Introduction to Pharmaceutical chemistry.

• **Pharmaceutical chemistry** :- It is the branch of science which makes use of laws of chemistry to study the drug which include chemical nature composition structure influence. own organisation and study their physical and chemical property method of quality control and condition of their use.

In short it is chemistry of drug pharmaceutical chemistry of drug is speacialist science which depends upon chemical discipline as well as 'medico-biological discipline.

Pharmaceutical chemistry

- Chemical discipline.
  - Inorganic
  - Organic
  - Medical
  - Physical
  - Colloid
- Medicobiological discipline.
  - Pharmacology
  - Toxicology

i) **Inorganic chemistry** :- It is a branch of science that makes use of laws of chemistry to study inorganic substances (drug) which include preparation, chemical nature, composition structure, influence on organism etc.

• **Pure Compand** ⇒ A compand is said to be pure which is free from foriger material.

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Impure Compound :- A compound is said to be impure which if is having foreign material.

Impurity :- A compound is said to be impure if any foreign material or compound is co-existing with pure compound (drug).

Source of Impurity

i) Raw material is used in manufacturing.
ii) Reagents used in manufacturing process.
iii) Process used in manufacturing.
iv) Chemical process is used in manufacturing.
v) Atmospheric condition during manufacturing process.
vi) Intermediates product in manufacturing.
vii) Defects in manufacturing process.
viii) Manufacturing hazards.
ix) Storage Condition.
x) Decomposition of product during storage.
xi) Adultation / accidental substitution.

Impurity :- It is defined as any substances coexisting with the original drug such as starting material, intermediate or any substance from due to any side reaction.

i) Raw material employed in manufacture
Impurities may to be associated with these of chemicals may Abe carry through the manufacturing process and contaminate

the final product.
Eg :- Rock salt contains small amount of calcium sulphate and magnisium chloride so that sodium chloride prepare from this salt contains small amount of calcium and magnesium compand.

2) Reagent used in manufacturing process :-
If reagent used in manufacturing process are not completely remove by washing these may find anti into final product.
Eg :- Precipated calcium carbonate may be prepared by interaction of solution of calcium chloride with sodium carbonate.

$$CaCl_2 + Na_2CO_3 \longrightarrow CaCO_3 + 2NaCl$$

precipates of $CaCO_3$ is washed with water to remove excess of sodium carbonate and soluble chloride. If this precipatate is not wash properly these may be present in final product as impurities.

3) Method or process used in manufacture :-
Some impurities are inaproperate into material during the manufacturing process.
eg. Water has been cheapest solvent available. So tap water contains calcium, magnisium, sodium chloride, sulphate, carbonate as impurity in very small amount.

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4) Chemical process used in manufacture :- For synthesis of drug many chemical reaction such as nitration, halogenation, oxydation reduction or hydrolysis are involved
Eg:- Tap water

5) Atmospheric Contamination during the manufacturing process :- In industrial area atmosphere is contaminated with dust particle and some gases like black smoke, hydrogen sulphide etc during the manufacturing or purification of pharmaceutical product these impurity enter into final product as impurity.

6) Intermidiate products :- In manufacturing process there are some intermediate which are produce in manufacturing process some times the intermediate may be carry through to final product.
Eg:- Potassium iodite is prepared by reaching iodine with pottasium hydroxide

$$3I_2 + 6KOH \rightarrow 5KI + KIO_3 + 3H_2O$$

the resulting Soln is evaporated to dryness and heated with charcoal. In this process if the intermediate product KIO_3 is not completely converted into KI then it may be carried through to the final product as impurity.

7) Defects in manufacturing process:-
In many manufacturing process there are defects like imperfect mixing, incompleteness, non adherence to proper temperature, pressure or reaction condition which may give chemical compand with impurities.
Example:- Zinc oxide may be prepared by heating mettalic zinc to bright red in current of air if their is lesser heat or air or both zinc mital is not completely converted into zinc oxides. If heat and air both are same

$$2Zn + O_2 \xrightarrow[air]{Heat} ZnO$$

8) Manufacturing hazards:- A well established system of check on manufacture and analytical control of product is usually sufficient to ensure that standards which are well maintained.

i) Particulate contamination → The presence of unwanted particulate mital can arise in number of way accidental inclusion of dust glass porcelin metallic and plastic fragments from sieves granulation tablated fandation filling machine or from product containers
ii) process error.
iii) Cross Contamination.
iv) Microbial Contamination.
v) Packing error.

