جامعة الجزيرة الخاصة
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Industrial Pharmacu (2)

SOLUTIONS
DISSOLUTION AND SOLUBILITY

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SOLUTIONS: DISSOLUTION AND SOLUBILITY

Introduction

Definitions: solutions, dissolution, solubility

Expressions of concentration

Dissolution

- Dissolution rates of solids in liquids
- Factors affecting *in vitro* dissolution rates of solids in liquids
- Methods for determining dissolution rate

Solubility

- Classification of substances according to solubility
- Factors affecting the solubility of solids in liquids

WHY STUDYING SOLUTIONS?

Many drugs are formulated as solutions.

Almost all drugs function in solution in the body; In general, a drug substance must be in solution form to be absorbed and to give their therapeutic effects

DEFINITIONS

Solution:

- A mixture of two or more components that form a single phase which is **homogeneous** down to the molecular (ionic) level, it contains two components:

1. The ***solvent :*** determines the phase of the solution and constitutes the largest proportion of the system.
2. The ***solute/s:*** dispersed as molecules or ions throughout the solvent; ***dissolved*** in the solvent.

A **solution** can be a solute of **any of the three states of matter (gas, liquid, solid) dissolved in a solvent of any of the three states of matter**. ❖

Most pharmaceutical solutions are **solid in liquid** solutions. ❖

DEFINITIONS

Dissolution

The transfer of molecules or ions from a solid state into solution.

Solubility

The ***amount*** of a substance that passes into solution when ***equilibrium*** is established between the solution and excess (undissolved) substance (***saturation).***

- ***Dissolution*** **describes** ***process***
- ***Solubility*** **measures the extent of dissolution process** ***(amount or concentration)***

EXPRESSIONS OF CONCENTRATION

Quantity per quantity

- weight or volume of solute that is contained in a given weight or volume of the solution (w/w, v/w, w/v or v/v).

1 g L^{-1} = 0.1 g per 100 mL = 1 mg mL^{-1} = 5 mg in 5 mL = 1 µg $µL^{-1}$

Percentage

- (% w/w, % v/w, % w/v or % v/v).

concentration in % *w*/v = $\frac{\text{weight of solute}}{\text{volume of solution}}$ x 100

EXPRESSIONS OF CONCENTRATION

Parts

- Parts of solute dissolved in parts of solution,

e.g. sucrose dissolves 2 parts in 1 part water = 2 g of sucrose dissolve in 1 g water (simple syrup: 66.7%w/w)

Molarity

- Number of moles of solute in 1 dm^3 (1 L) of solution (mol L^{-1})

Molality

- Number of moles of solute / mass of solvent (mol $kg^{-1)}$

EXPRESSIONS OF CONCENTRATION

Mole fraction

moles of solute / moles of solute + moles of solvent

Equivalents or Milliequivalents

1Eq (1 mEq) = ionic or molecular weight in g (in mg)/valency

Normality

Number of Eq / volume of solution (L)

Normality = Molarity when valency = 1

1- DISSOLUTION

Definition

The transfer of molecules or ions from a solid state into solution.

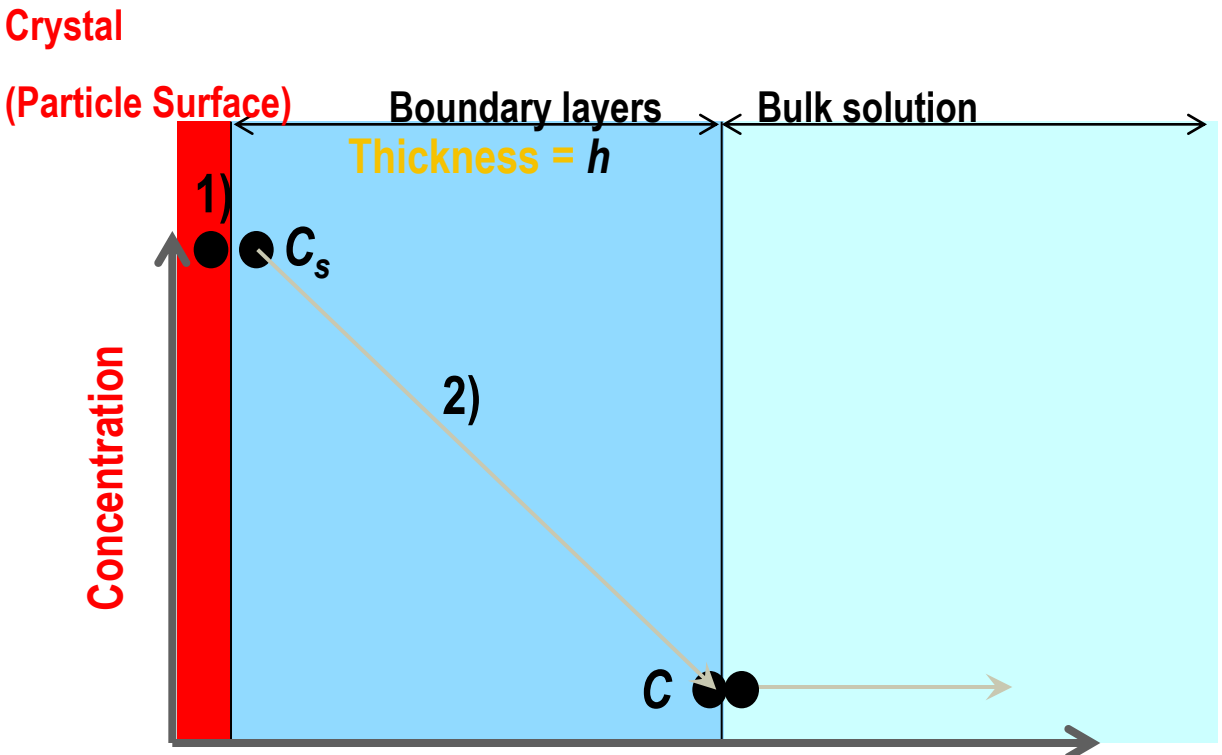
Dissolution **describes** ***process.***

