WELCOME
TO
Drx Notes

Chapter 1: Introduction to Pharmaceutical chemistry:

Syllabus:

- Scope and objectives
- Sources and types of errors: Accuracy, precision, significant figures .
- Impurities in Pharmaceuticals: Source and effect of impurities in Pharmacopoeial substances, importance of limit test, Principle and procedures of Limit tests for chlorides, sulphates, iron, heavy metals and arsenic.

Scope

The pharmaceutical chemistry is designed to impart basic knowledge on the chemical ,structure, storage conditions and medicinal uses of organic and inorganic chemical substances used as drugs and pharmaceuticals.

Also, the pharmaceutical chemistry discusses the impurities, quality control aspects of chemical substances used in pharmaceuticals.

Objectives

The pharmaceutical chemistry will discuss the following aspects of the chemical substances used as drugs and pharmaceuticals for various disease conditions .

1. Chemical classification, chemical name, chemical structure
2. Pharmacological uses, doses, stability and storage conditions
3. Different types of formulations / dosage form available and their brand names
4. Impurity testing and basic quality control tests

Sources and types of errors:

✓ It has been said that reliability, reproducibility and accuracy are the basis of analytical chemistry .

✓The task of the analytical chemist will be to devise methods which give results that are reliable, reproducible and accurate.

✓But every measurement made, no matter how systematically and carefully, is subject to some degree of uncertainty or error.

✓It is impossible to perform a chemical analysis that is totally free of errors or uncertinities .

✓Errors are caused by faulty calibration or standardization or by randam variations and uncertinities in results .

Errors

✓Errors refers to the difference between a measured value and the True or known value

✓Error often denotes the estimate uncertainty in a measurement or experiment .

Defination of errors :

The difference between the experimental mean and a true value is termed as absolute error .

Absolute error may be positive or negative .

Thus,

$$\text{Relative error} = \frac{\text{Measured mean value} - \text{True value}}{\text{True value}}$$

Accuracy

✓The term accuracy refers to the agreement of experimental result with the true value and it is usually expressed in terms of error .
✓In scientific experiments it is known that true value is not known .
✓It is simply the value that has been accepted and is usually a means calculated from the results of several determinations from many laboratories employing different techniques .

Precision

✓Precision may be defined as the degree of agreement between various results of the same quality .
✓That is it refers to the reproducibility of a result , good precision are not necessarily accurate.
✓A constant error may always yield reproducible results yet deviating accuracy .
✓An analytical chemist always attempts for reproducible results to assure the highest possible accuracy .

Example :

A chemist prepared a buffer solution of pH 4.62. When an analyst made replicate measurements of the pH of the solution by a pH meter, the following values were obtained: 4.59, 4.63 and 4 .60 Calculate the absolute error and the relative error for each of these values.

Solution :

Here the true value x, is 4.62

Absolute error (i) 4.59 - 4.62 = - 0.03

(ii) 4.63 - 4.62 = + 0.01

(iii) 4.60 - 4.62 = - 0.02

Relative error	Relative error (percent)	Relative error (part per percent)
(i) -0.03/4.62 = 0.0065	-0.0065 X 100 = -0.65	-0.0065 X 1000 = -6.5
(ii) 0.01/4.62 = 0.002	0.002 X 100 = 0.20	0.002 X 1000 = 2.0
(iii) -0.02/4.62 = 0.0043	- 0.0043 X 100 = - 0.43	- 0.0043 X 1000 = - 4.3

Classification of Errors

The errors which affect an experimental result may be conveniently divided into:

1.Systematic/determinant/non-random errors :

(a) Instrumental errors:

(b) Operational/Personal errors:

(c) Methodical Methodological errors :

2.Non-systematic/Indeterminant/Random/accidental errors.

1. Systemic or Determinant or Constant Errors:

These are those errors, as the name implies are determinable and can be either avoided or corrected.

These errors are non-random and occur when something is wrong with the measurement.

These errors may be additive/multiplicative depending on the nature of the error.

Sub-types of determinate errors:

(a) Instrumental errors:

Errors occur due to faulty instrument or reagents containing impurities.

Following factors are responsible for such errors:

- Balance arms of unequal lengths.
- Uncalibrated or improperly calibrated weights.
- Uncalibrated instruments like digital balance.
- Incorrectly graduated burettes.

