UNIT - I

Impurities in pharmaceutical Substance.

✡ History of Pharmacoepia

Inorganic chemistry → It is a branch of chemistry that deals with the study of inorganic compounds (do not have carbon-Hydrogen bond).

→ This covers a wide range of substances i.e. minerals, metal & salts.

→ so basically inorganic chemistry focuses on properties, structures, reaction and application of these compounds.

eg: KI, sodium nitrate, Na_2SO_4 etc.

History of Pharmacoepia

PHARMACOEPIA

→ It is an official publication.

→ It contains the list of medicinal drugs along with their standards, description, and guidline for preparation, quality control and dosage.

It includes.

1) Monographs: Detailed description of drug's chemical structure, physical property, purity standard and instruction for pharmaceutical preparation.

2) Standards: specification for identity, strength purity and quality of drug.

3) Testing methods: procedure for analysing and verifying the quality and efficacy of drugs.

4) Formulation: Guidelines on correct formulation of medication, its appropriate ingredient concentration and methods.

PHARMACOEPIA = Pharmakon → Drug

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Poiein → to make/create

Classification of pharmacopia

Each countries have published the pharmacopia for official standard of drugs.

e.g. 1) India Pharmacopia
2) British pharmacopia
3) Europian pharmacopia
4) USP
5) Japanis pharmacopia

INDIAN PHARMACOEPIA

→ History of I.P. began in year 1833, when East India Company dispensary recommended for publication.

→ 1844 : General conspect of medicinal plant published.

→ 1868 & 1869 : covers drug used in India along ⊂ it's suppliment.

→ 1885 : B.P. was made official in India.

→ 1927 : A Drug enquiry committee recomond the publication of National pharmacoepia.

→ 1946 : first time in India a suppliment list of B.P. published by G.O.I.

→ 1948 : Indian pharmacoepial committee was established.

→ 1954 : Reconstitution of committee under chairman ship of Dr. B.M. Ghose.

→ 1955 : The first edition of India pharmacoepia was published, it replaces the B.P.

→ 1960 : Suppliment of this I.P. published.

→ 1966 : Dr. B. Mukerjee appointed as chairman of second edition of I.P.

→ 1978 : Indian pharmacopeial committee was reconstituted for new edition and addenda at regular/short interval.

S.N. edition	Year publication	Addendum	Feature of edition
first	1955	1960	Contain both western + traditional drug used in India.
2nd	1966	1975	—— 〃 ——
3rd	1985	1989 1991	In this traditional system of drug was limited. New inclusion 1) New drugs manufactured/marketed 2) Herbal drugs & had definite Q.C. stand.
4th	1996	2000 2002 2005	Includes → Anti retroviral drugs and new plant for making medicinal products not covered by other pharmacopeia. → Committee decided to delet less used product monograph.
5th	2007	2008	- focused on drugs & covers National health care program & national essential medicine. → It contains monographs on anti-retroviral, anticancer, anti T.B. and herbal drugs. → Biological sera, blood products ete.

Edition	Year	Amendment	
6th	2010	2012	It comprises of three volume. Vol. I : It contains. Notice, preface, about I.P., acknowledgement Introduction, general chapters & Ref. Vol. II : General notice, General monograph, drug substance, dosage form & p'ceutical aids (A → M) Vol. III : General notice, drug substance, Dosage fom p'ceutical aids (N → Z), vaccine, sera, herbal products, blood & blood products. biotechnology product, veterinarian product and index.
7th	2014	-	→ It is presented in IV volumes. → Include product of biotechnology, herbs & herbal product, veterinarian, vaccins, antiretroviral, New drugs for NHP. → IP 2014 includes 2548 monograph of drug
8th	2018		→ published by IPC on behalf of Ministry of health & family welfare. → 4 volume, 220 New monographs 366 revised monographs 7 omissions.

British Pharmacopeia

→ It is for the United Kingdom & published annually BPC.

→ Latest edition supersedes the previous B.P.