DISSOLUTION RATES OF SOLIDS IN LIQUIDS

Dissolution mechanisms

١. **Liberation** of solute molecules from the solid phase. The solution in contact with the solid (boundary layers) will be saturated; Cs.

٢. **Diffusion** step (slower than 1st step): solute molecules migrate through the boundary layers (static layers) surrounding the crystal to the bulk of the solution, where its concentration will be C.



DISSOLUTION RATES OF SOLIDS IN LIQUIDS

Rate of dissolution

Fick's law (change in concentration of dissolved material with time)

$$\frac{dC}{dt} = k\Delta C$$

K: rate constant (s^{-1})

$\Delta C = Cs - C$

Cs > C: Dissolution

Cs = C: $\Delta C = 0$; equilibrium (saturation)

Cs < C: precipitation or crystallization; supersaturation

DISSOLUTION RATES OF SOLIDS IN LIQUIDS

Rate of dissolution

Noyes-Whitney equation (rate of mass transfer of solute molecules from a single spherical particle)

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

D : diffusion constant (m^2/s)

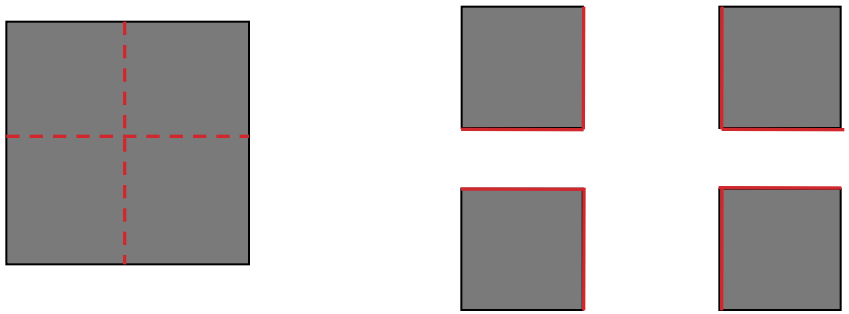
A: surface area

h: thickness of the boundary layer

VITRO DISSOLUTION RATES OF SOLIDS IN LIQUIDS

1. *A*, surface area

- **Size of particles:** surface area is increased when particle size is smaller.



A = 4L

A = 8L

FACTORS AFFECTING IN VITRO DISSOLUTION RATES OF SOLIDS IN LIQUIDS

2. C_s, solubility of solid in dissolution medium

- Temperature.
- Nature of dissolution medium.
- Molecular structure of solute.
- Crystalline form of solid.
- Presence of other compounds (e.g. impurities).

3. *C*, concentration of solute in solution at time *t*

- Volume of dissolution medium (sink conditions).
- Any process that removes dissolved solute from the dissolution medium: adsorption, partition into a second liquid, dialysis, replacement of solution.

FACTORS AFFECTING IN VITRO DISSOLUTION RATES OF SOLIDS IN LIQUIDS

4. D, diffusion constant (diffusion coefficient of solute in the dissolution medium)

- Viscosity of dissolution medium.
- Size of diffusing molecules.

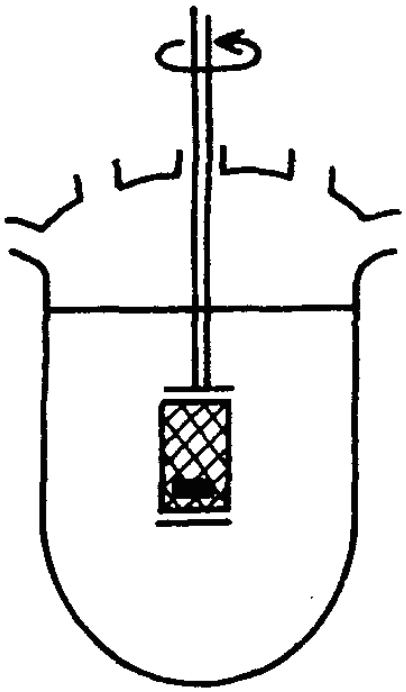
5. *h* Thickness of boundary layer:

- Reduced by agitation.

