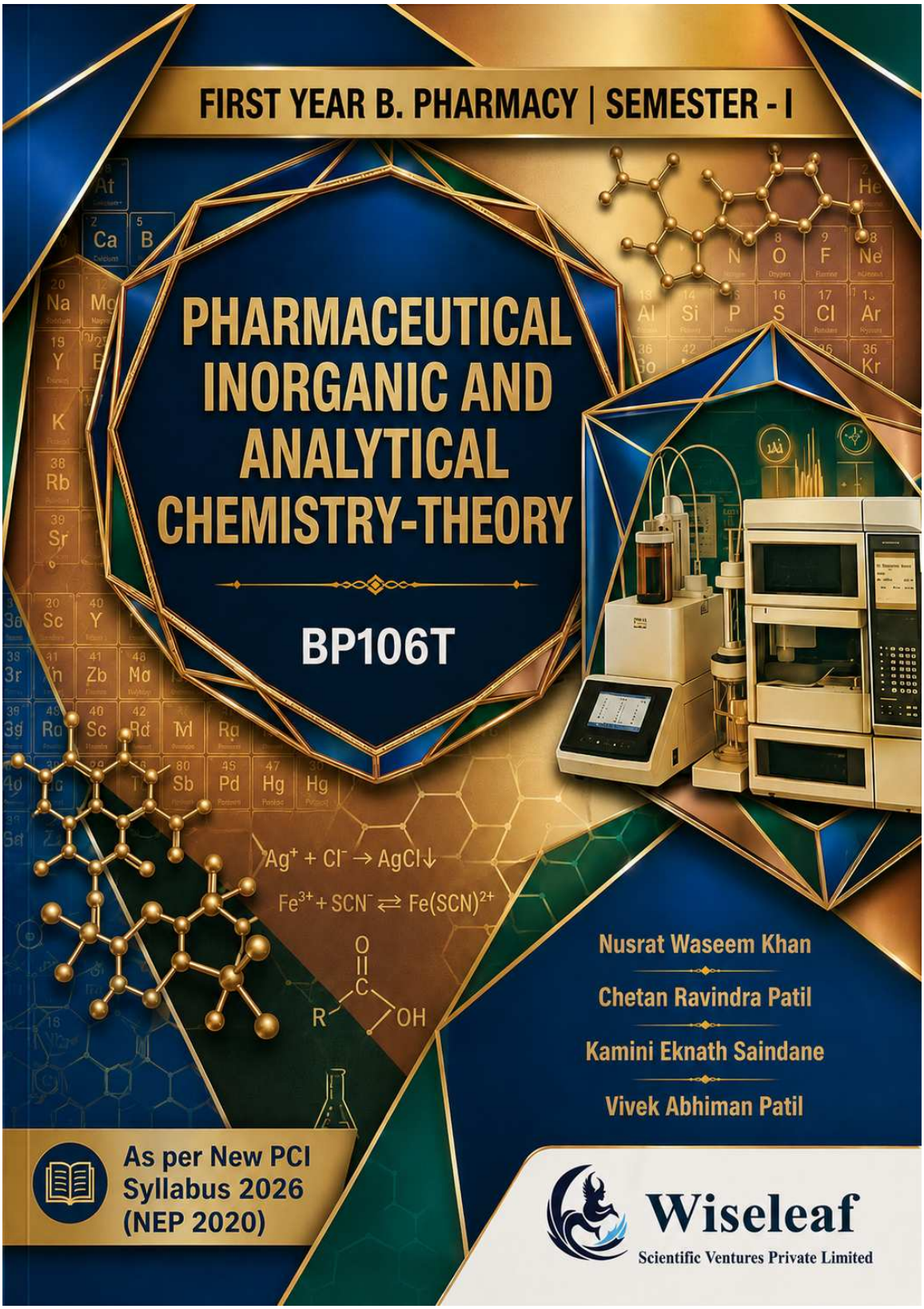
FIRST YEAR B. PHARMACY | SEMESTER - I
PHARMACEUTICAL INORGANIC AND ANALYTICAL CHEMISTRY-THEORY
BP106T
Ag+ + Cl- → AgCl↓
Fe3+ + SCN- ⇌ Fe(SCN)2+
Nusrat Waseem Khan
Chetan Ravindra Patil
Kamini Eknath Saindane
Vivek Abhiman Patil
As per New PCI Syllabus 2026 (NEP 2020)
Wiseleaf
Scientific Ventures Private Limited

PHARMACEUTICAL INORGANIC AND ANALYTICAL CHEMISTRY-THEORY

First Year B. Pharmacy
Theory Book as Per New Syllabus – 2026
Semester – I
BP 106 T

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Preface

Pharmaceutical sciences continue to evolve rapidly with advancements in drug discovery, analytical techniques, quality assurance, and healthcare standards. In this dynamic era, a strong understanding of Pharmaceutical Inorganic and Analytical Chemistry is essential for every pharmacy student, as it forms the scientific foundation for pharmaceutical analysis, drug standardization, quality control, and formulation development.

With this vision, we are delighted to present "Pharmaceutical Inorganic and Analytical Chemistry – Theory" for First Year B. Pharmacy students (Semester I, BP106T) as per the PCI New Syllabus – 2026. This book has been thoughtfully designed to bridge the gap between theoretical understanding and practical pharmaceutical applications while maintaining a student-friendly approach.

The journey of pharmacy education begins with understanding the chemistry behind medicines, their purity, standards, analysis, and therapeutic relevance. Keeping this in mind, the book systematically covers important topics such as pharmaceutical analysis, standard solutions, errors in analysis, pharmacopoeias, impurities in pharmaceuticals, limit tests, acid–base theories, buffers, isotonic solutions, and electrolyte balance. Each chapter has been prepared with special attention to conceptual clarity, examination orientation, and real-world pharmaceutical significance.

One of the unique aspects of this book is its simplified presentation style. Complex topics have been transformed into easily understandable explanations supported by definitions, mechanisms, examples, pharmaceutical applications, and important points for revision. The content is arranged in a logical and unit-wise sequence so that students can develop a step-by-step understanding of the subject.

In today's pharmaceutical profession, analytical precision and quality assurance play a crucial role in ensuring safe and effective medicines. Therefore, this book not only aims to help students succeed in university examinations but also encourages them to develop scientific thinking, analytical skills, and a professional approach toward pharmaceutical sciences.

We sincerely believe that this book will become a reliable academic companion for students, teachers, and pharmacy aspirants. If it inspires learners to explore the fascinating world of pharmaceutical chemistry with curiosity and confidence, our efforts will be truly rewarded.

We express our heartfelt gratitude to all mentors, colleagues, students, and well-wishers whose motivation and encouragement made this work possible. We also acknowledge the contribution of various standard references and academic resources that guided us during the preparation of this book. Suggestions for further improvement are always welcome and will be greatly appreciated for future editions.

"Knowledge in chemistry builds the foundation of safe medicines and better healthcare."

