PREFORMULATION

4th week

PHARMACEUTICS;

In the simplest terms; "pharmaceutics converts a drug into a medicine".

!!! Drug is the pharmacologically active ingredient in a medicine.

Drug = Medicinal agent = Active substance

Drug = Active pharmaceutical ingredient (API)

* Drugs are rarely administered as pure chemical substances alone and are almost always given as "formulated preparations" or "dosage forms" or "medicines".

** Dosage forms can vary from relatively simple solutions to complex drug delivery systems through the use of appropriate additives or excipients along with active substances in the formulations.

*** The excipients provide varied and specialized pharmaceutical functions.

The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation which is capable of large scale manufacture with reproducible product quality.

Numerous features are required to ensure the product quality;

- Chemical and physical stability with suitable preservation against microbial contamination
- Uniformity of dose of drug
- Acceptability to users, including both prescriber and patient
- Suitable packaging and labelling

* There are numerous dosage forms into which a drug substance can be incorporated for the convenient and efficient treatment of a disease.

** Dosage forms can be designed for administration by alternative delivery routes to maximize therapeutic response. They can be taken orally or injected, as well as being applied to the skin or inhaled.

*** It is necessary to relate the drug to the clinical indication being treated before the correct combination of drug and dosage form can be made since each disease often requires a specific type of drug therapy.

PREFORMULATION

* Prior to the development of dosage forms, it is essential that certain fundamental physical and chemical properties of potential drug molecules and other derived properties of the drug powder are determined.

** This first learning phase of a drug molecule is known as "*preformulation*".

* It is difficult to completely define what constitutes preformulation or where it starts and ends within a drug discovery / development program.

** The aim of preformulation is to provide key pharmaceutical information during development permitting progress decisions and ultimately leading into formulation studies for the final marketed product.

* Preformulation defines the steps to be undertaken before formulation.

** Preformulation is generally performed on potential active molecules or new drug candidates.

*** In the case of the formulation of generic products of existing drugs, sufficient information is usually known prior to formulation.

* The information required on preformulation will be designated to a certain extent by the final product, the proposed route of administration and the development plan of the company.

** For example, aqueous solubility and stability will be important for an intravenous (iv) injection, while properties such as powder flow and compressibility are critical for a tablet.

Preformulation;

- Gives pointers to the feasibility of the various dosage forms and to any potential problems of instability, poor in vivo dissolution and thus bioavailability.

- Should also give some guidance to the suitability of potential excipients to be used in formulation.

* It is important to gain as much information as possible from the materials which are in small amounts. In this context, preformulation study is often prioritized to yield the key information early in these studies.

** Two fundamental properties are mandatory for a new compound and should be determined first. These properties are; intrinsic solubility (C_o) and dissociation constant (pK_a).

*** This is the concept of "minimum preformulation".

Recommended list of information required in preformulation can be summarized as;

- UV Spectroscopy
- Solubility
- Melting point
- Assay development
- Stability (in solution and in solid state)
- Microscopy
- Powder flow, bulk density, angle of repose
- Compression properties
- Compatibility of excipients

UV SPECTROSCOPY

The first step in preformulation is to establish a simple quantitative analytical method.

Most drugs absorb UV light (190-390 nm) since they are generally aromatic or contain double bonds. In other words, UV absorption can be anticipated for the aliphatic or aromatic molecule which contains a double bond.

UV SPECTROSCOPY

Using the UV spectrum of the drug, it is possible to choose an analytical wavelength (often the wavelength of maximum absorption; λ_{max}) which is suitable to quantify the amount of drug in a particular solution.

Excitation of the molecule in solution causes a loss in the light energy and the net change from the intensities of the incident light and the transmitted light can be measured.

UV SPECTROSCOPY

The amount of light absorbed by a solution of drug is proportional to the concentration (C) and the path length of the solution (l) through which the light has passed.

UV SPECTROSCOPY

Lambert-Beer Law

$A = \log(I_o/I) = e.C.l$

A	=	Absorbance
I_o	=	Intensity of incident light
I	=	Intensity of transmitted light
C	=	Concentration
l	=	Path length of the solution
e	=	Molar extinction coefficient

UV SPECTROSCOPY

UV analysis is a very simple and convenient quantitative technique that is suitable at this early stage of preformulation but it suffers from being non-indicating of the molecule absorbing the UV light.

It must be replaced later in the process with an assay such as HPLC that will give a precise indication of the molecule and its degradation products.

CRYSTAL FORM AND POLYMORPHISM

Crystallization is a classical technique for compound purification from solution and generally the final step in the synthesis process of the drug.

Crystallization conditions are crucial to the pharmaceutical properties of a drug since they control the crystal form, habit and size.

