Pharmaceutical Pre-formulation

(Part 2)

Topics:

- Introduction
- Preliminary evaluation and molecular optimization
- Bulk characterization
- **Solubility analysis**
- **Stability analysis**

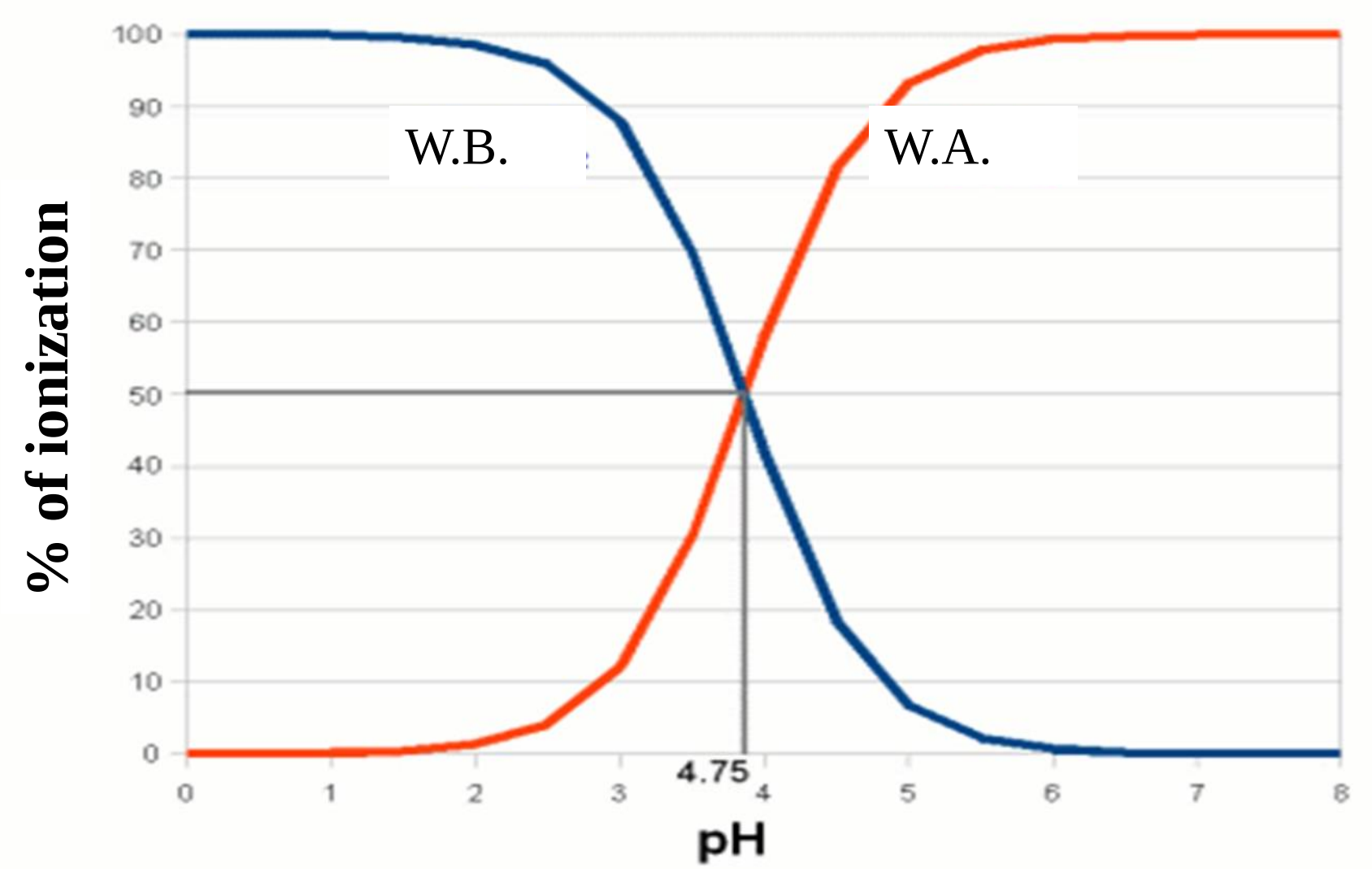
Solubility analysis

- ✓ it is important for orally administered drugs or drugs needed to be converted into solutions.
- ✓ It includes:
- ❖ pKa determinations
- ❖ pH solubility profile and common ion effects
- ❖ Effect of temperature
- ❖ Solubilization
- ❖ Partition coefficient
- ❖ Dissolution

