

Introduction to Pharmaceutical Chemistry

We Cover in this notes 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.

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Introduction to Pharmaceutical Chemistry

Introduction of Pharmaceutical chemistry: - Pharmaceutical chemistry is a Branch of chemistry which deals with the study of organic chemistry (Molecules & Compound) In combination with structural & chemical biology & pharmacology for producing pharmaceutical drugs & medicines.

Pharmaceutical chemistry comprises drug development & is the study of drugs. This includes drug discovery, metabolism, absorption, delivery.

They contain drug chemistry, quality, assurance, metabolism, pharmacology, and analytical techniques & cures & remedies disease.

Scope of Pharmaceutical chemistry:

- Quality Assurance & Quality control (QA & QC):- Processes & standards that ensure quality of drug compounds.
- Drug Discovery: - Identifying compound, especially those that treat disease.
- Industry:-
- Pharmaceutical chemistry Teacher for College institute etc.

Sources and types of errors, Accuracy, Precision, Significant figures.

Introduction of Errors— Errors is define as the deformity present in any measurements by addition of any internal or external factor. In the pharmaceutical science errors are induced by the defective equipment and methods.

In analytical chemistry errors are affects the material products reliability, reproducibility, and accuracy or precision.

During an analysis, the results are expected to be highly accurate and precise. However, it is not happening in all cases because due to presence of errors.

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These errors may be predictable or unpredictable. Depending on the calculative nature errors are categorized into two parts.

Absolute Errors— Difference between experimental mean value and true/actual value is known as absolute errors. Absolute errors may be positive and negative.

$$\text{Absolute errors} = \text{Measured mean value} - \text{True value}$$

Relative Errors— Relative error is defined by dividing the absolute errors by the true values. It is generally expressed as percentage, that is by multiplying the relative error by 100 or by expressing it as parts per thousand by multiplying the relative error by 1000.

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

Questions- In the tea leaves actual content of caffeine is 3.50% and if any analyst are analyses the tea leaves and determine the caffeine content is 3.75% then determine the absolute and relative error(in percentage an part per thousand) ?

Answer—Actual caffeine content—3.50

Measured caffeine content—3.75

- *Then absolute error is—3.75 – 3.50= 0.25.*
- *Relative error in percentage—0.25/3.50*100= 7.14*
- *Relative error in part per thousand—0.25/3.50*1000=71.42*

On the basis of nature and source errors are categorized into two principles.

1. Determinate or Systematic Errors.
2. Indeterminate or Random Errors.

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1. **Determinate or Systematic Errors**— Systematic errors are arises due to the wrong procedure, wrong measurement (pipettes, burette, volumetric flasks) and faulty instruments (calibrated balance and machinery system).

Systemic error is under the control of the analyst because it is easily detectable and can be eliminated to a large extent.

Sources of systematic Errors— sources are mentions below.

Instrumental Errors— Due to the use of defective equipment or low quality instruments, errors are arises in the analytical procedure. It is easily checkable by the analyst.

Proportional Errors— The absolute value of this kind of the errors changes with the size of the sample in such a fashion that the relative error remains constant. It is easily incorporated by a material that directly interferes in analytical process.

Personal Errors— Errors are induced due to the carelessness, or ignorance and lack of skilled. This error is also called operative error. It is occurs by who are handling the method of analysis.

Chemical/Reagent Errors— Chemical errors are based on the chemical reactivity between the using chemical and reagent.

Errors in Methodology— It is a most serious error in analysis, as the error arises due to faulty methods.

*Example—**incomplete reactions, Co-precipitation of impurities etc.***

Impurities and contamination may also altered the chemical reactivity and induce the errors.

2. **Indeterminate or Random Errors**— In this error we not define the specific well known reason and cannot be eliminated, so it is also called as accidental errors.
 - It is induced by the several successive measurements performed by the same analyst under the same conditions and identical experiments.

