

Impurities in Pharmaceutical SubstancesImpurity

Any foreign material or substance present in a chemical compound is called impurity.

eg - As, Pb, Fe, Cl⁻, SO₄⁻

Classification① Toxic/Harmful Impurity

- Very harmful to us.
- Can cause death even if taken once short period of time.
- Immediate toxicity.
- Injurious to health even in small quantity.
- Very low permissible limit in pharmaceutical preparation. eg - As, Pb.

② Cumulative Impurity

- May not cause immediate adverse effect.
- When taken for long period of time, may show toxic effect.
- Have more permissible limit than toxic impurities.
- eg - Fe, Heavy metals.

② Harmless / Non toxic

→ May be harmless but its presence in large quantity may reduce the therapeutic effect of a drug.

→ Can cause technical difficulties during formulation of a drug.

→ May change odour or taste.

→ May lower shelf life of a drug by causing drug decomposition. eg - Cl^- , SO_4^- .

Sources

① Raw material

If raw materials contain impurities, the same impurities may be present in final product.

eg - NaCl obtained from rock salt may contain Ca & K as impurities.

② Manufacturing process

(a) Reaction vessels:

→ Galvanized iron vessel may cause impurities like zinc (Zn^{2+}) to the final product.

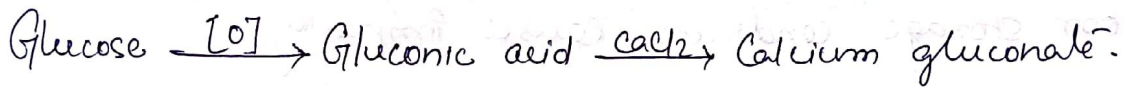
→ The vessels made up of copper & Lead may result in metallic impurities.

(b) Solvent:

- Tap water contain impurities like Cl^- , SO_4^{2-} , Ca^{+2} , Mg^{+2}
- Alcohol may be present as impurity in streptomycin.

(c) Reagents

- Unreacted reagents act as impurities.
- eg - Calcium gluconate and calcium lactose contain glucose as impurities.

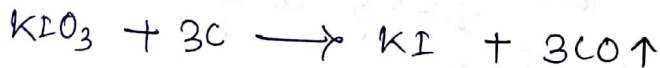
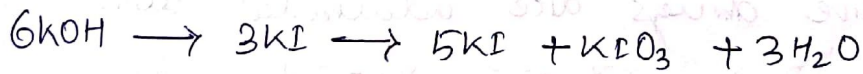


(d) Catalyst

Nickel (Ni) & potassium (K^+) catalyst may be present as impurities in carbencilline sodium (final product)

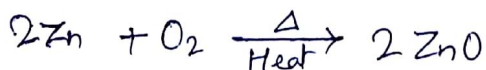
(e) Intermediate

While preparing potassium iodide (KI) potassium iodate (KIO_3) is formed as intermediate and act as impurity.



(f) Physical parameters

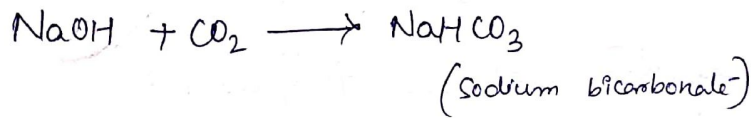
- Excess heating, boiling, pressure or unequal mixing causes impurities in final product.
- Eg., Conversion of Zinc into Zinc oxide.



③ Atmospheric Pressure

→ CO_2 , O_2 , H_2 and dust, moisture and microorganisms present in atmosphere causes impurity.

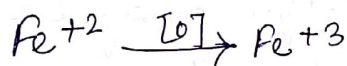
→ eg - Sodium hydroxide absorb CO_2



④ Storage

→ Poor storage condition causes impurity.

→ eg... Ferrous is oxidised to Ferric in presence of oxygen.



→ eg - Silver salts are decomposed by light hence stored in amber coloured bottle.

⑤ Deliberately Adulterated

→ Expensive drugs are adulterated with cheap drugs or low quality drugs.

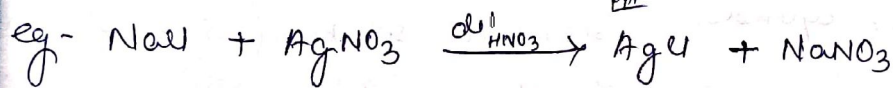
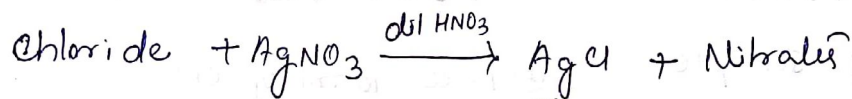
→ eg., Potassium bromide (KBr) is costly and is adulterated with sodium bromide (NaBr) which is cheaper.