CRYSTAL FORM AND POLYMORPHISM

- The materials which have atoms, ions or molecules aligned with a certain order are called as *crystal*.

- The basic structure of a crystal is the *unit cell*, which contains a fixed number of drug molecules and/or ions, which is then replicated in three dimensional to produce the crystal.

- Most pharmaceutical compounds can crystallize in one or more crystalline forms or *polymorphs*, which have the same chemical composition but different molecular arrangements, conformations or packing in the unit cell.

CRYSTAL FORM AND POLYMORPHISM

** Polymorphs have the same chemical structure but different internal crystal lattice.

** A polymorph is a solid material with at least two different molecular arrangements giving distinct crystal species.

Since polymorphism is a structural rather than chemical difference, it influences the drug's pharmaceutical properties and is optimally detected and examined by physicochemical testing.

The polymorphs of a compound have different properties in terms of;

- Melting point,
- Solubility,
- Density,
- Optical and electrical properties,
- Vapor pressure
- Solid state stability.

CRYSTAL FORM AND POLYMORPHISM

Pseudopolymorphs or solvates are also possible where the molecule cocrystallizes with solvent molecules (***hydrates*** if the solvent is water).

- In these instances chemical composition may vary.

- If the crystal is capable of losing the solvent to the atmosphere, a desolvated form may arise where the crystal has simply lost the solvent molecules.

Pharmaceutical Effects of Polymorphism

1- Dissolution and solubility

* If a solid (solute) is to dissolve in a liquid (solvent), the attractive forces holding the solute together must be overcome by the attractive forces between the molecules of the solid and solvent.

* It follows therefore that if the arrangement of drug molecules in the solid varies (i.e. polymorphism), the attractive forces holding the solid together will also vary and consequently dissolution and solubility will vary.

Pharmaceutical Effects of Polymorphism

2- Processing properties

- Polymorphism can affect the mechanical properties of crystal and therefore affect processing behavior such as mixing and compressibility during tableting.

- A simple rationale is that the more stable the polymorph, the more energy will be required to deform the crystal (during compression) and produce new surfaces that can form interparticle bonds that maintain the tablet.

Pharmaceutical Effects of Polymorphism

3- Stability

- Polymorphism can influence stability either by a direct effect on chemical reactivity and therefore the drug's basic chemical stability or via instability of the polymorphic form itself.

- Stability issues may also arise from polymorphic changes occuring during processing of the API, for example wet granulation or drying stages, into the final product.

Pharmaceutical Effects of Polymorphism

3- Stability

Generally, the more stable the polymorph, the greater the chemical stability, attributable to higher crystal packing or density and maintenance of the molecule in an optimized stable orientation.

CRYSTAL FORM AND POLYMORPHISM

Amorphous solids can be defined as materials that are not crystalline in nature and therefore have no defined long-range molecular structure.

There is a short-range molecular array between adjacent molecules. In other words, unlike the crystalline form, the molecules are arranged randomly.

- Because of this, they are generally "energetic" solids with higher dissolution rates and solubilities along with better compression properties than their crystalline counterparts.

- However, they tend to be less stable both chemically and physically.

CRYSTAL FORM AND POLYMORPHISM

* The amorphous state is common with large flexible molecules such as proteins and polymers; a protein can be an API and polymers can be employed as excipients.

** Various standard pharmaceutical processes such as lyophilization, spray drying and dehydration of hydrates can produce amorphous forms of normally crystalline materials.

EXAMINATION OF SOLID STATE PROPERTIES

The examination of these properties relies on physical testing methods;

- Melting point
- Vibrational spectroscopy
- Differential scanning calorimetry
- X-Ray scattering techniques
- Scanning probe microscopy (Atomic force microscopy)

Melting Point:

* A basic property of solids is the temperature at which the solid melts to become a liquid.

* During this process thermal energy is initially required to heat the solid to the melting point, at which temperature the thermal energy overcomes the forces holding the crystals together and induces a phase change from a solid to a liquid.

* During melting the material must still absorb heat (the heat of fusion) to fully overcome the forces in the crystal.

Melting Point:

- For crystals, melting point is defined, and although this implies precision, the melting process normally occurs over a range of a few degrees.

- For amorphous materials, there is no sudden phase change at any specific temperature, rather a gradual change in properties.

Melting Point:

* The determination of melting point by visually (either microscopically or by the naked eye) examining the material while it is being heated is a classical method.

* However, this technique will not generally permit the discrimination between polymorphic forms.

Melting Point:

The melting point of a drug can be measured using these techniques;

- Capillary melting
- Hot stage microscopy
- Differential scanning calorimetry (DSC) and differential thermal analysis (DTA)

Capillary melting:

- Capillary melting is a technique based on the observation of melting in a capillary tube in a heated metal block.

