

# **FACTORS WHICH INFLUENCE GI ABSORPTION OF DRUGS**

# Session Objectives

 @ the end of this session you will be able to identify:

 Physiologic Factors and Patient Characteristics

 Pharmaceutical Factors Affecting Drug BA

- The oral absorption process of drug from a pharmaceutical Df is very complex.
- However, the major steps occurring during oral drug absorption can be regarded as part of a serial process:
  - The dissolution of the drug from the DF
  - The solubility of drug as a function of its physicochemical characteristics
  - The drug's effective permeability to the intestinal mucosa and
  - The drug's pre-systemic metabolism.

- There are many factors that may affect the above processes, and finally affect the **rate and extent of oral drug absorption**.
- These factors can be divided into three categories:-
  - Physicochemical properties of a drug,
    - solubility
    - Particle size
    - polymorphism,
    - pKa,
    - lipophilicity, and soon.

- Formulation factors,
  - solution, capsule, tablet, suspension and so on.
  - Nature of excipients
  - Manufacturing procedures
- Physiological factors,
  - Gastrointestinal pH,
  - Gastric emptying,
  - Small intestinal transit time,
  - Blood flow

# Physiologic Factors and Patient Characteristics

## 1. Gastric emptying time

- Most drugs are best absorbed from the small intestine, any factor that delays movement of drug from the stomach to small intestine will influence the rate (and possibly extent) of absorption
- Gastric emptying may represent a limiting factor in drug absorption.
- Gastric emptying is quantitated by one of several measurements including
  - emptying time,
  - emptying half-life( $t_{50\%}$ ), and
  - Emptying rate.

- Emptying time is the time needed for the stomach to empty the total initial stomach contents.
- Emptying half-time is the time it takes for the stomach to empty one half of its initial contents.
- Emptying rate is a measure of the speed of emptying.
- Factors that affect gastric emptying need to be understood because of the implications on drug absorption as well as on optimal DF design.

- Gastric emptying principally depends on:
  - DF type (liquid vs. solid, unit DFs vs. multi particulate DFs)
  - fed/fasted state of stomach
  - Postural position
  - co-administered drugs
  - Diseases state.



- Factors delaying GE
  - Fats in diet
  - High viscosity of diet
  - Lying on left side
  - Disease: depression, hypothyroidism, gastric ulcer
  - Drug: **propantheline**, atropine (antimuscarinic)
- Factors promoting GE
  - Fasting
  - Lying on right side
  - Disease: anxiety, hyperthyroidism
  - Drug: Metoclopramide(antiemetic) .

✍ Delay in the gastric emptying time for the drug to reach the duodenum:

➤ Will slow the rate and possibly the extent of drug absorption

➡ Prolonging the onset time for the drug.

➤ Unstable drug will decompose in acid (e.g., penicillin)

➤ May irritate the gastric mucosa during prolonged contact (e.g., aspirin)

✍ **Liquids and small particles** less than 1 mm are generally not retained in the stomach

## ✍ **Drugs**

✍ **Anticholinergics:** Reduction in rate of emptying


✍ **Narcotic analgesics:** Reduction in rate of emptying


✍ **Metoclopramide:** Increase in rate of emptying


✍ **Ethanol:** Reduction in rate of emptying

## 2. Intestinal transit

- ✍ The small intestinal transit time is the time of transit between the **stomach** and the **caecum**
- ✍ It is an important factor with respect to drug bioavailability as the small intestine is the main site of absorption in the GIT for most drugs
- ✍ It is found to be relatively constant, at around 3 hours.

 The small intestine does not discriminate between solids and liquids, and hence between dosage forms, or between the fed and the fasted state.

 The drug must have a sufficient time (residence time) at the absorption site for optimum absorption.

 In the case of high motility in the intestinal tract, as in **diarrhea**, the drug has a very brief residence time and less opportunity for adequate absorption.

### 3. Perfusion of the Gastrointestinal Tract

- ✍ The blood flow to the GI tract is important in carrying absorbed drug to the systemic circulation.
- ✍ The splanchnic circulation receives about 28% of the cardiac output and is increased after meals.
- ✍ Once the drug is absorbed from the small intestine, it enters via the mesenteric vessels to the hepatic-portal vein and the liver prior to reaching the systemic circulation.