These errors can be avoided by using calibrated weights, glassware and pure reagents

(b) Operational/Personal errors:

When errors occur during operation or carrying out the experiment is called as **operational error.**

✓ e.g., transfers of solution, use of indicator, poor colour discrimination, reading uncertainty-while reading scale, incomplete drying of sample or precipitate, underweighting of precipitates, overweighing of precipitates, lack of skills and insufficient cooling of precipitates, mathematical errors in calculations, errors during transfer of solutions, etc.

✓ These errors are physical in nature and occur when proper analytical techniques are not followed.

✓Errors for which the individual analyst is responsible and are not connected with the method or procedure is called as **personal errors.**

✓ e.g., inability in judging colour change sharply in visual titrations, error in reading a burette,

(c) Methodical Methodological errors :

✓ These are the most serious errors of analysis.

✓Most of the above errors can be minimized or corrected for, but errors that are inherent in the method cannot be changed unless the conditions of the determinations are altered.

✓For example, Error occurs due to co-precipitation of impurities, side reactions, post-precipitation (in gravimetric analysis), volatilization, etc.

✓**Examples:** In the titrimetric analysis, errors occur due to failure of reaction, side reaction, the reaction of substances other than the constituent being determined, the difference between the observed endpoint and the stoichiometric equivalence point of a reaction., Sometimes a correction can be simple by taking blank reading to identify impurities introduced by solvents and reagents,

When errors become intolerable, another approach to the analysis must be made. But sometimes we forced to accept a given method in the absence of a better one.

2. Non-systematic/indeterminant/Random/Accidental Errors:

These are often called accidental or random errors, which represent experimental uncertainty that occurs in any measurements, These errors are shown by small differences in successive measurements made by the same analyst under almost similar conditions.

These errors cannot be predicted or determined. However, they can be considerably reduced by careful work and by the increase in the number of repeated determinations.

This kind of errors mainly affect the precision of measurement.

Example:

• During the course of series of replicate measurements, the temperature might fluctuate slightly, This would cause slight variations in the volumes associated with the use of pipette or burette, • Instrumental uncertainty is the major source of random error. a Experienced chemist touches the pipette against the side of the conical flask permit it to drain for a set time. However, the way in which they do this and the tim which is allotted for drainage may vary, even if only slightly, This variation will cause a variation in the volume delivered .

Difference between Determinant and In-determinant Errors

Determinant Errors	In-determinant Errors
These are also known as Systemic or These are also known as Non-non-random or Constant errors.	These are also known as Non systematic or random or accidental errors.
These errors are determinable and can These errors can never be determined and eliminated but can be minimized by careful work.	These errors can never be determined and eliminated but can be minimized by careful work .
These errors are recognized by the lack of agreement between the mean of a series of replicate determinations and the correct value.	These errors are recognized by variability in the replicate determinations, i.e., by the scatter of result about their mean .
These errors are quantified by a measure of accuracy such as absolute error or the relative error of the mean.	These errors are quantified by a measure of precision such as standard deviation or the relative standard deviation
The sources of these errors may be personal, instrumental and methodological bias,	The sources of these errors may be personal, instrumental uncertainties.

Significant Figures

It carries the meaning in a number and contributes to its precision . A significant figure denotes which figures are really giving information about how precise our measurements are the significant digits are indicated by underlining only those digits which are significant .

The significant figures can be easily identified by applying the following simple tricks :

Significant	Non -Significant
All non-zeros are significant e.g: 1,2,3,4,5,6,7,8,9	All starting zeros are non – significant e.g: 0.0123 , 0.00001
Trapped zeros/Zeros appearing in between non- zero digits are significant e.g: 101,2001,0.001002,90.001	All ending zeros without decimal point are non-significant e.g: 100,55600, 50100
Ending zeros with a decimal point are significant e.g: 6.300,50.000,96.60	

Sources of Impurities

The various sources of impurities in pharmaceutical substances are as follows:

A.Raw Materials

*Reagents Used
*Intermediate Products
*Reagents used to eliminate impurity
*Solvents Used
*Atmospheric Contamination

B. Method of Manufacturing

*Contamination from Matter
*Cross Contamination
*Contamination by Microbes
*Errors in Manufacturing
*Errors in Storage & Packaging

C. Manufacturing Hazards

*Reaction with Container
*Temprature

D. Instability of Products

*Chemical Instabilities
*Physical Instabilities

1. Raw Materials:

- ✓ Pharmaceutical substances are either isolated from natural sources or synthesized from chemical starting materials which have impurities.
- ✓ Impurities associated with the raw materials may be carried through the manufacturing process to contaminate the final product.

