Raw material analysis

Session agenda

1. What is Raw materials
2. Types of Raw materials
3. Difference between API & Excipient
4. Difference between Qualitative & quantitative analysis
5. Sources of Method of analysis
6. Analytical analysis of Raw materials
7. Documentation of Raw materials

Raw material analysis

RAW MATERIAL SECTION **MAIN ROLE** IS ANALYSIS OF ALL RAW MATERIALS USED IN PRODUCTION AND DECIDE IF THEY WILL BE ACCEPTED OR REJECTED .

raw materials types

Active pharmaceutical ingredient
API

Inactive pharmaceutical ingredient
Excipient

Packaging material
1ry-2ry-3ry

Active materials=Potent materials
Active pharmaceutical ingredients=**APIs**

MATERIALS THAT HAVE PHARMACOLOGICAL / THERAPEUTIC EFFECTS LIKE PARACETAMOL , BISOPROLOL AND HYDROCHLOROTHIAZIDE.

ANY MATERIAL THAT USED TO TREAT PATIENT HEALTH ISSUES.

Inactive materials

In active pharmaceutical ingredients=**Excipients**

MATERIALS THAT HAVE NO PHARMACOLOGICAL EFFECTS, BUT HAVE EFFECTS ON **PROPERTIES OF DOSAGE FORM** LIKE **BINDER**, **DISINTEGRANT**, **FILLER**, **BASE** ADDED TO CREAM TO SIMULATE IT'S ABSORPTION, **COAT MATERIALS LIKE ENTERIC COATED TABLETS** .

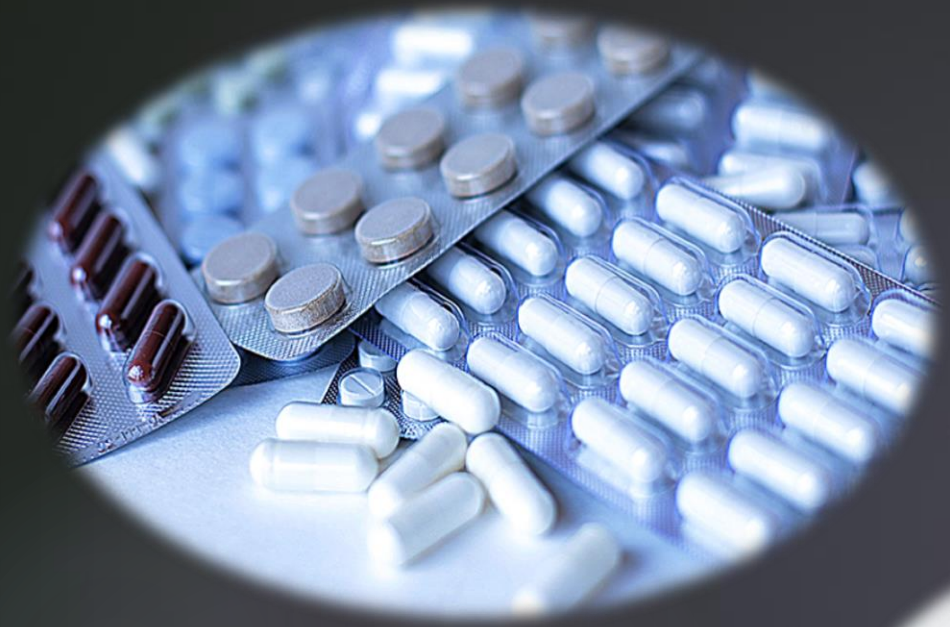
Packaging materials

- 1ry packaging materials
- 2ry packaging materials
- 3ry packaging materials

1ry packaging materials

First layer that make direct contact with dosage form ,It is very critical and very dangerous layer ,because it's direct effect on dosage form quality and safety .

Examples
Aluminum strips in tablets.
Plastic bottles in syrup.
Glass vials in Ampoules.
Tubes for creams and ointment.



Strips

Tubes

Glass vials

2ry packaging materials

2nd layer of packaging, consist of carton box and leaflet that contains all important information about the dosage form like ,side effects , therapeutic dose , pharmacological effects ,storage conditions etc..

