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A CONCEPT ON SOURCES OF IMPURITIES

T. Rupa Devi, B. Akhila, M.Pharm, (Ph.D)
Student of Dr.K.V.Subbareddy Institute Of Pharmacy
Assistant Professor, Department Of Pharmacy Practice
Dr.K.V.Subbareddy Institute Of Pharmacy

Abstract:
The impurities in pharmaceuticals are unwanted chemicals that remain with the active pharmaceutical ingredients (APIs) or develop during formulation or upon ageing of both API and formulation. The presence of these unwanted chemicals even in trace amounts may influence the efficacy and safety of pharmaceutical products. The control of impurities is currently a critical issue to the pharmaceutical industry. The International Conference on Harmonization (ICH) formulated guidelines regarding the control of impurities. This review outlines the description of different types and origins of impurities and degradation routes with specific examples.

Keywords: *Impurities, formulation, efficacy, degradation.*

Corresponding author:
T. Rupa Devi,
Student,
Dr. K.V. Subbareddy Institute of Pharmacy

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INTRODUCTION:

chemical compounds manufactured on a commercial scale contain different types of impurities, although the proportion of total impurities may be very small. These impurities include the raw materials, dust particles, moisture, etc.

The impurities commonly present in pharmaceutical preparations are of the following types:

(i) Toxic impurities, e.g. lead and arsenic salts.

(ii) Activity depressing impurities, e.g. presence of water in hard soap.

(iii) Impurities due to which the substance becomes incompatible with other substances.

(iv) Impurities causing technical difficulties in the use of the substance; e.g. presence of potassium iodate (KIO_3) in potassium iodide (KI) or presence of carbonate in solutions of ammonia.

(v) Impurities due to colouring or flavouring substances,

e.g. sodium salicylate is discoloured due to phenolic compounds; sodium chloride becomes damp due to the presence of magnesium salts.

(vi) Impurities due to humidity, e.g. presence of traces of moisture may cause many substances to lose their flowing qualities or they may be easily oxidizable.

(vii) Impurities which change the physical and chemical properties of the substances and make them unfit for medicinal use.

(Viii) Impurities Decreasing the shelf-life of a compound.

IMPURE CHEMICAL COMPOUND:

A compound is said to be impure if it is having foreign matter, impurities. A state of absolute purity is virtually unobtainable but may be approached as closely as desired provided sufficient care is taken during the manufacturing process. Even analytically pure samples of most compounds are having minute traces of impurities. Purification of chemicals is an expensive process. Therefore, a substance should not be purified more than needed as it brings about waste of time, material and money.

PURE CHEMICAL COMPOUND:

Chemical purity implies freedom from foreign matter. It means that a pure chemical compound refers to that compound which has no foreign matter, i.e ., impurities.

Absolutely pure chemical compounds are rarely met with in commerce. Even analytically pure samples of most compounds have minute traces of impurities. Purification of chemicals is an expensive process therefore a substance should not be purified more than required as it brings about waste of time, material and money.

The substances employed in the pharmaceutical field, must be almost pure so that they can be used safely. It becomes rather difficult to get an almost pure substance. We find substances and chemicals, having varying degrees of purity. For instance, substances such as cane-sugar (sucrose), dextrose, common salt and many inorganic salts, are found with over 99 per cent purity while many others are only having traces of impurities. The purity of substances has been dependent upon several factors, like their methods of manufacture and types of crystallisation for the purification process. In the pharmaceutical field, we have to deal with a large number of drugs, chemicals and other substances which find use in formulations. All such materials must be pure. However, it becomes almost impossible to obtain an absolutely pure material, as impurities are incorporated into them either during manufacture, purification. Or **Impurities**

Commonly Found in Medicinal Preparations:

The impurities usually occurring in medicinal preparations may be of the following types:

The impurities which are having a toxic effect and bring about unpleasant reactions when present beyond certain limits. The lead and arsenic salts have been examples of such impurities.

The impurities which, though otherwise harmless, occur in such proportions that the active strength of the substance is lowered and it is not having the same therapeutic activity as the pure substance. In other words, such impurities get contraindicated for economic reasons. For example, hard soap having much water has been uneconomical. Therapeutically, the sodium salt may be harmless and a larger percentage of water in hard soap may also be without any deleterious effect.

The impurities which are able to lessen the keeping properties of the substances. The impurities which are able to make the substance incompatible with other substances.

The impurities which may bring about technical difficulties in the use of the substance; presence of KIO_3 in carelessly prepared samples of KI or presence of carbonate in solutions of ammonia. The impurities like taste, odour, colour or appearance, which can be easily detected by the senses and make the substance un aesthetic or unhygienic. Sodium salicylate is usually discoloured due to phenolic impurities; sodium chloride becomes damp because of the presence of traces of magnesium salts.