pKa determinations

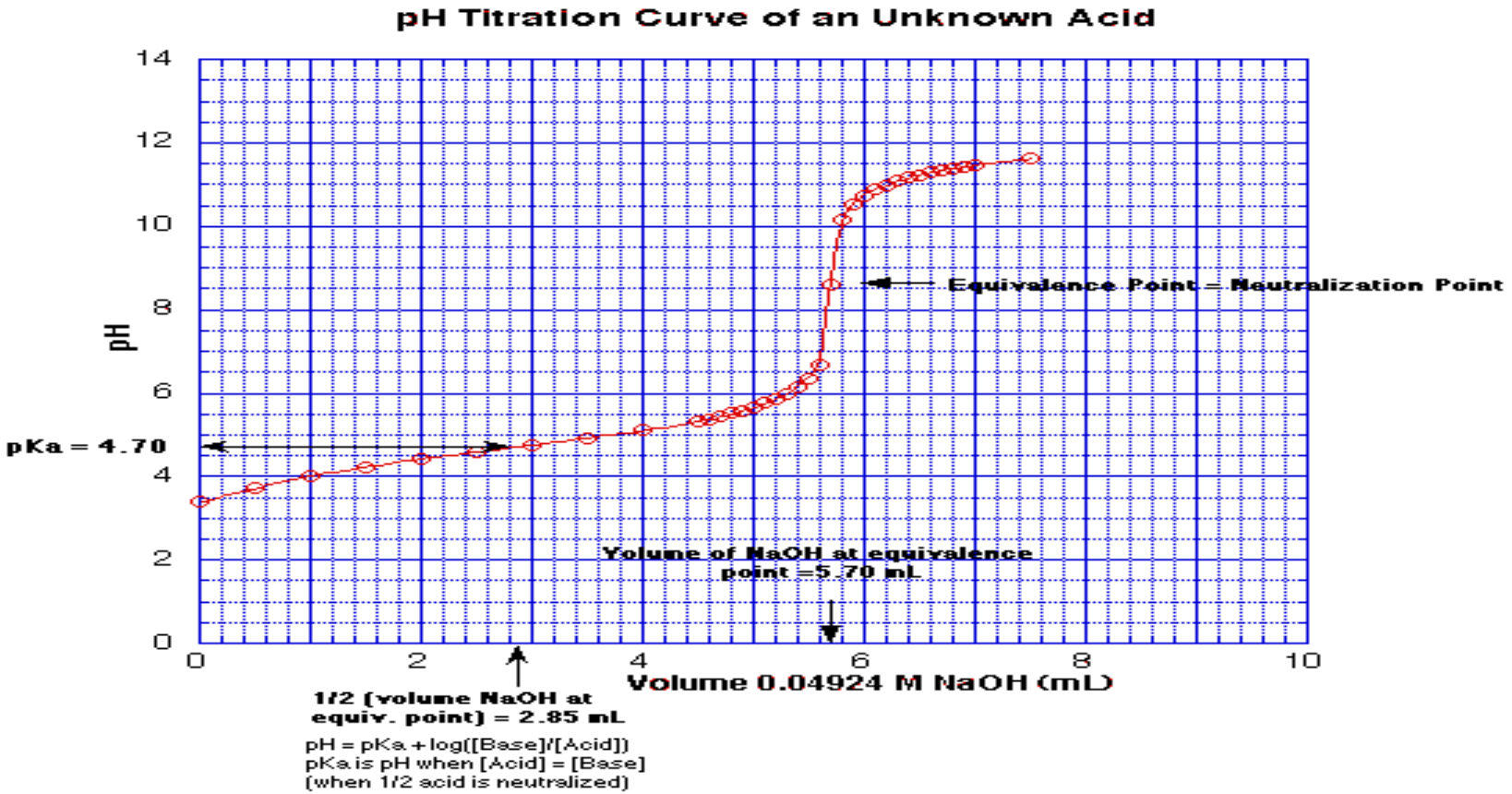
- ✓ It is important for drugs capable of ionization within a pH range (1-10), since solubility and then absorption can be changed by pH changes.
- ✓ As example, for a weakly acidic drug with pka value greater than 3, the unionized form is present within the acidic contents of the stomach, but the drug is ionized predominantly in the neutral media of the intestine.
- ✓ for basic drugs such as erythromycin, (pka ~ 8-9), the ionized form is predominant in both the stomach and intestine.

For w.a or w.b with pka **4.75**



The equations?? H.W

- ✓ pka can be determined using potentiometric pH titration (the drug is dissolved in water forming either w.a or w.b. which titrated and pH recorded).
- ✓ Conductivity, potentiometry and spectroscopy methods can be used. (all these at controlled conditions)???



pH solubility profile and Common ion effects

- ✓ The solubility of an acidic or basic drug depends on the pka of the ionizing functional group and the intrinsic solubilities for both the ionized and un-ionized forms.
- ✓ When the ionized or salt form of a drug is the solubility-limiting species in solution, the concentration of the paired counter ion (common ion) is usually the solubility determining factor. Ex. **Salt of basic amine** $BH^+ Cl^-$

$[BH^+Cl^-]_{solid} \rightleftharpoons [BH^+] + [Cl^-]$, $K_{sp}=[BH^+][Cl^-]$

$[Cl^-]$ increase ⟹ total solubility decrease

- ✓ Then, the solubility affected by pH, counter ion conc., drug conc., ionic strength, temp., and aqueous media composition.

