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Consideration of Pre-Formulation Parameters to Develop Solid Dosage Form

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Abstract: ***As the name indicates, Pre means before and Formulation means Processing. When any dosage form is to be designed, researchers are not aware about properties of drug substance and this is a crucial step to evaluate the drug substance for better dosage form design. Pre-formulation studies are to be conducted before designing dosage form. Pre-formulation studies include bulk characteristics, solubility characteristics and stability characteristics of drug substance. With the help of these studies a researcher would come to know about the physical and chemical properties of drug substance. A better dosage form can be designed by considering the evaluation outcomes of conducted pre-formulation parameters. This will furnish the pharmacokinetic and pharmacodynamic effects of designed dosage form and dosage form can show its desired therapeutic effect for patients. This whole protocol is known as Pre-formulation. Parameters which are evaluated for processing of dosage forms are called Pre-formulation parameters.***

Keywords: Conventional dosage form, Non-conventional dosage form, Bulk characteristics, Angle of repose, Crystalline

1. Preformulation

As the name indicates, Pre means before and Formulation means Processing. When any dosage form is to be designed, researchers are not aware about properties of drug substance and this is a crucial step to evaluate the drug substance for better dosage form design. Pre-formulation studies are to be conducted before designing dosage form. Pre-formulation studies include bulk characteristics, solubility characteristics and stability characteristics of drug substance. With the help of these studies a researcher would come to know about the physical and chemical properties of drug substance. A better dosage form can be designed by considering the evaluation outcomes of conducted pre-formulation parameters. This will furnish the pharmacokinetic and pharmacodynamic effects of designed dosage form and dosage form can show its desired therapeutic effect for patients. .This whole protocol is known as Preformulation. Parameters which are evaluated for processing of dosage forms are called Preformulation parameters.

Goals of Preformulation

- To choose correct form of drug substance.
- To evaluate its physical and chemical properties of drug substance.
- To study preformulation parameters very accurately and precisely so that drug product would be pharmacological efficient.
- To generate well understanding of drug substance stability under the conditions that will lead to development of desired drug delivery system.

Note:
If we want to design non-conventional drug delivery system, we have to study Preformulation accordingly:

- Conventional/Old Drug Delivery System
- Non-Conventional/New Drug Delivery System

Objectives of Preformulation

- To design an ideal drug delivery system. (*Here ideal terms refers to Stable, non-toxic, Therapeutically active and Pharmacologically active drug)
- Physicochemical characterization of drug substance in solid form as well as in solution form. Where in solid form, Flow properties can be evaluate and in solution form, Solubility can be measured.
- To find out the compatibility between drug and excipients of formulation.
- To find out the stability of drug substance.
- To provide adequate information about physicochemical properties of drug.

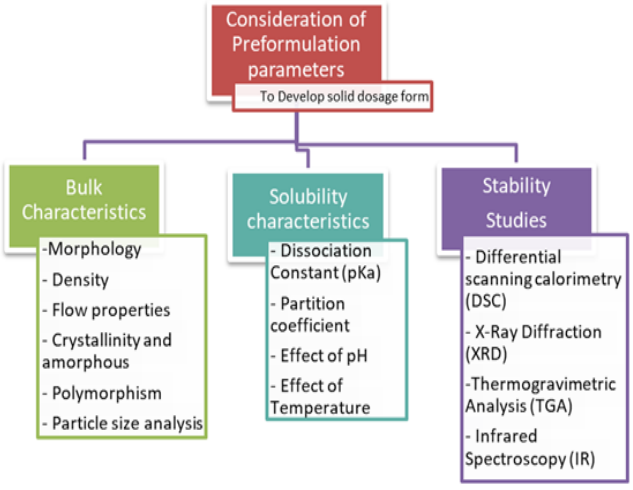


Figure 1

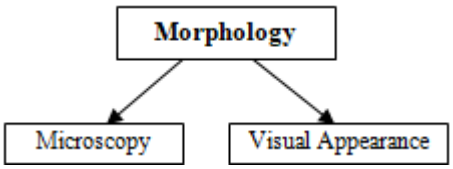
Bulk Characteristics:

Parameters which are to be evaluated for the physical properties of drug substances.