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Syllabus

Unit	PCI Syllabus Topic	Hours
I	**Introduction to pharmaceutical analysis** Different techniques of analysis, Methods of expressing strength of solutions, Primary and secondary standards with examples. **Errors** Sources of errors, types of errors, methods of minimizing errors, accuracy, precision and significant figures. **Impurities** Definition, types, contents and regulatory importance. Sources and types of impurities in Pharmaceuticals, limit tests for chloride, sulphate, iron, arsenic, lead, heavy metals, and modified limit test for chloride and sulphate.	7 h
II	**Acid-Base Chemistry and Buffer Systems in Pharmacy** Definition of acids, bases, buffers, pH Scale and its significance, Buffer equation, calculation of pH for Buffer solution. Isotonicity and its application in IV Fluids and Ophthalmic Solutions. **Major extra and intracellular electrolytes** Functions of major physiological ions, Electrolytes used in the replacement therapy: Sodium chloride*, Potassium chloride, Calcium chloride and Oral Rehydration Salt (ORS), Physiological acid base balance	8 h
III	**Acid base titrations** Theories of acid base indicators, classification of acid base titrations. Preparation and standardization of titrants viz. hydrochloric acid and sodium hydroxide. Theory involved in titrations of strong, weak, and very weak acids and bases, neutralization curves. Assay of Ammonium hydroxide. **Non-aqueous titrations** Types of solvents used, acidimetric and alkalimetric titration using nonaqueous solvents. Preparation and standardization of acidic and basic titrants. Estimation of weakly acidic and basic substances using nonaqueous titrants, estimation of Sodium benzoate. **Precipitation titrations and gravimetry** Principle and steps involved in gravimetric analysis, Mohr's method, Volhard's, Modified Volhard's, Fajans method. Estimation of barium sulphate by gravimetry. **Complexometric titrations** Classification, metal ion indicators, masking and demasking reagents, preparation and standardization of disodium EDTA. Estimation of Magnesium sulphate and Calcium gluconate*. **Redox titrations** Concepts of oxidation and reduction, Types of redox titrations viz. Permanganometry, Cerimetry, Iodimetry, Iodometry and titrations with potassium iodate.	14 h

Unit	PCI Syllabus Topic	Hours
IV	**Gastrointestinal agents** Acidifiers: Sodium acid phosphate and Dilute Hydrochloric acid. Antacids: Ideal properties of antacids, combinations of antacids, Sodium bicarbonate*, Aluminium hydroxide gel*. Agents promote bowel movements: Magnesium hydroxide, Sodium orthophosphate, Sodium Potassium tartrate and magnesium trisilicate. Antimicrobials: Mechanism, classification, Potassium permanganate, Boric acid, Hydrogen peroxide*, Chlorinated lime*, Iodine and its preparations. **Radiopharmaceuticals** Basics of radioactivity, applications of radioisotopes of Sodium Iodide I-131, Technetium-99m, Cobalt-60, Phosphorus-32 including safe handling, storage, and disposal of radiopharmaceuticals, adhering to regulatory guidelines for safety.	10 h
V	**Miscellaneous Compounds** **Expectorants:** Potassium iodide, Ammonium chloride*. **Emetics:** Copper sulphate*, Sodium potassium tartrate. **Haematinics:** Ferrous sulphate*, Ferrous gluconate. **Poison and Antidote:** Definition, classification of antidotes, Sodium thiosulphate	6 h

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UNIT I

Introduction to Pharmaceutical Analysis · Sources of Impurities · Limit Tests · Pharmacopoeias

1.1 Introduction to Pharmaceutical Analysis

Pharmaceutical analysis is the sub-discipline of chemistry that deals with the identification, determination, quantification and purification of substances that are intended for human or veterinary use. The discipline is the chemical conscience of the pharmaceutical industry, every batch of a drug substance, every dosage form, and every excipient that leaves a manufacturing site must first satisfy the analytical specifications laid down in a pharmacopoeia or in a regulatory dossier. Failures in analysis translate directly into failures at the patient level, and that is why pharmaceutical analysis carries a weight that ordinary classroom chemistry does not.

The substances examined by the pharmaceutical analyst originate from four broad sources. Natural sources contribute plant-derived actives (digitoxin from Digitalis purpurea, atropine from Atropa belladonna, vincristine from Catharanthus roseus). Microbial fermentation supplies antibiotics such as penicillin G from Penicillium chrysogenum, streptomycin from Streptomyces griseus and amphotericin B from Streptomyces nodosus. Mineral sources provide the inorganic pharmaceuticals that form the subject of this textbook, sodium chloride, calcium carbonate, ferrous sulphate, magnesium sulphate, zinc oxide. The fourth source, synthetic organic chemistry, accounts for the overwhelming majority of modern actives, from paracetamol to atorvastatin.

Whatever the origin of the drug, analysis is what converts the molecule into a medicine. A pure crystalline compound is not yet a medicine; it becomes one only when the analyst is able to certify, against a defined specification, that the right amount of the right substance is present, and that the wrong substances are present in amounts low enough not to harm the patient.

1.2 Scope and Purpose of Pharmaceutical Analysis

The scope of the discipline is wide. Five interconnected functions are commonly recognised.

Quality control. In-process and finished-product testing confirms that each batch of an active pharmaceutical ingredient (API) or a dosage form complies with the declared label claim and with the relevant monograph in the Indian Pharmacopoeia (IP), the British Pharmacopoeia (BP) or the United States Pharmacopeia–National Formulary (USP-NF). A typical example is the assay of paracetamol tablets, which must contain not less than 95.0 % and not more than 105.0 % of the labelled amount when tested by the official UV procedure.

Quality assurance. Quality assurance is broader than quality control. It covers the entire production chain, from raw-material qualification to the validation of the analytical method itself, and is built around the principles of Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP).

Regulatory compliance. No medicine is allowed in the supply chain unless it conforms to the standards of a recognised pharmacopoeia. In India, the standards of the IP are legally binding under the Drugs and Cosmetics Act, 1940; in the United Kingdom the same role is filled by the BP under the Human Medicines Regulations, 2012; in the United States the USP-NF is enforced by the U.S. Food and Drug Administration.

Stability testing. Stability studies make use of analytical methods to monitor the degradation of an API or a formulation over time under defined temperature and humidity conditions (typically 25 °C / 60 % RH for long-term studies and 40 °C / 75 % RH for accelerated studies, as per ICH Q1A(R2)). The data so generated fix the shelf life printed on the package.

Research and development. In the early stages of new drug discovery, analytical chemistry is used to monitor the progress of synthesis, to elucidate the structure of intermediates, and to characterise impurities. Without robust analytical support no pharmaceutical research programme can function.

1.3 Classification of Analytical Methods

The methods used in the pharmaceutical laboratory can be classified along two independent axes. The first axis distinguishes the type of information obtained, and the second distinguishes the technique used to obtain it.

1.3.1 Classification by the type of determination

On the basis of what the analyst sets out to find, three categories are recognised.

- Qualitative analysis answers the question, "what is in the sample?". It identifies the chemical entity present, but says nothing about its amount. Wet-chemistry tests for functional groups, identification tests in a pharmacopoeial monograph and spot tests on a TLC plate all fall under this heading.
- Quantitative analysis answers the question, "how much is in the sample?". It provides a numerical estimate of the concentration of the analyte. Assay by titration, by UV-visible spectrophotometry or by HPLC are examples in routine use.
- Semi-quantitative analysis is a hybrid. It does not produce a precise numerical value but tells the analyst whether the substance of interest is present above or below a prescribed limit. The limit tests described later in this chapter, for chloride, sulphate, iron, arsenic, lead and heavy metals, belong to this category.

1.3.2 Classification by the technique employed

A second classification, more useful in the day-to-day laboratory, separates the methods into instrumental and non-instrumental. The instrumental group depends on a measuring device that responds to a specific physical property of the analyte; the non-instrumental group relies on a chemical reaction whose course is

followed by simple observation, mass measurement or volume measurement. Figure 1.1 summarises both axes.