- ✍ Any decrease in mesenteric blood flow, as in the case of **congestive heart failure**, will decrease the rate of drug removal from the intestinal tract, thereby reducing the rate of drug bioavailability.
- ✍ Drugs are absorbed through the lacteal or lymphatic vessels under the microvilli.
- ✍ Absorption of drugs through the lymphatic system bypasses the first-pass effect due to liver metabolism
- ✍ The lymphatics are important in the absorption of dietary lipids and some lipophilic drugs.

## 4. Gastrointestinal pH

✍ The pH of fluids varies considerably along the length of the gastrointestinal tract.

✍ Gastric fluid:

✍ Fasted state: 1-3.5

✍ Immediately after meal: 3-7

✍ Small intestine: 4-8

✍ Colon: 6.5



✍ Chemical degradation due to pH-dependent hydrolysis can occur in the GIT → incomplete bioavailability

✍ Penicillin G (should not be given orally)

✍ Erythromycin and omeprazole (formulated as enteric-coated dosage forms)

## 5. Effect of Food on GI Drug Absorption

### 1. Complexation of drugs with components in the diet

☞ Drugs may bind to components within the diet.

☞ The fraction of the administered dose that becomes complexed is unavailable for absorption.

☞ Example: Tetracycline with Ca and Fe forms non-absorbable complexes

## 2. Alteration of pH

☞ Food tends to increase stomach pH by acting as a buffer.

## 3. Alteration of gastric emptying

☞ Some foods, particularly those containing a high proportion of fat, tend to reduce gastric emptying and thus delay the onset of action of certain drugs.

#### 4. Stimulation of gastrointestinal secretions

- ❧ GI secretions (e.g. pepsin) produced in response to food may result in the degradation of drugs that are susceptible to enzymatic metabolism → ↓ their bioavailability.
- ❧ The ingestion of fatty foods stimulates the secretion of bile.
  - ❧ Bile salts are surface active agents → ↑ dissolution of poorly soluble drugs → ↑ absorption
- ❧ Bile salts form insoluble (non-absorbable) complexes with some drugs, such as neomycin, kanamycin and nystatin.

## 5. Competition b/n food components & drugs for specialized absorption mechanisms

☞ Drugs that have a chemical structure similar to nutrients

## 6. Increased viscosity of gastrointestinal contents




☞ The presence of food in the GIT provides a viscous environment  $\rightarrow$   $\downarrow$  rate of drug dissolution  $\rightarrow$   $\downarrow$  BA

## 7. Food-induced changes in presystemic metabolism

- ☞ Certain foods ↑ BA of drugs that are susceptible to presystemic intestinal metabolism by interacting with the metabolic process.
- ⇒ **Grapefruit juice** inhibiting the intestinal CYP3A family  
→ ↑ BA of some drugs (terfenadine, cyclosporin, saquinavir and verapamil)



## 8. Food-induced changes in blood flow

-  Blood flow to the GIT and liver increases shortly after a meal  
→ ↑ the rate at which drugs are presented to the liver.
-  The enzyme systems responsible for their metabolism become saturated by the increased rate of presentation of the drug to the site of biotransformation
-  Some drugs (e.g. propranolol, hydralazine, dextropropoxyphene) escapes first-pass metabolism.

## 6. Effect of Disease States on Drug Absorption

✍ **Parkinson's disease:** difficulty swallowing and greatly diminished GI motility

✍ **Achlorhydric patients** → ↓ production of acids in the stomach;

➡ Stomach HCl is essential for solubilizing insoluble free bases.

➡ Dapsone, itraconazole, and ketoconazole may be less well absorbed in the presence of achlorhydria



✍ Proton pump inhibitors render the stomach achlorhydric which may also affect drug absorption.

✍ Co-administering orange juice, colas, or other acidic beverages can facilitate the absorption of some medications requiring an acidic environment.

✍ **HIV/AIDS** patients are prone to a number of GI disturbances, such as increased gastric transit time, diarrhea, and achlorhydria.

➡ Rapid gastric transit time and diarrhea can alter the absorption of orally administered drugs.