9) Storage Condition :- The chemical or substance when prepared is stored in different types of container depending upon nature of material, batch size, quantity.

Example :- The chemical ferrous sulphate slowly gets change into insoluble ferric oxide by air and moisture. Hence it may be stored in well closed amber colour bottle.

10) Decomposition of product during storage →
Some substances decompose on keeping the decomposition becomes greates in presence of light, air and oxygen.

11) Accidental substitution or adulteration →
It is possible to prevent accidental substitution by storing all more toxic substance together seperately or in lock of cup board.

- Effect of Impurity
Almost pure substance are difficult to prepare and that some amount of impurity always remains in the material. The impurity present in substance may exist following effects :-

i) Impurities having a toxic effect that can be injurious when present in certain limits.
ii) Impurities mainly decrease the therapeutic effect.
iii) Impurities are some time harmless if present in small quantity.

4) Impurities may cause change in physical and chemical property of substances their by making it medically useless.
5) Impurities may decrease shelf-life.
6) Impurities may cause change in order, colour and taste of substance which is unhygiine

Pharmacopoeia

Pharmacopoeia is a book of direction and sequirement of preparation of medicians (drug). So, it is generally publised by an authority.
Thus pharmacopoeia is a legislation of country which set standard and obligatory quality indices for drugs, raw material is used to prepare them and various pharmaceutical preparation.
These are presented seperatelly in general and specific articles:

Monograph

It is complete discription of specific pharmaceutical which include nomenclature, classification, physical characterics, dosage, purity, limits of purity, Assay, condition for storage.
The appendices may also include standards for apparatus, chemical techniques and process related to said pharmaceutical.

Pharmaceutical or Pharmacopoeia discription

Mostly all pharmacopoeia consist of three main sections

i) Introduction
ii) Monograph
iii) Appendix

i) Introduction: It is useful point of pharmaceutical progress its summised the various changes addition or deletion in current edition.

ii) Monograph: The word monograph is study of about the ~~mono~~ pharmacopoeial monograph eg [I.P 1985] give the following information about the drugs and pharmaceuticals aids.

1) The tital is stated in english and refers to the official name of compand sometimes sub titles are given. These are synonin and could be used in placed on main title.
eg: Calcium Carbonate can also be called precipitate ~~chow~~ chalk.

ii) formula weight or molecular weight
example: Magnesium chloride having formula $MgCl_2 \cdot 6H_2O$ and molecular weight → 202.30

iii) Category → This discribes the phasmacology or pharmaceutical.

iv) Dose are the quantities for the guidence of describe to acheive the desired therapeutic effect of drug.

v) Description → This gives a physical discription of substance like Crystalline or amorphous nature, smell, taste or colour.

vi) Solubility → It is described in popular term which are defined in pharmacopoie under general notice.

Term	Relative quantities of solvent for 1 part of solute
Very soluble	less than one parts
freely soluble	from 1 to 10 parts
Soluble	from 10 to 30 parts
Sparingly Soluble	from 30 to 100 parts
Slightly soluble	from 100 to 1000 parts.
Very slightly soluble	from 1000 to 10,000 parts.
practically Insoluble	More than 10 thousand parts.

vii) Standard → It is an important part of monograph which specify the quantative purity of title compound where the compound of definate composition.

eg → Potassium bromide is having not less than 98% potassium bromide calculated with reference to derived substance.

viii) Identification → This involves specific chemical test to identify substance.

9) PH → The PH value given in monograph are for guidence of manufacturing pharmist develope various dosages form and to avoid physiological composition.

10) Limitation ~~of~~ for impurities → for different chemical different limit test has been included different limit test for impurity are generaley represented as ppt (parts per million)

11) Assay → It is the step by step reaction discription of chemical analytical method for the active substance

12) Storage → This is the last item under monograph this direction are useful in pressuring the activity of chemicals, for inorganic pharmaceutical the pharmacopoeia use the term well closed container tighty container, Light resistance, cool place, single door container.

Appendix

The general notice and monograph are followed by comprehensive.

eg:- Appendix no.1 contain information for apparatus for test and assay.

History of Pharamacopoeia

In India, the first pharamacopoeia has been published as Bengal pharmacopoeia in 1844. The goverment of India Constitute a permanent pharmacopie in 1948 for preparing India pharmacopoeia vndin the chairmanship of Dr. B.N. Ghosh.