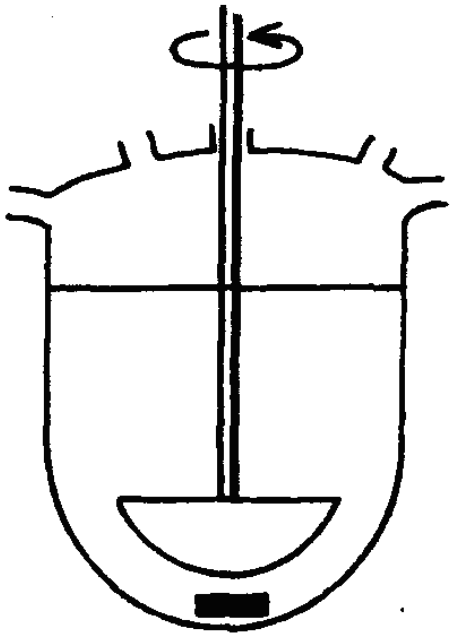
METHODS FOR DETERMINING DISSOLUTION RATE

Rotating basket and Paddle methods

- ods; described by pharmacopeias



(c) Rotating basket method



(d) Paddle method

DISSOLUTION RATE PROCEDURE

Place the stated volume of the Dissolution Medium (±1%) in the vessel of the specified apparatus given in the individual monograph, assemble the apparatus, equilibrate the Dissolution Medium to 37 ± 0.5.

Place 1 dosage unit in the apparatus, and immediately operate the apparatus at the specified rate given in the individual monograph.

Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the Dissolution Medium and the top of the rotating basket or blade, not less than 1 cm from the vessel wall.

Perform the analysis as directed in the individual monograph using a suitable assay method.

Repeat the test with additional dosage form units.

In general:

- Times: 10, 20, 30, and 45 minutes.
- Dissolved amount is not less than 80% is dissolved in 45 minutes.

2- SOLUBILITY

Definition

The ***amount*** of a substance that passes into solution when ***equilibrium*** is established between the solution and excess (undissolved) substance (***saturation).***

Solubility **measures the extent of dissolution process** ***(amount or concentration).***

CLASSIFICATION OF SUBSTANCES ACCORDING TO SOLUBILITY (IN PHARMACOPOEIAS)

Description	Approximate weight solvent (g) necessary to dissolve 1 g of solute
Very soluble	< 1
Freely soluble	Between 1 and 10
Soluble	Between 10 and 30
Sparingly soluble	Between 30 and 100
Slightly soluble	Between 100 and 1000
Very slightly soluble	Between 1000 and 10 000
Practically insoluble	> 10 000

SOLUBILITY OF SOLIDS IN LIQUIDS

Solutions of solids in liquids are the most common type encountered in pharmaceutical practice.

Determination of the solubility of a solid in a liquid

1. Preparation of a saturated solution

The following points should be observed in all solubility determinations:

A. The solvent and the solute must be **pure.**

B. A **saturated solution must be obtained** before any solution is removed for analysis.

C. Temperature must be adequately controlled.

SOLUBILITY OF SOLIDS IN LIQUIDS

2. Filtration:

It is used to remove undissolved compound. Precautions should be taken to ensure that:

A. it is carried out at the **temperature of the solubility determination**, in order to prevent any change in the equilibrium between dissolved and undissolved solute.

B. loss of a volatile component does not occur.

3. Measurement of concentration:

Variety of methods: gravimetric or volumetric analysis, electrical conductivity measurements, ultraviolet (UV) spectrophotometry and chromatographic methods (HPLC).

FACTORS AFFECTING THE SOLUBILITY OF SOLIDS IN LIQUIDS

1. Temperature
2. Nature of solute
3. Nature of solvent
4. Crystal characteristics
5. Particle size of the solid
6. pH
7. Complex formation
8. Solubilizing agents

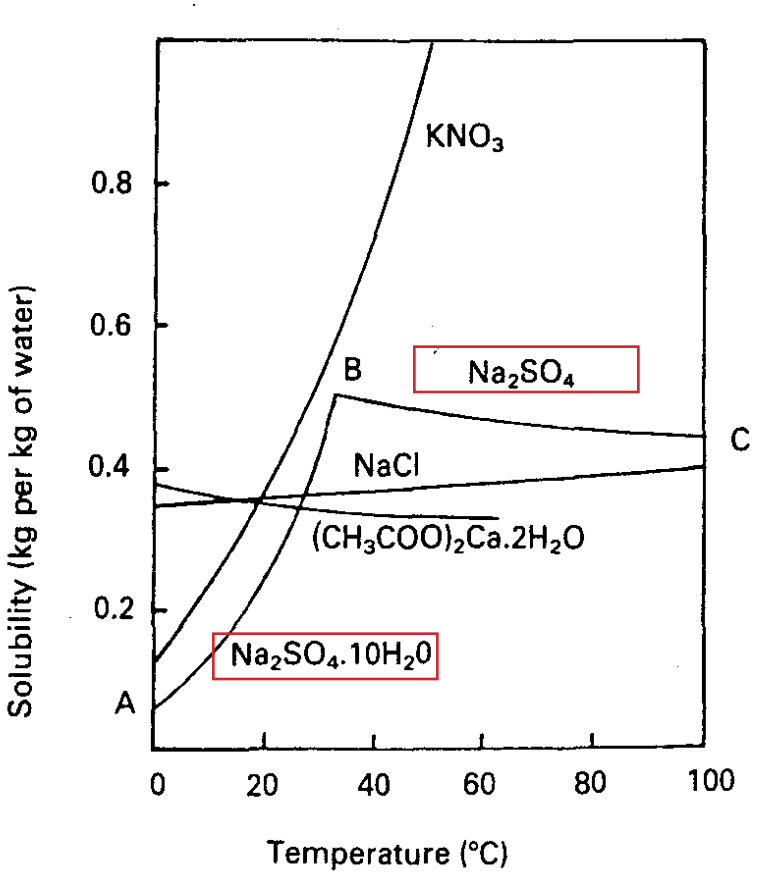
FACTORS AFFECTING THE SOLUBILITY OF SOLIDS IN LIQUIDS

1. Temperature

Temperature mostly **increases** solubility but **may also decrease** it depending on the nature of solute and solvent.