2. Method of Manufacture:

- ✓ The Process or method of manufacture may introduce new impurities.
- ✓ Due to impure reagents, catalysts and solvents, reaction vessels and reaction intermediates employed at various stages.

(A)Reagents employed in the manufacturing process:

- Calcium carbonate contains 'soluble alkali' as impurity Anions like Cl - and SO 4 -2 are common impurities in many substances because of the use of hydrochloric acid and sulphuric acid respectively
- Barium ion may be an impurity in hydrogen peroxide

(B) Regents used to eliminate other impurities:

- Barium is used to remove sulphate from potassium bromide, which can be found itself (barium) as impurity at the end of process.

(C)Solvents:

- Small amounts of solvents employed in preparation, and purification of the product may also result in the contamination of the pharmaceutical substances.

▪Water is the cheapest solvent which can be the major source of impurities as it contains different type of impurities like Ca 2+ , Mg 2+ ,Na + , Cl - , CO3 -2 and SO 4 -2 in trace amounts.

(D)Intermediates:

▪Sometimes, an intermediate substance produced during the manufacturing process may contaminate the final product

▪e.g. Sodium bromide is prepared by reaction of sodium hydroxide and bromine in slight excess.

▪ o 6 NaOH + 3 Br 2 → NaBrO 3 + 5 NaBr + 3 H 2 O …(1)

▪The sodium bromate an intermediate product is reduced to sodium bromide by heating the residue with charcoal.

▪ NaBrO 3 + 3 C → NaBr + 3 CO …(2)

▪If sodium bromate is not completely converted to the sodium bromide then it is likely to be present as an impurity.

(E) Atmospheric contamination during the manufacturing process:

- Atmosphere may contain dust (aluminium oxide, sulphur, silica, soot etc.) and some gases like carbon dioxide, sulphur dioxide, arsine and hydrogen sulphide.
- These may contaminate the final product during the manufacturing process.
- e.g. sodium hydroxide readily absorbs atmospheric carbon dioxide when exposed to atmosphere.
- $2\ NaOH + CO\ 2 \rightarrow Na\ 2\ CO\ 3 + H\ 2\ O$

3.Manufacturing hazards:

✓If the manufacturer is able to control and check impurities from the all above mentioned sources there exists certain manufacturing hazards which can lead to product contamination.

(A) Contamination from the particulate matter:

The unwanted particulate matter can arise by accidental introduction of dirt or glass, porcelain, plastic or metallic fragments from sieves, granulating, tabletting and filling machines and the product container.

(B) Cross-contamination of the product:

- ✓ Cross-contamination of product can occur by air-born dust arising out of handling of powders, granules and tablets in bulk.
- ✓ If 2 or more Products are manufactured in same time this type of contamination is possible.

(C) Contamination by microbes:

✓ Many products, like liquid preparations and creams intended for topical applications are liable to contamination by microbes from the atmosphere during manufacturing.

✓ Microbes like Bacteria, fungi, Algae etc can contaminate the final product.

(D) Errors in the manufacturing process:

✓ Sometimes in a liquid preparation, there is incomplete solution of the solute.

✓ A error on the efficiency of mixing, filling, tabletting, sterilization etc arise impurity in final product.

(E) Errors in the packaging:

✓ Similar looking products, such as tablets of the same size, shape and colour, packed in similar containers can result in mislabeling of either or both of the products

(4) Instability of the product:

(A) Chemical instability:

✓ Impurities can also arise during storage because of chemical instability of the pharmaceutical substance.

✓Many pharmaceutically important substances undergo chemical decomposition when storage conditions are inadequate.

✓This chemical decomposition is often catalyzed by light, traces of acid or alkali, traces of metallic impurities, air oxidation, carbon dioxide and water vapours.

(B) Changes in physical properties:

✓ Pharmaceuticals may undergo changes in physical properties during storage.

✓There can be changes in crystal size and shape, sedimentation, agglomeration and caking of the suspended particles.

