# DOSAGE FORM DESIGN

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## Biopharmaceutical and Pharmacokinetic considerations

### Dissolution:

**The process by which a drug particle dissolves**. For a drug to be absorbed, it must first **dissolved in the fluid** at absorption site.

As a **drug particle undergoes dissolution**, the drug molecules on the surface are the first to enter into solution, creating a **saturated layer** of drug solution that envelops the surface of the solid drug particle. This layer of solution is the **diffusion layer.**

From diffusion layer the **drug molecules pass throughout the dissolving fluid** and make contact with biologic membranes, and absorption ensues.

In a series of kinetic or rate processes **(Disintegration**, **Deaggregation**, **Dissolution** and **Absorption**) , **the rate at which the drug reaches the systemic circulation is determined by the slowest of the various steps involved in the sequence**. Such a step is called as the rate-determining or rate-limiting step (RDS).

**If dissolution is rapid** or if the drug is administered as a solution, **the rate at which the drug becomes absorbed** depends mainly on **its ability to traverse the membrane barrier and said to be** permeation rate-limited **or** transmembrane rate-limited**.**

**If dissolution slow** because of the physicochemical characteristics of the drug substance or dosage form, dissolution is a rate-limiting step **in absorption**

Drug remain in stomach :**2 to 4 hours** while in small intestine: **4 to 10 hours**.

**Various techniques used to determine gastric emptying time like:**

**Gamma scintigraphy**: tracking dosage forms labeled with gamma-emitting radionuclides.

The **gastric emptying time** for a drug is **rapid with fasting stomach**, **slower** as food **content is increased**.

Changes in **gastric emptying time** or **intestinal motility** can affect **drug transit time** and thus **opportunity for drug dissolution and absorption**.

**a.** Anticholinergic drug, **slows gastric emptying**, which **increases** drugs absorption from **stomach** and **reduce** drugs absorption from **small intestine**.

**b.** Drugs that **enhance gastric motility**, for example, laxatives, reduce amount of drug absorbed.

**c. Aging decrease absorption (geriatrics)**

- **Decrease** in **gastric emptying time** is **advantageous** for drugs absorbed from **stomach** but **disadvantage** for drugs prone to **acid degradation**, like penicillins and erythromycin, or inactivated by stomach enzymes, like L-dopa.

**The rate of dissolution:**

The rate of dissolution described by Noyes-Whitney equation :

$$\frac{dW}{dt} = \frac{DA(C_s - C)}{L}$$

Where:

**dw/dt** is the **rate of dissolution**,

**D** is the **dissolution rate constant**,

**A** is the **surface area of dissolving solid**,

**Cs** is **saturation concentration of drug in diffusion layer** (which may be approximated by the **maximum solubility of the drug in the solvent**, because the diffusion layer is considered saturated), and

**Ct** is the concentration of the drug in **dissolution medium** at **time t** (Cs - Ct is concentration gradient).

**L**: length of diffusion layer.

- Rate of dissolution governed by rate of diffusion of solute through diffusion layer.

**The dissolution rate increased by**:

**1.** Increasing **surface area** (reducing the particle size),

**2. Increasing the solubility of drug in diffusion layer**, by factors embodied in

dissolution rate constant, D, including the intensity of agitation of the solvent and diffusion coefficient of dissolving drug. For a given drug, the diffusion coefficient and usually concentration of the drug in diffusion layer will increase with **increasing temperature**.

**3. Increasing rate of agitation** of the dissolving medium will increase the rate of dissolution.

**4. Reduction in the viscosity** of solvent enhance dissolution rate of a drug.

**5. Changes in pH** or **nature of solvent** that influence the solubility of the drug may be used to increase dissolution rate.

## Handerson HasselBalch equation:

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$ **For acidic drugs**.

$$pH = pKa + \log \frac{unionized}{ionized}$$ **For basic drugs.**

**Example 1: A weak acid drug is present in urine with an ionized concentration of 4.8 M and a unionized concentration of 0.2 M. If the pH is 6.5. What is the pKa of the drug?**
Answer:
pH = pKa + log ( [ionized] / [unionized] )
6.5 = pKa + log ( [4.8] / [0.2] )
**pKa = 5.119**

**Example 2: A weak base drug has a pKa of 8.0. The unionized concentration in urine is 0.5 M, and the ionized concentration is 4.5 M. What is the pH?**
Answer:
pH = pKa + log ( [unionized] / [ionized] )
pH = 8 + log ( 0.5/4.5) = **7.045**

- Drug movement **not always affected by pH**.
- **Very weak** acids and bases **completely non ionized** at physiological pH, their

transfer rapid and **independent of pH**.

- **Strong acids** and bases are **completely ionized** and so their transfer is usually slow and **pH-independent**.
- Drugs include acids within the pK range 3 to 7.5 and bases in the pK range 7 to 11
- Stomach pH: 1-2
- Duodenum pH: 2-4
- Small intestine pH: 4-6
- Large intestine 6-7.8

| | $pK_a$ |
|---|---|
| **Acids** | |
| Acetylsalicylic acid | 3.5 |
| Barbital | 7.9 |
| Benzylpenicillin | 2.8 |
| Boric acid | 9.2 |
| Dicoumarol | 5.7 |
| Phenobarbital | 7.4 |
| Phenytoin | 8.3 |
| Sulfanilamide | 10.4 |
| Theophylline | 9.0 |
| Thiopental | 7.6 |
| Tolbutamide | 5.5 |
| Warfarin sodium | 4.8 |
| **Bases** | |
| Amphetamine | 9.8 |
| Apomorphine | 7.0 |
| Atropine | 9.7 |
| Caffeine | 0.8 |
| Chlordiazepoxide | 4.6 |
| Cocaine | 8.5 |
| Codeine | 7.9 |
| Guanethidine | 11.8 |
| Morphine | 7.9 |
| Procaine | 9.0 |
| Quinine | 8.4 |
| Reserpine | 6.6 |