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Biopharmaceutics

It is the science that considers the interrelationship of the **physicochemical properties of drug** , **the dosage form** in which the drug is given and **route of administration** on the **rate and extent** of drug absorption.

To illustrate the importance of the drug substance and the drug formulation on absorption, and distribution of the drug to the site of action, one must first consider the sequence of events that precede elicitation of a drug's therapeutic effect. First, the drug in its dosage form is taken by the patient either by an oral, intravenous, subcutaneous, transdermal, etc., route of administration. Next, the drug is released from the dosage form in a predictable and characterizable manner. Then, some fraction of the drug is absorbed from the site of administration into either the surrounding tissue, into the body (as with oral dosage forms), or both. Finally, the drug reaches the site of action. If the drug concentration at the site of action exceeds the ***minimum effective concentration*** (MEC), a pharmacologic response results. The actual dosing regimen (dose, dosage form, dosing interval) was carefully determined in clinical trials to provide the correct drug concentrations at the site of action.

For example, a drug such as isoproterenol causes an increase in heart rate when given intravenously but has no observable effect on the heart when given orally at the same dose level. In addition, the *bioavailability* (a measure of systemic availability of a drug) may differ from one drug product to another containing the same drug, even for the same route of administration.

Pharmacokinetics

Pharmacokinetics is the science of the kinetics of drug absorption, distribution, and elimination (e.g. excretion and metabolism).

Pharmacodynamics

Pharmacodynamics refers to the relationship between the drug concentration at the site of action (receptor) and pharmacologic response, including biochemical and physiological effect that influence on the interaction of drug with receptor.

The systemic absorption of a drug dependent on:

1.**physicochemical** properties of the drug.

2.**Nature** of drug product.

3. **Anatomy** and physiology of the drug absorption site.

All these considerations are important in manufacture and Biopharmaceutics evaluation of drug products. Understanding of the physiologic and pathologic factors affecting drug absorption to assure therapeutic efficacy and to avoid potential drug- drug and drug nutrient interactions.

Dissolution

In the most standard situation, a tablet is ingested and passes through the esophagus to the stomach. Because the stomach is an aqueous environment,

Dissolution is a process in which a solid substance becomes dissolved in a given solvent i.e. transfer of solute from the solid surface to the liquid phase. Rate of dissolution is the amount of drug substance that goes in solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition.

This is the first place where a tablet will dissolve

The rate of dissolution is a key target for controlling the duration of a drug effect and as such several dosage forms that contain the same active ingredient may be available differing only in the rate of dissolution. If a drug is supplied in a form that is not readily dissolved the drug may be released more gradually over time with a longer duration of action. Having a longer duration of action may improve compliance since the medication will not have to be taken as often. Additionally slow release dosage forms may maintain concentrations within an acceptable therapeutic range over a long period of time , as opposed to quick release dosage form which may result in sharper peaks and troughs in serum concentrations.

The rate of dissolution is describe by the Noyes - Whitney equation as shown below

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

Where $\frac{dW}{dt}$ is the rate of dissolution

A: surface area of solid.

C: is the concentration of solid in bulk dissolution medium.

Cs: is the concentration of solid in the diffusion layer surrounding the solid.

D: is diffusion coefficient.

L: is the diffusion layer thickness or called stagnant layer.

- As can be inferred by the Noyes- Whitney equation, the rate of dissolution may be modified primarily by altering the surface area of the solid. The surface area may be adjusted by altering the particle size (e.g. micronization). The rate of dissolution may also be altered by choosing a suitable polymorph of a compound. Specially , crystalline forms dissolve slower than amorphous form.
- Also coatings on a tablet or a pellet may act as a barrier to reduce the rate of dissolution. Coating may also be used to modify where dissolution take place. For example **enteric coated** may be applied to a drug so that the coating only

dissolves in the basic environment of intestines. This well prevent release of drug before reaching the intestines.

- Since solutions are already dissolved the do not need to undergo dissolution before being absorbed.