(C) Reaction with container material:

✓ The possibility of reaction between the container material and the contents can be possible.

✓ Preparations susceptible to reaction with metal surfaces

✓ e.g. salicylic acid ointment must not be packed in metal tubes.

✓ Plastic containers and closures have tendency to give undesirable additives, such as plasticizers, particularly in the presence of non-aqueous solvents.

(D) Temperature:

✓ The rate of chemical decomposition and physical changes of stored products depends upon the temperature.

✓The susceptible substances may have temperature storage requirements assigned to them in order to protect them against undesirable decomposition.

Limit test

➢ Limit = a value or amount that is likely to be present in a substance

➢ Test = to examine or to investigate

❖**Limit test is defined as** quantitative or semi quantitative test designed to identify and control small quantities of impurity which is likely to be present in the substance.

▪ Limit test is generally carried out to determine the inorganic impurities present in compound.

▪In short, limit test is nothing but to identify the impurities present in the substance and compare it with standard.

❖**Importance of Limit tests:**

▪ To find out the harmful amount of impurities .

▪To find out the avoidable/unavoidable amount of impurities.

Limit test for chloride

Principle

1: Chemical Interaction

Limit test for chloride depends upon the interaction of chlorides with silver nitrate in the presence of dilute nitric acid.

2: Precipitation/Opalescence

Deposition of solid particle of chloride as silver chloride.

3: Comparison of test sample with standard

Chloride as impurity is present in very small quantities. In the chemical interaction the precipitation of silver chloride appears as opalescence. It is compared under uniform conditions of illumination with standard opalescence in Nesslers cylinders to draw inference.

Proposition

Chemical Reaction:

$$\underset{\text{(Soluble)}}{Cl} + \underset{\text{(Soluble)}}{AgNO_3} \xrightarrow{\text{Dilute } HNO_3} \underset{\text{(Precipitate)}}{AgCl} + \underset{\text{(Soluble)}}{NO_3}$$

Procedure:

Standard solution :

1. Take 10 ml of chloride standard solution. (25 ppm CI) in labeled Nesslers cylinder (S).
2. Add 5 nil of distilled water.
3. Add 10 ml of dilute nitric acid and mix well.
4. Dilute to 50 ml with distilled water.
5. Add 1 ml of 0.1 M silver nitrate solution.
6. Stir immediately with glass rod and allow to stand for 5 minutes, protect from light.

Test solution of sodium bicarbonate :

1. Weigh accurately 1.25 g of sodium bicarbonate
2. Dissolve it in 15 ml of distilled water in a labeled Nesslers cylinder (1).
3. Add 2 ml of dilute nitric acid and mix well.
4. Dilute to 50 ml with distilled water.
5. Add I ml of 0.1 M silver nitrate solution
6. Stir immediately with glass rod and allow to stand for 5 minutes, protect from light.
7. View transversely, against a black background.
8. Compare the opalescence produced with that of standard solution.

Limit test for sulphate

Principle

1; Chemical Interaction

Limit test for sulphate depends upon the interaction of soluble sulphate with barium chloride in presence of alcohol and potassium sulphate.

2: Opalescence/ precipitation

Deposition of solid particles of sulphate as barium sulphate.

(barium chloride, alcohol and a small amount of potassium sulphate is used for this purpose, alcohol prevents supersaturation and potassium sulphate increases sensitivity of the test by giving ionic concentration in the reagent which just exceeds the solubility product of barium sulphate.)

3: Comparison of test Sample with standard

The opalescence/turbidity produced by sample under test is compared with standard sample opalescence/turbidity against the dark background.

Chemical Reaction:

$$BaCl_2 + SO_4 \longrightarrow BaSO_4 + 2Cl$$

Procedure:

Standard solution :

1.Take 1 ml of 25% w/v solution of barium chloride in the Nesslers cylinder (S).

