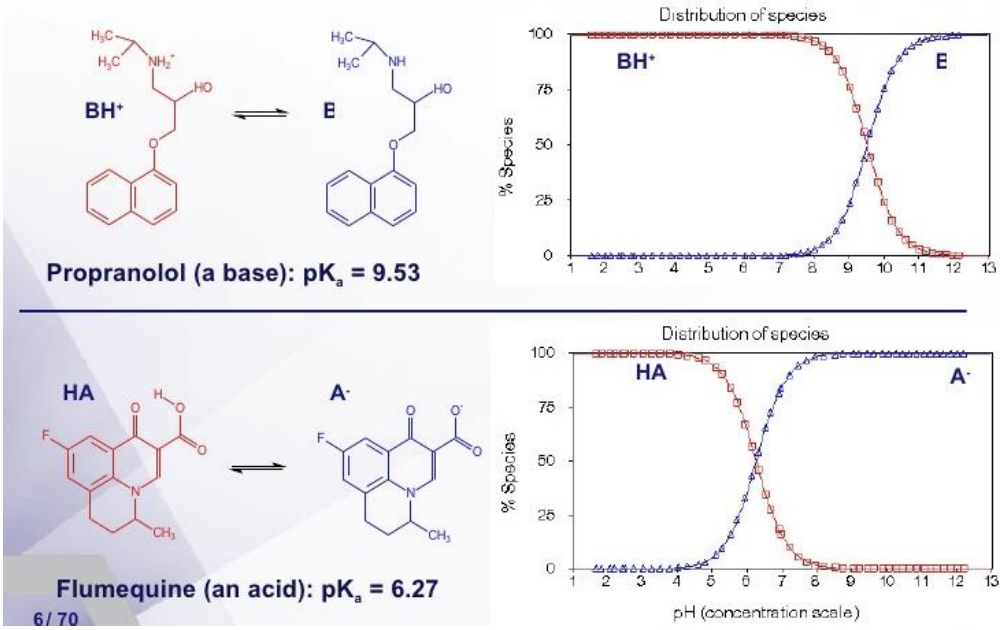


Figure 10. Ionisation of weak base (propranolol) and weak acid (flumequine) at different pH.

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 (**Figure 11**).

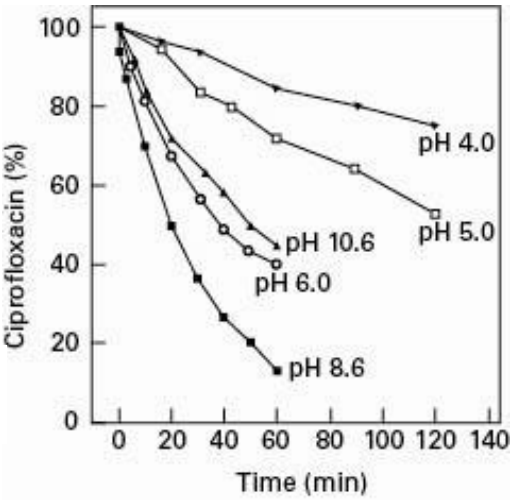


Figure ١١ . Stability of ciprofloxacin at different pH

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 surface area, the better the water saturation, and the more rapid the rate of drug dissolution.

Griseofulvin, nitrofurantoin, and many steroids 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

Properties of Polymorphs

1. They are chemically identical but they are different in the crystalline structure in the solid state.
2. Polymorphs have different melting points, solubility, hygroscopicity, density, hardness, and compression characteristics.
3. Polymorphs 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.

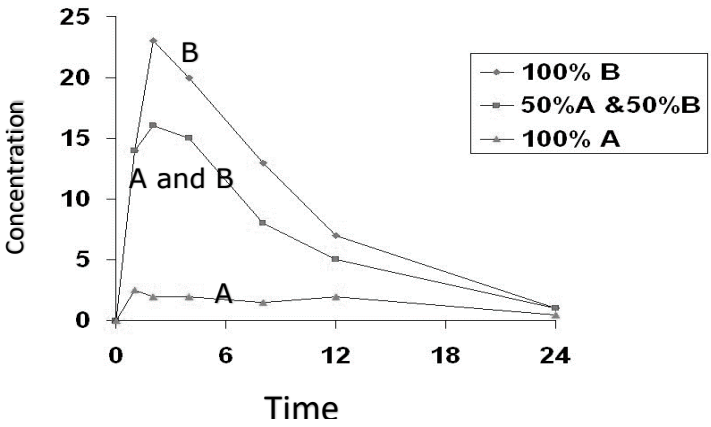


Figure١٢ . Plasma concentration-time profiles following oral administration of **A, B**, and a mixture of **A** and **B** polymorph forms of chloramphenicol.

- **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 (**Figure 13**).
2. Ampicillin trihydrate was reported to be less absorbed than the anhydrous form of ampicillin because of faster dissolution of the latter

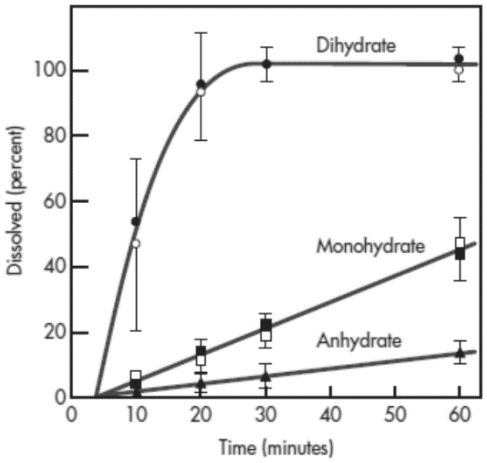


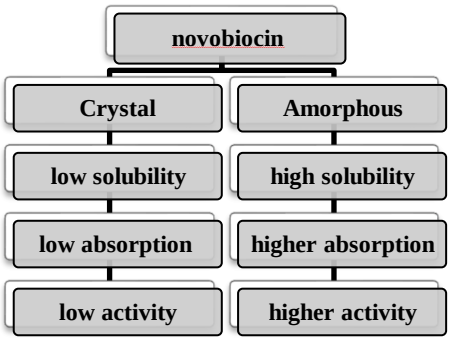
Figure ١٣ . Dissolution profile of mon-, di-, and anhydrate erythromycin

- **Amorphous solids**

Amorphous solids can be considered as supercooled liquids in which the molecules are arranged in a random manner as in the liquid state.

A drug that exists as an amorphous form (noncrystalline form) generally dissolves more rapidly than the same drug in a more structurally rigid crystalline form.

The presence of pharmaceutical substances as amorphous or crystalline form will affect the therapeutic activity. Example: the antibiotic novobiocin acid.



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.

Examples of excipients and their role in the dosage form

Excipient	Property in Dosage Form
Lactose	Diluent
Dibasic calcium phosphate	Diluent
Starch	Disintegrant, diluent
Microcrystalline cellulose	Disintegrant, diluent
Magnesium stearate	Lubricant
Stearic acid	Lubricant
Hydrogenated vegetable oil	Lubricant
Talc	Lubricant
Sucrose (solution)	Granulating agent
Polyvinyl pyrrolidone (solution)	Granulating agent
Hydroxypropylmethyl-cellulose	Tablet-coating agent
Titinium dioxide	Combined with dye as colored coating
Methylcellulose	Coating or granulating agent
Cellulose acetate phthalate	Enteric-coating agent