5. Dissolution

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5.1. Definitions

- A solution is defined as a mixture of two or more components that form a single phase which is homogenous down to the molecular level.
- Dissolution is the transfer of molecules or ions from a solid state into solution.
- Dissolution rate is the rate at which a solid dissolves in a solvent (change in mass divided by a change in time).
- So what's the difference between solubility and dissolution?

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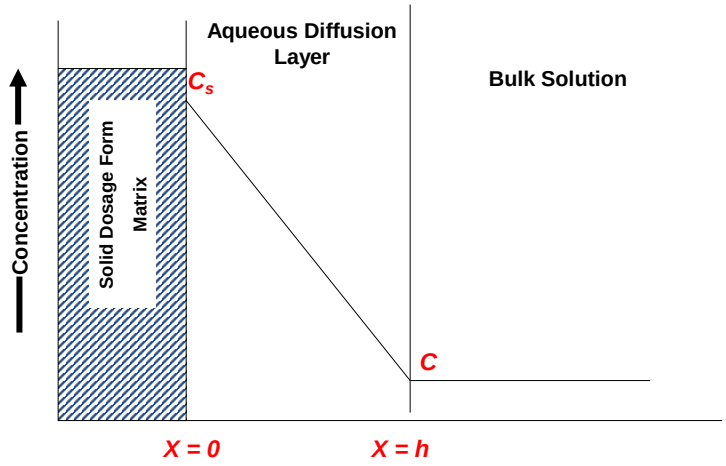
5.2. Dissolution Rate

$$J = \frac{dM}{dt.S} = -D\frac{dC}{dx}$$



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5.2. Dissolution Rate

- Dissolution rate is described in quantitative terms by the Noyes – Whitney equation:

$$J = \frac{dM}{dt.S} = -D\frac{dC}{dx}$$

$$\frac{dM}{dt} = DS\frac{(C_s - C)}{h}$$

- Where
  - ***M*** is the mass of solute dissolved
  - ***dM/dt*** is the rate of dissolution (mass/ time)
  - ***D*** is the diffusion coefficient
  - ***S*** is the surface area of the exposed solid
  - C_s is the solubility of the solid
  - ***C*** is the concentration of the solute in the bulk solution at time ***t***
  - ***h*** is the thickness of the diffusion layer (stagnant liquid film)

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5.2. Dissolution Rate

- An aqueous diffusion layer or stagnant liquid film of thickness h exists at the surface of a solid undergoing dissolution.
- The aqueous diffusion layer represents a layer of solvent in which the solute molecules exist in concentrations ranging from C_s to C. Beyond the static diffusion layer, at X greater than h, mixing occurs in the solution and the drug is found at a uniform concentration, C, throughout the bulk phase.
- The change in concentration (concentration gradient, dc/dx or $(C_s-C)/h$), in the diffusion layer is constant (i.e. steady state conditions).
- The thickness of the diffusion layer can change with mechanical agitation and stirring and this could affect the dissolution rate.

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5.2. Dissolution Rate

- The previous equation is similar to Fick's first law of diffusion.
- The equation can be written in concentration forms as :

$$\frac{dC}{dt} = DS\frac{(C_s - C)}{Vh}$$

Where V is the volume of dissolution medium.

- When $C << C_s$ (sink condition), the equation simplifies to

$$\frac{dC}{dt} = \frac{DSC_s}{Vh}$$

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5.2. Dissolution Rate

$$\frac{dC}{dt} = \frac{DSC_s}{Vh}$$

Factors affecting dissolution rate?

- Solubility (C_s).
- Diffusion coefficient (D).
- Surface area (S) (i.e. particle size).

- Thickness of diffusion layer (h) (i.e. rate of agitation or stirring).

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5.2. Dissolution Rate

- The saturation solubility of a drug is a key factor in the Noyes-Whitney equation.
- The driving force for dissolution is the concentration gradient across the boundary layer. Therefore, the driving force depends on the thickness of the boundary layer and the concentration of the drug already dissolved (C).
- When the concentration of the dissolved drug, C, is less than 20% of the saturation concentration, C_s, the system is said to operate under "sink conditions". The driving force for dissolution is greatest when the system is under sink conditions.