1) Morphology

Morphology is a term which indicates the physical appearance of drug substance which includes various

parameters like Shape of drug, size of drug, etc. It can be done by two techniques which are mentioned below:



Microscopy:

- Morphological characteristics of drug substance can be observed with light/compound microscope. This will provide the data for shape of drug substance particles. Exact symmetry can be identified with the help of electron microscopy. Scanning electron microscopy (SEM) can be used for particular symmetry of particles i.e. spherical, oblong, circular, cylindrical etc.

Visual Appearance:

- Through this parameter grittiness, color etc. of drug substance particles can be evaluated.

2) Density

Density is calculated to improve the flow properties of drug substance.

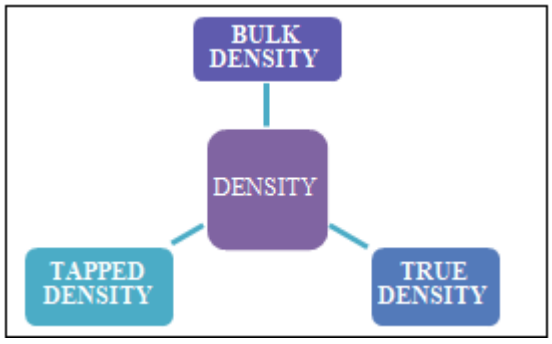


Figure 2

Bulk density

It is a ratio of the mass of untapped powder to tapped powder. It is expressed in gram per milliliter (g/ml). It may also be expressed in grams per cubic centimeter (g/cm^3). It can be determined by the volume of sieved powder sample into a graduated cylinder.

Tapped density

It is increased bulk density acquired after mechanically tapping a cylinder containing the powder sample. Practically, it is done by using bulk density apparatus in which graduated cylinder containing powder sample is tapped mechanically after noting the initial mass or volume. Then after 100 taps, volume or mass is noted down and then after 50 taps, volume or mass is observed until volume gets constant. The mechanical tapping is established by raising the graduated cylinder and let it drop by its own mass.

True density:

True density is measured by Helium pycnometer. As helium gas is passed in it to check the presence of any voids. Helium gas is not absorbed by powder surface because it is a noble gas. So, we get the actual weight of powder with any helium gas absorption.

3) Flow Properties

Flow properties are important to check how efficiently powder flows during formulation. Flow properties are greatly affected by density, particle size, particle shape, moisture. Flow properties of powder can be finding out by the parameters like Angle of repose, Hausner's ratio and Carr's index.

Angle of repose

It is a parameter used to evaluate interparticle force. Practically, it is measured by using funnel with wide mouth open is placed at distance of minimum 10cm above the platform and a piece of paper is placed under the funnel. Then pour the powder sample in funnel and let it flow through and gets collected on the paper. And outline the boundary where powder sample is present and measured the height of peak and diameter obtained with ruler. Then by applying following formula, angle of repose (Θ) can be estimated.

$$\theta = \tan^{-1}\frac{h}{r}$$

When angle of repose is less than 25 degree, then flow is said to be excellent and if angle of repose is more than 40 degree, then flow is said to be poor.

Table 1

Sr. No.	Angle of repose (degree)	Flow Character
1	<25	Excellent
2	25-30	Good
3	31-38	Passable
4	>38	Poor

Carr's index:

Carr's index evaluates the capability of powder to combine or unite. It can be calculated by following formula:

$$Carr's\ index = \frac{Tapped\ \ volume\ \ - Bulk\ \ volume}{Tapped\ \ volume}$$

Bulk volume is a volume of powder having no direct contact whereas tapped volume can be obtained by tapping in bulk density apparatus. A Carr's index less than 20% meant to have better flow.