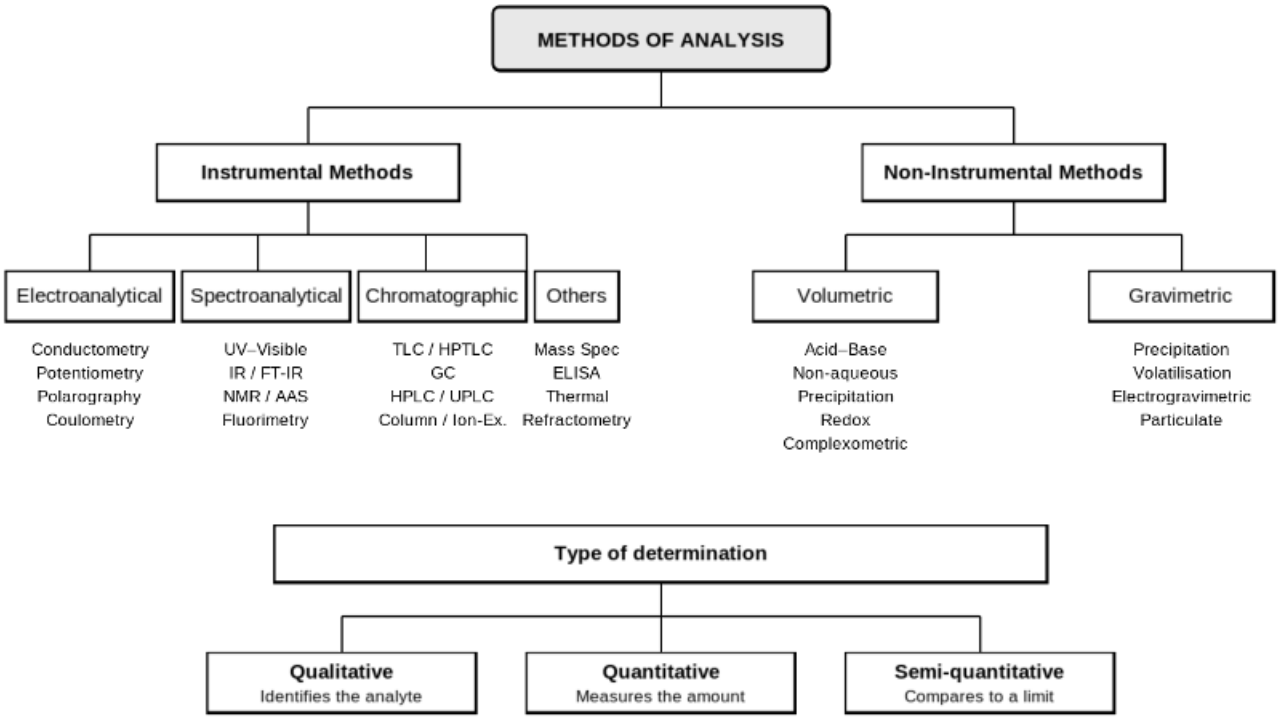

Fig. 1.1 Classification of methods used in pharmaceutical analysis

Within the instrumental group, four families are commonly recognised:

Electroanalytical methods potentiometry, conductometry, polarography, coulometry, amperometry. They measure the current, voltage, charge or conductance produced when the analyte takes part in a redox or ion-transport process at an electrode interface.

Spectroanalytical methods UV-visible, IR, FT-IR, NMR, atomic absorption spectroscopy (AAS), atomic emission spectroscopy (AES), turbidimetry, nephelometry, fluorimetry. They exploit the interaction of the analyte with electromagnetic radiation.

Chromatographic methods TLC, HPTLC, GC, HPLC, UPLC, ion-exchange chromatography. They separate the components of a mixture by partition between a stationary and a mobile phase before quantitating each band.

Other instrumental methods mass spectrometry, ELISA, thermal methods (DSC, TGA), refractometry, polarimetry.

The non-instrumental group is dominated by classical chemical methods, volumetric (titrimetric) and gravimetric. The four classes of volumetric analysis (acid–base, non-aqueous, precipitation and redox) form the subject of Unit III, and gravimetric methods are covered alongside them.

1.4 Methods of Expressing the Strength of Pharmaceutical Solutions

Every quantitative procedure rests on the analyst being able to express the concentration of a solution in unambiguous terms. The six expressions used most commonly in pharmaceutical work are listed below.

Table 1.1 Common modes of expressing concentration in pharmaceutical analysis.

Mode	Symbol	Definition	Worked example
Molarity	M	Number of moles of solute per litre of solution.	40 g NaOH dissolved and made up to 1 L = 1 M NaOH (M.W. = 40).
Normality	N	Number of gram-equivalents of solute per litre of solution. Useful where one analyte particle reacts with more than one acid or base equivalent.	49 g H_2SO_4 in 1 L = 1 N (eq. wt. = 49); the same solution is 0.5 M.
Molality	m	Number of moles of solute per kilogram of solvent. Independent of temperature.	58.44 g NaCl in 1 kg water = 1 m NaCl.
Formality	F	Number of formula weights per litre of solution. Used for ionic substances that dissociate on dissolution (e.g. NaCl).	58.44 g NaCl in 1 L = 1 F (rather than 1 M, since the salt dissociates).
Percent strength	%	% w/w (g of solute per 100 g of solution), % w/v (g per 100 mL), % v/v (mL per 100 mL).	Povidone-Iodine 5 % w/v solution (Betadine): 5 g of free iodine equivalent per 100 mL of preparation.
Parts per million	ppm	mg of solute per kg of solvent or µg per g. Used for trace analytes such as heavy-metal impurities.	A 1 ppm Pb^{2+} standard contains 1 mg Pb^{2+} in 1 L (since 1 L ≈ 1 kg for dilute aqueous solutions).

Two further expressions appear sporadically: parts per billion (ppb), used in elemental impurity analysis (ICH Q3D), and mole fraction (X), used when colligative properties such as osmotic pressure are under discussion. Concentrations expressed in milliequivalents per litre (mEq/L) are universal in clinical chemistry, sodium, potassium and bicarbonate in serum are reported on this scale, and the topic is developed further in Unit II in connection with body-fluid electrolytes.

1.5 Standard Solutions: Primary and Secondary

A standard solution is one whose strength is known with high accuracy. The pharmaceutical analyst depends on these solutions for every titrimetric assay and for the calibration of every instrumental method. Two categories are recognised on the basis of how the strength is established.

1.5.1 Primary standards

A primary standard is a chemical substance of very high purity (in the range 99.95–100.05 %) which can be weighed directly and used to prepare a solution of accurately known concentration without further titrimetric standardisation. To qualify as a primary standard a substance must satisfy a strict set of criteria.

- It must be easily obtainable in a pure state and easy to dry, usually between 105 °C and 110 °C; hydrated salts seldom qualify because the water of crystallisation cannot be driven off without partial decomposition.
- It must remain unchanged on exposure to air during weighing, that is, non-hygroscopic, non-efflorescent, resistant to atmospheric oxidation and unreactive towards atmospheric carbon dioxide.
- Its total impurity content must not exceed 0.01–0.02 % and must be measurable by sensitive tests.
- It must have a high relative molecular mass so that the unavoidable weighing error of ±0.1–0.2 mg contributes a negligible relative error. For example, weighing 0.2 g of a substance of molecular mass 200 gives a 0.1 % relative error; the same absolute error on a substance of molecular mass 20 would give a 1 % error.
- It must be readily soluble under the conditions of the titration, and the reaction with the titrant must be stoichiometric, rapid and quantitative.

The principal primary standards used in volumetric analysis are summarised in Table 1.2.