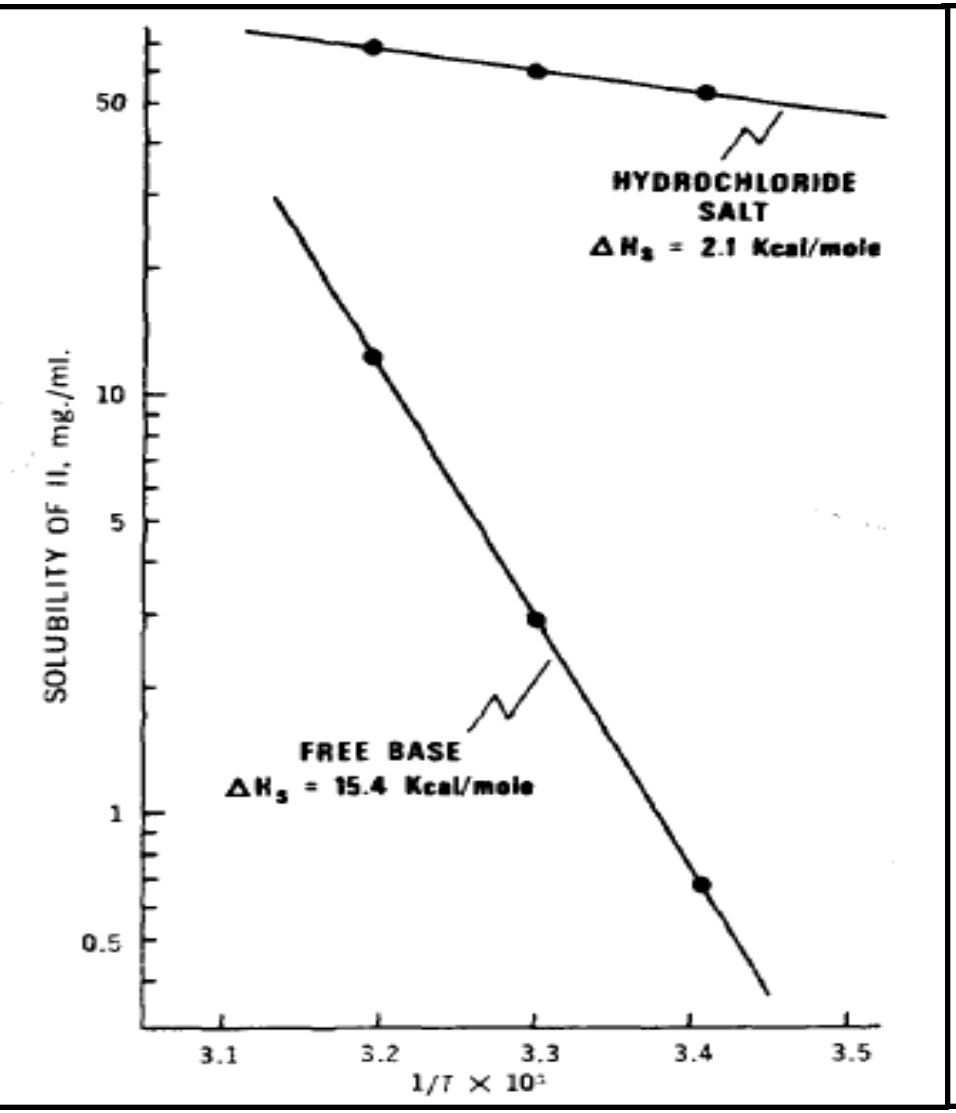
- ✓ For drug **(Doxycycline, pka 3.4),** there is common ion effect for an amine hydrochloride salt on solubility.
- ✓ The solubility in aqueous medium **(pH 2 or less)** logarithmically decreased as a function of pH (which was adjusted with hydrochloric acid) because of corresponding increases in the chloride ion concentration.
- ✓ In gastric juice **(pH, 1-2 and [Cl^-]= 0.1-0.15M),** doxycycline hydrochloride dihydrate has a solubility of about **4mg/ml**, which is **a factor of 7 less than its solubility in D.w**.
- ✓ In addition to that, protonated form (of solubility product) of doxycycline can form dimeric species (due to self association) at certain pH.