Table 2

Sr. No.	Carr's Index (%)	Flow Character
1	0-10	Excellent
2	11-15	Good
3	16-20	Fair
4	21-25	Passable
5	26-31	Poor
6	32-37	Very poor
7	>38	Extremely poor

Hausner's ratio

It is a ratio between the tapped density and bulk density. It is used to measure cohesiveness between particles. It can be calculated by following formula:

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

Ratio lower than 1.25 meant to be good flowability whereas ratio more than 1.4 has poor flow.

Table 3

Sr. No.	Hausner Ratio	Flow Character
1	1.00-1.11	Excellent
2	1.12-1.18	Good
3	1.19-1.25	Fair
4	1.26-1.34	Passable
5	1.35-1.45	Poor
6	1.46-1.59	Very Poor
7	>1.60	No flow

4) Crystallinity

It is an arrangement of particle of drug in a sequential manner. If drug is crystalline then its more stable but drug is insoluble. Crystalline substances have high stability, less hydration energy and less solubility. Crystallinity can be confirmed by X-Ray Diffraction (XRD).

X-Ray Diffraction: A technique used to determine the atomic and molecular structure of crystal, in which crystalline atoms cause a beam of incident x-rays to diffract into many specific directions. The atomic planes of a crystal cause an incident beam of x-ray to interfere with one another as they leave the crystal. This phenomenon is called the X-Ray diffraction. Stream of X-rays directed at a crystal it diffracts and scatters as they encounter atoms. The scattered rays interfere with each other and produce spots of different intensities that can be recorded on a photographic film. XRD measures the average spacing between layers and rows of atoms which determines the orientation of single crystal or grain.

5) Polymorphism

Some of the elements are available in different forms that can be named as allotropes of element. For example: Carbon. Generally, they have same properties under liquid or gaseous state but they act unstable under solid state. Almost every drug can crystallize into their different forms. Polymorphs with their properties like melting point, density, stability and solubility i.e. thermodynamic and physicochemical properties can enhance the quality of pure drug form. The stable form of polymorphs is generally named as its metastable form which have higher solubility than the other forms or less soluble than the original form. Whereas metastable form get converted into its thermodynamic stable form in a short duration of time. Excipients present in may speed up the process of transition to solid state on the basis of its thermodynamic stability of metastable forms. Solvates can also be termed as pseudo polymorphs. They are crystalline solids in nature present within the crystalline structure either stoichiometric or non-stoichiometric proportions of solvent. When the solvent used is water then the solvate is called as hydrate. Hydrates can have fast or slow dissolution rate as compared to anhydrous form. For instance, theophylline anhydrate dissolves faster than its hydrate form Where as erythromycin dihydrate have faster dissolution rate than its anhydrate form. The physical stability depends on the temperature or humidity of surroundings and its transition state. Where polymorphs are of two types: first is ENANTIOTROPHS (i.e. every form is stable at different temperature and pressure range. For example: sulfur) and second type is MONOTROPHS (i.e. only one form is stable at all temperature ranges below its melting point while other forms are unstable. For example: chloramphenicol, palmitate).

6) Particle Size Analysis

Particle size plays a vital role in determining the physical and chemical properties of drug substance which can get affected by size and other morphological factors of particles. Particle size also matters to get accurate drug dissolution rate, bioavailability, taste, texture, color and stability. Content uniformity also depends on the particle size. Some properties like sedimentation rate (i.e. rate at which particles of drug gets accumulated at the surface) and flow properties also gets affected by particle size and morphology of drug particle. In order to save product efficacy we need to find the morphological features of drug substance which can be done by various techniques like light microscope having calibrated grid, sieving method, Coulter current, sedimentation process and also by scanning electron microscope. In light microscopy, we need to carefully prepare a slide containing sample of drug substance and observe under microscope properly to get accurate size of particle. It can be done on small samples whereas sieving method is done on large samples. With the help of scanning electron microscope we can confirm the surface morphology related to surface area.