➡ Indinavir, for example, requires a normal acidic environment for absorption

✍ **Congestive heart failure patients:** have reduced splanchnic blood flow, develop edema in the bowel wall and intestinal motility is slowed.


➡ The reduced blood flow to the intestine and reduced intestinal motility result in a decrease in drug absorption.

## 7. Drugs Affecting Absorption of other Drugs

✍ **Anticholinergic drugs** in general may reduce stomach acid secretion and stomach emptying and motility of the small intestine.

✍ **TCA's** (imiprimine, amitriptyline, & nortriptyline) and phenothiazines have anticholinergic side effects → slower peristalsis in the GI tract.

💡 Slower stomach emptying may cause delay in drug absorption

 **Metoclopramide**: stimulates stomach contraction, relaxes the pyloric sphincter, and increases intestinal peristalsis,

➡ → ↓ effective time for the absorption of some drugs

➡ → ↓ peak drug concentration and the time to reach peak drug concentration.

## Antacids

❧ Antacids containing aluminum, calcium, or magnesium may complex with drugs such as tetracyclines, fluoroquinolones, and indinavir, resulting in a decrease in drug absorption.

❧ So how can we avoid these interactions?

❧ **Cholestyramine**, a nonabsorbable ion-exchange resin for the treatment of hyperlipemia, adsorbs warfarin, thyroxine, and loperamide, → ↓ absorption of these drugs

# Pharmaceutical Factors Affecting Drug BA

 These factors include:

1. The type of dosage forms (eg, solution, suspension, suppository, capsule .tablets),
2. The nature of the excipients in the drug product,
3. The physicochemical properties of the drug molecule,
4. The route of drug administration.

# Physicochemical Nature of the Drug

## Dissolution and solubility

- ✧ Solid drugs need to dissolve before they can be absorbed.
- ✧ The dissolution of drugs can be described by the **Noyes-Whitney equation**