Solubility curves for various substances in water

The decahydrate (sodium sulfate) Na_2SO_4, $10H_2O$ (endothermic) is converted into the anhydrous form Na_2SO_4 at 32.5°C (exothermic)



FACTORS AFFECTING THE SOLUBILITY OF SOLIDS IN LIQUIDS

2. Molecular structure of solute (chemical modification)

Solubility can be increased or decreased by changing the molecular structure.

A. Increased solubility

1. Addition of hydrophilic groups

Phenol (hydrophilic hydroxyl group) is 100-fold more soluble in water than benzene.

2. Formation of a salt:

The most used salts are:

- **Hydrochloride salt for basic drugs.**
- **Sodium salt for acidic drugs.**

Salt	solubility (mg/ml)	pKa
Chlordiazepoxide (base) (hypnotic)	2.0	٤.٨
Hydrocholride	165	-6.1
Maleate	57.1	1.92
Tartarate	17.9	3.0
Benzoate	6.0	4.2

Aqueous solubilities of salicylic acid and its sodium salt are 1:550 and 1:1, respectively.

FACTORS AFFECTING THE SOLUBILITY OF SOLIDS IN LIQUIDS

B. Decreased solubility:

Advantages:

1. **Masking the taste of a parent drug, e.g. chloramphenicol palmitate is used in paediatric suspensions rather than the more soluble and very bitter chloramphenicol base.**

2. **Protecting the parent drug from excessive degradation in the gut, e.g. erythromycin propionate is less soluble and consequently less readily degraded than erythromycin.**

FACTORS AFFECTING THE SOLUBILITY OF SOLIDS IN LIQUIDS

3. Nature of solvent (cosolvent)

'Like dissolves like'

Solubility can be enhanced by using cosolvents, a mixture of miscible solvents.

For example, the aqueous solubility of metronidazole is about 100 mg in 10 mL, can be increased to 500 mg in 10mL by incorporation of one or more water-miscible cosolvents (ethanol).

FACTORS AFFECTING THE SOLUBILITY OF SOLIDS IN LIQUIDS

4. Crystal characteristics

Some crystalline medicinal chemicals are capable of forming different types of crystals, depending on the conditions (temperature, solvent, time) under which crystallization is induced.

This property, whereby a single chemical substance may exist in more than one crystalline form, is known as "Polymorphism".

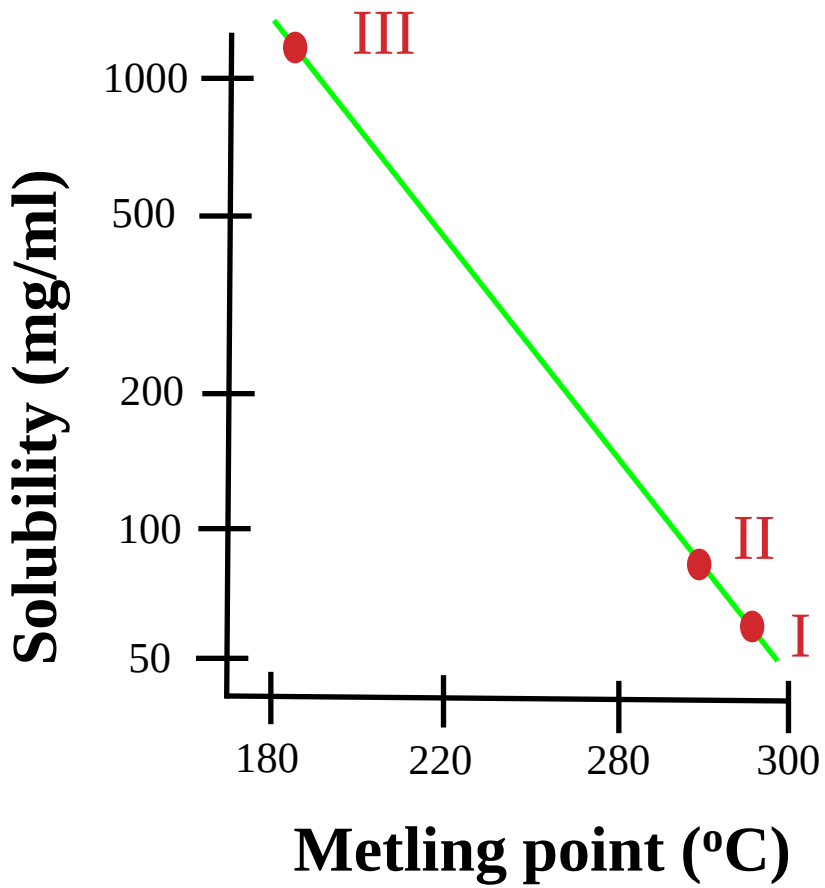
The absence of crystalline structure of a compound results in an amorphous form.

Many drugs exhibit polymorphism, e.g. steroids, barbiturates and sulfonamides.

Polymorphs possess different free energies, and this difference is reflected by changes in stability, melting point and solubility.