Limit test for chloride

Principle:

→ Limit test for chlorides depend on the interaction of chloride with silver nitrate (AgNO_3) in the presence of Nitric acid (HNO_3).

→ This results in the precipitation of chloride as silver chloride.



→ Small quantity of silver chloride appears as opalescence.

→ Sample opalescence is compared with standard opalescence.

→ Sample opalescence < standard opalescence [Limit test will pass]

Use of nitric acid (dil HNO_3)

→ Nitric acid produces common ion effect and suppress dissociation of silver ions.

→ Prevents precipitation of other acid radicals such as phosphates, sulphate with silver nitrate.

→ In presence of HNO_3 , only chlorides get precipitated & other precipitates are not produced.

Procedure

Standard chloride solution

→ (25 ppm Cl) 0.05845 % w/v chloride solution

→ 10 ml of 0.05845 % w/v chloride solution is used to produce standard opalescence.

Sample/Test

Standard

① Take 10 ml of sample solution in Nessler cylinder.

① Place 10 ml of chloride standard solution (0.05845 % w/v) in Nessler cylinder.

② Add 10 ml of dilute nitric acid.

③ Dilute to 50 ml mark with distilled water.

④ Add 1 ml of silver nitrate solution (5 % w/v)

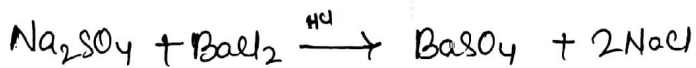
⑤ Stir the solution with glass rod & allow to stand for 5 minutes.

⑥ Compare the opalescence of sample & standard solutions.

Limit Test For Sulphate

Principle

- Depends on the interaction of sulphates with barium chloride (BaCl_2) in the presence of HCl .
- This results in the precipitation of sulphates as barium sulphate (BaSO_4)



Use of HCl

- In the presence of HCl , only sulphates are precipitated.
- HCl prevents precipitation of other acid radical by common ion effect with BaCl_2 solution. So less barium ions are formed.
- Prevents precipitation of other acid radicals such as phosphates, oxalates.

[Very small quantity of sulphate ions are present] → Barium sulphate appears as turbidity.

Sample turbidity < ^(Less impurity) Standard turbidity [Limit Test will pass]

Sample turbidity > ^(More impurity) Standard turbidity

Procedure (Reagent preparation)

Standard sulphate solution →

0.1089 % w/v potassium sulphate solⁿ.

→ 1ml of 0.1089 % w/v potassium sulphate solution is added to produce standard turbidity.

Take two Nessler cylinders and label them as 'sample' and standard.

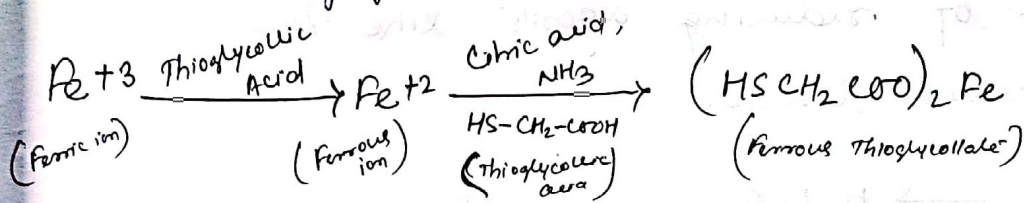
Test/sample

Standard

- ① Take 1ml of 25% w/v BaCl₂ solution in each Nessler cylinder.
- ② Add 1.5 ml ethanolic sulphate standard solution in each cylinder, mix & stand for 1 minute.
- ③ Add 15 ml of sample solution ③ Add 15 ml of standard prepared as per IP monograph. sulphate solution.
- ④ Add 0.15 ml of 5M acetic acid.
- ⑤ Dilute upto 50 ml with distilled water, stir with glass rod & allow to stand for 5 minutes.
- ⑥ Compare the turbidity.

Iron

Principle: Based on interaction of iron (Fe^{+2}) with thioglycollic acid in presence of citric acid and ammonia to form purple coloured ferrous thioglycollate.



Role

- Thioglycollic acid: Conversion of Fe^{+3} to Fe^{+2} * Formation of purple colour salt.
- Ammonia (NH_3): Provide alkaline medium for reaction.
- Citric acid: Prevent ppt of iron with ammonia.