Table 1.2 Common primary standards used in pharmaceutical volumetric analysis.

Titration type	Titrant being standardised	Primary standard used	Drying conditions
Acidimetry	HCl, H_2SO_4	Anhydrous sodium carbonate (Na_2CO_3)	270 °C, 1 h
Alkalimetry	NaOH, KOH	Potassium hydrogen phthalate ($KHC_8H_4O_4$)	120 °C, 2 h
Permanganometry	$KMnO_4$	Sodium oxalate ($Na_2C_2O_4$) or arsenic(III) oxide	105 °C, 2 h
Iodometry	$Na_2S_2O_3$	Potassium dichromate ($K_2Cr_2O_7$), potassium iodate (KIO_3) or potassium bromate ($KBrO_3$)	120–150 °C, 1 h
Iodimetry	I_2	Arsenic(III) oxide (As_2O_3)	Desiccator over P_2O_5
Argentometry	$AgNO_3$	Sodium chloride (NaCl, AR grade)	500 °C, 1 h
Complexometry	Disodium EDTA	Calcium carbonate ($CaCO_3$)	110 °C

1.5.2 Secondary standards

A secondary standard is a solution whose strength has been established by titration against a primary standard. Most working laboratory reagents, sodium hydroxide, hydrochloric acid, potassium

permanganate, sodium thiosulphate, silver nitrate, cannot be used as primary standards. Sodium hydroxide, for example, picks up moisture and carbon dioxide from the air the moment a fresh bottle is opened, so the concentration of even a freshly prepared solution begins to drift within hours.

The differences between the two classes are summarised in Table 1.3.

Table 1.3 Comparison of primary and secondary standards.

Property	Primary standard	Secondary standard
Purity	99.95–100.05 %	Generally < 99 %; contains adventitious impurities
Stability	Stable on storage and on exposure to air	Less stable; concentration drifts on storage
Method of preparing a solution	Weighed accurately and dissolved to volume	Concentration determined by titration against a primary standard
Reactivity	Low; does not react with air, CO_2 or moisture	Often hygroscopic or reactive (e.g. NaOH absorbs CO_2)
Molecular weight	Preferably high so that weighing error is small	Variable; not a defining criterion
Examples	Na_2CO_3, $KHC_8H_4O_4$, As_2O_3, $Na_2C_2O_4$, $K_2Cr_2O_7$	NaOH, HCl, $KMnO_4$, $Na_2S_2O_3$, $AgNO_3$, I_2

A sodium hydroxide solution, therefore, can be standardised in two ways. It may be titrated directly against weighed potassium hydrogen phthalate (a primary standard), or it may be titrated against a previously standardised hydrochloric acid solution (which is itself a secondary standard, standardised against anhydrous sodium carbonate). The latter chain of standardisations is permissible only when the error is propagated through the chain transparently.

1.6 Errors in Pharmaceutical Analysis

No analytical measurement is free of error. The mark of a competent analyst is not the absence of error but the ability to recognise its source, estimate its magnitude and report the result with the correct number of significant figures. The discussion that follows is built on the framework of Mendham et al., Vogel's Textbook of Quantitative Chemical Analysis [2], and is restricted to the basics required at undergraduate level.

1.6.1 Definition and sources

Error is defined as the difference between the measured value and the accepted true value. The absolute error carries the same units as the measurement; the relative error is dimensionless and is usually expressed as a percentage.

The principal sources of error encountered in the pharmaceutical laboratory are five.

Analyst-related. The training and experience of the analyst influence every step from sampling through endpoint detection. An inexperienced operator over-titrates by 1–2 drops where an experienced one stops within a fraction of a drop.

Instrument-related. Burettes that have not been calibrated against the temperature of use, pH meters with drifting electrodes, single-beam UV-spectrophotometers used without a wavelength check, and analytical balances that have not been verified against class-E2 weights all introduce systematic errors.

Reagent-related. Reagents that have aged on the shelf, indicator solutions that have started to decompose, and distilled water that has picked up atmospheric CO_2 are responsible for many of the puzzling results seen in undergraduate practical classes.

Procedure-related. An analytical procedure that has not been validated, or one that has been validated but not followed step-by-step, is a frequent source of large unexplained errors.

Sample-related. A sample that does not represent the bulk of the batch, for example, the top scoop of a tablet drum without prior mixing, gives a result that cannot be related back to the manufacturing batch.

1.6.2 Types of error

Errors are classified, on the basis of their behaviour on repetition of the measurement, into two large groups, determinate and indeterminate.

Determinate (systematic) errors have an assignable cause and a fixed sign and magnitude. They affect every measurement in the same way and, once identified, can be corrected for. Sub-classes are listed in Table 1.4.

Table 1.4 Sub-types of determinate (systematic) error.

Sub-type	Origin	Illustrative example
Personal error	Personal habit of the analyst	Habitual over-reading of the meniscus by one division
Instrumental error	Faulty or uncalibrated instrument	A burette delivering 50.00 mL when set to 50.10 mL
Reagent error	Impurity in the reagent or attack of reagent on the container	KOH stored in soft glass extracts silicate
Constant error	Fixed in magnitude regardless of sample size	Loss of 0.1 mg of precipitate during transfer
Proportional error	Varies in step with the amount of analyte; relative error is constant	Co-precipitation of an interferent in a gravimetric assay
Methodological error	Defect in the method itself	Incomplete reaction at the endpoint of a slow titration
Additive error	Independent of the analyte amount	Buoyancy correction not applied during weighing

Indeterminate (random) errors do not have an identifiable single cause. They arise from many uncontrollable variables acting together, small temperature fluctuations, vibration of the bench, electronic noise in the detector, and they produce scatter around the mean. Random errors cannot be eliminated; the best one can do is to reduce their magnitude by repeated determinations and to estimate their size by statistical methods such as the standard deviation, the standard error of the mean and the confidence interval.

1.7 Methods of Minimising Errors

Nine techniques are routinely used to keep error within acceptable bounds.

1. **Calibration of apparatus.** Burettes, pipettes, volumetric flasks and balances are calibrated against certified reference weights and certified volume standards. Calibration certificates are renewed annually.
2. **Blank determination.** The procedure is repeated step-by-step on a sample-free reagent system. The volume of titrant consumed gives the contribution of reagent and glassware impurities, and is subtracted from the sample reading. A useful blank value should be small; a large blank reduces precision.
3. **Control determination.** The procedure is run on a sample of known composition that is similar to the unknown. The ratio of the result on the control to the certified value provides a correction factor.
4. **Independent method check.** The same analyte is determined by two independent methods. If a chloride is determined gravimetrically as AgCl and also titrimetrically by Mohr's method and the two results agree within experimental error, confidence in the result is high.
5. **Parallel determinations.** Three replicate determinations are normally run; the agreement between them indicates precision but not necessarily accuracy.
6. **Standard addition.** A known amount of the analyte is added (spiked) to the sample. The recovery (the amount measured after spiking minus the original amount, expressed as a percentage of the spike) provides an estimate of accuracy and of matrix interference. The method is invaluable in spectrophotometric and polarographic determinations of trace analytes.
7. **Internal standard.** A substance similar in chemical character to the analyte but resolvable from it is added in a constant amount to every standard and every sample. Quantitation is by the ratio of the analyte signal to the internal-standard signal. The method dominates HPLC and GC of biological matrices.
8. **Amplification methods.** When the analyte is below the detection limit, a chemical amplification step is introduced. For example, every iodate ion can be amplified to six iodine atoms by reaction with iodide in acid, the iodine then being titrated with thiosulphate.
9. **Isotope dilution.** A measured amount of a radioactive isotope of the analyte is added; the analyte is then isolated and its specific activity measured. The drop in specific activity gives the amount of

the unlabelled analyte originally present. The method is widely used in pharmacokinetics and metabolic studies.