SOURCES OF IMPURITIES IN PHARMACEUTICAL CHEMICAL SUBSTANCES:

A knowledge of those impurities which occur in pharmaceutical substances in general use is readily available from actual batch analyses. Experience in the manufacture of any one particular substance often shows that not all the expected impurities are present in practice.

But for a substance newly available it is important that one should be able to deduce the impurities with which it is likely to be contaminated. A list of the possible impurities can be readily compiled from a knowledge of the raw materials used, the method of manufacture and the stability of the product. The type and amount of impurity present in the chemicals or pharmaceutical substances, depends upon several factors. Some of such factors are described as follows:

1. Raw materials employed in manufactured:

Impurities known to be associated with these chemicals may be carried through the manufacturing process and contaminate the final compound. For example, rock salt contains small amounts of calcium sulphate and magnesium chloride, so that sodium chloride prepared from this source will almost certainly contain traces of calcium and magnesium compounds. Impurities such as arsenic, lead, heavy metals etc. are present in raw materials, and are hence found in substances. It therefore becomes necessary to use pure chemicals and substances as raw materials for the manufacturing process.

Traces of lead, copper, and silver usually present in bismuth compounds are derived from the raw materials used in their manufacture. Process employed in the manufacture of a substance also determines the kind of impurities that may be present in it.

Example 1. Copper sulphate may be prepared by the action of sulphuric acid on copper turnings. Cu + 2H2SO4 -> CuSO4 + 2H2O + SO2

Copper turnings are known to have iron and arsenic as impurities. These impurities may be present in negligible or appreciable quantities. If appreciable quantities are present in the raw material (copper turnings in this case), they may enter the final products ($CuSO_4$.5H2O). Due to this, I.P. prescribes a limit of tolerance for arsenic as impurity to be not more than 8 parts per million in copper sulphate. Similarly, it prescribes a limit for iron as impurity.

Example 2. Zinc sulphate may be prepared by the action of sulphuric acid on zinc metal or zinc oxide (raw materials).

Zn + H2SO> ZnSO4 + H2

Zn+ H2SO4- > ZnSO4 + H2O arsenic Both and zinc iron and as zinc impurities. oxides are If known these to impurities have aluminium, are present copper, in appreciable magnesium, amounts manganese, in the nickel, raw materials (ZnSO4.7H2O). (zinc metal or zinc oxide), these impurities are likely to be carried to the final product.

2. Reagents used in the manufacturing Process:

If reagents used in the manufacturing process are not completely removed by washing, these may find entry into the final products.

Example 1. Ammoniated solution. mercury may be prepared by adding a solution of mercuric chloride to dilute ammonia HgCl2+2NHOH -> NH, HgCl + NH,Cl + 2H2O vlibro1 at our InTON(soluble) (soluble) ammoniated (soluble) mercury this The precipitate is washed of ammoniated with cold mercury water (precipitate) (final (final to remove product product) ammonium contains ammonium hydroxide. ammonium hydroxide.

Example 2. Precipitated calcium carbonate may be prepared by calcium chloride with sodium carbonate.

CaCl2 + Na,CO2 -> CaCO3 + 2Nacl

(soluble) (soluble) (ppt) (soluble

The precipitated calcium hydroxide is associated with sodium carbonate and the soluble chlorides Therefore, this precipitate is washed with water to remove excess sodium carbonate and the soluble chlorides. If this precipitate is not washed properly, these may be present as impurities. Due to this, I p has prescribed limits of tolerance for the soluble alkali (NaCO2) and for the chlorides as impurities in these cases.

3. Method or the process used in manufacture:

Many drugs and chemicals (especially organic) are manufactured from different raw materials, during the manufacturing using Many different drug processes. methods certain and chemical drugs The or processes. type a multiple-step-synthesis (especially and Some amount impurities of impurity procedure are incorporated present in the which drugs produces or chemicals intermediate varies in compounds. Furthermore, the intermediates, new synthesis. The for impurities purification Impurities will due get off to incorporate the of contamination the intermediates product into side by has the reactions reagents been final also compound also and essential, is occur solvents used, Usually, otherwise in the at various substances. side impurities reactions stages. This present of occur may the process as described below:

A. Reagents employed in the process: 'Soluble alkali' in calcium carbonate arises from sodium carbonate used in the process. Calcium carbonate is obtained by interaction of a soluble calcium salt and a soluble carbonate, and the product is therefore liable to contain traces of soluble alkali, which the washing process has failed to remove.

B. Reagents added to remove other impurities: Potassium bromide is liable to contain traces of barium, which is added in the course of the manufacturing process to remove excess sulphate which in turn arises from the barium used.

C. Solvents: Water has been the cheapest solvent available and has been used wherever possible, especially in the manufacture of inorganic chemicals. Tap water has Ca2+, Mg2+, Na+, Cl -, SO2 and CO- as impurities in very small amounts. Hence even if a good deal of washing of the final product is done by tap water the final product may still contain traces of such impurities.