2. Add 1.5 ml of ethanolic sulphate standard solution(10 ppm SO4) mix and allow to stand for 1 minute.

3. Add 0.15 ml of 5 M acetic acid.

4. Add sufficient water to produce 50 ml, stir immediately with glass rod.

5. Allow to stand for 5 minutes.

Test solution of sodium bicarbonate :

1. Take 10 ml of purified water in a labeled Nesslers cylinder (T).
2. add 0.1 ml of 2M hydrochloric acid.
3. And add 0.1 ml of 25% w/v barium chloride solution.
4. Observe the appearance of the solution for 1 hour. (Appearance of solution does not change for at least 1 hour)

Limit test for Iron

Principle:

1: Chemical Interaction

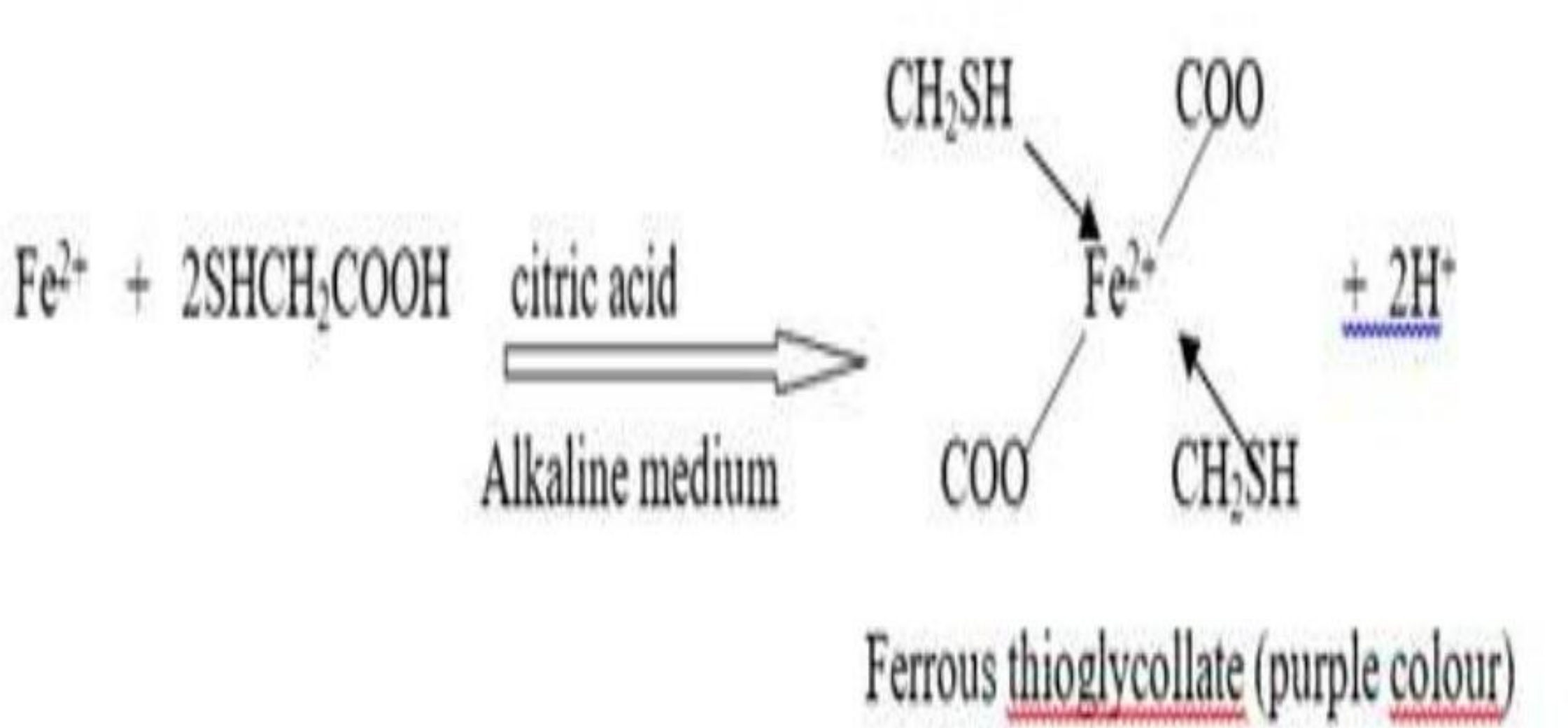
Limit test for iron based upon the chemical reaction of iron in ammonical solution in presence of iron free citric acid with thioglycollic acid, it forms ferrous thioglycolate complex.

2: Colouration A purple colour is formed due to formation of ferrous thioglycolate complex. The original state of iron is unimportant as thioglycollic acid reduces ferric to ferrous . This test is vary sensitive making use of 20 % citric acid, which forms, complex with other metal ion, eliminates interference of other metal ions.

