PREFORMULATION

5th week

HYGROSCOPICITY

* If a solid drug absorbs water from air, it is termed "hygroscopic", and conversely, if it loses water, it is termed "efflorescent". A substance which absorbs sufficient moisture from the atmosphere to dissolve itself is "deliquescent".

** Both situations represent a type of physicochemical instability since variation in water content inevitably leads to variations in potency (i.e. the percentage of drug present for any given weight), which if uncontrolled makes drug handling difficult.

HYGROSCOPICITY

*** In addition, variations in water content can lead to further physical and chemical instability.

Variations in moisture level of an hygroscopic substance effect some properties such as chemical stability, flow property and compressibility.

HYGROSCOPICITY

* Since this is a dynamic phenomenon, it will be influenced by the relative humidity of the ambient air.

* If a drug is not affected by variations in relative humidity, it is termed "nonhygroscopic", which is the optimal property for new drugs.

* There is an interesting paradox to this since nonhygroscopicity imparts stability, while hygroscopicity (or hydrophilic) properties are required for dissolution and solubility.

HYGROSCOPICITY

* To assess hygroscopicity, the drug is placed in open containers with a thin powder bed to assure maximum atmospheric exposure and is exposed to a range of controlled relative humidity environments, with or without temperature variation, permitting both sorption and desorption of water to be measured.

* The choice of the analytical method (i.e. gravimetry, TGA, Karl Fischer titration, gas chromatography) for monitoring the moisture level of drug depends on the desired precision level and the amount of moisture adsorbed onto the drug sample.

HYGROSCOPICITY

The amount of adsorbed moisture depends on the atmospheric humidity, temperature, surface area and moisture adsorption mechanism.

HYGROSCOPICITY

* It is difficult to change this particular property since it is a function of the drug, salt and crystal form.

* The results of the studies should provide information on the optimal storage and handling conditions for the drug and indicate the type of packaging required, glass or plastic.

PARTICLE SIZE AND SHAPE

* A basic physical feature of a solid is that for any given weight of material as the diameter of the particles; when the particle size decreases, the surface area increases.

- Since a solid's interaction with its external environment occurs at surfaces, particle size is an important characteristic controlling a variety of properties, for example, dissolution and adhesion.

PARTICLE SIZE AND SHAPE

- The sedimentation rate of a suspension depends on the particle size of the dispersed phase.

- Particle size also has a significant effect on the flow properties of powders which is an important issue for manufacturing process technologies of capsules and tablets.

PARTICLE SIZE AND SHAPE

If the compound is for pulmonary delivery via inhalation, since only a particular size fraction (generally <10 μm diameter) will reach the lungs, particle size is therefore an important parameter.

PARTICLE SIZE AND SHAPE

- If powders consisted of spherical particles, a simple statement of radius would describe the particles.

- However, pharmaceutical powders generally consist of particles with varying nonspherical shapes and sizes. Any size measurement technique has to account for this situation.

PARTICLE SIZE AND SHAPE

This is an interesting mathematical and statistical problem which leads to the utilization of a variety of descriptors based on geometrical relationships, for example, using surface area or volume of the particle under measurement and a nominally equivalent ideal sphere.

Measurement of Particle Size

‼ A key feature of any particle size measurement is the method adopted to present the particle in a stable non-agglomerated (i.e. as individual particles) format for measurement.

‼ If this is not attained, measurement by any method is suspect.

Measurement of Particle Size

- Sieve analysis
- Optical microscopy
- Sedimentation method
- Coulter counter
- Laser diffraction
- Dynamic light scattering
- Gas permeability
- BET adsorption
- Image analysis

Measurement of Particle Size

Optical Microscopy:

- This is the simplest technique and will visually provide an indication of crystallinity, shape and other features such as surface smoothness.

- The classical optical determination of size relies on a comparison of the particles, under microscopic examination, with discs (usually a graticule within the eyepiece) of a known size and the counting or comparison of a statistically significant number ($n>625$).

Measurement of Particle Size

Optical Microscopy:

- This is a tedious process and if the particles deviate from disc-like shapes, it also becomes difficult.