Test

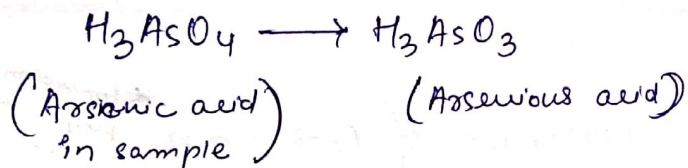
Standard

- ① 1g NaCl (sample) dissolve upto 40 ml with distilled water.
- ② 2ml, 20% w/v citric acid (iron free)
- ③ 0.1 ml thioglycollic acid.
- ④ Add NH_3 solution to make the soln alkaline medium.
- ⑤ Dilute upto 50 ml with distilled water, mix and allow to stand for 5 minutes.
- ⑥ Observe purple colour vertically and compare.

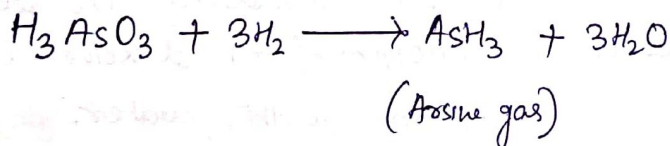
DMCT TEST FOR ARSENIC

Principle:

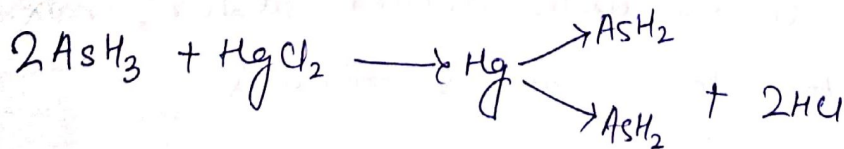
(i) The arsenic impurity present in the sample is first converted into arsenious acid by the action of reducing agents like zinc, HCl, potassium iodide.

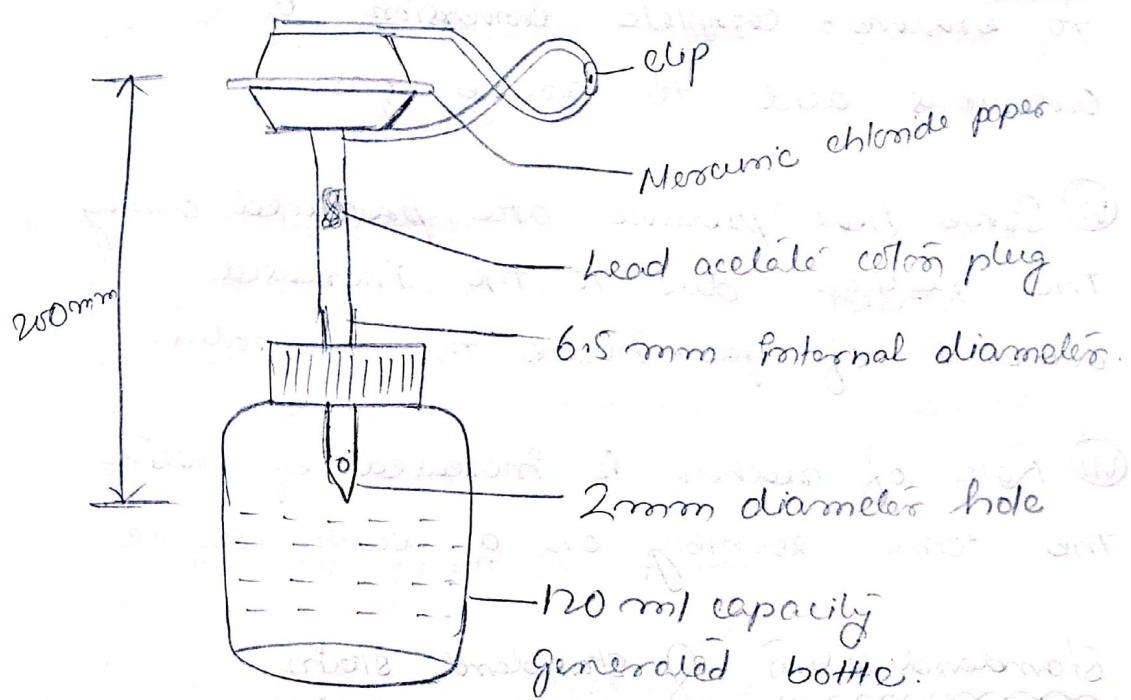


(ii) The arsenious acid is then reduced to arsine gas by the action of nascent H_2 which is produced by the reaction between zinc & HCl.



(iii) The liberated arsine gas reacts with mercuric chloride paper and forms yellow stain.