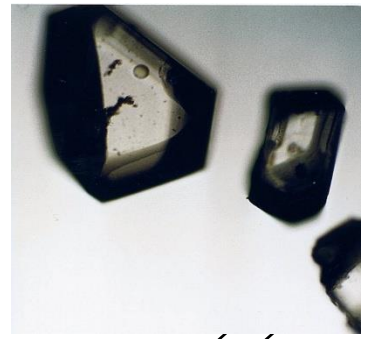
These differences are manifest as long as the drug is in the solid state (solid dosage forms and liquid suspension). Once solution is effected, the different forms become indistinguishable one from another.

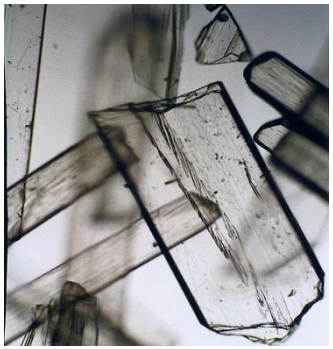
Only one form of a pure drug substance is stable at a given temperature and pressure, with the other higher-energy forms, called metastable forms, converting in time to the stable crystalline form, even in a completed pharmaceutical preparation, although the time required for a complete change may exceed the normal shelf-life of the product.

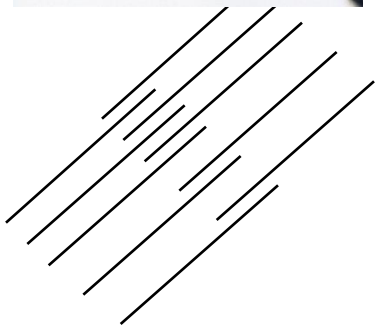


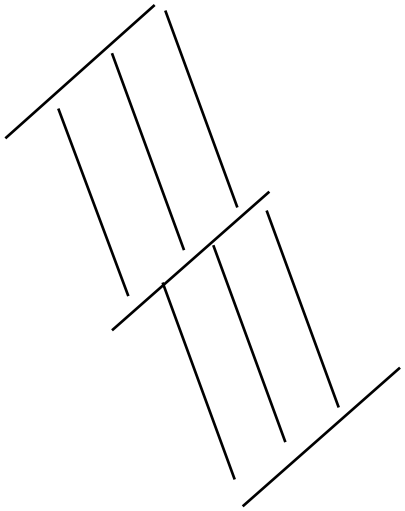
The relation between melting point and solubility in three (Vit B2). polymorphs of riboflavin

METASTABLE FORMS ARE TRANSFORMED TO THE STABLE FORM









Stable form

Metastable form

The use of metastable forms generally results in higher solubility and dissolution rates than the respective stable crystal forms of the same drug.

On the other hand, the stable polymorph is more resistant to chemical degradation and because of its lower solubility is frequently preferred in pharmaceutical suspensions of insoluble drugs.

In all instances, the advantages of the metastable crystalline forms in terms of increased bioavailability of the drug must be balanced against the increased product stability when stable polymorphs are employed.

Since the amorphous form of a chemical is usually more soluble than the crystalline form, different extents of drug absorption may result with consequent differences in the degree of pharmacologic activity obtained from each. Two antibiotic substances, novobiocin and chloramphenicol palmitate, are essentially inactive when administered in crystalline form, but when they are administered in the amorphous form, absorption from the gastrointestinal tract proceeds rapidly, with good therapeutic response.

In other instances, crystalline forms of drugs may be used because of greater stability than the corresponding amorphous forms. For example, the crystalline forms of penicillin G as the potassium salt or sodium salt are considerably more stable than the analogous amorphous forms. Thus, in formulation work on penicillin G, the crystalline forms are preferred

FACTORS AFFECTING THE SOLUBILITY OF SOLIDS IN LIQUIDS

5. Particle size of the solid

The solubility (as well as dissolution rate) of a substance is increased with decreasing particle size.

Micronized **powders with large surface area are frequently used in their solid products. Micronized powders consist of drug particles reduced in size to about** ***5 microns*** **and smaller.**

The use of micronized drugs is not confined to oral preparations. For example, ophthalmic and topical ointments use micronized drugs for their preferred release characteristics and nonirritating quality

FACTORS AFFECTING THE SOLUBILITY OF SOLIDS IN LIQUIDS

6. pH

A large number of drugs are either weak acids (20%) or weak bases (75%), and therefore their solubilities in water can be influenced by the pH of the system.

Improving solubility: for a weak base by lowering the pH, for a weak acid by increasing pH.