- The traditional manual method has been replaced by the advent of computer-based image analysis systems which remove human based size comparison errors, greatly speed up the analysis and permit rapid statistical data processing.

Measurement of Particle Size

Coulter Counter:

- Samples are prepared for analysis by the Coulter counter by dispersing the material in a conducting medium such as isotonic saline with the aid of ultrasound and a few drops of surfactant.

- A known volume (0.5 to 2 ml) of this suspension is then drawn into a tube through a small aperture (0.4 to 800 microns in diameter), across which a voltage is applied.

Measurement of Particle Size

Coulter Counter:

- As each particle passes through the hole, it is counted and sized according to the resistance generated by displacing that particle's volume of conducting medium.

- Given that the instrument has been calibrated with standard spheres, the counter provides a histogram output (frequency versus size) within the limits of that particular aperture tube.

Measurement of Particle Size

Coulter Counter:

* Although the Coulter method is quick and statistically meaningful, it assumes that each resistance arises from a spherical particle, thus nonspheres are sized inaccurately.

* Other limitations with the Coulter counter are;

- the tendency of needle shaped crystals to block the aperture hole,
- the dissolution of compound in the aqueous conducting medium,
- stratification of particles within the suspension.

Measurement of Particle Size

Laser Light Scattering:

- If a particle is suspended (in a liquid or gas) in a laser beam, it scatters the light, an effect dependent on the difference between the laser's wavelength and the size of the particle.

- If the particle is larger (generally 0.5 – 1000 μm diameter) than the wavelength, the light is forward scattered with only a small change in angle to produce a Fraunhofer diffraction pattern.

Measurement of Particle Size

Laser Light Scattering:

- If the particle is smaller (0.001-5 μm diameter) than the wavelength, it will, due to its size, undergo Brownian motion. The scattered light fluctuates at a rate dependent on the particle size since smaller particles move faster. This is termed *"dynamic light scattering"* and detection and quantification of the light fluctuation pattern yields the particle's velocity of movement or diffusion coefficient.

- In both cases computer based mathematical processing of the detected signal can then extract the particle size distributions.

Measurement of Particle Size

- Additional methods of particle size analysis are image analysis and sieve analysis.

- Sieve methods are used primarily for large samples of relatively large particles (~100 microns).

Measurement of Surface Area

* Kinetic processes involving drug in the solid state, such as dissolution and degradation, are directly related to available surface area.

** If drug particles have a shape that can be defined mathematically, then light microscopy size analysis or Coulter coulter analysis with appropriate geometric equations may provide a reasonable estimation of surface area.

Measurement of Surface Area

- A more precise measurement of surface area is made by Brunauer, Emmett and Teller (BET) nitrogen adsorption, in which a layer of nitrogen molecules is adsorbed to the sample surface at -196 °C.

- Once surface adsorption has reached equlibrium, the sample is heated to room temperature, the nitrogen gas is desorbed and its volume is measured and converted to the number of adsorbed molecules via the ideal gas law.

Measurement of Surface Area

While BET measurements are usually precise and quickly obtained with current commercial equipment, errors may arise from the use of impure gases and volatile surface impurities (e.g. hydrates).

Observation of Surface Morphology

- Surface morphology may be observed by scanning electron microscopy (SEM), which serves to confirm qualitatively a physical observation related to surface area.

- For example, bulk lots of drug recovered by different crystallization processes that have been used in an attempt to improve yield may result in surface morphologies that provide greater area for surface reactions such as degradation, dissolution or hygroscopicity.

Observation of Surface Morphology

During preparation for SEM analysis, the sample is exposed to high vacuum during the gold coating process, which is needed to make the samples conductive, and concomitant removal of water or other solvents may result in a false picture of the surface morphology.

DENSITY

1- Bulk density

2- Apparent bulk density

3- Tapped density

4- True density

BULK DENSITY

- The density of a powder sample generally expressed as bulk density.

- Bulk density is calculated by pouring the drug into a graduated cylinder via a large funnel and measuring the volume (v) and weight (m) (g/ml).