3ry packaging materials

External carton.

Difference between active and inactive materials in analysis

API " Active pharmaceutical ingredient"

APIs are potent materials because they have a pharmacological effects on human body ,small quantities make large effects.
Example:-product with 5mg concentration differs from 10mg ,differs from 20 mg .
Therapeutic dose and daily intake is related to APIs concentration ,so it is very critical.

Official monograph used for analysis focus on detection of potency=Assay % in APIs.
Any deviation must be taken in consideration.

EXCIPIENTS=INACTIVE PHARMACEUTICAL INGREDIENT

Excipients are non potent materials because most of them haven't a pharmacological effects on human body.
Example :-addition of large amount of sugar.

Official monograph used for analysis focus on **quality** of excipient.

API " Active pharmaceutical ingredient"

Role of API is pharmacological effect so,
Official monograph used for analysis focus on purity of APIs , also Impurities concentrations and their allowed limits.

EXCIPIENTS=INACTIVE PHARMACEUTICAL INGREDIENT

ROLE OF EXCIPIENTS IS THEIR EFFECTS ON DOSAGE FORM PROPERTIES ,LIKE 1-ADDITION OF MATERIAL THAT HAS BUFFER EFFECT TO MAINTAIN PH IN SPECIFIC DOSAGE FORM

2-ADDITION OF MATERIAL THAT ADJUST VISCOSITY.

3-ADDITION OF FILLER TO INCREASE TABLET VOLUME.

SO OFFICIAL MONOGRAPH FOCUS ON **IDENTIFICATION** AND **QUALITY** TESTS.

Qualitative Analysis

- Analysis that focus on identity of materials like **Identification tests and Tests for properties (physical properties)** .

Examples of **Identification test :-**

Iodine addition to starch, if it gives blue color ,then it is starch.

Flame test for sodium ,if gives you golden yellow ,then material contains sodium.

Examples of **physical properties :-**

Particle size detection ,

Quantitative Analysis

Analysis that focus on material concentration or count.

- Examples:-
- 1-Detection of **Assay %** for specific active material in dosage forms.
- 2-Detection of **Impurity limit** .
- **3-Microbial count to** detect contamination.

Sources of Method of analysis

Official monographs

Non official monograph (Supplier methods)

Official monographs

USP → United status pharmacopeia

BP → British Pharmacopeia

EP → European pharmacopeia

JP → Japanese pharmacopeia

Non Official monographs

FROM SUPPLIER WHO MANUFACTURE RAW MATERIAL.

Analytical analysis of Raw materials

1-Identity test.

2-Purity test.

3-Assay=Potency test.

4-Quality test.

Identity tests

Qualitative or Quantitative ?

- **Identification is considered a qualitative test , because it focus on identity of the material**

- Appearance test
- Solubility test
- Identification test

Identity tests (cont.)

Appearance test is identification test , because each material has specific color and specific appearance, if we found any deviation in appearance, it is probable that it may be the material but damaged or it may be not the material at all.

Example :- material must be fine powder in specification , we found it yellow powder .

Here **2 probabilities** can be present, either it is not target material, or it is our target material but damaged.

Identity tests (cont.)

Solubility test is identification test for specific material

e.g. material dissolve in water and not dissolve in ethanol.

It is considered also a quality test , because if we found our material that dissolves in water has some turbidity or partially soluble , this mean **low quality**.

Identification Tests for material characteristics"

It is considered Test for material characteristics, if we have Starch and want to make sure if it is starch or not , Identification test here is iodine test ,if we notice blue color ,so it is starch.

If we want to detect presence of sodium in any raw material, we make Flame test, if we notice golden yellow color ,so it contains sodium.

Identification test as comparative test Examples:-
(Infrared) IR

IR (Infrared)

If you want to detect any API like Bisoprolol using IR , you prepare known standard(Bisoprolol std) , test from your unknown material , put them in IR , both standard material and your unknown expose to IR radiation ,give an emission , finally you will have a graph that called a finger print for each substance in IR.

Compare Standard graph with test graph ,then you will know if your material Bisoprolol or not.