The first edition of Indian pharmacopoeia is published in 1955 which contains large no. of crude drugs and their preparation silent features of first edition of pharmacoppeia (1955) it contains 986 monograph titals of monograph in latin language

Weight and measures in matric system list of preparation geiven at the end of some of monograph

- Silent feauture of 2nd edetion of Indian Pharmacopoeia.
- Published in 1966 and its suplimeat were published in 1966 and 1975.
- Titals of monograph are changed from latin into english.
- Name of drug come first in title eg. → Aminophyline Injection
- 93 new monogsaph were added

Limit test → There are the qualitative and semiqualitive test deign to identify and conbol small quanting of impurity which is Lightly to be present in substance.

Limit test involve simple comparison of opotensence, turbidity or colour change with fixed standard. These are in carried out in nesselar cylinder.

In performing Limit test only distilled water or pusify water is used because ordinary tap water contains number of ion

If the intensity of colour is more than Standard it means the sample contain impurities.

→ Limit test for Chloride:

Limit test for chloride has been base on simple reaction between silver nitrate and soluble chloride to obtain simple chloride which is insoluble in delute nitric acid.

$$Cl^- + AgNO_2 \xrightarrow{+HNO_3} AgCl + HNO_3^-$$

Solute Silver chloride nitrate Silver chloride

The silver chloride produce in the preesence of delute nitric acid makes the test solute turbid. The extand of turbidity depends upon the amount of chloride present in substance is compared with a standard solution produce by addetion of silver nitrate to standard solution haveing chloride ion and nitric acid.

• Test Solution:

Specified substance (1g) + 10 ml of water + 1ml of nitric acid (HNO_2)

→

Diluted to 50 ml in Nesselar Cylinder (A)
+
1 ml of Silver Nitrate ($AgNO_3$) soln
↓ set aside for 5 mint
Turbidity

- Standard Solution

1 ml of 0.0584% w/v soln of sodium chloride
+
1 ml of Nitric acid (HNO_3)
↓
Diluted to 50 ml in Nesselar cylinder (B)
+ 1 ml of silver nitrate soln
↓ set aside for 5 mint
Turbidity

Compare the turbidity of both test soln and standard solution terminated the sample is passed the limit test.

Limit test for Sulphate.

The limit test for sulphate is carried out on the basis of reaction between barrium chloride and soluble sulphate. In the presence of HCl it gives Barium Sulphate.

$$BaCl_2 + SO_4^{2-} \xrightarrow{HCl} BaSO_4 + Cl^-$$

Barrium Chloride — Soluble Sulphate — Barrium Sulphate

then the comparision of turbedity produce by given amount of substance is done with standard turbidity.

The barrium chloride test soln in the I.P has been replaced by barrium sulphate reagent which is having barrium chloride, sulphate free alcohol and soln of potassium sulphate.

1) Potassium Sulphate has been added to increase sensitiveity of test.
2) Barrium sulphate is precipated by barrium sulphate reagent.
3) Alcohal helps to prevent super saturation.

Test solution.

Specified substance (1g) + 2ml HCl

↓

Deluted to 45 ml of distilled water + 5ml soln of barrium sulphate reagent

↓ set aside for 5 min

Turbidity

standard solution

1 ml of 0.1089% w/v soln of K_2SO_4 + 2ml HCl

Diluted to 45 ml distilled water + 5 ml Sol^n of $BaSO_4$ reagent

↓ set aside for 5 min.

Turbidity

Preparation of test soln

A soln of specied substance is prepared in water and 2ml of dilute hydrochloric acid is added.

Dilute to 45ml with water, add 5 ml of Barrium Sulphate soln in the soln and set aside for 5 min

~~the turbidity produce by sample soln should not the greater than standard soln.~~

Preparation of standard soln

Place 1 ml of 0.01089% w/v sol. of K_2SO_4 and 2ml of dilute HCl is added.

In another nessalar Cylinder dilute to 45 ml of water. add 5ml of barrium sulphate reagent and set aside for 5ml.

The turbidity produce by sample sol should not greater than standard soln

Modify limit test for chloride and sulphate

A specified amount of substance is dissolve in distilled water and volume made up to 50ml of nessular cylinder. Depending upon the nature of substance some modification have to be adopted for preparation of soln.

Alkaline Substance have to be dissolved in acid so that effervescence ceases and much of free acid is left in soln. As is described in the test.

