Physical Pharmacy

Drug Release and Dissolution
Drug Release

Drug release is the process by which a drug leaves a drug product and is subjected to absorption, distribution, metabolism, and excretion, eventually becoming available for pharmacologic action.

Immediate release refers to the instantaneous availability of drug for absorption or pharmacologic action. Immediate-release drug products allow drugs to dissolve with no intention of delaying or prolonging dissolution or absorption of the drug.

Modified release dosage forms include both delayed and extended release drug products.

Delayed release is defined as the release of a drug at a time other than immediately following administration.

Extended-release products are formulated to make the drug available over an extended period after administration.

Finally, controlled release includes extended and pulsatile release products. Pulsatile release involves the release of finite amounts of drug at distinct time intervals that are programmed into the drug product.
Drug Release
The Higuchi (Equation) Model

- Higuchi developed a theoretical model for studying the release of water-soluble and poorly soluble drugs from a variety of matrices, including semisolid and solids.

- A powdered drug is dispersed throughout the matrix of an erodible tablet. The drug is assumed to dissolve in the polymer matrix and to diffuse out from the surface of the device.

- As the drug is released, the distance for diffusion becomes increasingly greater. The boundary that forms between drug and empty matrix therefore recedes into the tablet as drug is eluted.
Drug Release

The Higuchi (Equation) Model

- Recall Fick's first law:  
  \[ \frac{dM}{S dt} = \frac{dQ}{dt} = \frac{DC_s}{h} \]

- It can be applied to the case of a drug embedded in a polymer matrix at \( t=0 \), where \( dQ/dt \) is the rate of drug released per unit area of exposed surface of the matrix.

- Because the boundary between the drug matrix and the drug-depleted matrix recedes with time, the thickness of the empty matrix, \( dh \), through which the drug diffuses also increases with time.

- Whereas \( C_s \) is the solubility or saturation concentration of drug in the matrix, \( A \) is the total concentration (amount per unit volume), dissolved and undissolved, of drug in the matrix.

- As drug passes out of a homogeneous matrix, the boundary of drug (represented by the dashed vertical line) moves to the left by an infinitesimal distance, \( dh \).
Drug Release
The Higuchi (Equation) Model

- The Higuchi equation:
  \[ Q = [D(2A - Cs)Cs t]^{1/2} \]
  Ordinarily, \( A \) is much greater than \( Cs \)
  \[ Q = [D(2ACst)]^{1/2} \]

- The instantaneous rate of release of a drug at time \( t \) is
  \[ \frac{dQ}{dt} = \left( \frac{ADC_s}{2t} \right)^{1/2} \]
Example

(a) What is the amount of drug per unit area, $Q$, released from a tablet matrix at time $t = 120$ min? The total concentration of drug in the homogeneous matrix, $A$, is 0.02 g/cm$^3$. The drug's solubility, $C_s$, is $1.0 \times 10^{-3}$ g/cm$^3$ in the polymer. The diffusion coefficient, $D$, of the drug in the polymer matrix at 25°C is $6.0 \times 10^{-6}$ cm$^2$/sec or $360 \times 10^{-6}$ cm$^2$/min.

$$Q = [D(2AC_s t)]^{1/2}$$

$$[2(0.02 \text{ g/cm}^3)(360 \times 10^{-6} \text{cm}^2/\text{min})x(1 \times 10^{-3} \text{g/cm}^3 \times 120 \text{min})]^{1/2}$$

(b) What is the instantaneous rate of drug release occurring at 120 min?

$$\frac{dQ}{dt} = \left(\frac{ADC_s}{2t}\right)^{1/2} = \left(\frac{(0.02)(360 \times 10^{-6})(1 \times 10^{-3})}{2 \times 120}\right)^{1/2}$$

$$= 5.5 \times 10^{-6} \text{ gcm}^{-2} \text{ min}^{-1}$$
Dissolution refers to the process by which a solid phase (e.g., a tablet or powder) goes into a solution phase such as water.

In essence, when a drug “dissolves,” solid particles separate and mix molecule by molecule with the liquid and appear to become part of that liquid.

If particles remain in the solid phase once they are introduced into a solution, a pharmaceutical suspension results.

Only drugs in solution don’t need to dissolve and can be absorbed, distributed, metabolized, excreted, or even exert pharmacologic action.
Dissolution

- When a tablet or other solid drug form is introduced into a beaker of water or into the gastrointestinal tract, the drug begins to pass into solution from the intact solid.

- Unless the tablet is a contiguous polymeric device, the solid matrix also disintegrates into granules, and these granules deaggregate in turn into fine particles.

- Disintegration, deaggregation, and dissolution may occur simultaneously with the release of a drug from its delivery form.
Dissolution

- The effectiveness of a tablet in releasing its drug for systemic absorption depends somewhat on the rate of disintegration of the dosage forms and deaggregation of the granules.

- Frequently, dissolution is the limiting or rate-controlling step in the absorption of drugs with low solubility because it is often the slowest of the various stages involved in release of the drug from its dosage form and passage into systemic circulation.