Stagnant layer : is concentration of the drug in saturation form

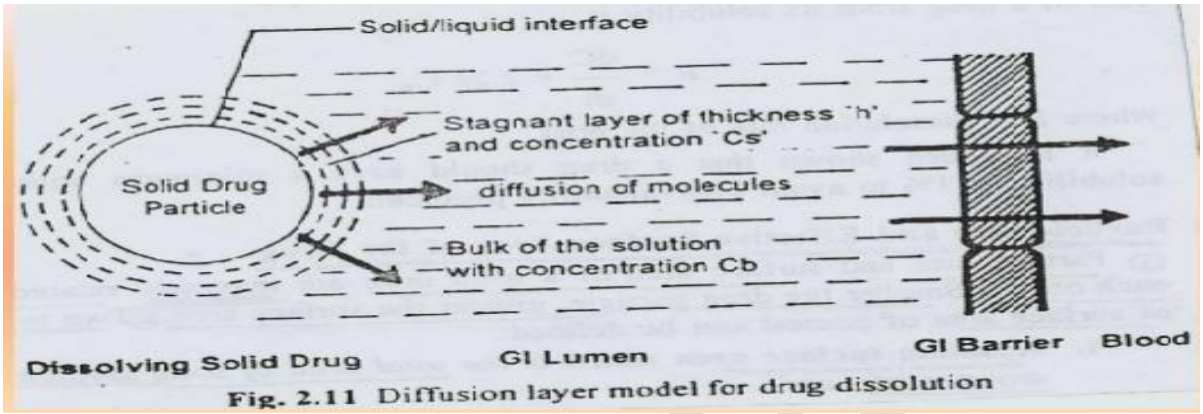

Fig. 2.11 Diffusion layer model for drug dissolution

This model assessed by Noyes Whitney equation. The assumptions are Drug particles – spherical and equal in size. Dissolution process controlled by diffusion of molecules. No chemical reaction between drug and solvent particles. Thickness of diffusion layer and solubility of drug in diffusion layer are constant. It involves two steps :-

1. Solution of the solid to form stagnant film or diffusive layer which is saturated with the drug

2. Diffusion of the soluble solute from the stagnant layer to the bulk of the solution

Ionization

☒ The gastrointestinal tract is lined with epithelial cells. Drugs must pass through these cells in order to be absorbed into the circulatory system. One particular cellular barrier that may that may prevent absorption of a given drug is the cell membrane. Cell membrane are essentially lipid bilayers which form a semipermeable membrane. Pure lipid bilayers are generally permeable only to **small, uncharged solutes**. Hence whether or not a molecule is ionized will affect

its absorption, since ionic molecules are considered charged molecules by definition.

- ☒ The Henderson – Hasselbalch equation offers a way to determine the proportion of a substance that is ionized at a given pH. In the stomach, drugs that are weak acid (such as aspirin) will be present mainly in their non-ionic form, and weak bases will be in their ionic form. Since non-ionic species diffuse more readily through cell membranes, weak acids will have a higher absorption in highly acidic stomach.
- ☒ However the reverse is true in the basic environment of the intestines,

  Weak bases (such as caffeine) will diffuse more readily since they will be non-ionic.

- ❖ **Prodrugs** of a compound may be developed by medicinal chemists that may be more readily absorbed and then metabolized by the body into the active compound. However changing the structure of a molecule is less predictable than altering dissolution properties, since changes in chemical structure may affect the pharmacodynamics properties of a drug.

Henderson – Hasselbalch Equation

Describes the derivation of pH as a measure of acidity (using pKa, the acid dissociation constant) in biological and chemical systems.

$$pH = pKa + \log\frac{[A-]}{[HA]}$$ for acidic drugs

$$pH = pKa + \log\frac{unionized}{ionized}$$ for basic drugs

Here, pKa is -log (ka) where Ka is the acid dissociation constant that is

$$pKa = -\log(ka) = -\log\{\frac{[H3O+][A]}{[HA]}\}$$

$$HA + H_2O \rightleftharpoons A^- + H_3O^+$$

In these equations, A^- denotes the ionic form of the relevant acid. Bracketed quantities such as [base] and [acid] denote the molar concentration of the quantity enclosed.

The movement of a drug is not always affected by pH. Very weak acids and bases are essentially completely non ionized at physiological pH values and so their transfer is generally rapid and independent of pH. In contrast, strong acid and bases are completely ionized and so their transfer is usually slow and pH – dependent.

Sensitivity to pH is likely to be seen only with drugs whose non-ionized fraction changes substantially within the normal physiological range of pH values. Such drugs include acids within the pK range 3 to 7.5 and bases in the pK range 7 to 11. Finally the non-ionized species must be lipid soluble.

Stomach pH**: 1-2**

Duodenum pH**: 2-4**

Small intestine**: 4-6**

Large intestine**: 6- 7.8**

Reference text: Shargel L, Yu AB, (Eds.), Applied Biopharmaceutics and Pharmacokinetics.