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

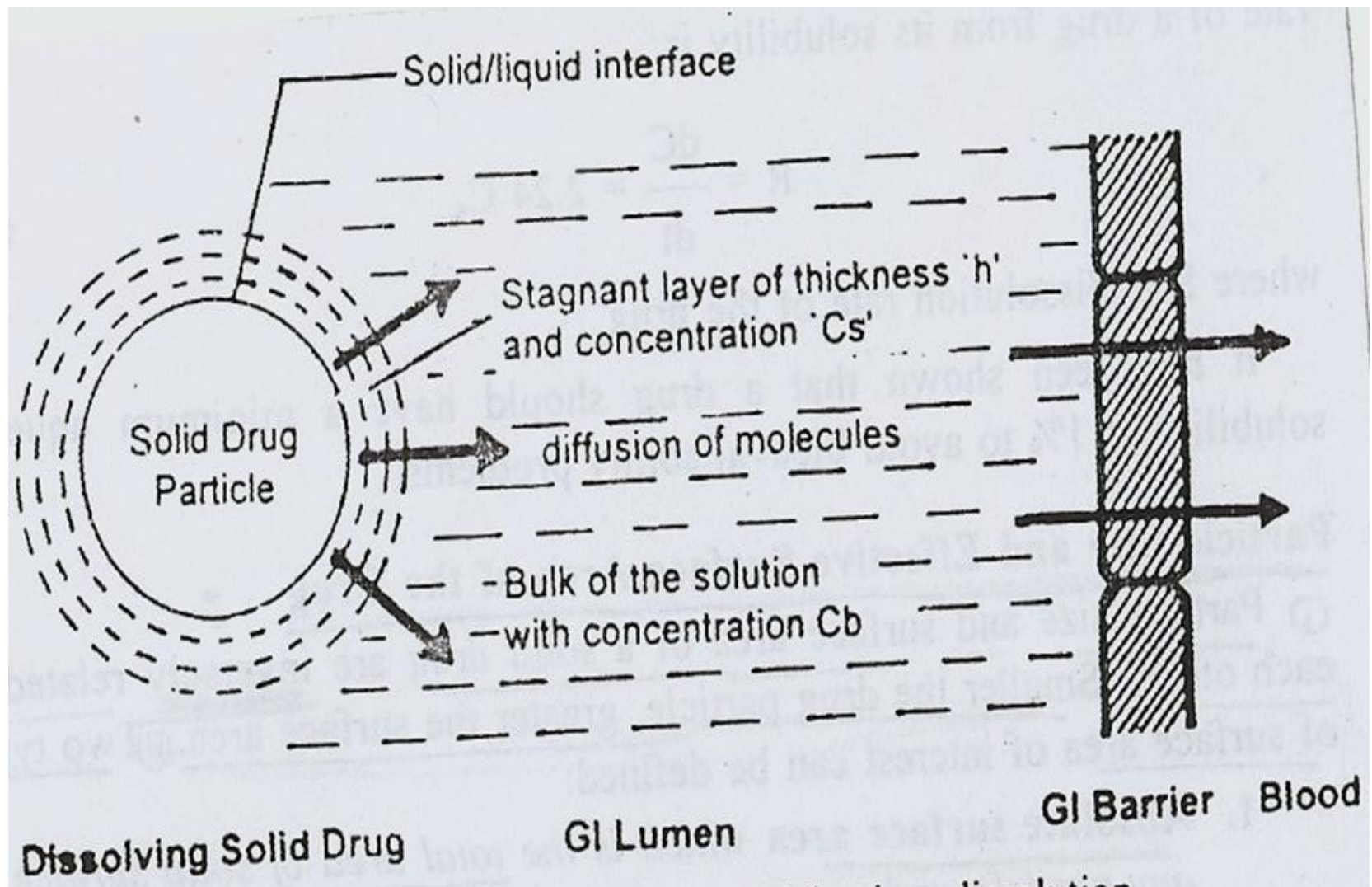


Figure: diffusion layer model for drug dissolution



## Solubility, pH, and Drug Absorption

- ❧ A basic drug is more soluble in an acidic medium, forming a soluble salt.
- ❧ Acidic drug is more soluble in the intestine, forming a soluble salt at the more alkaline pH
- ❧ Solubility may be improved with the addition of an acidic or basic excipient.
- ❧ Solubilization of **aspirin**, for example, may be increased by the addition of an alkaline buffer.

## pH-Partition Theory of Drug Absorption

✧ The dissociation constant ( $pK_a$ ), the lipid solubility of a drug, and the  $pH$  at the absorption site often dictate the magnitude of the absorption of a drug following its availability as a solution.

✧ The interrelationship among these parameters ( $pH$ ,  $pK_a$  and lipid solubility) is known as the  $pH$ –partition theory of drug absorption

✍ pH-partition theory of drug absorption is based on:

✍ The drug is absorbed by **passive transfer**

✍ The drug is preferentially absorbed in **unionized** form

✍ The drug is sufficiently **lipid soluble**.

✍ The fraction of drug available in **unionized form** is a function of both the **dissociation constant** of the drug and **the pH** of the solution at the site of administration.

✍ The dissociation constant, for both acids and bases, is often expressed as  $-\log K_a$ , referred to as **pKa**

## For Weak Acids

☞ Ionization of weak acids is described by an adaptation of a classical **Henderson–Hasselbalch** equation:

$$pH - pKa = \log \left( \frac{\alpha}{1 - \alpha} \right)$$

☞ Where  $\alpha$  is the fraction of ionized species and  $(1 - \alpha)$  is the fraction of unionized species.

✍ The equation may, therefore, be written as:

$$\frac{\alpha}{1 - \alpha} = 10^{(pH - pK_a)}$$

$$\frac{\alpha}{1 - \alpha} = \text{antilog}^{(pH - pK_a)}$$

☞ When  $\text{pH}=\text{pK}_a$ ,  $\alpha = 0.5$ , or 50% of the drug is in ionized form

☞ When  $\text{pH}$  is 1 unit greater than  $\text{pK}_a$ ,  $\alpha=0.909$ , or 90% of the drug, is in ionized form

☞ When  $\text{pH}$  is 2 units greater than  $\text{pK}_a$ ,  $\alpha=0.99$ , or 99% of the drug, is in ionized form

☞ When  $\text{pH}$  is 1 unit below  $\text{pK}_a$ ,  $= 0.9$ , or 90% of the drug, is in unionized form

☞ When  $\text{pH}$  is 2 unit below  $\text{pK}_a$ ,  $=0.99$ , or 99% of the drug, is in unionized form

 **Therefore**

➡ As the pH of the solution increases, the degree of ionization (percentage ionized) also increases.