Insoluble substance are generally treated with water and then filtered and filtrate is used for test, because of presence of insoluble substance modify the turbidity and colour

Sarce of Organic Acid like sodium benzoate and salicylate are the salts of organic acid. Librates free water insoluble organic acid during acidification which is filtered and filtrate is used for test.

Coloured Substance like crystal violent are carbonised and ash so produced is treated in water

Deeply colored substance have to be decolourised before test example potassium permagnate is reduced by boiling with alcohal and filterate is used.

Reducing Substance like hypophosporus acid which reacts with silver nitrat in Limit test for chloride should be oxidised with nitric acid or some other oxidising agents before carrying out the test.

Limit test for Iron

The limit test for Iron is based on the reun b/w Iron in ammonical solution. In the presence of cytric acid with thioglycollic acid when a pale pink to deep reddish purple colour is formed due to ferrous compand

The produce from specified amount of substance from the test is compared by doing the standard sol^{n}. If the colour from test sol^{n} is less dask then standard then sample passes the test.

Cytric acid does not allow the precipitation of Iron by ammonia by forming a complex with it.

Thioglycollic acid is useful analog of glycollic acid which is prepaid by action of potassium hydrogensulphide on monochloroacidic acid.

$$CH_2Cl.COOH + KSH \longrightarrow CH_2SH\,COOH + KCl$$

Thioglycollic acid is colourless liquid having unpleasent odour.

the colour produce from specified amount of substance is compared with standard colour obtain from non amount Iron.

Chemical reaction

$$Fe^{2+} + 2CH_2SHCOOH \longrightarrow Fe(CH_2SHCOO)_2 + 2H^+$$

ferrous thioglycollic acid.

Preparation of Standard soln of Iron

It is prepare by adding 0.173 g of ferric ammonium sulphate to 1.5 ml of HCl and adding sufficient water to produce thousand soln. Each ml of solution contains 0.02 g mg of iron.

Method of preparation of test soln

A specified amount of substance is taken in nessler cylinder and to it 2ml 20% ~~ferric~~ acid is added. the soln are mixed made alkaline with iron free ammonia and dilute 5ml with water

Method of preparation of standard soln →

Place 2ml of standard soln of iron have water 2ml 20% w/v sibic acid and 2 drop of thioglycolic acid soln with alkalin with ammonia and adjusted to 50ml with water allowed to stand and compain the standard and test soln

Limit test for Heavy metals.

It has been based upon the reaction of metal ions with hydrogen sulphide [H_2S] under the precribe condition of test by forming metal sulphide [$PbS + H_2$]

Example → Lead

$$Pb + H_2S \longrightarrow PbS + H_2$$

Metal ion — Hydrogen Sulphide — Metal Sulphide

The test soln is compared with standard soln the metallic impurities is substance express parts of lead per million parts of test for substance.

The IP has adopted three method for Limit test for heavy metal

i) Method I is use for the substance which gives clear colourless soln under specified condition.

ii) Method II is used for substance which do not give clear colourless soln under specified condition

iii) Method III is used for substance which do not give clear colourless soln under specified condition that give clear & colourless soln in sodium hydroxide medium.

Method II → this method is applicable for the sample which give clear colourless soln under specified condition of test.

Preparation of test soln

Take 25 ml of soln which is prepared as per the processue given under IP adjust the

PH b/w 3 to 4 by adding dilute acetic acid or dilute ammonia soln to stop dilute made up the volume upto 50 ml

Preparation of standard soln

Take 2ml of standard lead soln by pipette in nessler cylinder and dilute it with water to produce 25 ml and adjust the PH b/w 3 to 4 by adding dilute acetic acid or dilute ammonia soln dilute with water and mix well then made up the volume up to 50 ml

Method IInd The standard soln can be prepared as ~~described~~ directed under Method IS.

Preperation of test soln test soln may be prepared by using specified quantity of substance with sulphuric acid ignition flame till completely charred and few drops of nitric acid and head to 500 allow to cool and 4 ml of hydrofluric acid and evaporate the dryness mothion the residue with 10ml of HCl acid digest for 2 min neutralised with ammonia soln and make just acitic with acetic acid adjust the PH b/w 3 to 4 filter if necessary adjust the volume to filtrate to 35 ml and 10 ml hydrogen sulphide soln dilute to 50 ml water and compare the colour with standard soln

Method II[nd]

→ Preparation of standard soln →

It is prepared by using 2ml of lead soln adding 5ml dilute sodium hydroxide and making the volume up to 50 ml with water.