- This technique gives information about the melting range but it is difficult to assign an accurate melting point using this technique.

Hot stage microscopy;

- This is the visual observation of melting under a microscope equipped with a heated and lagged sample stage.

- The heating rate is controllable and other transitions can be observed and recorded.

- It is more precise since the phase transitions (first melt, 50% melt and completion) can be registered on a recorder as the melting proceeds and due to the high magnification the values are more accurate.

Differential scanning calorimetry (DSC) and differential thermal analysis (DTA);

- Neither of the previos methods is as versatile as either DTA or DSC.

- The other advantage of these methods is that the sample size required is only 2-5 mg.

* DTA measures the temperature difference between the sample and a reference as a function of temperature or time when heating at a constant rate.

* DSC is similar to DTA, except that the instrument measures the amount of energy required to keep the sample at the same temperature as the reference, i.e. it measures the enthalpy of transition.

Differential scanning calorimetry (DSC) and differential thermal analysis (DTA);

- When no physical or chemical change occurs within the sample then there is neither a temperature change nor input energy to maintain an isotherm.

- However, when phase changes occur then latent heat supresses a temperature change and the isothermal energy required registers as an electrical signal generated by thermocouples.

- Crystalline transitions, fusion, evaporation and sublimation are changes in state which can be quantified.

Vibrational Spectroscopy:

- Infrared (IR) spectroscopy
- Raman spectroscopy

Infrared (IR) spectroscopy;

* IR spectroscopy is applied by chemists as a structure determination technique for a molecule.

* IR absorption results in changes in a molecule's vibrational and rotational energy levels, which permits examination of the molecular bonds.

* If these are constrained because of differences in crystal structure and hence orientation, then the effects on the vibrational and rotational energy levels can be determined.

Infrared (IR) spectroscopy;

* The common method of analyzing a sample is to use *Fourier transform IR coupled with a reflectance technique* so that the solid sample is not subjected to any processing that may alter polymorphic properties.

* Since this is a light-based technique, it can also be applied through a microscope.

Raman spectroscopy;

* If a monochromatic source of light impinges on a sample, it interacts with the molecules to produce excited vibrational energy states, and the scattered light can be modified by this effect.

* If the interaction is such that the molecule returns to its original energy state, then Rayleigh scattering occurs and the scattered light has the same wavelength as the incident light.

Raman spectroscopy;

* However if the molecule does not return to its original energy state but a higher one, then the wavelength of the scattered light will also change producing Raman scattering.

* Only a very small percentage of the incident light is Raman scattered and since a small amount of energy has been absorbed by the sample, the scattered wavelength is at a lower wave number.

Differential Scanning Calorimetry (DSC):

* DSC is a thermoanalytical technique that measures the difference in the amount of heat required to increase the temperature of a sample and reference as a function of a change in temperature, generally linearly increasing.

* Both the reference and the sample are maintained at the same temperature over the desired temperature range and the reference must have a characterized heat capacity in the range.

Differential Scanning Calorimetry (DSC):

* If the sample undergoes a physical change or a chemical change, for example, melting or degradation, then more (if the transition is endothermic) or less (if the transition is exothermic) heat will be required to maintain the sample temperature in comparison to the reference.

* By measuring heat flow against temperature, it is possible to calculate the enthalpy of the phase transition and the temperature at which it occurs.

Differential Scanning Calorimetry (DSC):

* This provides a very sensitive method of examining the physical properties of solid samples, which can be further improved by modulating the heat flow to discriminate between reversible and irreversible thermal effects.

* DSC is therefore a powerful research and analytical tool that is employed to characterize pharmaceutical solids and determine the polymorphic behavior.

Differential Scanning Calorimetry (DSC):

DSC is one of a family of thermally based techniques such as;

- Differential thermal analysis; heat flow, rather than temperature, is maintained at a constant rate
- Thermogravimetric analysis; sample weight is measured as a function of temperature

that can be employed to study the solid pharmaceutical materials.

X-Ray Scattering Techniques:

* X rays are part of the electromagnetic radiation spectrum with wavelengths around 10^{-10} m or 1 Angstrom (Å).

* X ray scattering techniques are a family of analytical methods that provide information about the structure of solid and chemical composition.

X-Ray Scattering Techniques:

* The diffraction pattern obtained is a means of measuring distances between atoms or planes in the crystal.

* This means that the diffraction pattern obtained for every crystalline form of a compound is unique and can be employed to identify the compound and polymorphic forms and calculate the dimensions on the unit cell.

Scanning Probe Microscopy (Atomic Force Microscopy – AFM):

A recent microscopic technique is AFM which scans a sample's surface at an atomic level.