↘ Hence, weak acids are preferentially absorbed at low pH.

 For weak bases

$$pK_a - pH = \log \left( \frac{\alpha}{1 - \alpha} \right)$$

$$\frac{\alpha}{1 - \alpha} = 10^{(pK_a - pH)}$$

$$\frac{\alpha}{1 - \alpha} = \text{antilog}^{(pK_a - pH)}$$



☞ When  $\text{pH}=\text{pK}_a$ ,  $\alpha = 0.5$ , or 50% of the drug is in **ionized** form

☞ When  $\text{pH}$  is 1 unit below than  $\text{pK}_a$ ,  $\alpha=0.909$ , or 90% of the drug, is in **ionized** form

☞ When  $\text{pH}$  is 2 units below than  $\text{pK}_a$ ,  $\alpha=0.99$ , or 99% of the drug, is in **ionized** form

☞ When  $\text{pH}$  is 1 unit above  $\text{pK}_a$ ,  $= 0.9$ , or 90% of the drug, is in **unionized** form

☞ When  $\text{pH}$  is 2 unit above  $\text{pK}_a$ ,  $=0.99$ , or 99% of the drug, is in **unionized** form

 Therefore:

➡ As the pH of the solution increases, the degree of ionization (percentage ionized) decreases.

↙ Therefore, weak basic drugs are preferentially absorbed at higher pH.

 Examples:

💜 **Aspirin**, a weak acid with pK<sub>a</sub> of  $\approx 3.47$ – $3.50$ , has a greater fraction ionized in a more alkaline (higher pH) environment

💜 **Erythromycin**, a weak base with pK<sub>a</sub> of  $8.7$ , has a greater fraction ionized in a more acidic (lower pH) environment

## *Limitations of pH-PH*

- \* Extent to which drug exists in unionized form is not only factor determining rate and extent of absorption.
  - Despite high degree of ionization, **weak acids are well** absorbed from SI
  - Intestinal absorption of weak acid is often higher than in stomach
  - Huge SA in SI more than compensates for high degree of ionization

## NOTE ;

- A weak acid such as aspirin ( $pK_a$  3.5) is approximately 99% unionized in the gastric fluid at pH 1.0 but only 0.1% of aspirin is unionized at pH 6. (small intestine). Despite this seemingly unfavorable ratio of unionized to ionized molecules, aspirin and most weak acids are absorbed predominantly in the small intestine.

- This is due to a large surface area, a relatively long residence time and absorption of the ionized species  
(factors not considered by the pH–partition theory).

## Stability, pH, and Drug Absorption

- ✧ The stability–pH profile is a plot of the reaction rate constant for drug degradation versus pH.
- ✧ If drug decomposition occurs by acid or base catalysis
- ✧ E.g., erythromycin has a pH-dependent stability profile:
  - ✧ Acidic medium (in the stomach): decomposition
  - ✧ Neutral or alkaline pH: stable
  - ✧ Erythromycin tablets are enteric coated to protect against acid degradation in the stomach

## Particle Size and Drug Absorption

- ❧ The effective surface area of a drug is increased enormously by a reduction in the particle size.
- ❧ Because dissolution takes place at the surface of the solute (drug), the greater the surface area, the more rapid is the rate of drug dissolution
  - Many poorly soluble, slowly dissolving drugs are presented in *micronized form to increase SA*
    - - Digoxin (Cardiac glycoside)

## Polymorphism and Drug Absorption

- ❧ Polymorphism refers to the arrangement of a drug substance in various crystal forms or polymorphs
- ❧ Polymorphs have the same chemical structure but different physical properties, such as solubility, density, hardness, and compression characteristics.



✍ The crystal form that has the lowest free energy is the most stable polymorph

✍ 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.

✍ E.g., The  $\beta$  form of chloramphenicol is more soluble and better absorbed

10Q