TLC =thin layer chromatography

If you want to detect any substance by **TLC**, you will dissolve known material (Standard) in suitable solvent and dissolve also your unknown material, then **drop them** in stationary phase(Silica paper) , then you allow mobile phase to spread, you will notice spots appear in paper,

Comparing Standard spot with your unknown spot will tell you if it is your target material or not.

There are **3 factors** that must be in your consideration during comparison :-

1-Spot position ,this depends on affinity between material , stationary and mobile phase.

2-Spot color.

3-Spot size.

UV spectrophotometer

Each material that has a **chromophore** ,can **absorb UV radiation** at specific **wave length**, if you want to identify materials with UV, prepare Known standard material and solution from your unknown material and read them in UV.

If you notice the same reading ,so it is your target material.

HPLC=High performance liquid chromatography

If you want to identify your material with more accurate and advanced technique, use **HPLC** ,first you prepare **standard solution** (Known material) and **solution from unknown material** , inject at HPLC and compare Standard chromatogram with test chromatogram in **Retention time**(location of peaks) and **Area under the curve**.

Purity Test

QUANTITATIVE TEST, IT IS A TEST THAT DETECT PRESENCE OF IMPURITIES AND ESTIMATE THEIR QUANTITY TO MAKE SURE IT IS WITHIN SPECIFICATION LIMIT OR NOT.

Types of Impurities

1- General impurities ." Inorganic impurities and residual solvents"

2-Related impurities . "organic impurities"

General impurities

Impurities that arises during manufacturing of raw material , due to addition of some chemicals that help in manufacturing process like , addition of catalyst ,substances that helps in solubility, or presence of unwanted residuals that developed from any step of manufacturing.

Examples:- Chloride- sodium- heavy metals-calcium-sulfate

All General impurities analysis methods are present in official monographs with limits.

Related impurities

Impurities that related to material itself , they arise during manufacturing of raw material or after manufacturing.

Examples:-

1-Isomers like levofloxacin & o-floxacin

2-Byproducts arise from starting materials during manufacturing .

3-Degradation products developed within shelf life .

Most of related impurities analysis methods are present in official monographs with limits.

Best way for related impurities identification and quantitation is by **HPLC** technique

Steps briefly:-

1-search in official monograph to use specific method.
2-prepare your material to detect impurities.
3-the chromatogram will show principle peak (large one) and other small peaks in different retention times ,these are impurities(**degradation products**) or your **isomer** if your material has isomer.

Example "detection of impurities in specific material "

After you follow the official method of preparation and after injection , you will obtain chromatogram like this **as an example** , **assume your principle peak (large one) is called Bisoprolol ,it's area is=200, your impurity peak area (small peak)=1**

Then %of impurity =1/200 *100 =0.5%

review the limit of impurity in monograph, result should not exceed this limit.

Is TLC used to detect impurities?

It can be used ,but in a narrow scale because it is difficult to detect amounts of impurities by this technique.

Assay test=Potency test

A QUANTITATIVE TEST ,

IT IS CRITICAL TEST FOR APIS, BECAUSE APIS HAVE A PHARMACOLOGICAL EFFECT AND DETERMINATION OF CONCENTRATION IS VERY IMPORTANT.

ASSAY % SHOULD BE 100%.

Assay test in raw material

- Raw material is Pure so there is no interference that may affects the analysis result.
- Assay can be performed by different ways like using chemical reaction like titration, or by instruments like UV spectrophotometer, HPLC etc..
- Assay results should be 100%

ASSAY TEST IN FINISHED PRODUCT

- Finished product is composed of APIs and Excipient that may affect the analysis result.
- Assay performed mostly through separation method to separate tested material before analysis
- So it is mostly performed by instruments like HPLC,UPLC,GC.
- And in rare case we can use another techniques.

HPLC technique for Assay% detection

Steps briefly:-

1-search in official monograph to use method specific for raw material (**Bisoprolol**) for example.
2-prepare Standard solution(Known) **Bisprolol std.**
3-Prepare sample solution(Unknown) **Bisoprolol raw material**.
4- perform the test as in monograph
5-Inject both standard and sample solution.
6-compare both standard and sample chromatogram.
7-Calculate **Assay %**

Assay % Example

Area of Bisoprolol standard 1000

Area of test(Bisoprolol raw material) =990

Assay%=Test Area/standard Area *Standard wt/ volume * volume of test /test wt * standard purity/Lable claim amount *100

Assay%=990/1000*100 =99% in consideration to above factors mentioned in equation.