Solubility Characteristics:

It is a necessary step of preformulation which is used to check the aqueous solubility of drug for its therapeutic effectiveness. Drugs having aqueous solubility can enter systemic circulation which results in its therapeutic effect. Drugs without aqueous solubility cause incomplete absorption. If a solute gets dissolves, inter molecular forces of attraction of substance can be overcome by forces of attraction between solute and solvent molecules. Solubility can be affected by various factors like temperature, physical and chemical properties, pressure, acidity or basicity of the solution. Solubility characteristics can be studied by various parameters like *pKa determination, pH, partition coefficient, effect of temperature***.** Solubility characteristics can also be studied by various analytical methods like HPLC, UV spectroscopy and gas chromatography.

7) pKa Determination

With the help of this we can determine the amount of ionized and unionized drug at a pH range of 1 to 10. With the change in pH absorption can be affected. Henderson Hasselbach equation helps to determine pKa value i.e. the concentration of ionized and unionized drug at particular pH.

$$\text{For Acidic Compounds: } pH = \frac{pKa + \log [ionized\ drug]}{[unionized\ drug]}$$

$$\text{For Basic Compounds: } pH = \frac{pKa + \log [unionized\ drug]}{[ionized\ drug]}$$

Drugs having pKa value greater than 3 i.e. weakly acidic drugs, the unionized form remains in the stomach and drug gets ionized in intestine i.e. in basic medium. Drugs with pKa value 8-9, the ionized form of drug remains intermediate between both stomach and intestine example: erythromycin and Papaverine.

8) Effect of pH

The pH of media decides the degree of ionization and the solubility of acidic and basic drugs. It also helps to find out the dissociation constant (pKa) which is useful during parenteral formulation.

9) Effect of Temperature

The temperature decides the nature of solute and solvent. Endothermic substances (i.e. absorbs heat during dissolution process) increase in temperature tends to increase in solubility whereas in exothermic substances (i.e. give off heat during dissolution process) with increase in temperature tends to decrease in solubility. Thermolabile substances cannot be used and special care must be given during application of heat as prolonged heat can destroy the drug substance.

10) Partition Coefficient:

It is a parameter used to determine drug lipophilicity and tells us about its capability to enter cell membrane. Generally, it is defined as ratio of unionized drug present between the oily phase and water phase.

$$P_{o/w} = {}^{C_{oil}}/_{C_{water}}$$

It can be determined by shake flask method. In this method, dissolved drug is shaken with particular drug along with other solvent having different partition coefficient for 30 minutes. Left undisturbed for 5 minutes. Two layers will form, one aqueous and other is oily layer. Aqueous layer is centrifuged and assayed to find out drug content. This method have various applications which are mentioned below:

- Used to determine solubility of both aqueous and mixed solvent.
- Structure activity relationship (SAR) of homologous series can be determined.
- With the help of this information, we can find extract crude drug.

2. Stability Characteristics

Stability studies are quantitative assessment of chemical stability of new drug. To determine stability we have to perform some tests which are explained below:

Differential Scanning Calorimetry:

It is a thermal analysis which measures the heat loss or gain which is caused from any physical or chemical changes within a sample which is considered as a function of temperature. With this method, difference in amount of heat required increasing the temperature of sample pan and a reference pan is taken as a function of temperature. Both sample and reference pan attains nearly same temperature.

Construction:

The main assembly of DSC is composed of silver heating block which provides heat to the sample and reference pan. Platform of pan is known as a thermoelectric junction which is connected to the silver heating block. Two wires are attached to each platform; one is chromal wire and second is alumel wire. The temperature of reference and sample pan can easily be measured independently.