Gutzzeit apparatus

Procedure

- (i) Required amount of sample is added in the wide mouthed bottle.
- (ii) To this, add 1g of K_2CO_3 & 10g granulated Zn.
- (iii) Immediately close the bottle with stopper assembly.
- (iv) Acid present in the test solution & zinc reacts, produces nascent H_2 which reacts with arsenious acid present in the sample & liberates arsine gas, which passes through the tube and reacts with mercuric chloride paper and produces yellow stain.

(v) Reaction is maintained for 40 minutes to ensure complete conversion of arsenious acid to arsine gas.

(vi) Some heat pressure are produced during the reaction due to the increased amount of gas inside the apparatus.

(vii) Rate of reaction is increased by placing the total assembly on a warm surface.

Standardization of standard stain

(i) Standard stain is prepared by using dilute arsenic solution (0.132g in 1000 ml)

(ii) 1 ml is diluted to 100 ml.

(iii) The comparison of the stain is done after the completion of the test immediately, so the test and standard should be carried out simultaneously.

Precaution

(i) If the stain present in the filter paper becomes dark, the test should be repeated by using pure reagents.

(ii) The most suitable temp for carry out this test is 40°C .

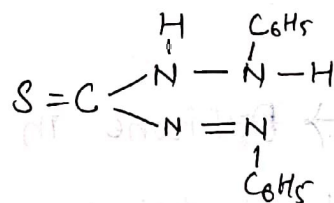
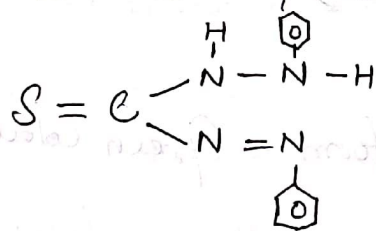
(iii) Cotton wool dipped in lead acetate solution is used to trap any hydrogen sulphide gas liberated with arsine gas.

(iv) Care must be taken that the filter paper remains quite dry during the reaction.

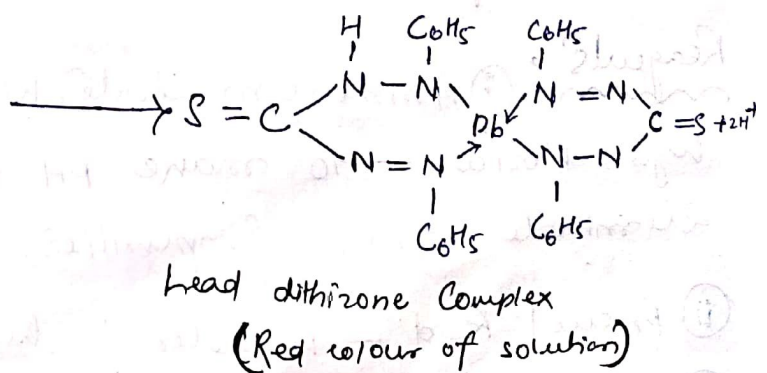
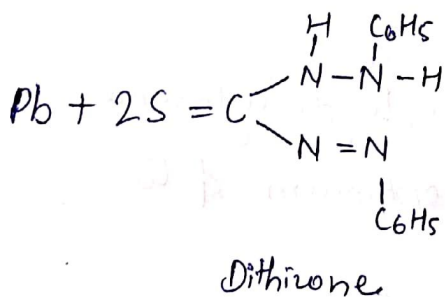
(v) All the reagent used for this test should be free from arsenic.

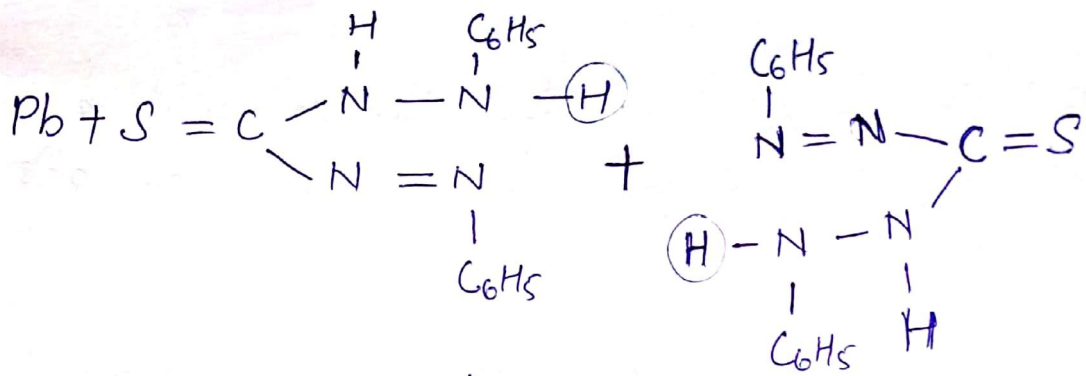
LEAD TEST FOR LEAD (separating funnel)