1.8 Accuracy, Precision and Significant Figures

The terms accuracy and precision are often used loosely. In the analytical laboratory they have precise meanings. Accuracy is the closeness of a measured value to the accepted true value, and is usually expressed as the percentage relative error. Precision is the closeness of replicate measurements to one another, and is usually expressed as the standard deviation or the relative standard deviation. A set of measurements may be precise without being accurate (a tightly grouped pattern of shots far from the bull's-eye), accurate without being precise (a scattered pattern centred on the bull's-eye) or, desirably, both accurate and precise.

Table 1.5 Accuracy contrasted with precision.

Property	Accuracy	Precision
What it measures	Closeness to the true value	Closeness of replicate measurements
Expressed as	Absolute or relative error	Standard deviation or relative standard deviation
Improved by	Eliminating determinate (systematic) errors	Eliminating indeterminate (random) errors
Affected by	Bias of the method or operator	Random fluctuation of instrument and environment
Target metaphor	Hitting the bull's-eye	A tight grouping of shots

1.8.1 Significant figures

A significant figure is any digit in a measured quantity that is known with certainty plus the first digit that is uncertain. A burette graduated in 0.1 mL is read to the nearest 0.01 mL by estimating between the lines; a reading of 24.36 mL therefore has four significant figures - the 2, 4 and 3 are certain, and the 6 is estimated.

Five rules cover almost every situation encountered at undergraduate level.

10. All non-zero digits are significant. The number 5489.213 has seven significant figures.
11. Zeros between non-zero digits are significant. The number 0.08006 has four significant figures (the 8, the two zeros in the middle, and the 6).
12. Leading zeros that fix the decimal point are not significant. The number 0.00065 has two significant figures.
13. Trailing zeros to the right of a decimal point are significant. The number 1000.0 mL has five significant figures.

14. Trailing zeros in a whole number without a decimal point are ambiguous. 1000 mL may have one, two, three or four significant figures; the ambiguity is resolved by expressing the number in scientific notation, 1.0×10^3 mL (two significant figures), 1.000×10^3 mL (four).

1.9 Pharmacopoeia: Concept, Evolution and Importance

The English word pharmacopoeia comes from the two Greek roots pharmakon, "drug", and poiein, "to make". A pharmacopoeia is a legally binding compendium of standards for drugs, drug substances and dosage forms, issued under the authority of a government or an intergovernmental body. Each entry, known as a monograph, defines the identity, the purity and the strength expected of the substance, and prescribes the analytical methods by which compliance is to be demonstrated.

The historical roots of the idea reach back at least four thousand years. The Ebers Papyrus of about 1550 BCE catalogues more than seven hundred Egyptian remedies. The Chinese Shen-Nung Pen-Tsao Ching describes some three hundred and sixty medicines. The Nuovo Receptario published in Florence in 1498 is regarded by historians as the first official pharmacopoeia in the modern sense. The Pharmacopoeia Augustana of Augsburg followed in 1564, and the London Pharmacopoeia in 1618. The United States Pharmacopeia first appeared in 1820, the Pharmacopoeia of India in 1868, and the British Pharmacopoeia in 1864.

1.9.1 Functions of a Pharmacopoeia

Setting standards. A pharmacopoeia lays down the legally enforceable identity, purity and strength of each drug and each dosage form within its scope.

Protecting public health. By preventing the manufacture and sale of substandard or adulterated medicines, the pharmacopoeia is the first defence of the patient.

Providing a reference for compounding. It gives manufacturers and hospital pharmacists the formulae and procedures needed for the preparation of dosage forms.

Supporting regulatory enforcement. The standards are admissible as evidence in courts of law; a batch that fails the pharmacopoeial test is, by definition, of substandard quality.

1.10 Major Pharmacopoeias of the World

Seven pharmacopoeias, plus a small number of associated reference works, account for the bulk of medicinal-product specifications in international commerce. The current editions are tabulated below.

Table 1.6 Major pharmacopoeias of the world with the editions current as of 2026.

Pharmacopoeia	Abbrev.	Country / region	Publisher / custodian	Current edition (year)
Indian Pharmacopoeia	IP	India	Indian Pharmacopoeia Commission (IPC), Ghaziabad: under the Ministry of Health and Family Welfare	10th edition, IP 2026, 4 volumes; released 2 Jan 2026 [3]
British Pharmacopoeia	BP	United Kingdom and Commonwealth	Medicines and Healthcare products Regulatory Agency (MHRA), London	BP 2026, 6 volumes; legally effective 1 Jan 2026 [4]
United States Pharmacopeia–National Formulary	USP-NF	United States	U.S. Pharmacopeial Convention, Rockville, Maryland	USP-NF 2026, Issue 1 (Jul 2025) [5]
European Pharmacopoeia	Ph. Eur.	39 European countries	European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe, Strasbourg	12th edition (annual cycle: Issues 12.1, 12.2, 12.3) [6]
Japanese Pharmacopoeia	JP	Japan	Pharmaceuticals and Medical Devices Agency (PMDA) on behalf of MHLW	JP 18 (effective 7 Jun 2021) + Supplements I (2022) & II (2024); JP 19 planned 2026 [7]
International Pharmacopoeia	Ph. Int.	WHO Member States	World Health Organization, Geneva	11th edition (March 2023); focuses on WHO essential medicines [8]
Extra Pharmacopoeia (Martindale)		Worldwide reference	Royal Pharmaceutical Society of Great Britain	Martindale: The Complete Drug Reference; periodic updates

1.10.1 Indian Pharmacopoeia (IP)

The Indian Pharmacopoeia is the official book of drug standards for India. It is published by the Indian Pharmacopoeia Commission, an autonomous body under the Ministry of Health and Family Welfare, located at Sector 23, Raj Nagar, Ghaziabad. The standards laid down in the IP are made legally enforceable by virtue of the Drugs and Cosmetics Act, 1940 and the rules framed under it. The first edition was published in 1955; the latest, the tenth edition, was released on 2 January 2026 in four volumes and is known as IP 2026 [3].

The IP is organised in four broad parts: the general notices (provisions and definitions that apply across all monographs), the general chapters (analytical procedures and apparatus), the monographs (the specifications themselves) and the appendices (tables of solubility, melting points, reagents and reference materials). The ninth edition (IP 2022) introduced 92 new monographs, and its Addendum 2024 added a further 75 [9].

1.10.2 British Pharmacopoeia (BP)

The British Pharmacopoeia is published by the MHRA on behalf of the Department of Health. The first edition appeared in 1864. The 2026 edition, in six print volumes, became legally effective on 1 January 2026 and incorporates approximately four thousand monographs whose standards are enforceable under the Human Medicines Regulations, 2012 [4]. Volume I carries the preliminaries, Volumes II–IV carry the monographs (including herbals, blood products, vaccines and radiopharmaceuticals), Volume V the appendices and analytical methods, and Volume VI the veterinary section.

1.10.3 United States Pharmacopeia–National Formulary (USP-NF)

The USP-NF combines the United States Pharmacopeia (drug substances and dosage forms) with the National Formulary (excipients). It is published by the U.S. Pharmacopeial Convention at 12601 Twinbrook Parkway, Rockville, Maryland, and its standards are enforceable by the U.S. Food and Drug Administration. From 2020 onwards the USP-NF has moved to a continuous on-line publication cycle; the current edition is USP-NF 2026, Issue 1, with quarterly supplements [5].