DSC Curve

Graph is made between temperature v/s heat flow. There is base line present in between which shows whether the substance is endothermic or exothermic. If the curve raise above the base line then the substance is exothermic, mainly crystalline substances are exothermic and if the curve goes below the base line then the substance is known to be endothermic, mainly amorphous substances are endothermic. Typical DSC curve is divided into three phases which are mentioned below:

- Glass transition phase (T_g) – below the base line
- Crystallization phase (T_c) – above the base line
- Melting phase (T_m) – below the base line

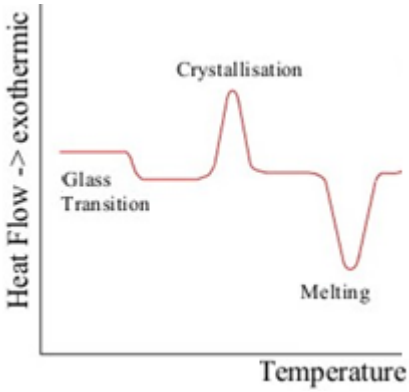


Figure 3

In glass transition phase, amorphous substances are employed. It is a endothermic process where energy is absorbed in the form of heat which leads to change in their state as it become molten rubber from a brittle substance. It is a reversible process. In crystallization phase, crystalline substances are employed. It is a exothermic process where Molten substance give out enough energy to change their form from unarranged to a arranged form which leads to a formation of crystals. They give off heat after changing into crystals. The temperature at highest peak is considered as a polymer crystallization temperature. In melting phase, endothermic process again comes as polymer absorbs extra amount of heat then polymer crystals fall apart and it again starts melting and eventually reaches to the its thermal transition i.e. a melting phase. If any co-solvent is used in formulation to evaluate compatibility of drug with co-solvent. We have:

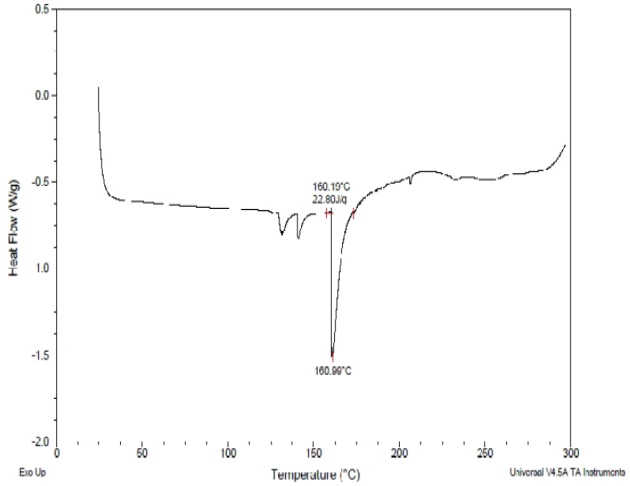


Figure 4: DSC of Poly Ethylene Glycol – 400

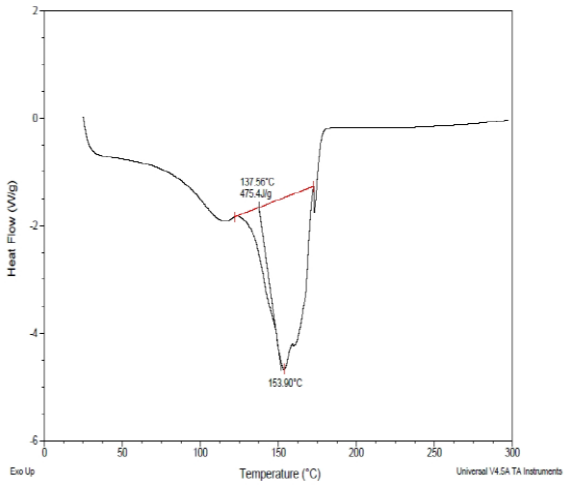


Figure 5: DSC of Propylene Glycol

If the peak of curve is tapered then the substance is Crystalline in nature whereas if the peak of curve is broad then the substance is amorphous in nature. If the curve is overlapping then there is no compatibility of drug with co-solvent and if the curve is not overlapping each other then the drug is compatible with co-solvent.

Applications

- We can study DSC of liquid crystals
- To study the oxidative stability of samples
- It is used in pharmaceutical and polymer industry as a way of determining melting point.
- To study drug polymer interaction.
- To study food dynamics by food science.

Infrared Spectroscopy

It is a spectrophotometric technique used to determine the functional groups of chemical constituents. It is widely employed in quality control and manufacturing processes. This technique can also determine different polymorphic forms of a compound.