→ Method for preparation of test solution.

It is prepared by 25ml sol prepared as directed in I.P or take specified quantity of substance disolve in 20ml water add 5ml of dilute sodium hydroxide soln and make up to volume upto 50 ml to each above soln in nesslar cylinder at 5 drops of sodium sulphide soln mix well and set aside for 5 min the colour produce by test soln is not darked than standard solution

Lead Solution

Weight accurately about 400 mg of lead nitrate in distilled water containing two ml of nitric acid and dilute upto 250 ml. Take 10 ml of this soln and dilute up to 100ml further take 10 ml of this soln and dilute up to 500 ml with distilled water.

Dilute acetic acid

Take 57 ml of global acetic acid and volume make upto 100 ml

Limit test for Arsenic

Arsenic is well known undesirable and harmful substance which is present in medicine substances. All pharmacopoeia describe a limit test for it many qualitative and quantitative test of arsenic are known. However, the pharmacopoeia method is based on the gutzeit test.

Principal of test

This test is based on the fact that arsenic in oxidized state can be easily reduced to arsine gas when this gas is passed over mercuric chloride paper. It produces a stain which ranges in colour from yellow to brown. The intensity and length of which are proportional to the amount of arsenic.

The british pharmacopoeia suggest mercuric bromide paper

the chemical reaction involved in this method is based on following steps when the sample is dissolved in acid the arsenic present in sample gas converted to arsenic acid which gets reduce by reducing agents like potassium iodize to arseniaus acid. The nascent hydrogen form during the reaction further reduce to arseniaus acid to arsene gas which reacts with mercuric chloride paper giving a yellow stain

H_3AsO_3

$H_3AsO_3 + 3H_2 \longrightarrow AsH_3 + 3H_2O$

Arsenic acid — Arsine gas

$H_3AsO_4 + H_2SnO_2 \longrightarrow H_3AsO_3 + H_2SnO_3$

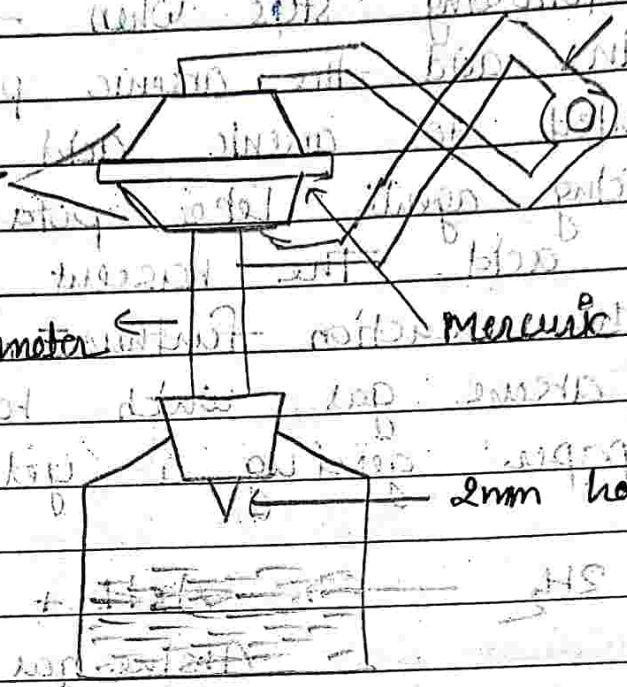
Arsenic acid — stannous acid — Arseniaus acid

$H_3AsO_3 + 3H_2 \longrightarrow AsH_3 + 3H_2O$

the depth of yellow stain on mercuric chloride paper will depend upon the quantity of arsenic present in the paper

A wide mouth glass bottle which is filled with rubber bung and glass tube with 20mm length with internal diammeter 6.5 mm and out diameter is 8mm passed through it upper end of this tube is open and lower

end is tapped by or reduced by diameter to 1 mm at the side of lower and a hole of 2 mm diameter is made from where the lower end is started tapering



Arsenic limit test apparatus

Cotton wall in moisture with lead acitate solution dryed and packed into glass tubes. Lead assitate cotton trap hydrogen sulphide gas if any which can interface with test by giving stain on mercuric chloride paper upper end of tube is fitted with two rubber bungs and act like tube of 6.5 mm diameter with the hulps of clip in closing flat mercuric chloride paper in it.