1.10.4 European Pharmacopoeia (Ph. Eur.)

The European Pharmacopoeia is the common standard for the 39 signatory countries of the Convention on the Elaboration of a European Pharmacopoeia. It is published by the EDQM in Strasbourg. The cycle has changed from a three-yearly edition with eight supplements to an annual edition of three issues (Issues 12.1, 12.2, 12.3 making up the 12th edition) [6].

1.10.5 Japanese Pharmacopoeia (JP)

JP 18, the eighteenth edition, came into force on 7 June 2021 under Ministerial Notification 220 of the Ministry of Health, Labour and Welfare. Supplement I was published in December 2022 and Supplement II in 2024. JP 19 is scheduled for publication in 2026 [7].

1.10.6 International Pharmacopoeia (Ph. Int.)

The International Pharmacopoeia is published by the World Health Organization with the objective of providing recommended specifications and test procedures for the medicines on the WHO Model List of Essential Medicines. It is not directly legally binding in any country; rather, its monographs are adopted by member states as the basis for their own national standards. The current edition is the 11th, published in March 2023 [8].

1.10.7 Associated reference works

British National Formulary (BNF). A joint publication of the British Medical Association and the Royal Pharmaceutical Society, the BNF gives prescribing information for medicines in current use in the United Kingdom. It is updated twice a year.

National Formulary of India (NFI). Published by the IPC for the use of prescribers in India.

Martindale: The Complete Drug Reference. A comprehensive international reference covering drugs in current use, drugs under development and drugs of historical interest. The 39th edition was published in 2017.

Merck Index. An encyclopaedia of chemicals, drugs and biologicals; the 15th edition (2013) is the most recent print edition.

1.11 Sources and Types of Impurities in Pharmaceutical Substances

A pure chemical compound is one that contains no foreign matter. The pharmaceutical analyst rapidly learns that absolute purity is an unreachable ideal, every batch of every drug substance carries some impurities, and the question is never "is it pure?" but rather "are the impurities within the limits prescribed by the pharmacopoeia?". An impurity is any substance present in a drug other than the drug itself. The principal impurities encountered in inorganic pharmaceuticals are lead, arsenic, iron, chloride, sulphate and the heavy metals (Cu, Cd, Hg, Bi, Sb, Sn).

Eleven distinct sources contribute to the impurity profile of a finished substance. They are summarised in Figure 1.2 and explained in the paragraphs that follow.

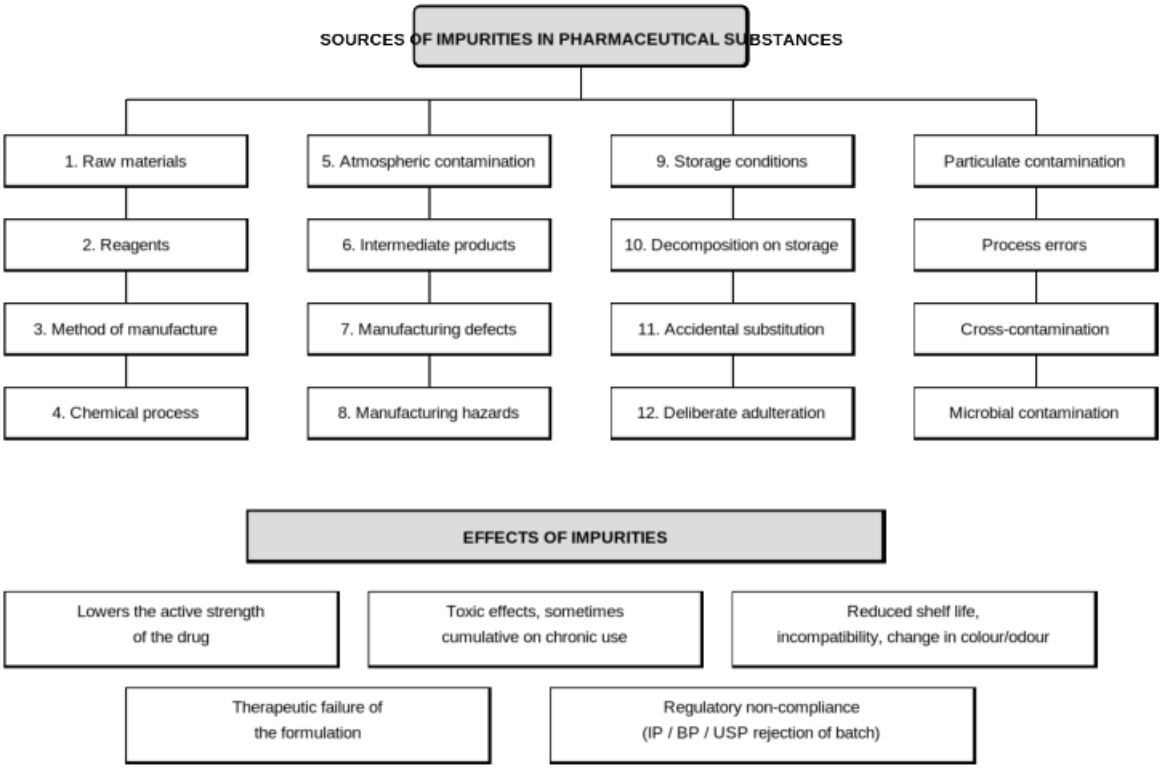

Fig. 1.2 Sources of impurities in pharmaceutical substances and their effects on the finished medicine.

1.11.1 Raw materials used in manufacture

Impurities that are present in the starting materials are very often carried through unchanged into the finished substance. Rock salt, for example, is a natural source of sodium chloride for the inorganic industry. It contains residual calcium sulphate and magnesium chloride, and sodium chloride manufactured from it without prior purification therefore carries calcium and magnesium as impurities.

A second illustrative case is the preparation of copper sulphate ($CuSO_4 \cdot 5H_2O$) from copper turnings:

$$Cu + 2\ H_2SO_4\ (hot,\ conc.) \rightarrow CuSO_4 + 2\ H_2O + SO_2$$

Commercial copper turnings carry trace iron and arsenic, both of which find their way into the product. For this reason the IP places an upper limit of 8 ppm on arsenic in copper sulphate and prescribes the Gutzeit test (Section 1.13.5) as the test of compliance.

1.11.2 Reagents used in the manufacturing process

When a reagent used during processing is not completely removed by washing, it appears as an impurity in the product. The preparation of ammoniated mercury ($HgNH_2Cl$), used in dermatological ointments, illustrates the point:

$$HgCl_2 + 2\ NH_4OH \rightarrow Hg(NH_2)Cl\downarrow + NH_4Cl + 2\ H_2O$$

Inadequate washing of the precipitate with cold water leaves ammonia and ammonium chloride as impurities. The IP therefore prescribes a specific test for ammonia in the monograph for ammoniated mercury.

1.11.3 Method or process of manufacture

Many synthetic drugs are prepared in multi-step sequences. Each step generates its own intermediates and by-products. Unless the intermediates are themselves purified, their impurities are inherited by the next step and ultimately by the final product. Side reactions add a second layer of contamination. The analyst is therefore expected to know not only what is intended to be in the bottle but also what could be in the bottle.

1.11.4 Chemical processes used in manufacture

Reactions such as nitration, halogenation, oxidation, reduction and hydrolysis introduce reagents that, even in trace amounts, may persist into the product. The tap water that is used as the solvent of last resort in much industrial work carries chloride, magnesium and calcium ions, and these are commonly seen as residual impurities in inorganic pharmaceuticals.