Softened water is obtained by allowing tap water to pass through the sodium form of zeolite which removes divalent cations (Ca2+, Mg2+) from tap water in exchange for sodium. The softened water contains Na+ and Cl ions as impurities. As a result of final product may still contain sodium salts as impurities.

Demineralised water is obtained by passing tap water through columns packed with ion exchange resins. The water obtained by this process is free from Ca2+, Mg2+, Na+, Cl -, SO,2- and CO22 -. Thus, the final product is free from these impurities. However, water obtained by this process may still contain organic impurities and the final product may contain organic impurities.

D. Action of solvents and reagents on reage vessels: During the manufacturing process, some of the solvents and reagents may undergo reaction with the metals of the reaction vessel and may dissolve these metals which appear as impurities in the final products.

Inorganic compounds are usually manufactured in metallic reaction vessels such as copper, iron, galvanised iron, tinned iron, aluminium and nowadays more usually stainless steel. Iron is known to contain arsenic impurity and, therefore, the inorganic compounds manufactured in the iron vessel contain arsenic and iron as impurities. Therefore, I.P. has prescribed limit tests for arsenic and iron for most of the inorganic chemicals.

If inorganic substances are prepared in the reaction vessels made of soda glass, these vessels may release some alkali as impurity. However, if reaction vessels are made of hard glass, they don't release any impurities but these are highly expensive.

4.Chemical processes used in the manufactured:

For synthesis of drugs, many chemical reactions such as nitration, halogenation, oxidation, hydrolysis are involved. In this chemical process different chemicals are used. Tap water is invariably used in the various processes and it often has chloride, calcium and magnesium, which may find access to the substance being manufactured, and limits for these impurities have been prescribed in a large number of cases. For instance, potassium iodide is manufactured from iodine which is obtained from kelp, a seaweed cyanide that tends to get formed when nitrogenous organic matter is burnt with alkaline. Limit tests have been prescribed for cyanides in potassium iodide.

5. Atmospheric Contamination during the Manufacturing Process:

In industrial areas, the atmosphere is contaminated with dust particles (aluminium oxide, silica glass particles, porcelain particles, plastic fragments, etc.) and some gases like hydrogen sulphide, sulphur dioxide and black smoke (soot). During the manufacture or purification of pharmaceutical products, these impurities enter the final products as impurities.

There are many pharmaceutical products which when manufactured are contaminated with atmospheric carbon dioxide and water vapour. For example, sodium hydroxide absorbs atmospheric carbon dioxide.

2NaOH + CO2> Na, CO3 + H2O

Because of this reaction, sodium hydroxide should not be exposed for a long duration during its manufacture. Because of this reason, I.P. has prescribed that sodium hydroxide should not contain more than 3% of sodium carbonate.

6. Intermediate products in the manufacturing Process:

There are some intermediates which are produced during the Manufacturing Process. Sometimes, these intermediates may be carried through to the final product.

Example. Potassium iodide is prepared by reacting iodine with potassium hydroxide.

6KOH + 31, - > 5KI + KIO, + 3HO

The resulting solution is first evaporated to dryness and then heated with charcoal.

KIO, + 3C -> KI + 3CO

In this process, if the intermediate product KIO3, is not completely converted into KI, then it may be carried through to the final product as an impurity. This impurity is not desirable and hence pharmacopoeia prescribes a test for iodate in potassium iodide.

7. Defects in the manufacturing Process:
In many manufacturing processes, there are defects like imperfect mixing, incompleteness, to proper temperature, pressure, pH or reaction conditions, etc. which may yield chemical compounds with impurities in them.

Example 1. Calcium chloride (CaCl2 6H2O) is prepared by adding pure calcium carbonate to the slight excess of dilute hydrochloric acid followed by stirring and filtration. The filtrate on concentration yields crystals of CaCl2 6H2O.

CaCO3 + 2 HCI Ca Cl + H2O + CO2

The aim of adding a slight excess of calcium carbonate is to consume hydrochloric acid so that it does not enter filtrate. However, if these ingredients (CaCO2 and HCI) are not mixed perfectly, then some hydrochloric acid may still remain unreacted which first passes to the filtrate and finally to the crystals of calcium chloride. Therefore, I.P. has prescribed a test for acidity in CaCl2.6HO

Examples 2. Zinc oxide may be prepared by heating metallic zinc to bright redness in a current of air. The vapours of zinc burn to form zinc oxide which is collected as a fine white powder.

2Zn + 02 -> 2ZnO

However, if there is lesser heat or air or both, zinc metal is not completely converted into zinc oxide. Thus, the final product, Zno may still contain metallic zinc as impurity. Therefore, IP has prescribed a test for zinc metal in zinc oxide.