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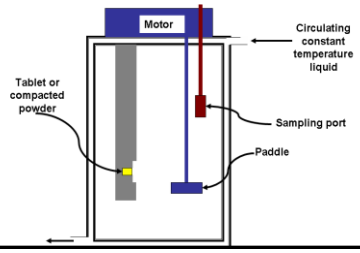
5.2. Dissolution Rate

$$\frac{dC}{dt} = \frac{DSC_s}{Vh}$$

- The Noyes – Whitney equation assumes both h and S are constant. This dissolution rate is known as intrinsic dissolution rate.
- To determine the intrinsic dissolution rate experimentally, both ***h*** and ***S*** are maintained constant.
- ***S*** is maintained constant by placing a compressed pellet in a holder that exposes a surface of constant area.
- ***h*** is maintained constant by using a standard agitation throughout the dissolution rate testing.



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5.2. Dissolution Rate

- The method used for the determination of the intrinsic dissolution rate (constant ***h*** and ***S***) adheres to the requirements of the Noyes-Whitney equation:
  - It provides valuable information on the active drug itself.
  - However, it does not give any on dosage forms which are mixtures containing other material.
  - It does not simulate the actual dissolution of material in practice.

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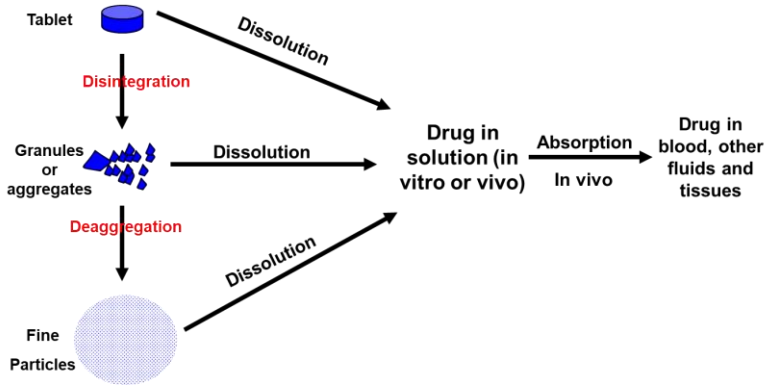
5.2. Dissolution Rate

- In fact, in many cases the static diffusion layer thickness (h) is altered by the force of agitation and the surface area (S) changes as the drug powder, granule or tablet dissolves. Accordingly, the surface area, S, does not remain constant as powder, granule, or tablet dissolves.



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5.3. Dissolution of Solid Dosage Forms

- When a tablet or other solid dosage form is introduced into a beaker of water or into the gastrointestinal tract, the drug begins to pass into solution from the intact solid.
- The solid matrix ***disintegrates*** into granules and these granules ***deaggregate*** in turn into fine particles.
- Dissolution could occur from the intact tablet, granules and fine particles.
- Disintegration, deaggregation and dissolution may occur simultaneously.

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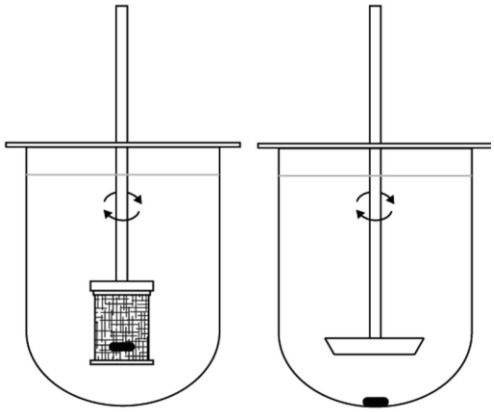
5.3. Dissolution of Solid Dosage Forms

To simulate the drug dissolution from solid dosage forms, paddle and basket dissolution apparatus are used.



USP Method 1: Basket Apparatus

USP Method 2: Paddle Apparatus

Brunaugh A.D., Smyth H.D.C., Williams III R.O. (2019) Preformulation in Drug Product Design. In: Essential Pharmaceutics. AAPS Introductions in the Pharmaceutical Sciences. Springer, Cham. https://doi.org/10.1007/978-3-030-31745-4_2

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USP Dissolution Apparatus 2 (paddle)

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