Henderson-Hasselbac equations:

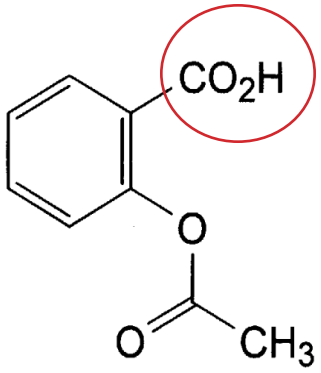
For weak acids:

$$pH = pKa + \log [R\text{-}COO^-] / [R\text{-}COOH]$$

For weak bases:

$$pH = pKa + \log [R\text{-}NH_2] / [R\text{-}NH_3^+]$$

The two equations can be re-written as the following integrated equation:



$$pH = pKa + \log [R\text{-}COO^-] / [R\text{-}COOH]$$

٣.٥ Aspirin a weak acid with pKa =

In the stomach with a pH of 2, then for aspirin:

$$\log [R\text{-}COO^-] / [R\text{-}COOH] = pH - pKa = 2 - 3.5 = -1.5$$

So, the ratio of unionized to ionized form is:

$$[R\text{-}COO^-] : [R\text{-}COOH] = \text{antilog} = 1:31.62$$

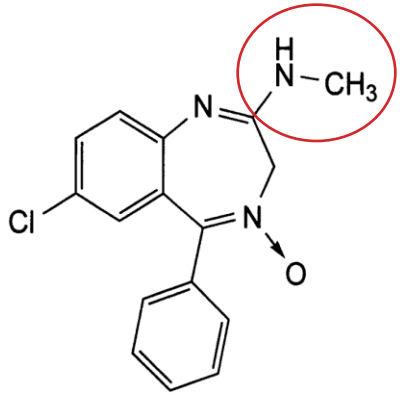
In acidic pH most aspirin is in the unionized form.

In the intestines and at a pH of 6:

$$\log [R\text{-}COO^-] / [R\text{-}COOH] = pH - pKa = 6 - 3.5 = 2.5$$

And, the ratio of unionized to ionized form is:

$$[R\text{-}COO^-] : [R\text{-}COOH] = \text{antilog} = 316.22:1$$



$$pH = pKa + \log [R\text{-}NH_2] / [R\text{-}NH_3^+]$$

٤.٨ Chlordiazepoxide (hypnotic) a weak base with pKa =

In the stomach with a pH of 2, then for chlordiazepoxide:

$$\log [R\text{-}NH_2] / [R\text{-}NH_3^+] = pH - pKa = 2 - 4.8 = -2.8$$

So, the ratio of ionized to unionized form is:

$$[R\text{-}NH_2] : [R\text{-}NH_3^+] = \text{antilog} = 1{:}630.95$$

In acidic pH most chlordiazepoxide is in the ionized form.

In the intestines and at a pH of 6:

$$\log [R\text{-}NH_2] / [R\text{-}NH_3^+] = pH - pKa = 6 - 4.8 = 1.2$$

And, the ratio of ionized to unionized form is:

$$[R\text{-}NH_2] : [R\text{-}NH_3^+] = \text{antilog} = 15.85{:}1$$

FACTORS AFFECTING THE SOLUBILITY OF SOLIDS IN LIQUIDS

7. Complex formation

The apparent solubility of a solute in a particular liquid may be increased or decreased by the addition of a third substance which forms an intermolecular complex with the solute.

It is essential that complex formation is easily reversible, so that the free drug is released during or before contact with biological fluids.

Examples is complexation of iodine with a 10-15% solution of polyvinylpyrrolidone to improve the aqueous solubility of the active agent.

FACTORS AFFECTING THE SOLUBILITY OF SOLIDS IN LIQUIDS

8. Solubilizing agents

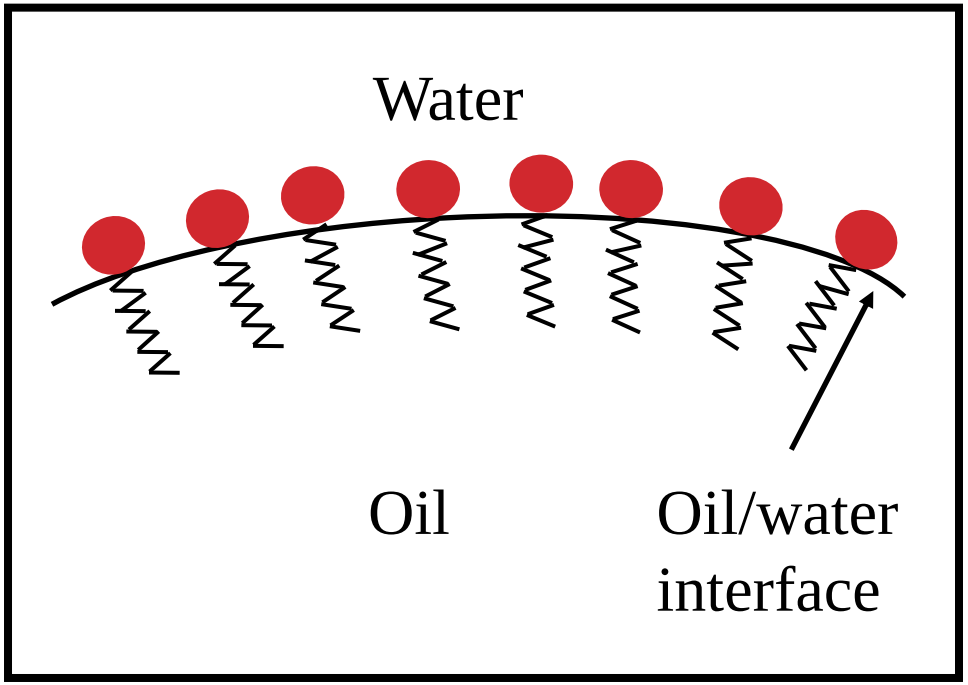
8.A. surfactants

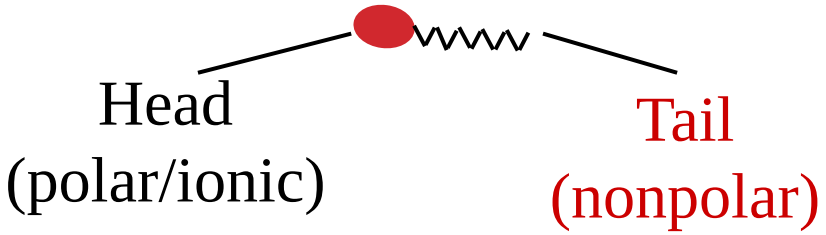
By the addition of a surface-active agent which forms micelles. In aqueous systems, non-polar molecules will dissolve in the interior of the micelle, which consists of the lipophilic hydrocarbon moiety.