8. Manufacturing hazard:
Even in a well-run manufacturing house, certain hazards exist which can give rise to product contamination. A well establish system of checks on manufacture and insistence on adequate analytical control of the product is usually sufficient to ensure that standards are well-maintained. Control analysis must be designed to more exclude likely contamination hazards, but ranging even so from specifications the accidental for drugs inclusion and formulation of particulate product matter to microbial contamination, or ever. labelling errors.

(a) Particulate contamination: inclusion of dirt, presence or glass, of unwanted particulate matter can arise in a number of granules, from tabletting and filling machines, or even porcelain, from product metallic containers. and plastic This fragments type of contamination from sieves, may equipment stem or containers, either Clarity bulk but of materials solutions is more likely used for injection into the be the formulation has result been of particularly particles or from the being important use shed of improperly through wear clean and tear of equipment.

(b) Process errors: Gross errors arising from incomplete solution of a solute in a liquid preparation must be detected readily by the normal analytical control procedures. Minor errors, however, could escape notice, if the manufacturing tolerance for the quantity of active ingredient in the product has been wide, and analysis reveals that the lower limit has only just been reached. Whilst errors of this sort are undesirable, they are probably only of serious concern in the case of solutions of potent medicaments. The preparation of such solutions, therefore, calls for special precautions, such as filtration to avoid the danger of undissolved solute contaminating part of the batch. Uneven distribution of suspended matter during manufacture can similarly become the source of batch variation, or even variation within a batch.

(c) Cross-contamination: The handling of powders, granules and tablets in large-bulk frequently creates a considerable amount of air-borne dust, which, if not controlled, can lead to cross-contamination of products. The danger is well-known to experienced manufacturers, particularly of steroidal and other synthetic hormones. Precautions, such as the use of face-masks and special extraction equipment, already in use to protect operators from undesirable effects of certain drugs of this type, are also suitable the United for more States general are required to by limit the cross-contamination. Food and Drugs Administration Manufacturers (FDA) of penicillin to institute adequate control of the manufacture, handling and storage of drugs and their preparations to limit cross contamination of penicillin or other products by another. Manufactured. The application on the of special same premises. Limit tests places a check on contamination

(d) Microbial Contamination: The pharmaceutical requirement of sterility tests for all products intended for end-sterilisation parenteral administration processes or and produced ophthalmic under septic preparations, conditions, irrespective provides an whether they level are of prepares concentration for application such preparations. to broke skin, Many or mucous other membrane products, especially are liable to be liquid to bacterial preparations mould and adequate and fungal contamination of topics creams

from the atmosphere (or, less frequently, from contaminated equipment) during manufacture. As the materials are self-sterilising, but many products capable of antibacterial antifungal agents microbiological spoilage of the product is to be completely avoided. Certain materials, which are particularly prone to microbial contamination, may constitute a health hazard unless they're carefully controlled. These are mainly substances of natural origin, which are known to be liable to contamination for usually freedom from specific specified organisms.

9. Storage conditions:

The chemicals, substances when prepared, have to be stored in different types of containers, depending upon the nature of the material, batch size and the quantity. Various types of materials are used for storage purposes. These may be plastic, polythene, iron vessels, stainless steel, aluminium, copper etc. Reaction of these substances with the material of the storage vessel occurs and the products formed are found as impurities in the stored material. This reaction may occur directly or by the leaching out effect on the storage vessel. Alkalines stored in ordinary glass containers, extract lead from it, which is found in the final product. Similarly, strong chemicals react with iron containers, and extract iron. There are many chemical substances which undergo changes due to careless storage. Ferrous sulphate slowly gets changed into insoluble ferric oxide by air and moisture. Surgical solution of the chlorinated soda rapidly deteriorates upon exposure to light and heat, and hence has to be stored in well-closed amber coloured bottles in a cool place. Solution of potassium hydroxide should be stored in well stoppered bottles of green glass to avoid a solvent action on lead glass. Ether and chloroform decompose in presence of light and air causing their contamination with the products of decomposition. There are certain guiding principles regarding storage and if they are observed, deterioration of substances could be minimised if not completely eliminated. All chemicals are stored in tightly-closed containers made of metal or dark glass and avoid extremes of temperatures, as inorganic chemicals are not much influenced by ordinary temperature changes. Sunlight affects a large number of chemicals: for example, bismuth carbonate gets blackened on long exposure on a shelf exposed to sunlight.

Inadequate storage conditions and their effects are outlined as follows:

(a)Filth: Stored products may become contaminated with dust, the bodies of insects, and even animal and insect excreta, unless adequate precautions are taken. Modern packaging is usually capable of excluding all such contamination from finished pharmaceutical products, but bulk storage of raw materials, and especially that of vegetable drugs, is far more likely to lead to such contamination, and an appropriate test for filth is desirable for all materials so stored.