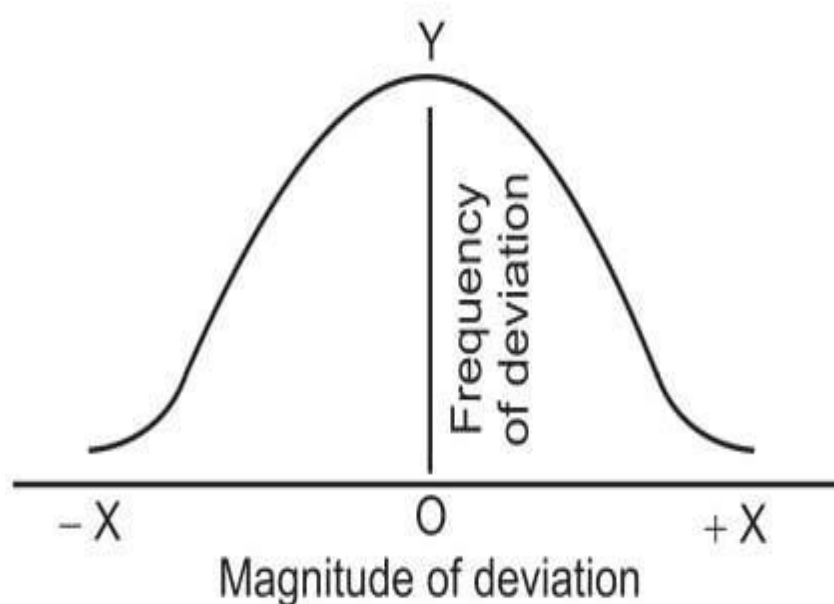
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Such accidental errors will follow a random distribution pattern and the mathematical law of probability can be applied to get net conclusion regarding the results.

Indeterminate errors are defined by this graph.

The magnitude of errors (abscissa) and the frequency of deviation (ordinate) have the shape of a normal frequency distribution curve or probability curve. This graph is also called as CURVE OF ERROR. Graph represent that's



- Very large errors are unlikely to occur.
- Smaller errors occur with greater frequency than the large errors.
- The errors on the positive and negative side occur with equal probability.

Accuracy

Accuracy— Nearest or accurate value which are matches to the true value of any experiments is defined the term accuracy.

Accuracy is also described as degree of agreement between a measured value and the accepted true value. In scientific experiments, since no measurement is

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completely accurate, the true value is not known within certain limits. It is the simple taken as a value that has been accepted and is generally a mean calculated from the results of several determinants from many laboratories using different techniques.

The comparison is normally done with regard to the error and the accuracy is inversely proportional to the error.

Precisions.

Precisions are defined as the agreement amongst a cluster of experimental results, however, it does not imply anything with respect to their relation to the 'true value' precisions designates 'reproducibility' of a measurement, where accuracy, but ironically a high degree of precision may not necessarily suggest accuracy.

Precision define the ranging nearest value of any experiment to the initial value.

Example—Analyst perform the experiment on milk with respect to water and conclude that—88.3, 85.4, 86.8, 88.5, 87.9.

Actual water percentage in milk is 87

Then precision range is—85.4 to 88.5.

SIGNIFICANT FIGURES.

In the analysis, significant figures play a very important role in accuracy and precision. The number of significant figures can be defined as, "the number of digits necessary to express the result of a measurement consistent with the measured precision".

Each digit denotes the actual quality that it specifies.

It should be clear that zeroes are employed to denotes the significant parts of measurement—to denotes ten, hundred, thousand, etc or merely to locate the decimal point.

Examples - 25.05 and 1350—Zero shows significant number and it contains the four significant numbers.

0.0034 — Zero only denotes the decimal point

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Examples — If any burette we measured the exact 7ml and 7.3ml because burette are graduate in smallest graduation per ml are divided into 0.1ml ten equal parts. But some are measured in the form of significant figures.

7.34 — it contains the three significant figures of which two are certain and one are uncertainty.

How to minimizing the errors--

- Calibration of Instruments, apparatus.
- Personal care (skilled) required.
- Choosing the suitable and usable materials.
- Exhausted the impurities contamination.
- Study chemical evaluation and analysis.
- Proper methodology.

Impurities in pharmaceuticals

Impurities — Impurities is defined as the presence of undesired/unexpected material during any procedure and may alters the final products.

The substances that are used in the pharmaceuticals should be pure enough to be used safely but it is difficult to obtain an absolute pure substances.

Generally the impurities is the accidental factors and some time it is depends on the several method of the manufacture, and types of crystallization or purification process.

Most of impurities cause the harmful effect in the pharmaceutical preparation so it is a challenging tasks for pharmaceutical to removing the impurities.

Alternatively, a reasonably acceptable purity can be achieved by controlling various sources or reasons that add to the impure nature of an active pharmaceutical ingredients, or drugs as well as excipients used in pharmaceutical formulations . pharmacopoeia have fixed the limit for their impurities.

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Sources of impurities.