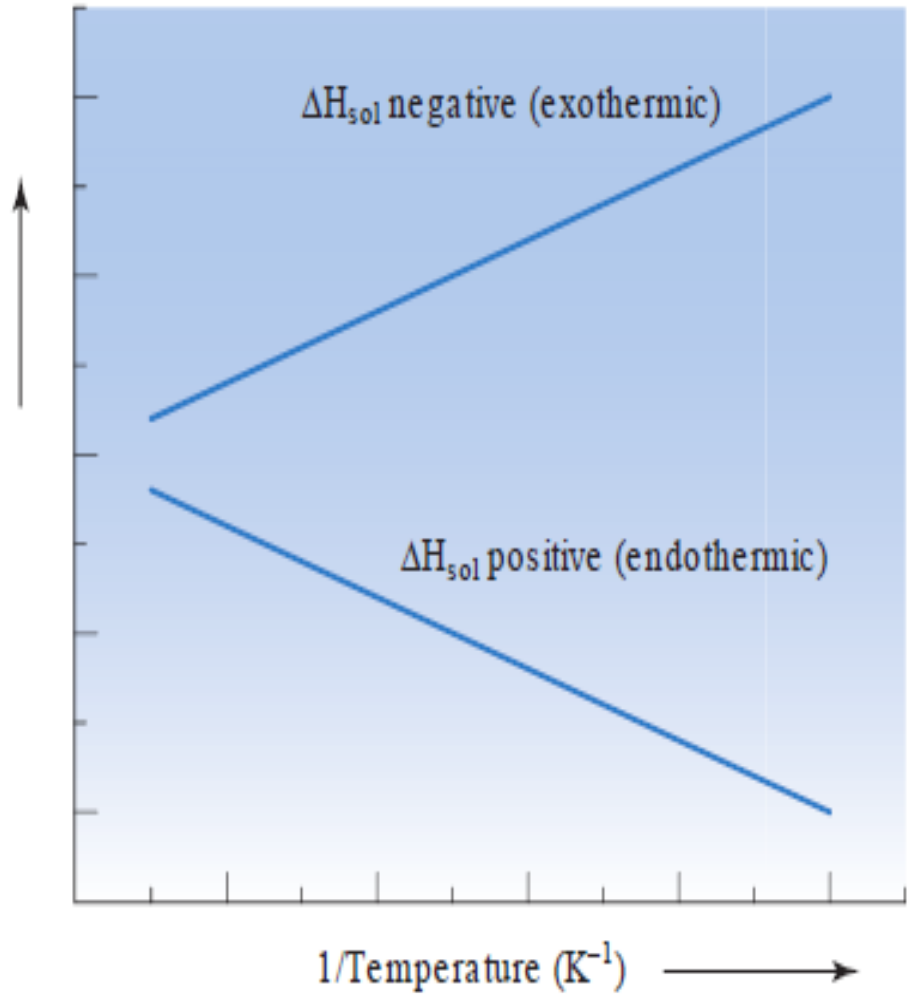
Effect of temperature

- The heat of solution, ΔH_s, represent the heat released or absorbed when a mole of solute is dissolved in a large volume of solvent (endothermic or exothermic reactions).
- Heats of solutions are determined from solubility values for saturated solutions equilibrated at controlled temperatures over the range of interest.
- Typically the temperature range should include **5, 25, 37 and 50°C** and the equation involved:

$$\ln S = \frac{-\Delta Hs}{R}\left(\frac{1}{T}\right) + C$$

The heat of solutions are varied with variation of drug chemical form (salt or free form).(T or F)?