(b)Chemical instability: Impurity can also arise during storage as a result of chemical instability, and a number of pharmaceutically important substances are known to undergo chemical decomposition when stored under non-ideal conditions. The nature of the decomposition, which is often catalysed by light, traces of acid or alkali, air oxidation, water vapour, carbon dioxide and traces of metallic ions can frequently be predicted from a knowledge of the chemical properties of the substance. The accent is on limitation or, if possible, total avoidance of all such decomposition, by adopting suitable storage procedures and conditions. The light sensitive materials should be stored in darkened glass vessels or metal containers to inhibit photochemical decomposition. An interesting example of special precautions to exclude light is the use of opaque capsule shells to protect chlordiazepoxide from decomposition by light. Material liable to oxidation or to attack by moisture or carbon dioxide may, if it is especially sensitive, requires displacement of air from the container by nitrogen; for less sensitive products, it is usually sufficient to prescribe storage in a sealed container.

Oxidation is also preventable by the inclusion of appropriate antioxidants, including such phenols as Butylated Hydroxy anisole (BHA), Butylated Hydroxytoluene (BHT) and Thymol, which are capable of undergoing free radical oxidation at the expense of the material (e.g., Liquid Paraffin) they are being used to protect. Sodium meta bisulphite, another antioxidant, is suitable for use in aqueous solution (e.g., Procaine and Adrenaline Injection), depending for its action on the oxidation which, as sodium bisulphite, it undergoes to sodium bisulphate. Exceptionally, suitable additives may be used to neutralise the toxic products of oxidation as in the stabilisation of chloroform. When pure it readily forms traces of phosgene by a reaction which is light catalysed. In practice, therefore, a stable and non-toxic product is obtained by the addition of 1 or 2 percent of ethanol, which suppresses the decomposition reaction, and at the same time converts any traces of phosgene to the harmless ethyl carbonate.

(c) Reaction with container materials: The possibility of reaction between container and contents constitutes a hazard which cannot be ignored. Creams

and ointments liable to react with metal surfaces, e.g., salicylic acid ointment must not be packed in metal tubes, unless they have been lacquered internally to inhibit reaction. Solutions of alkali sensitive materials, particularly if subjected to any form of heat treatment during preparation, e.g., atropine sulphate injection, which is sterilised by autoclaving, must be packed in glass ampoules, which comply with the test for hydrolytic resistance, European Pharmacopoeia (E.P.). This is the resistance offered by the glass to release of soluble mineral substances into freshly distilled water in the container, and is determined by titration. Glass containers are recognised in three grades, I, II and III. Type I is neutral glass, with high hydrolytic resistance arising from the composition of the glass. Type II glass also has high hydrolytic resistance, but this is due to surface treatment of the glass. It can be distinguished from Type I in a crushed glass test. Type III glass has somewhat more limited hydrolytic resistance than glass of Types I and II.

All glass containers for injectable preparations must comply with the test for hydrolytic resistance. Aqueous injectable solutions must be packed in containers consisting of glass either of Type I or II. Type III glass may be used only for non-aqueous solutions and injection solids which are stable in this standard of glass.

Plastic containers and closures require careful evaluation, because of the tendency to yield undesirable additives, such as plasticisers, a tendency which increases markedly in the presence of non-aqueous solvents. The plastic materials, mainly polyethylene, polypropylene, polystyrene and polyvinyl chloride, are used in conjunction with appropriate additives, which may consist of antioxidants, colours, plasticisers, lubricants, impact modifiers, and mould release agents. Not all these additives are used in the manufacture of any one type of container, but plastic containers for pharmaceutical use irrespective of their composition must be free from undesirable properties which affect the safety and efficacy of the medicament
Plastic containers for injections should be sufficiently translucent to permit visual inspection of the contents, and if greater than 500 ml capacity, must also comply with tests which limit animal toxicity in the cat, for Ether-Soluble Extractive, and for Metal Additives with special reference to barium and to the heavy metals tin, cadmium and lead.

Rubber closures, widely used in the packing of multi dose injections, are, on the other hand, more prone to absorb medicaments, and also antioxidants and bactericides from solution, unless suitably pre heated by immersion in solutions of the compounds concerned.

(d)Physical changes: The occurrence of change in physical form of the drug during storage is not unknown. Changes in crystal size and form, agglomeration and even caking of suspended particles, which are not always preventable, may lead to marked changes in the efficiency of the product. The particle size, and consequently surface area, may be a critical factor in determining the rate of absorption, and hence blood levels, of a drug of low solubility such as Griseofulvin. Multidose suspensions, which are inefficient through rapid setting or claying, likewise constitute a safety hazard, giving rise first to the possibility of underdosage and later to overdose, as successive doses are withdrawn from the container. Injectable emulsions in which the globule size has increased in storage may similarly be dangerous in that they could be the cause of fat embolism.