Impurities may enter or formed in a drug substance during any of the following three stages---

1. During manufacturing.
2. During purification and processing.
3. During storage.

1. During manufacturing-

Raw material employed— Impurities present in raw materials may be carried through the manufacturing process to contaminate the final product. Impurities such as As, Pb, Heavy metals, chlorides associate in the manufacturing unit.

Example- Rock salts contains the small amount of calcium sulphate and magnesium chloride. Thus sodium chloride prepared from this source will contain traces of calcium and magnesium compounds.

Example- Copper sulphate may be prepared by the action of sulphuric acid on copper turnings. Copper turning are known to have iron and arsenic impurities.

Reagents used in manufacturing process- The quality and purity of reagents used for manufacturing the drug substances are very important. If reagent used in the manufacturing process contains some impurities these may find entry into the final products

Example- Sulphuric acid is used in many chemical processes. This acid often has lead present in it. Anions like chlorine and sulphate are common impurities in many substances because of the use of hydrochloric acid and sulphuric acid respectively in processing.

Solvents used in the manufacturing process- Naturally, solvents play an important role next to the main reagents as most of the chemical reactions involved in these processes are solvent based. If proper quality/purity of solvents is not assured, they may add to the impurities. Solvents like toluene, n-butanol contain water as an azeotrope. Alcoholic solvents also may be contaminated with water

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and ethyl acetate can contain acetic acid in small amounts. Thus, quality of solvents needs to be assured and controlled.

Reaction equipment- The reaction vessels employed in the manufacturing process may be metallic or mild steel with glass lining. Some solvents and reagents employed in the process may react with the metals of the reaction vessels, leading to their corrosion and passing traces of metal impurities into the solution, contaminating the final product.

Example- Acid like HCl if by chance contain a small amount of fluoride, it can itch the glass lining and begin the metallic contamination. Lead, antimony, bismuth etc. can crop up as impurities from the vessels.

Intermediate products in manufacturing process- Some intermediate which are produced during the manufacture may be carried out through the final product as impurities. In the manufacturing process of potassium iodide, the intermediate iodate is the main impurity.

Manufacturing Hazards- In industrial areas, the atmosphere is contaminated with dust particle, silica glass, carbon gases. During the manufacture of pharmaceutical products, these impurities may enter the final products and alters the product potency.

2. During purification and processing—

Often if not properly controlled, impurities also get added during the purification processes, mainly through the purifying reagents, solvents or vessels used.

Reagent used to remove other impurities- Sometime some chemicals are added to remove or to participate another substance. This may be also give rise to source of impurity.

For example- BaCl_2 is added to remove excess of sulphate in AlCl_3 , hence AlCl_3 is likely to contain Barium as an impurity.

Solvents used in the process of purification— Often the solvents used for purification can be sources of impurities. These solvents range from organic solvents to acid (organic as well as mineral) and of course water.

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Water is the cheapest solvent and most widely used. Therefore, it is known as universal solvent.

Contamination due to vessels and equipment(filters, centrifuges, dryers etc) used for purification— During the purification processes, if the vessels are defective or not perfectly cleaned and dried they may add impurities like metallic ions, rust, glass particle, moisture etc.

3. During storage and packing—

Errors in packaging materials- During the process of packaging or filling and sealing, proper material which can ensure complete foolproof packaging without access to the atmosphere and light will ensure the stability of the product. Thus, quality and strength of packaging material is very important. For example- if the aluminum foil for the tablet strip or capsule for a liquid formulation bottles is of substandard quality it can add to impurities.

Faulty packaging process- Most of the pharmaceutical packaging processes are assembly lined automated process, generally involving pressing and sealing with heat. If the process parameters are not optimized or tampered with, then it may lead to contaminations and can be hazards.

Microbial contamination- Microbial contamination, mainly in the form of fungal and bacterial growth may be due to the result of improper storage conditions as well as faulty packaging. The products for parenteral administration and ophthalmic preparations have to undergo sterility testing.

Effects of impurities-

- Impurities are sometime harmless, but are present more than certain limits then it lowered the active strength of the substance. The therapeutics effects of the drug also altered by the impurities.
- Impurities may bring about an incompatibility in the original substance and cause the deterioration in the substance.
- Some impurities take direct participation in the chemical reaction and change the chemical behavior of the original substances.

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- Impurities, even when present in traces, may show a cumulative toxic effect after a certain period.
- Some impurities promote the microbial growth and that are responsible for the deterioration of the substances.
- Some impurities may be able to catalyze the degradation, thereby shortening the shelf life of the drug substance.
- Some impurities by virtue of their unstable nature like hygroscopic nature, oxidisable nature etc. Can bring about change in the physical properties like change in appearance, taste, odour, stability etc. of drug substance causing technical difficulties in its use as well as formulation.