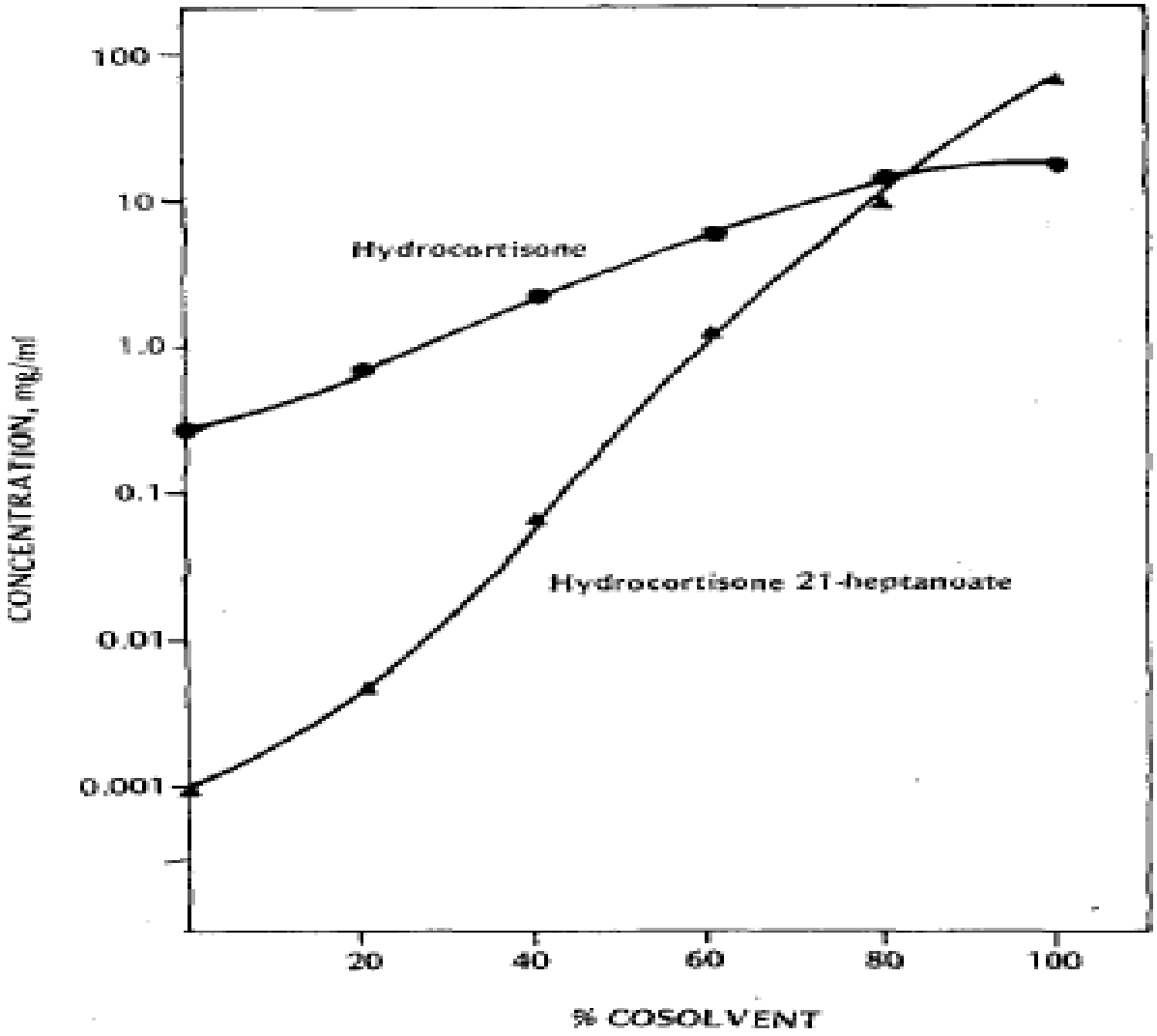




Solubilization

How we can increase the solubility extent in water?

- ✓ Addition of co-solvent (depending on chemical structure of drug?).
- ✓ Addition of surfactant
- ✓ Complexation



Partition coefficient

- ✓ A measurement of a drug's lipophilicity and an indication of its ability to cross cell membranes is the oil/water partition coefficient in systems such as octanol/water and chloroform/water.
- ✓ It is defined as the ratio of **unionized** drug distributed between the organic and aqueous phases at equilibrium. $P_{o/w} = \left(\frac{C\ oil}{C\ water} \right)_{equilibrium}$
- ✓ it is determined by shake-flask method, chromatographic methods (TLC, R-HPLC) using different phases (stationary and mobile)