(e)Temperature effects: The rate at which chemical and also physical change occurs in stored products is conditioned by temperature, and labile products may have temperature storage requirements assigned to them to guard against unnecessary decomposition. The use of subjective instructions such as store in a cool place are capable of ambiguous interpretation on the part of the operator, and more precise interpretations are generally placed on these phrases.

Products required for topical use, must, if prepared under temperate conditions, be capable of withstanding the effects of change to tropical temperatures. Thus, pastes and ointments must be so formulated as to retain their consistency at higher temperatures, and appropriate standards laid down for them. The high humidity often encountered in tropical countries also constitutes yet another hazard in that it is conducive to mould contamination of the product, and suitable precautions may be necessary in formulation.

10 Decomposition of the product during storage:
Some substances decompose on keeping. The decomposition becomes greater in the presence of light-air or oxygen. The result of decomposition brings about contamination of the final product. Substances which contain water of crystallisation lose it on being kept open, while deliquescent substances absorb water from the atmosphere, and get liquified. Crude vegetable drugs are especially susceptible to decomposition. Many organic substances get spoiled, due to decomposition on exposure to the atmosphere, e.g., amines, phenols, potent drugs etc. The

decomposition products thus appear as impurities in the substances.

Decomposition, and loss of potency, through insufficient attention to chemical stability of pharmaceutical chemicals or additives under the conditions of manufacture represent a further source of impurity. Careful attention to process design, and to the handling of compounds liable to decompose, for example, by hydrolysis, oxidation, or in the case of optically-active drugs such as Ergometrine Maleate and Adrenaline Acid Tartrate, by racemisation, is essential if products are to conform to the highest standards. The use of ionising radiations for sterilising pharmaceutical products may also lead to decomposition with consequent loss of the medicament and possible formation of toxic breakdown products.

11. Accidental substitution or deliberate adulteration with spurious or useles material's: It is possible to prevent accidental substitution by stocking all more toxic substances together separately, or in a locked cupboard. Deliberate adulteration is carried out at many places in India due to improper enforcement of Drugs and Cosmetic acts, therefore purchases have to be carried out vigilantly.

Impurities cannot be memorised, but a knowledge of it with the knowledge of sources of raw materials, their nature, composition etc. must be thorough, specially their keeping qualities in presence of light, air and moisture so as to be able to trace the sources of impurities in the substances met with by him in his professional work.

There are many pharmaceutical chemicals which are adulterated with cheaper substances. For example, the expensive potassium bromide may be adulterated with cheaper sodium bromide. In order to avoid the chances of adulteration of potassium bromide, I.P. has prescribed a test for sodium in them. Similarly, crude drugs, essential oils, fats and other substances may be adulterated with those substances in which analytical control is difficult to be maintained.

In order to identify the impurities likely to be found in a pharmaceutical preparation, one should have complete knowledge of raw materials, the process used for its manufacture, the chemical properties of the substances, especially its behaviour under normal and abnormal conditions of storage and possible adulterated cheap materials. It is a wasteful exercise to identify every possible impurity in each pharmaceutical substance.

EFFECTS OF IMPURITIES:

Almost all pure substances are difficult to prepare and that some amount of impurity always remains in the material. The impurities present in the substances may exert the following effects:

- Impurities having a toxic effect, can be injurious when present above certain limits.
- Impurities, even present in traces, may exert a cumulative toxic effect after a certain period.
- Impurities are sometimes harmless. However, if these are present in such large proportions that the active strength of the substance gets lowered, its therapeutic effect gets decreased.
- Impurities may cause a change in the physical and chemical properties of the substance, thereby making it medically useless.
- Impurities may bring about technical difficulties in the formulation, and use of the substances.
- Impurities may cause incompatibility with other substances.
- Impurities may decrease the shelf life of the substance.
- Impurities, though harmless in nature, may cause changes in odour, colour, taste etc., thereby making the use of the substance unethical, as well as unhygienic.

Permissible Impurities in Pharmaceutical Substances: As a general rule, medicinal compounds should not only free from undue amounts of toxic and undesirable substances but should also be of a reasonably pure quality. As it is not possible to avoid impurities,it becomes necessary to have substances that are reasonably pure. The pharmacopoeia committee takes the following points into consideration, with respect to the problem which is caused by impurities in substances.

1. The impurities, like lead and arsenic, which are having deleterious effects should not be present in amounts likely to be harmful. Pharmacopoeias usually prescribe limits for such impurities and in testing substances for these impurities the aim has been to see whether the impurities have been less than the prescribed limit or exceeds it.

2.For harmless impurities the aim has been to fix their limits so that, their presence does not interfere in the therapeutic usefulness of the drug. Here again, the limits have been prescribed and fixed. This is done depending upon the nature of the impurity, the type of substance, the use of substance etc.