Principle: Based on the reaction between lead (Pb) and Diphenylthiocarbazone (Dithizone) in alkaline medium to form lead dithizone complex, which is red in colour. ^(Vider)

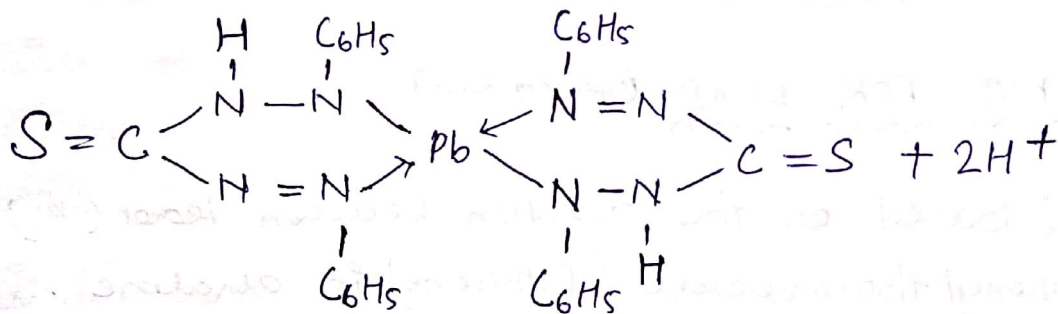


Reaction





↓ Alkaline



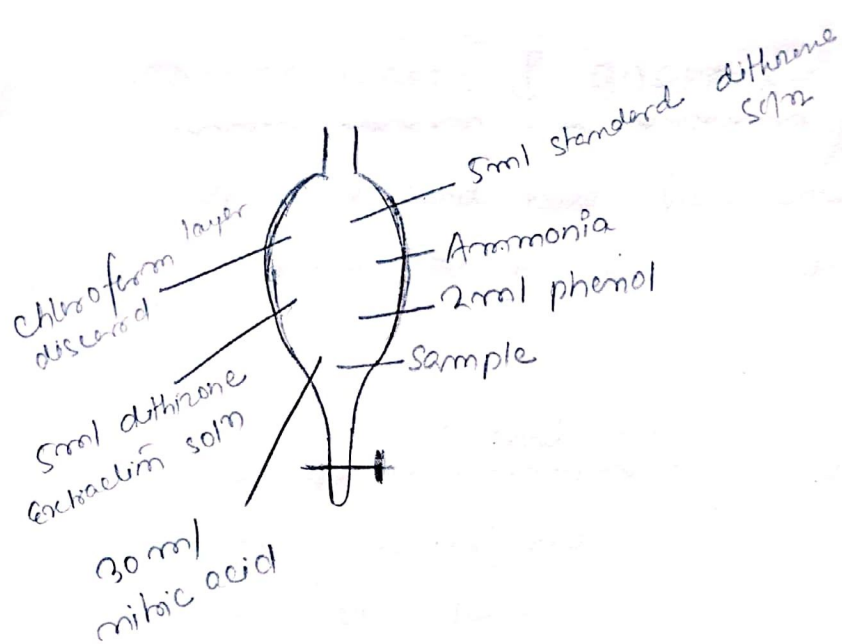
(Lead dithione complex)

Colour → Dithione in chloroform - Green colour
Lead dithione complex - Purple (violet)

* Resulting soln form, from above is in Red col^r

Reagents: (i) Ammonium citrate, KCl, hydroxylamine, hydrochlorid — to make pH optimum & to eliminate other impurities.

- (ii) Phenol Red — Indicator to help col^r development.
- (iii) Dithione Extraction Soln — To extracting lead as impurities from substance.



Test

Standard

(i) A known quantity of sample solution is transferred in a separating funnel.

(i) A standard lead solⁿ is prepared to the amount of lead permitted in the sample under examination.

(ii) Add 6ml of ammonium citrate.

(Same)

(iii) Add 2ml of potassium cyanide and 2ml of hydroxylamine hydrochloride.

(Same)

(iv) Add 2 drops of phenol red.

(Same)

(v) Make solⁿ alkaline by adding ammonia solution.

(Same)

(vi) Extract with 5ml of dithizone until it becomes green.

(vii) Combine dithizone extracts are shaken for 30 mins with 30 ml of nitric acid and the chloroform layer is discarded.

(viii) To the acid solⁿ, add 5ml of standard dithizone solⁿ.

(ix) Add 4ml of ammonium cyanide.

(x) Shake for 30 minutes.

(xi) Observe the colour.