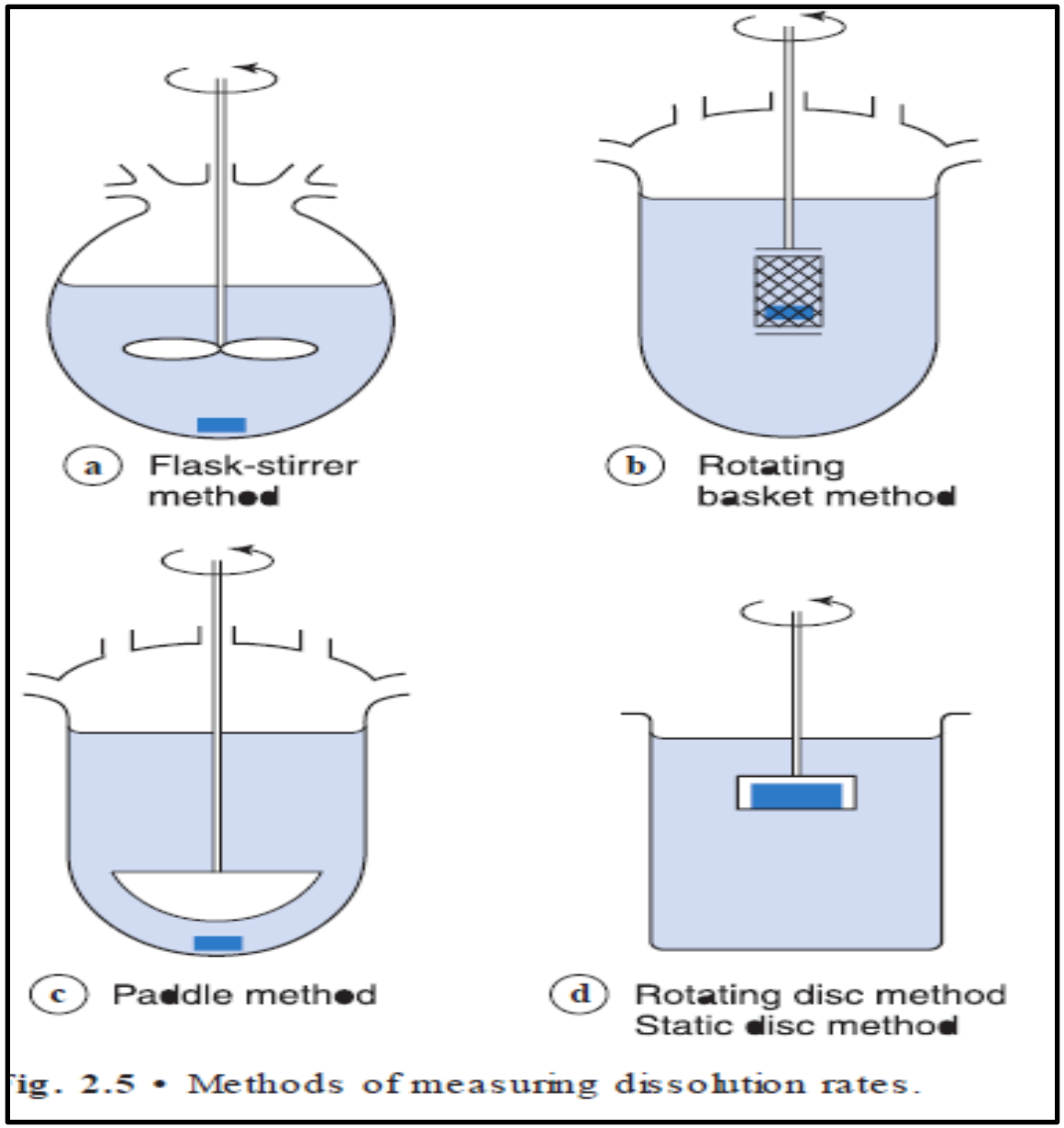
Dissolution

- ✓ Dissolution of a drug particle is controlled by several physicochemical properties, including chemical form, crystal habit, p.s. and S.A., solubility and wetting properties.
- ✓ By modification of Noyes-Whitney equation, we can calculate IDR for drugs (the parameters of equation are constant).

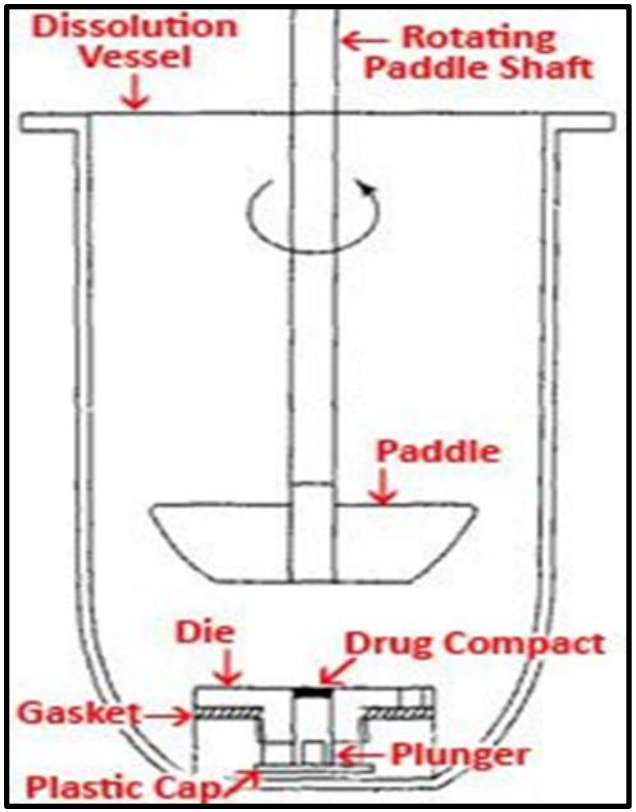
$\frac{dC}{dT} = \frac{DA}{hV}(C_s - C)$, at constant stirring speed and viscosity, we get constant D and h while A may be changed by disintegration? How it is being constant?, sink conditions are maintained so that **Cs-C = Cs**, then as result :

$$IDR = KC_s$$

✓ Experimentally, a constant S.A. is obtained by compressing powder into a disc of known area with a die and punch apparatus.



ig. 2.5 • Methods of measuring dissolution rates.