3.Another consideration is the practicability of getting substances without impurities at reasonable costs. It is possible to prepare substances (through a series of steps of purification) without any impurity, but this may be achieved at an exorbitant cost. Considering this aspect, the limits of various impurities have been prescribed.

4. Deliberate adulteration, employing materials that are having similar qualities, also accounts for the presence of impurities in the substances, e.g., adulteration of sodium salt with potassium salt, calcium salts with magnesium salts etc. Such adulteration, which brings impurities into substances, needs not exhibit less therapeutic activity, but it has been reasonable to expect unadulterated material from an ethical point of view. Pharmacopoeias guard against this type of impurity, by using tests for identification.

METHODS USED TO PURIFY THE INORGANIC SUBSTANCES:

In inorganic chemistry the solvent most used for washing or crystallisation has been water. The unit operation of distillation has been also not of much practical value in inorganic chemistry because it is used for the purification of a very few substances, e.g., acid chlorides, bromine, carbon di sulphide, mercury, nitric acid, and special chemicals such as anhydrous hydroxylamine and hydrazine hydrate. Inorganic substances may be purified by the following unit operations:

(a) Washing
(b) Drying
(c) Re crystallisation
(d) Sublimation.

Let us discuss these one by one,

Washing: This method is used especially when water soluble substances have to be washed away and a water insoluble substance is needed. An example is the prepared chalk obtained from native calcium carbonate a water in soluble substance is washed with water and dried and is required to have not less than 97 percent of CaCO3 on dry basis while basis while precipitated calcium carbonate as water insoluble substance is required to have not less than 98.5 percent of CaCO2 after drying in a manner which is similar to that used for prepared chalk. As limestone and (native calcium carbonate) are having variable composition, the tests for purity are generally many.

Drying: Inorganic chemicals may be generally dried in air, special precautions have to be taken to exclude dust. When anhydrous chemicals are required or expensive chemicals are manufactured on a small scale, drying is usually performed under vacuum. Drying has been an important unit operation and needs care and precaution so that chemicals may not deteriorate due to oxidation, caking or mould growth.

Recrystallisation of solid substances from water: It has been the most common method of purifying soluble salts. Very few inorganic substances could be recrystallised from non-aqueous solvents. With a few exceptions, the solubility of a salt in a solvent gets increased with increase in temperature and hence a saturated solution of the salt is obtained at a higher temperature and the solution is allowed to cool slowly after which crystals of a greater purity could be obtained.

Sublimation: The application of this method of purification has been applicable to a very few substances, e.g., arsenic trioxide, iodine, mercuric chloride, mercurous chloride, and sublimed sulphur. The organic compounds purified by this process have been camphor, benzoic acid. It is possible to get very pure materials by this process.

OFFICIAL SUBSTANCES:

These are medicinal substances and pharmaceutical aids which are included in the monograph of the latest edition of the pharmacopoeia of the country. There is a difference between chemical individual and an official substance with the same name. An individual chemical can be pure to any specified purity whereas the official substance is a commercial product which has to comply with certain purity standards prescribed in the pharmacopoeia and may often have some other substances added four specific reasons. For Example, the chemical compound of chloroform is CHCI, having certain purity. On the other hand, the official substance in the pharmacopoeia is chloroform containing 1-2% of ethyl alcohol to prevent the formation and to inactivate any phosgene gas (carbonyl chloride) that is formed with the atmospheric oxygen during storage.

An official substance is specified with capital initials, e.g., Chloroform, Sodium Chloride, Aluminium Hydroxide. However, if the reference/meaning is clear form of the context, the capital initials are not used or repeated unnecessarily. Wherever the word 'official' is used, it is synonymous with "pharmacopoeia" and/or "compedial". On the label of an article, if there is the designation or suffix IP in conjunction with the official title, it implies that the article complies with IP standards.

The term 'official substance' is used for a single drug or a drug entity or active pharmaceutical ingredients (API) or a pharmaceutical aid for which monograph

title does not include indication of the nature of a dosage form such as tablet, capsule, injection, ointment, cream, lotion, drops, spray, etc.

The term "official preparation" is used for a drug product (dosage form) which is the finished or partially finished preparation or product of one or more official substances formulated for the use of patients.

An article is an item for which a monograph is provided, whether an official substance or an official preparation.

TESTS OF PURITY:

The pharmacopoeias of the various countries prescribe "Tests of Purity " for substances so as to ensure their reasonable freedom from the undesirable impurities. The "Tests for Purity " have been in fact the tests for the presence of impurities and fix the limits of tolerance for these impurities. Arsenic and lead have been dangerous even when ingested in traces, and have been, therefore, made use of in smaller limits in medicinal substance. Another consideration in prescribing a limit for an impurity has been the practicability of commercial production of a substance of a particular standard of purity. An interesting example is that B.P. 1932 fixed certain limits for impurities in calcium hydroxide which were found difficult to comply with and therefore got relaxed in later editions.