Principle

It is a way of determining the amount of IR radiation absorb or emitted by a sample and this is considered as a function of wavelength. The IR spectrum is based on the molecular vibrations dependent on atomic mass, bond strength and intramolecular/intermolecular interaction.

Table 4

Functional group	*Frequency (cm^{-1})*	*Intensity*
Water OH	3700-3100	Strong
Alcohol OH	3600-3200	Strong
Carboxylic acid OH	3600-2500	Strong
N-H	3500-3350	Strong
-CH aldehydic	2900-2800	Variable
-COOR ester	1750-1720	Strong
C=O ketone	1745-1715	Strong
$-NH_2$ amide	1700-1500	Strong
C=C alkene	1680-1600	Weak
C=C aromatic	1600-1400	Weak
CH_2 bend	1480-1440	Medium
CH_3 bend	1465-1440, 1390-1365	Medium
C-O-C	1250-1050	Strong
C-OH	1200-1020	Strong
NO_2	1600-1500, 1400-1300	Strong
C-F	1400-1000	Strong
C-Cl	800-600	Strong
C-Br	750-500	Strong
C-I	=500	Strong

Instrumentation

The main assembly of IR is consists of a beam splitting plate and a pair of mirror. The difference in the path lengths of two arms can be adjusted mechanically. This gives rise to a time dependent variations in transmitted optical intensity called Interferogram. The interferometer is illuminated by mono chromatic source such as single frequency laser. The interferogram is between sin waves of intensity v/s mirror position.

Working:

- Light passes through beam splitter, which splits the light in two directions.
- One beam goes to stationary mirror, then back to beam splitter. The other goes to moving mirror.
- When these two meet up again at beam splitter, they recombine.
- The difference in the path lengths creates variation thus give rise to interferogram.
- The recombined beam passes through the sample and sample absorbs all different wavelength of its spectrum.
- Detector reports variation in energy v/s time for all wavelengths simultaneously.

X-Ray Diffraction

A technique used to determine the atomic and molecular structure of crystal, in which crystalline atoms cause a beam of incident x-rays to diffract into many specific directions. The atomic planes of a crystal cause an incident beam of x-ray to interfere with one another as they leave the crystal. This phenomenon is called the X-Ray diffraction. Stream of X-rays directed at a crystal it diffracts and scatter as they encounter atoms. The scattered rays interfere with each other and produce spots of different intensities that can be recorded on a photographic film. XRD measures the average spacing between layers and rows of atoms which determines the orientation of single crystal or grain.

Principle:

In this, x-ray beam is diffracted at a particular angle when an x-ray is allowed to pass through crystal. 3D structure causes diffraction. As a result diffractogram is obtained that consists of peaks where sharp peak symbolizes crystal structure and intensity of peak can be measured which indicate the purity of substance.

Uses:

- To determine purity of substance.
- To distinguish between crystalline and amorphous substance.
- To check compatibility of excipients with drug.

Thermo Gravimetric Analysis (TGA)

TGA is carried out in air or oxygen or free nitrogen at different heating rates. The amount and particle size of material can affect the thermogram. With the help of this analysis, we can also find out the temperature at which material starts decomposing. TG curve is obtained on a

apparatus called thermo balance. It mainly comprises of recording balance, furnace, recorder and temperature controller. The components of TGA are described as:

- There are two types of balances: one is reflection/extension type and another is null balance.
- Sample holder: It mainly decides the nature and shape of TG curve. Most commonly used sample holders are gauze crucible, polyplate sample holder, labyrinth crucible.

Thermo gravimetric analysis measures difference in mass as sample is heated cooled and held at constant temperature. This difference is depending on the environment conditions provided. When heat is provided to sample, alteration in chemical structure, composition and crystal lattice occurs like during oxidation, decomposition and fusion. And the result is compared with an inert reference.

3. Limitations

- Some liquids can be measured with the help of TGA. In practice, it is hard to detect liquid samples.
- Like in TGA, sample is required in small amount. So, it is difficult to detect compounds with heterogeneous composition.

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