Limit Test :

- Limit test is defined as quantitative or semi- quantitative tests which are performed to identify and control small amount of impurities which are likely to be present with the substance to be analysed.
- For to substance clarification and purity limit test perform a key role in the pharmaceutical analysis. Generally limit tests are carried out to identify the inorganic impurities present in the substance.
- Limit tests are not based on the numerical value.
- In these tests we are perform the comparison (Turbidity/Opalescences/Colour intensity) between the standard solution & test sample.
- Limit test of chloride and sulphates is based upon the measurement of opalescence or turbidity produce is the known amount of substance (by adding to reagent) and comparing it with the standard opalescence or turbidity. For comparison of turbidity for different substances to be used is varied and not the standard turbidity.

Importance of limit test.

- Limit test denotes the incompatibility of the solution in the presence of another substances.

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- Limit test are defined the amount of impurities which are present in the solution.
- Limit test make difference between avoidable and non- avoidable of impurities.
- Overall limit test are help in the purity and clarity of the solution.

Pharmacopeia standard for preparation of test solution during the limit test:

A specified amount of the substance is dissolved in distilled water, and volume makeup to 50ml in Nessler' cylinder.

For alkaline substances like Hydroxide, Carbonates etc. are dissolved in the sufficient quantity of acid so that effervescence ceases and free acid is present.

For insoluble substances like kaolin a water extract is prepared filtered and then the filtrate is used.

Salts of organic acids like sodium benzoate, sodium salicylate etc. liberated free water insoluble organic acid during acidification which is filtered off and the filtrate is used for the test.

Coloured substances like crystal violet, malachite green, dithizone etc. Are carbonized and the ash so produced is extracted in water.

Reducing Substance like Nitrite, Hypophosphate etc. are Oxidized with oxidizing agents and the solution is prepared and used.

Substance like potassium permanganate are reduced by boiling with alcohol and filtrate is used.

Limit test of chloride

Requirement:

Apparatus- Nessler's cylinder, pipette, stirring rod, beaker, stand.

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Chemicals- Dilute nitric acid (10%) Silver nitrate(5%), test sample, standard sample(Sodium chloride).

Chemical reactions



Principle— The limit test of chloride is based upon the chemical reaction between the soluble chloride ion with a silver nitrate reagent in a nitric acid media. The insoluble silver chloride renders the test solution turbid (depending upon the amount of silver chloride formed and therefore, on the amount of chloride present in the substance under test.

The turbidity is compared with the standard turbidity produced by the addition of silver nitrate, to the known amount of chloride ion (sodium chloride) solution. If the test solution shows less turbidity than the standard, the sample passes the test.

Procedure:

Test	Standard
Dissolve the test sample in water and transfer to the Nessler cylinder. Then add 1ml of dilute nitric acid and make the volume 50ml by adding water. Finally add 1ml of silver nitrate and stir immediately with stirring rod and set aside for 5 minutes. Observe the opalescence developed and compare with that of the test sample.	1ml of standard sample (0.05845% w/v) add in another cylinder. Then add the 10ml of nitric acid and make up the volume 50ml by adding water. Finally add 1ml of silver nitrate and stir immediately with stirring rod and set aside for 5 minutes. Observe the opalescence developed and compare with that of the standard sample.

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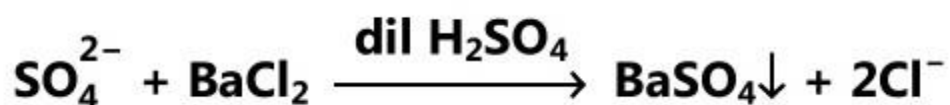
Limit test for Sulphate.

Requirement:-

Apparatus — Nessler's cylinder, pipette, stirring rod, beaker, stand.

Chemicals — Dilute hydrochloric acid test sample, standard sample, barium chloride.

Chemical reaction:-



Principle— In the limit test for sulphate, the solution of the substances under test is mixed with barium chloride reagent in the presence of dilute hydrochloric acid then turbidity produced.

After this, perform standard experiment in similar manner with a known quantity of sulphate ion(using potassium sulphate). The substance passes the limit test if it produce turbidity that is less than the standard.---

Limit Test For Iron.