1.11.5 Atmospheric contamination

Industrial atmospheres often carry dust, sulphur dioxide, hydrogen sulphide and unburnt carbon. Solid pharmaceuticals exposed to such atmospheres absorb these contaminants. Sodium hydroxide is the classical example, even a freshly prepared solution begins to take up atmospheric carbon dioxide:

$$2\ NaOH + CO_2 \rightarrow Na_2CO_3 + H_2O$$

The IP therefore allows a maximum of 3 % w/w sodium carbonate in pharmaceutical-grade sodium hydroxide.

1.11.6 Intermediate products

Where the synthesis is not driven to completion, the unconverted intermediate ends up in the final product. The conversion of potassium iodate to potassium iodide by reduction with charcoal:

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

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

If the second step is not driven to completion, the potassium iodide of commerce contains residual potassium iodate, against which the IP monograph has a specific iodate test.

1.11.7 Defects in the manufacturing process

Imperfect mixing, incomplete reaction, inappropriate temperature, pressure or pH all leave their fingerprints on the impurity profile. In the manufacture of zinc oxide by combustion of metallic zinc:

$$2\ Zn + O_2 \rightarrow 2\ ZnO$$

an insufficiency of air or of heat leaves residual metallic zinc, which the IP screens by a specific identification test on the monograph for zinc oxide.

1.11.8 Manufacturing hazards

Five distinct hazard categories are recognised by the GMP literature:

Particulate contamination fragments of dust, fibre, glass, porcelain or plastic generated by sieves, granulators and tableting machines. Eye drops and parenterals demand particularly tight clarity specifications.

Process errors for example, incomplete dissolution of a solute, leading to a non-homogeneous syrup.

Cross-contamination airborne dust from one product settling into another during open-handling. Penicillin handling is an extreme case; even a few µg in another product can sensitise a patient.

Microbial contamination a particular concern for oral liquids, ophthalmic preparations, parenterals and herbal materials such as senna, acacia and tragacanth, which are routinely screened for Salmonella.

Packing errors the wrong tablet in the wrong bottle, or a leaflet that does not match the contents. Recalls under this heading dwarf those under any other.

1.11.9 Storage conditions

Even a perfectly manufactured substance can deteriorate during storage. The container itself is a source, alkali solutions held in soft glass extract lead silicate from the bottle, and strong acids stored in metal vessels extract iron. Salicylic acid ointments must not be packed in metal tubes because salicylates corrode aluminium. Light-sensitive substances (vitamin A, riboflavin, nifedipine) are dispensed in amber glass; deliquescent substances (calcium chloride, sodium hydroxide) demand desiccated containers.

1.11.10 Decomposition during storage

Chemical decomposition during storage may be hydrolytic, oxidative, photolytic or thermal. The products of decomposition are themselves impurities, and may be toxic. Adrenaline injection oxidises in air to a pink, then red, then brown solution as the catechol is oxidised to adrenochrome. The IP therefore prescribes specific tests for colour and for adrenochrome in adrenaline injection.

1.11.11 Accidental substitution or deliberate adulteration

Accidental substitution is averted by keeping toxic substances in clearly labelled, locked cupboards. Deliberate adulteration is a regulatory and a legal matter, costly substances are replaced with cheaper ones, the classical example being the substitution of potassium bromide by sodium bromide.

1.12 Effects of Impurities on Pharmaceutical Products

The presence of impurities, even within the pharmacopoeial limit, has six measurable consequences.

- Toxic effects. Lead, arsenic, mercury, cadmium and bismuth produce acute and chronic toxicities at concentrations only marginally above the pharmacopoeial limit, and some of these effects (especially lead encephalopathy and arsenic dermatological lesions) are cumulative.
- Lowering of active strength. An impurity that does not contribute to the therapeutic action displaces an equivalent amount of the active substance, so that the label claim is no longer met.
- Reduction of shelf life. Impurities frequently act as catalysts for the degradation of the active. Trace iron catalyses the autoxidation of ascorbic acid; trace copper catalyses the oxidation of adrenaline.
- Incompatibility. The impurity may react with another formulation component. Trace iron in calcium gluconate, for example, can produce a brown discolouration on storage with antioxidant-containing parenteral solutions.
- Physico-chemical change. Crystal form, melting point, solubility and the dissolution profile may all shift in the presence of certain impurities. The polymorphic conversion of ritonavir from Form I to the less soluble Form II in 1998 is the most famous industrial example.
- Sensory change. Colour, odour and taste shifts on storage are perceived by the patient as evidence of "spoilage" and lead to non-compliance with the prescribed regimen.

1.13 Tests for Purity in the Pharmacopoeia

Every pharmacopoeial monograph carries a battery of tests of purity. Nine categories are commonly seen:

- sensory tests, colour, odour, taste, appearance;
- physico-chemical constants, melting point, boiling point, refractive index, specific rotation, iodine value, saponification value, acid value;
- acidity, alkalinity and pH;
- loss on drying and loss on ignition;
- sulphated ash and total ash;
- tests for water content (Karl Fischer or azeotropic);
- specific cation and anion tests;
- limit tests for inorganic impurities, chloride, sulphate, iron, heavy metals, arsenic, lead;
- tests for related substances and residual solvents (ICH Q3A, Q3C).

1.14 Limit Tests: Principle and Practice

A limit test is a semi-quantitative analytical procedure designed to detect and to estimate the maximum permissible amount of a specific impurity in a pharmaceutical substance. The test does not produce an

absolute number for the impurity content; it answers the simpler, but for the pharmacopoeia, sufficient, question of whether the impurity is present in an amount that is acceptable.

Limit tests share four common features. First, the impurity to be tested is converted into a detectable form, a coloured complex, a precipitate that imparts opalescence or turbidity, or a coloured stain on a piece of paper. Second, an identical conversion is performed in parallel on a freshly prepared standard solution of the impurity at a concentration equal to the maximum permitted in the substance. Third, the test and the standard are made up to the same final volume in matched Nessler cylinders (50 mL graduated glass cylinders with a flat optical base, see Fig. 1.3). Fourth, the test and the standard are compared visually, by looking down the long axis of the cylinder against a white background. If the test produces a colour or opacity no greater than the standard, the sample is held to comply.

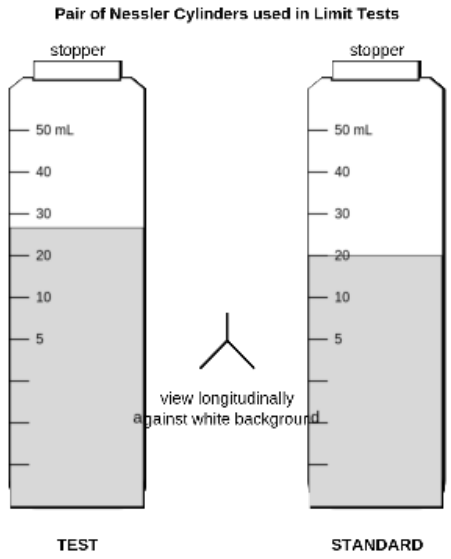

Fig. 1.3 Pair of Nessler cylinders (50 mL) used for visual comparison of turbidity, opalescence and colour in the limit tests.

The Nessler cylinder is to the limit test what the burette is to the titration. It has a graduated body, a flat ground base for longitudinal viewing, and a ground-glass stopper. The matched pair must be of identical glass thickness, identical inner diameter and identical graduation, because the eye compares optical path-lengths, not absolute amounts.