The amount of surfactant to be used for this purpose must be carefully controlled. A large excess is undesirable because of cost and possible toxicity. An insufficient amount of surfactant may not solubilize all the drug, or may lead to precipitation either on storage or on dilution of the product.

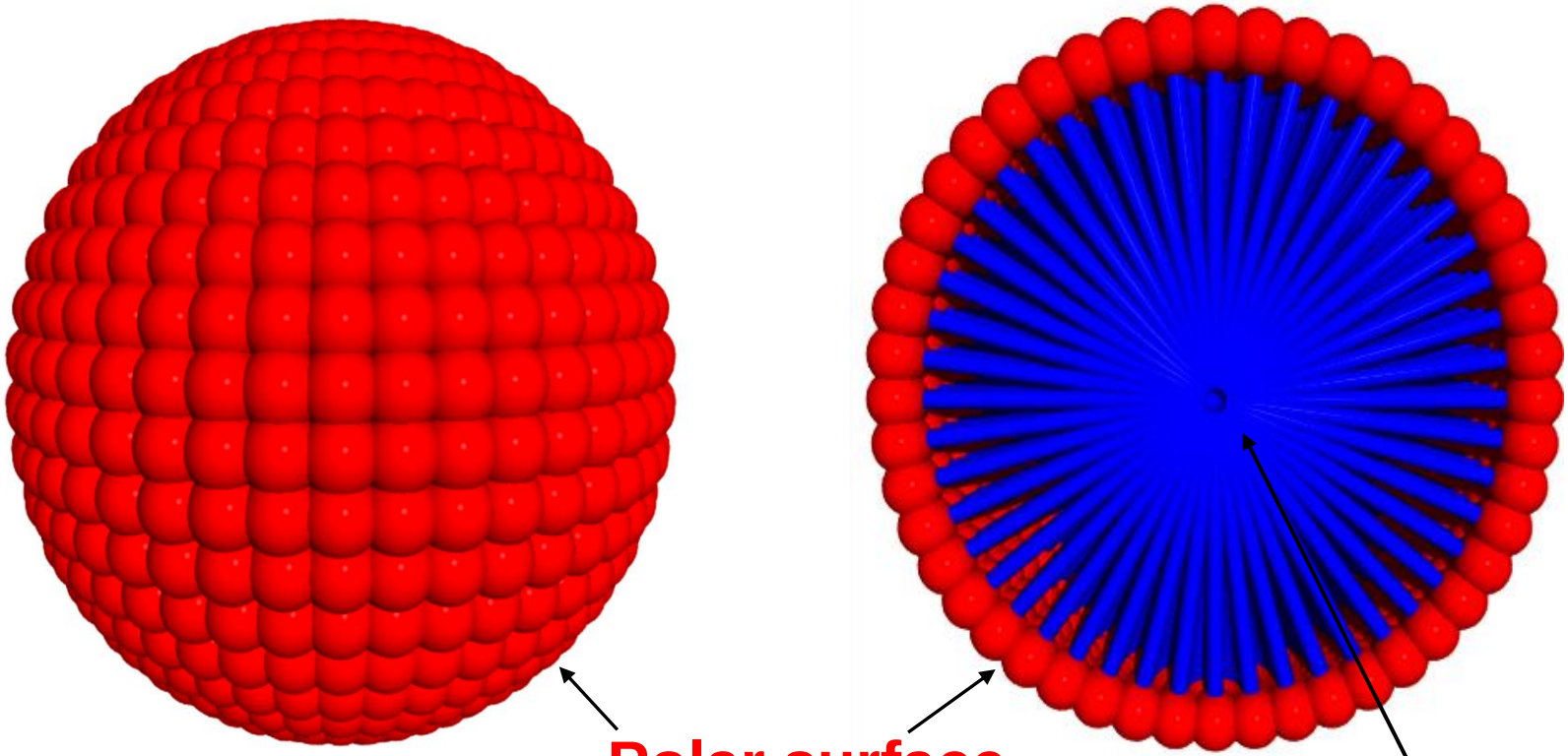
SURFACTANTS

Surface-active agents commonly known as surfactants are a group of substances that, when present at a low concentration in a system, adsorb onto the surfaces or interfaces of the system and reduce to a marked degree the surface or interface tension.