The governing factor for these tests, has been to determine how much impurity has been likely to be harmful, or to bring about technical and other difficulties, when the substance is used. Pharmacopoeias do not aim at ensuring freedom of a substance from every possible impurity in a substance, but to test for few major impurities which have been likely to interfere in their use. It means that the tests for purity often refer to a few of the impurities to ensure that drugs do not have drawbacks due to impurities. Some of the tests which may be run to ascertain the purity of a substance are given below: Certain tests which are performed on the substances are:

1. Colour, odour and waste:

When other tests for purity are not available, then the tests of odour, colour etc., are used. Though they are having limited value, they are useful in determining whether the substance has been reasonably pure, hygienic etc. or not.

2. Physico-chemical constants:

Solubility of the substances in different solvents, determination of melting and boiling points for organic substances, optical rotation for optically active substances and refractive index for liquids, have been some reliable values which can reveal the purity of substances. Determination of the acid value, iodine value, saponification value, acetyl value, ester value etc for vegetable oils have been general constants and a variation in their value, signifies the presence of impurities. The extent of the variation in these values is generally dependent upon the nature and extent of impurities present in the substances. However, a very low concentration of impurities may fail to alter these constants and thereby remain undetected, unless tested specifically, by special tests.

Determinations of physical constants ensure whether the substances have been reasonably free from other substances, although they fail to indicate the nature of impurities present.

3.Acidity, alkalinity and pH

Reactions which involve acids and alkalis often have considerable Substances of a great amount help prepare for determining the form of acid chemical or alkali, the extent of impurity. the impurity. Hence Further, the tests solutions for acidity of certain or alkalinity substances have a definite pH, at a given concentration. The presence of an impurity, will cause a change in the pH and thus it can be detected.

Determination of the acidity or alkalinity or pH constitutes an important test for ascertaining the purity of medicinal substances.

4.Humility:

Estimation of the moisture or humidity content of some crude drugs provide valuable information about the conditions of their storage and in turn about their therapeutic potency.

5.Anions and Cations:

Many synthetic drugs, both inorganic and organic, may be prepared using strong acids like hydrochloric, sulphuric, nitric acid etc. The presence of chloride and sulphate ion have been common. Tests for these ions (anions) are usually carried out especially in testing synthetic organic compounds. Similarly tests for sodium, ammonium (cations) are usually carried out to detect impurities in inorganic compounds (test for sodium in potassium salt and vice-versa, calcium in magnesium salts etc). Tests for heavy metals, such as lead, iron, copper, and mercury are also carried out, because these are very common impurities in substances.

The number and the kind of tests depend upon the following factors:

(a) Kind of metals used in the preparation of the substances;

(b) Amount of metals generally known to occur in the substance;

(c) Dose of the substance.

6. Insoluble Constituents or Residues:
A substance which in the pure state gives a clear solution with a given solvent produces a turbid solution in the presence of insoluble impurities. The turbidity may be attributed either to insoluble ingredients or sometimes even to pluff or other particles from filtering materials, wrappings etc. The measurement of opalescence helps to indicate the extent of impurities and thus provides a good check on the purity of soluble substances.
If the insoluble residue is high, then this can be determined by filtering and weighing the insoluble residue.

7.Ash, water insoluble Ash:
Determination of ash in crude vegetable drugs, organic compounds and some inorganic compounds, serves a good indication about the extent of impurities of heavy metals or minerals in nature. There for this determination is usually used for a number of substances. In certain cases, water-insoluble ash is also determined, to ascertain water-insoluble heavy metals or mineral types of impurity.

In organic substances alkali salts are often present as impurities; hence, in their case, determination of ash though time-consuming and laborious may be preferable.

8. Organic Impurities:
Necessary tests have been necessary to know the impurities in the process of production for those substances which have been either significant in the use of the medicinal compound or which serve as an criteria for its freedom from other impurities.

9. Arsenic:
The arsenic content may be expressed in parts per million. Monographs on many substances are not include any test for arsenic because of the advanced method in preparing acids. It is included only for those substances where experience has shown that commercial articles may get contaminated with arsenic. The permissible limit has been found to depend upon the following factors:(i) size and frequency of the dose; and (ii) difficulty of removing it from the substance during processing. Barium sulphate is administered in doses up to 130 mg at a time and hence must not contain arsenic more than 1 ppm.

From the above discussion, it is concluded that depending upon the type of material or substance, pharmacopoeias have been including tests for purity of particular nature, salicylic acid in acetyl salicylic acid, phenetidine in phenacetin, acraldehyde in glycerine, p-aminophenol etc. In general, it could be said that impurities of chloride, sulphate, iron, heavy metals, lead and arsenic, have been common in drugs and chemicals. Pharmacopoeias of various countries, therefore, prescribe limit tests for these which are to be carried out by a particular method.

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