Quality test

Quality test is done for any raw material to detect it's quality before using in manufacturing process , mostly done for Excipients.

Quality test also is considered an identification test.

Examples of Quality tests

e.g.

1-RI (Refractive index).

2-Polarity test.

3-Viscosity test.

4-Density test.

5-Melting point-boiling point-Freezing point.

6. Water content.

1-RI (Refractive index) by Refractometer

RI is considered identification and Quality test , when light emission occur then pass through sample ,it bends and RI can be measured and we obtain specific reading . A refractometer is used to determine a concentration of a particular substance within a given solution or detect purity of substances.

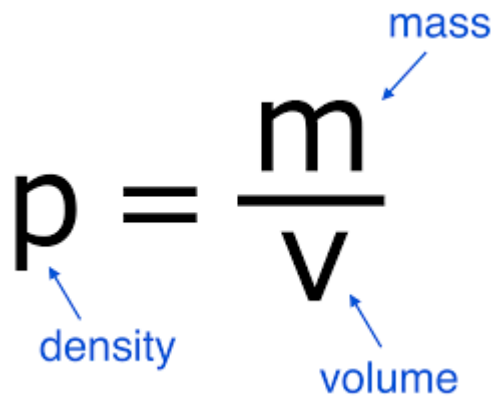
2-Polarity test by polarimeter

A polarimeter is a device used for determining the polarization direction of the light or the rotation of an optically active substances , it can detect quality of substances and determine if it is pure or not , also it is identification test.

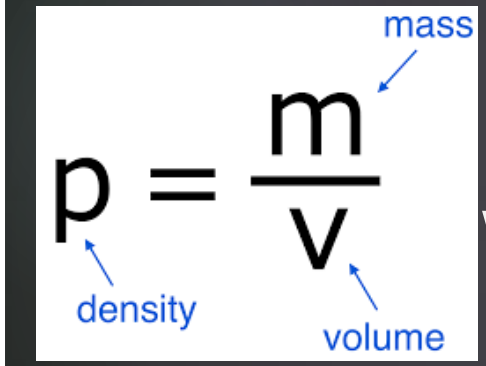
3-Density test

- **Is considered identification and quality test, for example if you want to make sure that you have glycerin or not or you want to detect it's purity , so you need to make density test.**
  - **1-Absolute Density.**
  - **2-Relative Density=Specific gravity.**

$$Specific\ Gravity = \frac{density\ of\ the\ object}{density\ of\ water}$$



Absolute Density
1-Done for liquid and solid materials .



Example
Volume of liquid in cylinder is 10ml
Weight of cylinder empty=80gm
Weight of cylinder and liquid =100gm.
Then weight of liquid=100-80=20gm
Density=20/10=2gm/ml

RELATIVE DENSITY=SPECIFIC GRAVITY

1-DONE FOR LIQUIDS ONLY.

$$Specific\ Gravity = \frac{density\ of\ the\ object}{density\ of\ water}$$

Example
Weigh liquid in specific flask.
Then weigh water in the same flask.
determine weight of flask and it's volume.
Then calculate relative density =**mass of material/mass of water** at the same volume and at Specific temperature.

4-Viscosity test by viscometer

Viscosity is **a measure of a fluid's resistance to flow.**

It is considered identification and quality test.

Water content

1. Bounded water

Karl Fischer reaction

$H_2O + SO_2 + I_2 \rightarrow SO_3 + 2HI$

2. Moisture content

Loss on drying test

Loss of material weight by drying in oven

Water content calculated by subtracting weight before and after drying

Documentation of Raw material section

1. Material monograph
2. Method of analysis (MOA)
3. Laboratory sheet
4. Test & instruments printouts
5. Certificate of analysis (COA)
6. Out Of Specification in case of material show non-conforming results

Thanks