Requirement:-

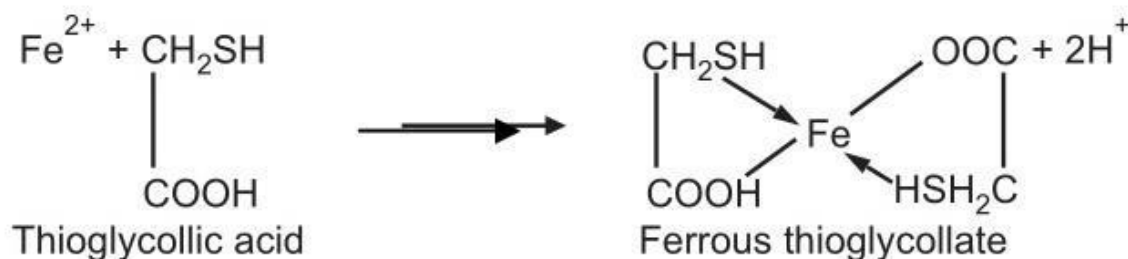
Apparatus — Nessler's cylinder, pipette, stirring rod, beaker, stand.

Chemicals— Test sample, standard sample, iron-free citric acid, iron-free ammonia solution, thioglycollic acid.

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Chemical reaction---



Principle— This test is based upon the reaction of iron in an ammonia solution, with thioglycollic acid which forms a pink to deep reddish purple colored complex of iron – thioglycollate .

Iron present in ferrous form and quite stable for long period in the absence of air .the color are destroyed by oxidizing agent and strong alkali. The original state of iron is unimportant, as thioglycollic acid reduces Fe^{2+} to Fe^{3+}

Then compared the test solution with standard solution (ferritic ammonium sulphate). It's the color from test solution is less dark than the standard, then the sample passes the test.

Procedure:

Test	Standard
<ul style="list-style-type: none">• Test sample dissolved in water in Nessler cylinder and make up the volume 40 ml.• Then add 2ml of 20% w/v solution of iron free citric acid and 0.1ml thioglycollic acid then mix.• Make alkaline with iron free-ammonia solution and make up volume 50ml.• Observe the intensity of the purple color developed by viewing vertically and compare with that of the test sample.	<ul style="list-style-type: none">• Take 2ml of standard iron solution in Nessler cylinder and make up volume 40ml by adding water.• Then add 2ml of 20% w/v solution of iron free citric acid and 0.1ml thioglycollic acid then mix.• Make alkaline with iron free-ammonia solution and make up volume 50ml.• d.Observe the intensity of the purple color developed by viewing vertically and compare with that of the standard sample.

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Inference of other metal cation is eliminated by making use of 20% citric acid which forms complex with other metal ions. Earlier ammonium thiocyanate reagent was used for the limit test of iron. Since thioglycolic acid is more sensitive reagent for iron .it has replaced ammonium thiocyanate in the test.

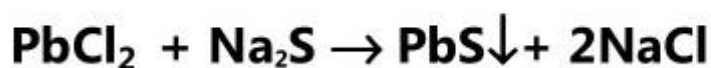
Limit test for heavy metal.

Requirement:

Apparatus— Nessler's cylinder, pipette, stirring rod, beaker, stand.

Chemicals—Test sample, standard sample, dilute acetic acid, dilute ammonia , dilute sodium hydroxide hydrogen sulphide solution.

Chemical reactions-----



Principle- The limit test for heavy metal is based upon the reaction of the metal ion with hydrogen sulphide, under the prescribed conditions of the test, resulting in the formation of metal sulphides. These remains distributed in a colloidal state and produce a brownish coloration

The heavy metal are the metallic inclusion that are darkened with sodium sulphide (TS) in acidic solution or hydrogen sulphide saturated solution as their quantity is expressed in terms of the quantity of lead (Pb).

The metallic impurities in substances are expressed as parts of lead per million parts of the substances. The usual limits as per I.P is 20ppm.

Procedure---

Method-1

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Test	Standard
<p>Take solution in Nessler cylinder and make up the volume 25ml by adding the water. PH adjust between 3 to 4 by using either dilute acetic acid or dilute ammonia solution Mix well and make the volume by water up to 35ml.</p> <p>Finally add 10ml of freshly prepared hydrogen sulphide solution and mixed, and make up 50ml solution by adding water and allow it to stand for 5 minutes.</p> <p>Observe the quantity of the black ppt of lead sulphide formed and compare with that of the standard.</p>	<p>2ml of standard lead solution take and diluting up to 25ml by adding the water. PH adjust between 3 to 4 by using either dilute acetic acid or dilute ammonia solution</p> <p>Mix well and make the volume by water up to 35ml.</p> <p>Finally add 10ml of freshly prepared hydrogen sulphide solution and mixed, and make up 50ml solution by adding water and allow it to stand for 5 minutes.</p> <p>Observe the quantity of the black ppt of lead sulphide formed and compare with that of the standard.</p>