→ 2020 edition have 25 New & 331 amended BP monographs

→ It has Six Volumes

Vol. I & II → Medicinal substance

Vol. III → formulated preparation
- Blood related product
- Immunological & radiopharmaceuticals
- Surgical, Homeopathic prep''

Vol. IV → Appendices
I.R. spectra
Index

Vol V → B.P. (Veterinarian)

Vol VI → B.P., B.P. (Veterinarian)
(CD-ROM) Version

UNITED STATE PHARMACOEPIA

→ USP for United State, published annually.
→ first edition — 15 dec 1820 (latin & English)
→ from 1820 to 1942 it was published at ten year intervals.
→ from 1942 to 2000 it was published at 5 year intervals.
→ from 2002, it was published annually.
→ Electronic version of USP-NF on flopy disk was introduced in 1992.
→ The current version, USP 43-NF 38 will become official on November 1, 2020.

SOURCE & TYPES OF IMPURITIES

Impurity: These are unwanted chemicals that remain ∈ Active Pharmaceutical Ingredient (API) that developed during formulation and upon aging the API.

→ These can affect the efficacy of drug / pharmaceutical products.

CLASSIFICATION OF IMPURITIES

→ According to ICH guideline, Impurities are of following types.

1. Organic Impurities
2. Inorganic Impurities
3. Residual solvents.

1. Organic Impurities

→ These are arise during manufacturing process or storage of drug substance.

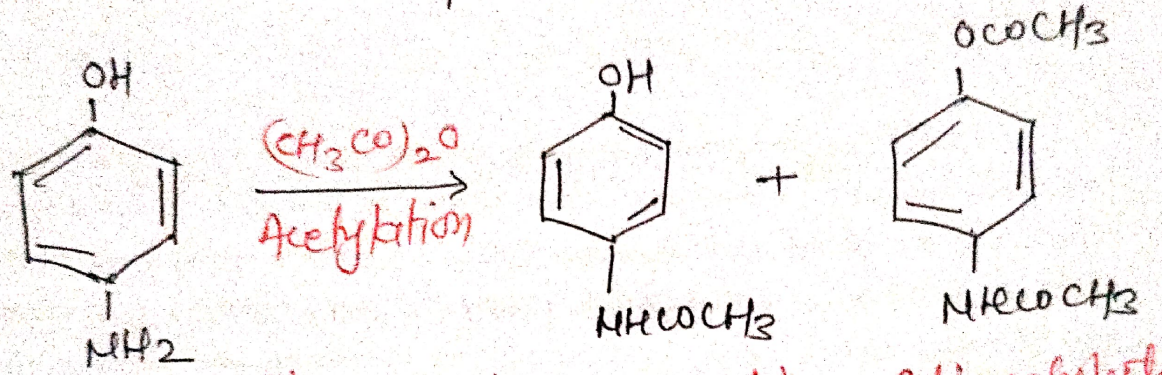
eg. starting material, byproduct, intermediate degradation product, Reagent, Catalyst etc.

Ex.

(a) By product Impurities

→ In Synthetic chemistry, getting a singl end product is rare ∈ 100% yield.

→ There is always a chance of some by-Product ∈ desired end product.



(P-amino phenol) (Paracetamol) {diacetylated Paracetamol}

By product

(b) Degradation product

→ These are produced on storage or aging of different pharmaceutical products.

eg. Degradation of penicillin and cephalosporin.

Penicillin react ∈ moisture to form penillic acid, penicino-aldehyde, & panicillamine, etc

(c) Intermediate Product

→ These products are formed during the reaction and some time they didn't get converted into end products.

$$6\,KOH + 3I_2 \longrightarrow 5KI + KIO_3 + 3H_2O$$

Potf. iodide — Pottasium iodate

$$KIO_3 + 3C \longrightarrow KI + 3CO$$

(pottasium iodide)

(d) Reagent, Ligand and Catalyst

→ These are chemical s carry out the reaction.

→ Generally these impurities are less common but sometime produce a problem as impurities.

(e) Enantiomer Impurities

→ These are related product of end product- s may act as impurities.

eg. (R) & (S) enentiomer of Naproxan, (S)-naproxen treat arthritis but R-naproxan causes liver poisoning.

2. INORGANIC IMPURITIES

→ Inorganic impurities involve reagent, ligands, catalyst, heavy metal, other residual metals, inorganic salts, filter-aid & charcoal.

(a) Reagent, ligand, catalyst

In following reaction the precipitation of $CaCl_2$ is washed to remove excess of Na_2CO_3 and $CaCl_2$. If precipitate is not properly washed it may remain as impurity.