Stability analysis

- Is usually the first quantitative assessment of chemical stability of a new drug.
- It includes both solution and solid state experiments under conditions typical for the handling, formulation, storage and administration of a drug candidate.
- Generally, it includes:

1. **Stability in toxicology formulations**
2. **Solution stability**
3. **Solid state stability**

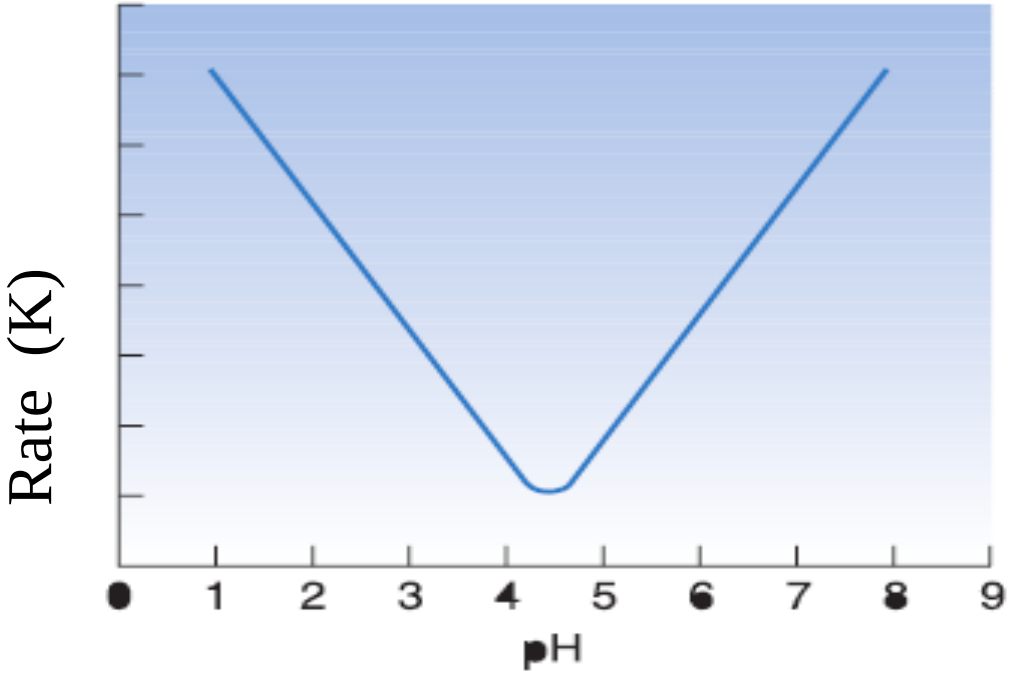
Stability in toxicology formulations

- ✓ A drug is administered to the animal in their feed, or by oral **gavage** of a solution or suspension of the drug in an aqueous vehicle.
- ✓ Water, vitamins, minerals (metal ions), enzymes and a multitude of functional groups are present in feed, which can severely reduce the shelf- life of a drug.
- ✓ Solution and suspension formulations are checked for ease of manufacture and then stored in flame-sealed ampoules at various temperatures.

Solution stability

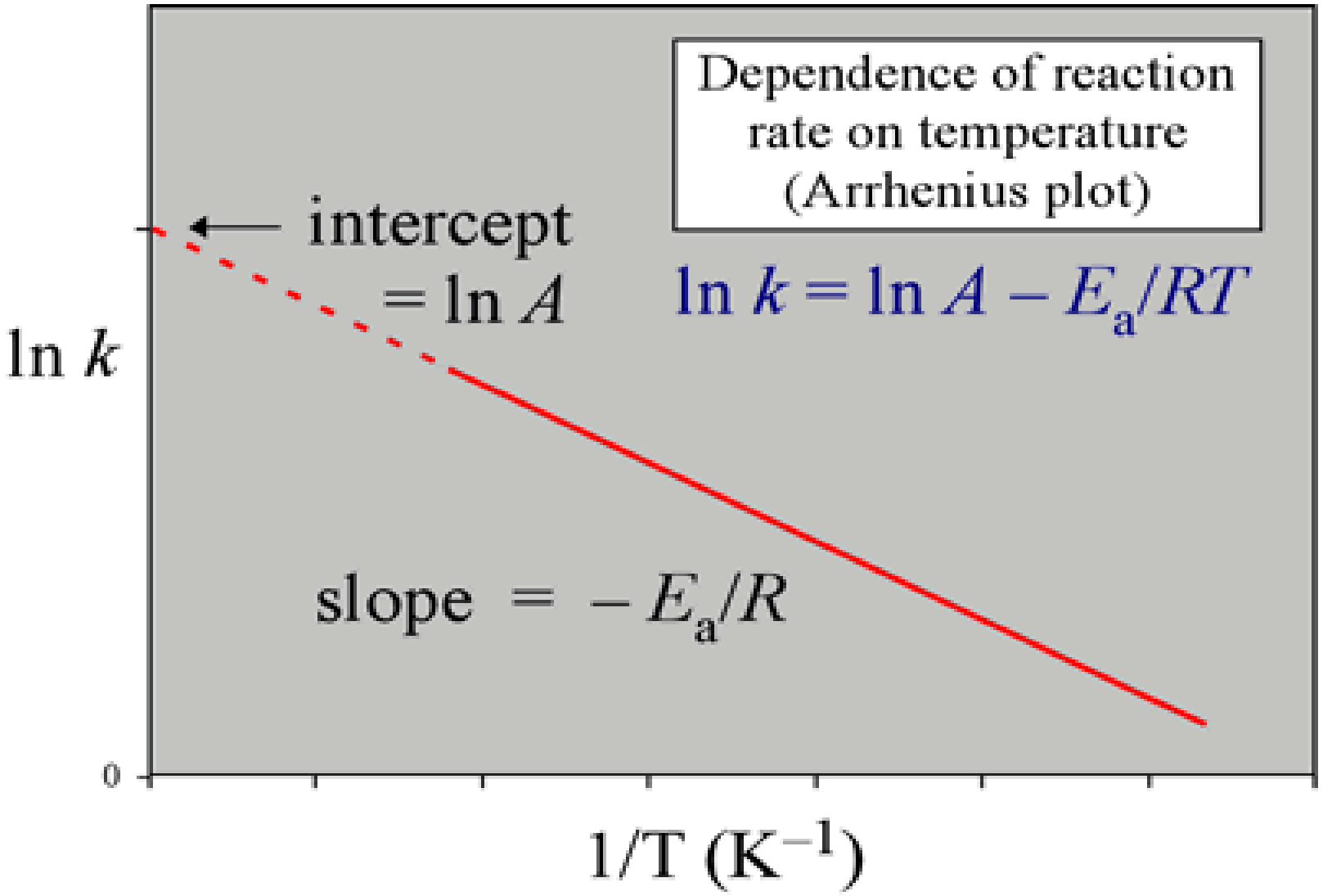
- ✓ It is important for identification of conditions necessary to form a stable solution including the effects of (pH, ionic strength, co-solvent, light, temperature and oxygen).
- ✓ pH for maximum stability is determined using different types of buffers at constant conditions(?).