Method-2

Test	Standard
<p>Take the test sample and 20ml water maintain in Nessler cylinder.</p> <p>Then add 5ml of dilute sodium hydroxide and make up the volume up to 50ml</p> <p>Finally add the 5 drops of sodium sulphide solution and stir well and set aside for 5 minutes.</p> <p>Observe the darkness of color and compare with that of the standard.</p>	<p>Take the 2ml of standard solution in 20ml of water in nessler cylinder.</p> <p>Then add 5ml of dilute sodium hydroxide and make up the volume up to 50ml</p> <p>Finally add the 5 drops of sodium sulphide solution and stir well and set aside for 5 minutes.</p> <p>Observe the darkness of color and compare with that of the standard.</p>

Limit test for arsenic.

Requirement-

Apparatus— Arsenic limit test apparatus, white filter paper, pipette, stirring rod, beaker, stand.

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Chemicals—Test sample, standard sample, Lead acetate solution, potassium iodide, zinc, mercuric chloride.

Chemical reaction-----



Arsenic acid is reduced by the reducing agent like potassium iodide, stannous chloride, etc to arsenous acid. Further it reduces arsenous acid to arsine(AsH_3) gas, which reacts with mercuric chloride paper, producing a yellow stain.

Principle— The pharmacopoeial method is based on the Gutzeit test. In this test, arsenic gas released which when passed over a mercuric chloride test paper, produces a yellow stain. The intensity of the stain is proportional to the amount of arsenic presents.

The rate of evolution of gas is maintained by using a particular size of zinc, and any impurities coming along with the gas is trapped by placing a lead acetate soaked cotton plug in the apparatus.

Apparatus:

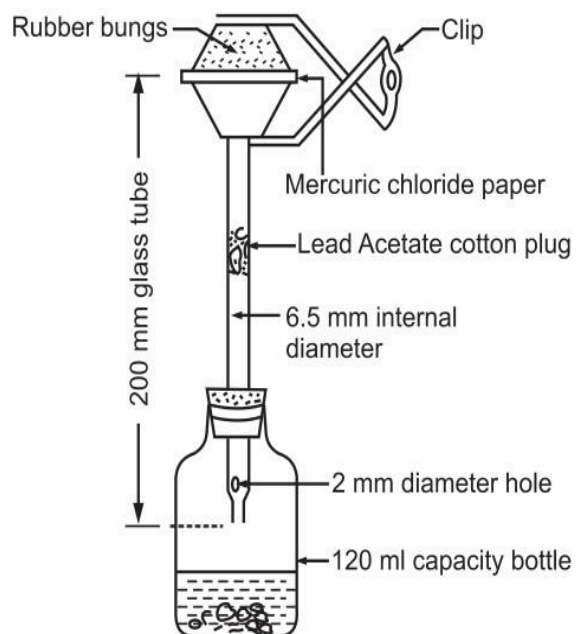
An apparatus as per the specification of I P is used for the limit test for arsenic.

A wide mouth bottle of 120 ml capacity fitted with rubber bung carrying a glass of tube 200 mm long and 6.5 mm internal diameter with a hole of 2 mm at one end is used in the test. The other end of the glass tube is cut smooth and

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carries rubber bungs (25 x 25 mm). Mercuric chloride paper is sandwiched between the rubber bungs. The rubber bungs are held in place by means of a clip



Take 50ml of arsenic limit test apparatus bottle.

Procedure-

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Test	Standard
<p>Dissolve the test solution in water and stannate hydrochloric acid and kept in wide mouthed bottle of apparatus.</p> <p>Then add 1gm of potassium iodide, 5ml of stannous chloride and 10gm of zinc is added(all these reagent should be arsenic free).</p> <p>Keep the solution aside for 40minutes.</p> <p>Compare the stain obtained on the mercuric chloride paper with that in the apparatus containing the test solution.</p>	<p>Dilute standard arsenic solution are kept in wide mouthed bottle of the apparatus.</p> <p>Then add 1gm of potassium iodide , 5ml of stannous chloride and 10gm of zinc is added(all these reagent should be arsenic free)</p> <p>Keep the solution aside for 40minutes.</p> <p>Compare the stain obtained on the mercuric chloride paper with that in the apparatus containing the test solution.</p>

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