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

- $CaCl_2$ → Calcium Chloride
- Na_2CO_3 → Sod. Carbonate
- $CaCO_3$ → Calcium Carbonate
- $NaCl$ → Sodium Chloride

(b) Heavy metals

The main source of heavy metal is the H_2O used in the processes and the reactors, where acidification & hydrolysis takes place

(c) Other Materials (e.g. filter aids, charcoal)

Activated charcoal, & Carbon, filter & filtering aids such as centrifuge bags used during manufacturing, fibres and black particles in bulk drug manufacturing are essential to avoid.

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8. Residual Solvents

→ Solvent are organic volatile chemical substance used during manufacturing process.

→ These are of following types.

(1) Class-1 solvent : Benzene (1-2 ppm)
CCl_4 (1-4 ppm)

→ These are avoided due to toxic effect.

(2) Class-2-solvent : $CHCl_3$, CH_3OH, pyridine Toluene, acetonitrile, are mostly used.

(3) Class-3-solvent : CH_3COOH, CH_3COCH_3, Isopropyl alcohol Butanol, C_5H_5OH, are permitted at daily exposure 50 mg or less per day.

4. OTHER IMPURITES

(a) Excipient impurity : Peroxide, Aldehyde, heavy metal

(b) Elemental Impurities :

As, Al, Ca, Na, Pb

(c) Packaging Material

→ leachable and extractable substance from primary packaging may react to form secondary product.

(Na2O, SiO2, MgO, CaO)

Effect of Impurities

1) It can be injurious above a limit
2) Can cause incompatibility ~ other substance.
3) It may cause physical (change in) and chemical property.
4) It may ↓ shelf life of products.

SOURCE OF IMPURITIES

→ A compound is said to be impure. if it have foreign matters. i.e. impurities.

→ There are several sources of impurities.

① Raw Material used in manufacturing
② Reagent used in manufacturing.
③ Intermediate product in manufacturing.
④ Defect in manufacturing process.
⑤ Solvents.
⑥ Action of solvent on "reagent" and reacting vessels.
⑦ Atmospheric contamination
⑧ Defective storage of final products.

(1.) Raw Material used in Manufacturing.

→ If impurities are present in raw material (ores, metals) ⊆ can come ⊂ final product.

Ex.

$ZnSO_4$ are prepared from ZnO or Zn metal.

$$Zn + H_2SO_4 \longrightarrow ZnSO_4 + H_2$$

$$ZnO + H_2SO_4 \longrightarrow ZnSO_4 + H_2O$$

* Both Zn & ZnO contains (Al), copper (Cu) & magnisium (Mg), Mn, Ni, As & Fe as impurities.

(2) Reagent used in manufacturing process

→ If reagent used in manufacturing process is not completely removed it comes in final product.

Ex. When $CaCl_2$ react ⊂ Na_2CO_3, a precipitate of $CaCO_3$ is formed, then $CaCO_3$ is washed properly to remove excess of Na_2CO_3.

(3) Intermediate products in Manufacturing Process

e.g. potassium iodide is prepared by reacting iodine & KOH

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

$$KIO_3 + 3C \longrightarrow KI + 3CO$$

(KIO_3 → intermediate)

(4) Defect in Manufacturing Process

Defect such as imperfect mixing, incompleteness of reaction, non-adherence to proper temperature, pressure & pH.

e.g.

$$2Zn + O_2 \longrightarrow 2ZnO$$

If Zinc Metal is not completely converted to ZnO, a small amount of Zn metal remain as impurity in final product.

(5) Solvent

→ H_2O is majorly used as solvent it have Ca, SO_4, HCO_3^-, Mg, Ca etc as impurities.

6. Action of solvent and reagent on Reacting vessel

→ Some reagent and solvent may react ε container in ς they are stored

→ strong acid lead out alkali from borosillicate glass; copper & zn vessels react ε slightly acidic substance.

7. Atmospheric contamination

→ In Industrial areas atmosphere is contaminated ε dust particles (Al_2O_3, silica, porcelin, plastic fragements etc)

e.g. NaOH absorbs atmospheric CO_2 (contaminant) to form Na_2CO_3 & bicarbonate.