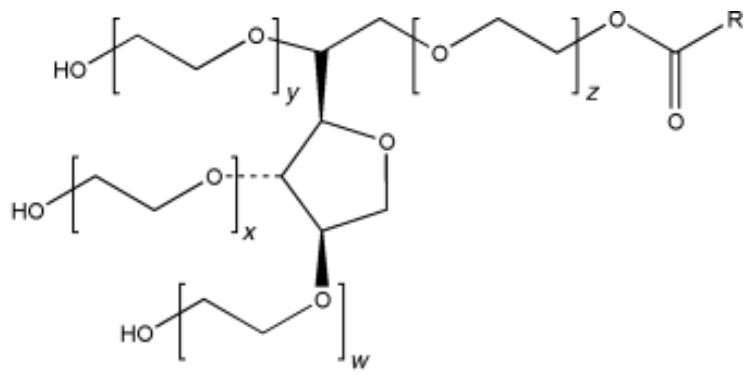




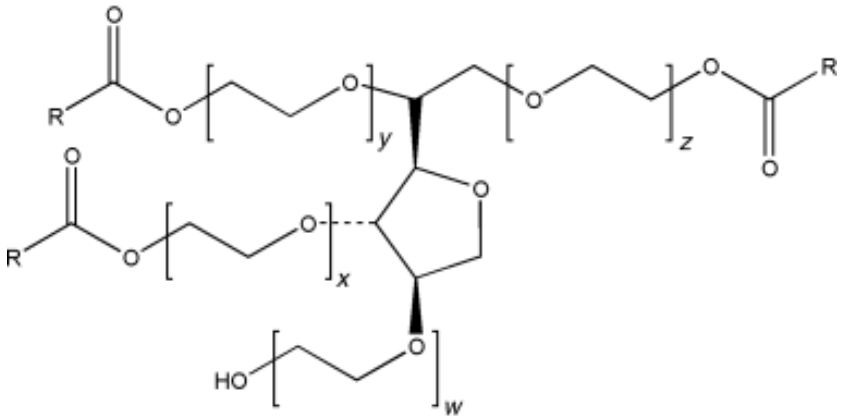
MICELLES



Micelle diameter is about 5 nm



Polyoxyethylene sorbitan monoester



Polyoxyethylene sorbitan triester

R = fatty acid

Examples include the solubilization of fat-soluble vitamins using polysorbates (tweens).

E.g. polysorbates 20, 40, 60, 65, 80, and 85.

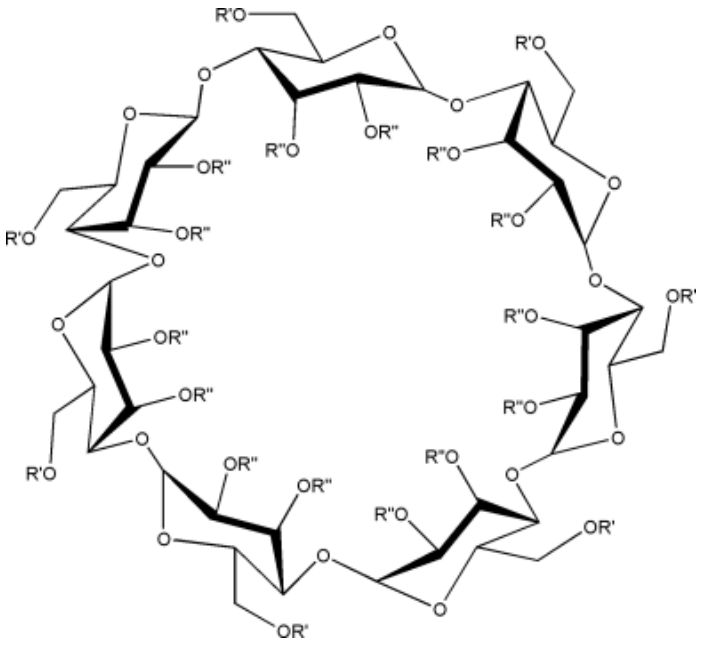
FACTORS AFFECTING THE SOLUBILITY OF SOLIDS IN LIQUIDS

8. Solubilizing agents

8.B. Cyclodextrins

Cyclodextrins are manufactured by the enzymatic degradation of starch using specialized bacteria.

There are three natural cyclodextrins, the α, β (structure to the right) and γ forms, the ring structures of which are composed of 6, 7 and 8 glucose units, respectively, as well as an expanding series of derivatives.

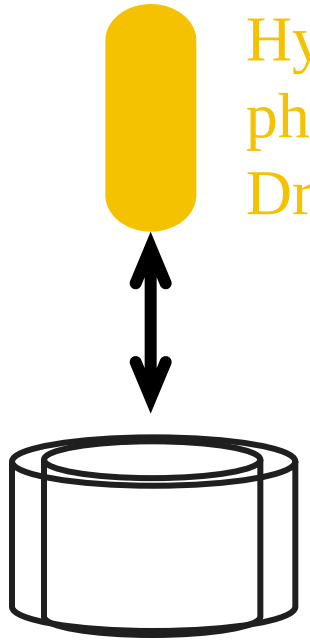


β Cyclodextrin (R'=R"= H)

FACTORS AFFECTING THE SOLUBILITY OF SOLIDS IN LIQUIDS

- Cyclodextrins **form cyclic structures**, **resembling hollow cylinders**. As the **inside surface of the ring is hydrophobic**, owing to the presence of -CH groups, drugs that are poorly soluble in water can be accommodated here. **The outer part of the structure is hydrophilic** and therefore freely soluble in water.

- **Poorly soluble drugs of appropriate size enter into the interior of these structures**, forming soluble complexes, usually with one 'host' molecule per cyclodextrin molecule.



Cyclodextrin