Acid-base catalysis (pH rate profile)



- ✓ Ionic strength depends on the molar concentrations of ion (with valency), it must be constant specially for injectable solutions (about 0.15).
- ✓ Co-solvent can affect solubility and stability (hydrolysis prevention), solvents effects originated from dielectric constants values?, toxicity and compatibility. So the selected cosolvent must be selected at controlled conditions like (temperature not causes evaporation, sealing/packaging).
- ✓ The studies include photodegradation and oxidation depending on the drug, so if found (must be prevented ? how).

- ✓ Then, Arrhenius equation ? is used for studying the effect of temperature on solution at controlled conditions.
- ✓ The fractions of remaining drugs are assayed using UV, HPLC (the best?).
- ✓ After determination of the rate constant at 25°C, the shelf life can be calculated using the equation: $\mathbf{t_{10\%} = 0.105/K_{25}}$
- ✓ Depending on the results, we can decide if, the drug can prepared in soluble, stable and effective form or not.


Dependence of reaction rate on temperature (Arrhenius plot)
intercept
= ln A
ln k = ln A – Ea/RT
ln k
slope = – Ea/R
0
1/T (K–1)

Solid state stability

- ✓ Includes identification of the suitable conditions for storage of solid drugs and drug-excipients compatibility.
- ✓ Solid state changes may include changes in the bulk properties.(so must be assayed as before)
- ✓ The reaction rates are much slower and more difficult to interpret.(why?)
- ✓ Generally, it involve placing of a new drug (certain weight) in open screw cap vials and then exposed directly to a variety of temperatures, humidities, and light intensities for long period of time.

Table 49.2 Long-term test conditions for the various climatic zones, as defined by the World Health Organization (2009)

Climatic zone	Definition	Long-term test conditions	
		Temperature (°C)	Relative humidity (% R.H)
I	Temperate climate	21	45
II	Subtropical and Mediterranean climate	25	60
III	Hot and dry climate	30	35
IVA	Hot and humid climate	30	65
IVB	Hot and very humid climate	30	75

Table 49.3 Examples of recommended minimum stability testing schedules for pharmaceutical products

Storage time (months)	Products intended to be stored in a refrigerator		Product intended to be stored in ambient conditions	
	Long-term 5 °C	Accelerated Zone II 25 °C/60% RH Zone IVA 30 °C/65% RH Zone IVB 30 °C/75% RH	Long-term Zone II 25 °C/60% RH Zone IVA 30 °C/65% RH Zone IVB 30 °C/75% RH	Accelerated 40 °C/75% RH
0	√	√	√	√
3	√	√	√	√
6	√	√	√	√
9	√		√	
12	√		√	
18			√	
24			√	
36			√	

- ✓ Effect of oxygen and light can be studied for effected drugs and then protected within study at various (T and RH).
- ✓ RH has its reaction rate constant (K_H), so as increased by increasing of water in atmosphere as the degradation increased.
- ✓ Solid drug-excipient compatibilities (physical or chemical) must be evaluated using different assay methods for pure drug alone, physical mixtures (at certain ratio) and formulas.

The end