- Because dissolution is a kinetic process, the rate of dissolution reflects the amount of drug dissolved over a given time period. In certain cases, an equation can be exactly derived that describes the dissolution time dependence.
In dissolution it is assumed that an *aqueous diffusion layer* or *stagnant liquid film* of thickness $h$ exists at the surface of a solid undergoing dissolution.

This thickness, $h$, represents a stationary layer of solvent in which the solute molecules exist in concentrations from $C_s$ to $C$.

Beyond the 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.
Dissolution Rate

**Noyes and Whitney Equation**

The equation for the rate at which a solid dissolves in a solvent can be written as (Noyes and Whitney relationship):

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

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

where \( M \) is the mass of solute dissolved in time \( t \), \( dM/dt \) is the mass rate of dissolution (mass/time), \( D \) is the diffusion coefficient of the solute in solution, \( S \) is the surface area of the exposed solid, \( h \) is the thickness of the diffusion layer, \( C_s \) is the solubility of the solid (i.e., concentration of a saturated solution of the compound at the surface of the solid and at the temperature of the experiment), and \( C \) is the concentration of solute in the bulk solution and at time \( t \). The quantity \( dC/dt \) is the dissolution rate, and \( V \) is the volume of solution.
At the solid surface-diffusion layer interface, $x = 0$, the drug in the solid is in equilibrium with drug in the diffusion layer.

The gradient, or change in concentration with distance across the diffusion layer, is constant, as shown by the straight downward-sloping line (as represented by Noyes and Whitney equations).

Therefore, when $C$ is considerably less than the drug's solubility, $C_s$, the system is represented by sink conditions, and concentration $C$ can be eliminated from equations and thus

$$\frac{dM}{dt} = \frac{DSC_s}{h}$$
**Calculate Dissolution Rate Constant**

A preparation of drug granules weighing 0.55 g and having a total surface area of 0.28 m$^2$ (0.28 $\times$ 10$^4$ cm$^2$) is allowed to dissolve in 500 mL of water at 25°C. After the first minute, 0.76 g has passed into solution. The quantity $D/h$ can be referred to as a dissolution rate constant, $k$.

If the solubility, $C_s$, of the drug is 15 mg/mL at 25 °C, what is $k$?

\[
\frac{dM}{dt} = \frac{760mg}{60\text{ sec}} = 12.67\text{ mg/sec}
\]

\[
\frac{dM}{dt} = \frac{DSC_s}{h}
\]

$12.67\text{ mg/sec} = k \times 0.28 \times 10^4 \text{ cm}^2 \times 15 \text{ mg/cm}^3$

$K=3.02\times10^{-4}$ cm/sec
After a solid dosage form such as a tablet is administered by mouth to a patient, it must first disintegrate into larger clusters of particles known as aggregates.

Deaggregation then occurs and individual particles are liberated.

Finally, particles dissolve, releasing the active drug into solution.

Dissolution is a time-dependent (or kinetic) process that represents the final step of drug release, which is ultimately required before a drug can be absorbed or exert a pharmacologic effect.
Dissolution tests are used for many purposes in the pharmaceutical industry: in the development of new products, for quality control, and to assist with the determination of bioequivalence.

Recent regulatory developments have highlighted the importance of dissolution in the regulation of post-approval changes and introduced the possibility of substituting dissolution tests for clinical studies in some cases.

Therefore, there is a need to develop dissolution tests that better predict the in vivo performance of drug products. This could be achieved if the conditions of the gastrointestinal tract were successfully reconstructed in vivo.

Numerous factors need to be considered if dissolution tests are to be considered biorelevant. They are the composition, hydrodynamics (fluid flow patterns), and volume of the contents in the gastrointestinal tract.
Methods and Apparatus

The objective of most pharmacopeial dissolution monographs is to establish procedures for evaluating batch-to-batch consistency in the dissolution of drug products.

- USP Dissolution methods are known as the USP basket (method I) and paddle (method II) methods and are referred to as “closed-system” methods because a fixed volume of dissolution medium is used.

- In practice, a rotating basket or paddle provides a steady stirring motion in a large vessel with 500 to 1000 mL of fluid that is immersed in a temperature-controlled water bath.

- The use of alternative dissolution methods should be considered only after USP methods I and II are found to be unsatisfactory.

- Biorelevant dissolution media were discussed in the previous section. Other commonly used media include (a) water, (b) 0.1 N HCl, (c) buffer solutions, (d) water or buffers with surfactants, and (e) low-content alcoholic aqueous solutions.

- The temperature of the medium is usually maintained at body temperature (37°C) for dissolution testing.
Dissolution (711) —

Medium: pH 5.8 phosphate buffer (see Buffer Solutions in the section Reagents, Indicators, and Solutions); 900 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Procedure — Determine the amount of $C_8H_9NO_2$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 243 nm on filtered portions of the solution under test, suitably diluted with Dissolution Medium, if necessary, in comparison with a Standard solution having a known concentration of USP Acetaminophen RS in the same Medium.

Tolerances — Not less than 80% (Q) of the labeled amount of $C_8H_9NO_2$ is dissolved in 30 minutes.