(Note:-',purple colour is developed only in alkalne medium, so ammonia solution is used, but ammonia solution forms precipitate with iron, therefore citric acid is added to form ammonium citrate buffer which stabilizes ferrous thioglycolate complex).

3: Comparison with standard The colour produced by sample under test is compared with the coloured produced by the standard solution.

Chemical Reaction :



Procedure:

Standard solution :

1.Take 2.0 ml of iron standard solution (20 ppm Fe) in labeled Nesslers cylinder (5).

2. Acid 2 ml of a 20% wiv solution of iron-free citric acid.

3. And add OA ml of thioglyconic add, mix well, make alkaline with iron free ammonia solution.

4. Dilute to 50 ml with water and allow to stand for 5 minutes

Test solution of Zinc Sulphate :

1.Weigh accurately 2.5 g of zinc sulphate and dissolve in sufficient carbon dioxide free water to produce 50 ml In a beaker. Take 2.0 ml of solution and diluted to 10 ml with water in a labeled Nesslers cylinder (T),

2. Add 2 ml of a 20% wlv Solution of iron-free citric acid.

3. And add 0.1 ml of thioglycollic acid, mix well and make alkaline with iron free ammonia solution.

4. Dilute to 50 ml with water and allow to stand for 5 min.

5. View the colour intensity against white background and compare with that of standard.

Limit test for Heavy Metals

Principle:

1: Chemical Interaction

Limit test for heavy metal is based upon the reaction between hydrogen sulphide and certain heavy metals such as lead. iron, copper, nickel. cobalt and bismuth resulting in the formation of sulphides of the respective metals in presence of dilute acetic acid.

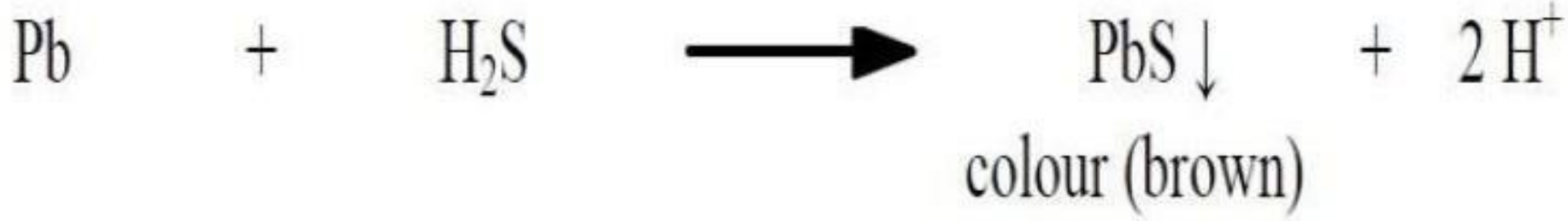
2: Colouration

The sulphides so formed are distributed in a colloidal state and produce brownish coloured solution.

3: Comparison of sample with standard

The intensity of colour produced in test is compared with intensity of colour produced in standard solution.

Chemical Reaction :



Procedure:

Standard solution :

1. In to a 50 ml labeled Nesslers cylinder (S) Pipette 1.0 ml of lead standard solution (20 ppm Pb).
2. Dilute with distilled water to 25 ml.
3. Adjust the pFt with dilute acetic acid or dilute ammonia solution in between 3.0 to 4.0.
4. Dilute with distilled water about 35 ml and mix with glass rod.
5. Add 10 ml of freshly prepared hydrogen sulphide solution,
6. Mix and dilute to 50 ml with water.
7. Allow to stand for 5 minutes.

Test solution of Sodium Chloride :

1. Accurately weigh 4 g of sodium chloride and add to labeled Nesslers cylinder (T).
2. Add 2 ml of dilute acetic acid and mix well, then add sufficient water to produce 25 ml.
3. Adjust the pH with dilute acetic acid or dilute ammonia solution in between 3.0 to 4.0.
4. Dilute with water to 35 ml and mix well.
5. Add 10 ml of freshly prepared hydrogen sulphide solution.
6. Mix and dilute to 50 ml with water.
7. Allow to stand for 5 minutes.
8. View downwards over a white surface and compare with that of standard.