BULK DENSITY

- Bulk density of a compound varies substantially with the method of crytallization, milling or formulation.

- Usually bulk density is of great importance when one considers the size of a high dose capsule product or the homogeneity of a low dose formulation in which there are large differences in drug and excipient densities.

- Once a density problem is identifed, it is often easily corrected by milling, slugging or formulation.

APPARENT BULK DENSITY

It is determined by pouring presieved (40 mesh) bulk drug into a graduated cylinder via a large funnel and measuring the volume and weight (g/ml).

TAPPED DENSITY

- It is determined by placing a graduated cylinder containing a known mass of drug or formulation on a mechanical tapper apparatus, which is operated for a fixed number of taps (~1000) until the powder bed volume has reached a minimum.

- Using the weight of drug in the cylinder and this minimum volume, the tapped density can be calculated.

TRUE DENSITY

- True density is calculated after exiting the pores and channels between the particles of powders.

- It is frequently desirable to know the true density of a powder for computation of void volume or porosity of packed powder beds.

- Experimentally, the true density is determined by suspending drug particles in solvents of various densities and in which the compound is insoluble.

- Wetting and pore penetration may be enhanced by the addition of a small quantity of surfactant to the solvent mixtures.

TRUE DENSITY

- After vigorous agitation, the samples are centrifuged briefly and then left to stand undisturbed until floatation or settling has reach equilibrium.

- The sample that remains suspended corresponds to the true density of the material.

POWDER FLOW PROPERTIES

-Pharmaceutical powders may be broadly classified as free-flowing or cohesive (non-free-flowing).

- Most flow properties are significantly affected by changes in particle size, density, shape, electrostatic charge and adsorbed moisture which may arise from processing or formulation.
- As a result, a free-flowing drug candidate may become cohesive during development, thus necessitating an entirely new formulation strategy.

POWDER FLOW PROPERTIES

- Preformulation powder flow investigations should quantitatively assess the pharmaceutical consequences of each process improvement and provide direction for the formulation development project team.

- This direction may consist of a formulation recommendation such as granulation or densification via slugging.

POWDER FLOW PROPERTIES

- Flow properties can be characterized by a simple flow rate apparatus consisting of a grounded metal tube from which drug flows through an orifice onto an electronic balance, which is connected to a strip chart recorder.

- Another measurement for the flowability of the powder is Carr's Compressibility Index.

Carr's Index (%) = (Tapped density – Bulk density / Tapped density) x 100

Carr's Index (%)	Type of Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable*
23-35	Poor*
33-38	Very poor
>40	Extremely poor

*Flowability may be improved by glidants e.g. 0.2% Aerosil

- A similar index has been defined by Hausner;

Hausner index (ratio) = Tapped density / Bulk density

* If the Hausner ratio is less than 1.25, it indicates good flow.

* If the Hausner ratio is greater than 1.5, it indicates poor flow.

* If the Hausner ratio is between 1.25 and 1.5, addition of a glidant normally improves the flow property.

- The another technique is to determine the angle of repose.

- When only gravity acts upon it, a static heap of powder will tend to form a conical mound.
- In this method, the powder is allowed to flow / fall under gravity from a nozzle onto a flat surface and the angle of inclination of the resultant powder cone is measured.

- The lower the angle, the better the flow properties, with angles less than 30^{o} constituting good flow.

Angle of Repose (Degree)	Type of Flow
<20	Excellent
20-30	Good
30-34	Passable*
>40	Very poor

*Flowability may be improved by glidants e.g. 0.2% Aerosil

COMPRESSION PROPERTIES OF POWDERS

- The compression properties of powders is especially important for tablet production.

- Information on the compression properties (elasticity, plasticity or fragmentation) of the pure drug is extremely useful.

- The compression properties of most drug powders are generally poor and necessitate the addition of compression aids.

While it is true that the tabletted material should be capable of plastic (permanent) deformation, it should also exhibit a degree of brittleness (fragmentation).

- When the dose is less than 50 mg, tablets can usually be prepared by direct compression with the addition of modern direct compression bases.

- At higher doses the preferred method would be wet massing.