Limit test for Arsenic

Principle:

1: Limit test for arsenic is based on semiquantitative determination of arsenic impurities in the test sample of drug. The sample is dissolved in stannated acid, which converts the arsenic impurities to arsenious acid or arsenic acid depending upon valency state of arsenic impurity present in the test

2:When acidic solution of sample treated is with reducing agent (stannous chloride) converts pentavalent arsenic acid into the trivalent arsenious acid.

3:The arsenious acid is then converted into gaseous arsenious hydnde (arsine gas) with the help of nascent hydrogen (which is produced by zinc and hydrochloric acid.

4:Arsine gas is carried through the tube by the steam of hydrogen and out through the mercuric chloride paper. A reaction occurs between arsine and mercuric chloride, which produces yellow colour stain.

5:The stain produced by test sample compared with that of standard arsenic solution. The limit of arsenic is expressed as part per millions.

Chemical Reaction :

LIMIT TEST FOR Arsenic

$$H_3AsO_4 \longrightarrow H_3AsO_3$$

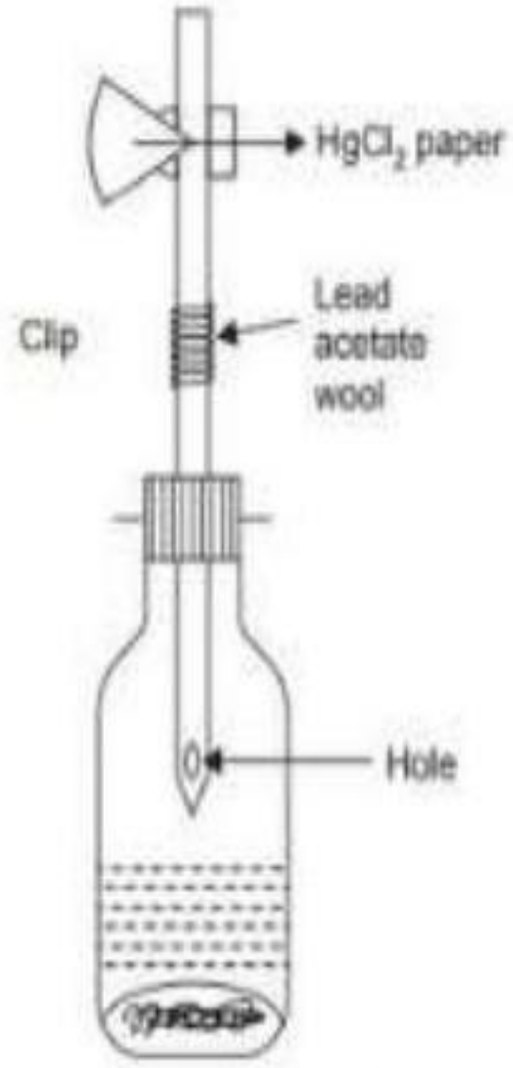
Arsenic Acid — Arsenious Acid

$$H_3AsO_3 + 6[H] \longrightarrow AsH_3 + 3H_2O$$

Arsenious Acid — Arsine Gas

$$AsH_3 + HgCl_2 \longrightarrow Hg(AsH_2)_2 + 2HCl$$

Arsine Gas



Procedure:

Standard solution :

1.Take 1 nil of arsenic standard solution (10 ppm As).
2. Dilute to 50 ml with water in the glass bottle/flask.
3.Add 5 ml of 1M potassium iodide.
4. And add 10 g zinc (AsT), mix it wel.
5. Immediately assemble the apparatus and immerse the bottle/flask in a water bath at a temperature such that a uniform evolution of gas is maintained.
6.Allow the reaction to take place for 40 minutes.
Note: - AsT = Tested for arsenic.

Test solution of Sodium Acetate :

1.Accurately weigh 5 g of sodium acetate and dissolve in 50 ml water in the glass bottle/flask.
2. Add 15 ml of stannated hydrochloric acid (AsT).
3. To this add 5 ml of 1 M potassium iodide.
4. Add 10 g of zinc AsT.
5. Immediately assemble the apparatus and immerse the bottle/flask in a water bath at a temperature such that a uniform evolution of gas is maintained.
6. Allow the reaction to take place for 40 minutes. after 40 minutes any stain produced by test sample on mercuric chloride paper is compared with that of standard.