1.14.1 Limit Test for Chlorides

Principle. Soluble chloride in the sample reacts with silver nitrate in the presence of dilute nitric acid to produce an opalescence of silver chloride. The opalescence in the test is compared with that produced by a known amount of chloride in a parallel standard.

$$Cl^- + AgNO_3 \rightarrow AgCl\downarrow \text{ (white opalescence)} + NO_3^-$$

Role of dilute nitric acid. The medium is acidified with dilute HNO_3 to prevent the precipitation of other silver salts that could form in neutral or alkaline conditions, Ag_2CO_3, AgOH and Ag_3PO_4, and which would give a false positive.

Reagents

- Dilute nitric acid 10 % v/v;
- Silver nitrate solution 5 % w/v in water;
- Standard NaCl solution: 58.45 mg NaCl per 100 mL water (= 0.05845 % w/v), prepared by dissolution of analytical-grade dry NaCl. 1 mL of this solution ≡ 10 µg Cl^-.

Procedure

Two matched 50 mL Nessler cylinders are taken; one is labelled "Test", the other "Standard". The two are processed in parallel as shown in Figure 1.4 and described below.

15. Test: dissolve the quantity of substance prescribed by the monograph in water; transfer to the Test cylinder.
16. Standard: pipette 1.0 mL of the 0.05845 % w/v NaCl solution into the Standard cylinder.
17. Add 10 mL of dilute nitric acid to each cylinder and dilute each to approximately 50 mL with distilled water.
18. Add 1 mL of silver nitrate solution to each cylinder, stir immediately with a glass rod, and allow both to stand for 5 minutes.
19. View each cylinder longitudinally against a white background and compare the opalescence of the Test with that of the Standard.

Interpretation. If the opalescence in the Test is not greater than that in the Standard, the substance complies with the limit. If the opalescence in the Test is more dense, the substance fails the limit test.

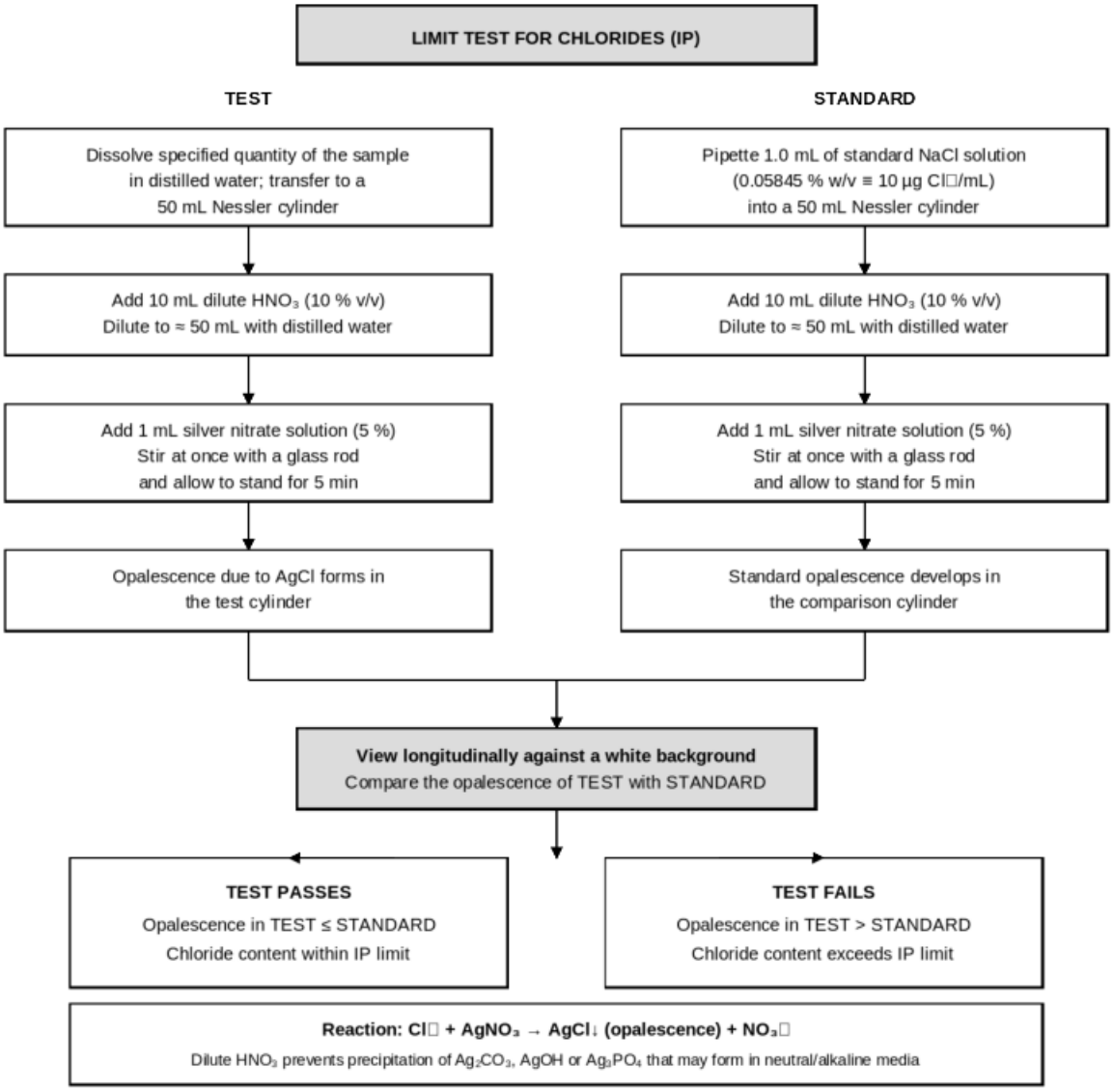

Fig. 1.4 Procedural flowchart for the limit test for chlorides.

1.14.2 Limit Test for Sulphates

Principle. Soluble sulphate in the sample reacts with barium chloride in the presence of dilute hydrochloric acid to produce a fine turbidity of barium sulphate. The turbidity in the test is compared with that of a parallel standard.

$$SO_4^{2-} + BaCl_2 \rightarrow BaSO_4\downarrow \text{ (turbidity)} + 2\ Cl^-$$

Role of the barium sulphate reagent. The reagent is a mixture of barium chloride solution, sulphate-free alcohol and a small amount of potassium sulphate. The alcohol suppresses super-saturation, so that the turbidity that develops is fine and reproducible; the small amount of potassium sulphate acts as a seeding agent, raising the sensitivity of the reaction.

Reagents

- Dilute hydrochloric acid;
- Barium sulphate reagent: 15 mL of 0.5 M barium chloride solution + 55 mL water + 20 mL sulphate-free alcohol + 5 mL of 0.0181 % w/v potassium sulphate; diluted to 100 mL with water and mixed;
- Standard sulphate solution: 0.1089 % w/v potassium sulphate in water (≡ 60 µg SO_4^{2-} per mL).

Procedure

20. Test: dissolve the prescribed quantity of substance in water; transfer to the Test cylinder.
21. Standard: pipette 1.0 mL of 0.1089 % w/v potassium sulphate into the Standard cylinder.
22. Add 2 mL of dilute hydrochloric acid to each cylinder and dilute each to approximately 45 mL with water.
23. Add 5 mL of barium sulphate reagent to each, stir immediately with a glass rod, and allow both to stand for 5 minutes.
24. View longitudinally against a white background and compare the turbidity.

Interpretation. Turbidity in the Test no greater than that of the Standard indicates compliance.

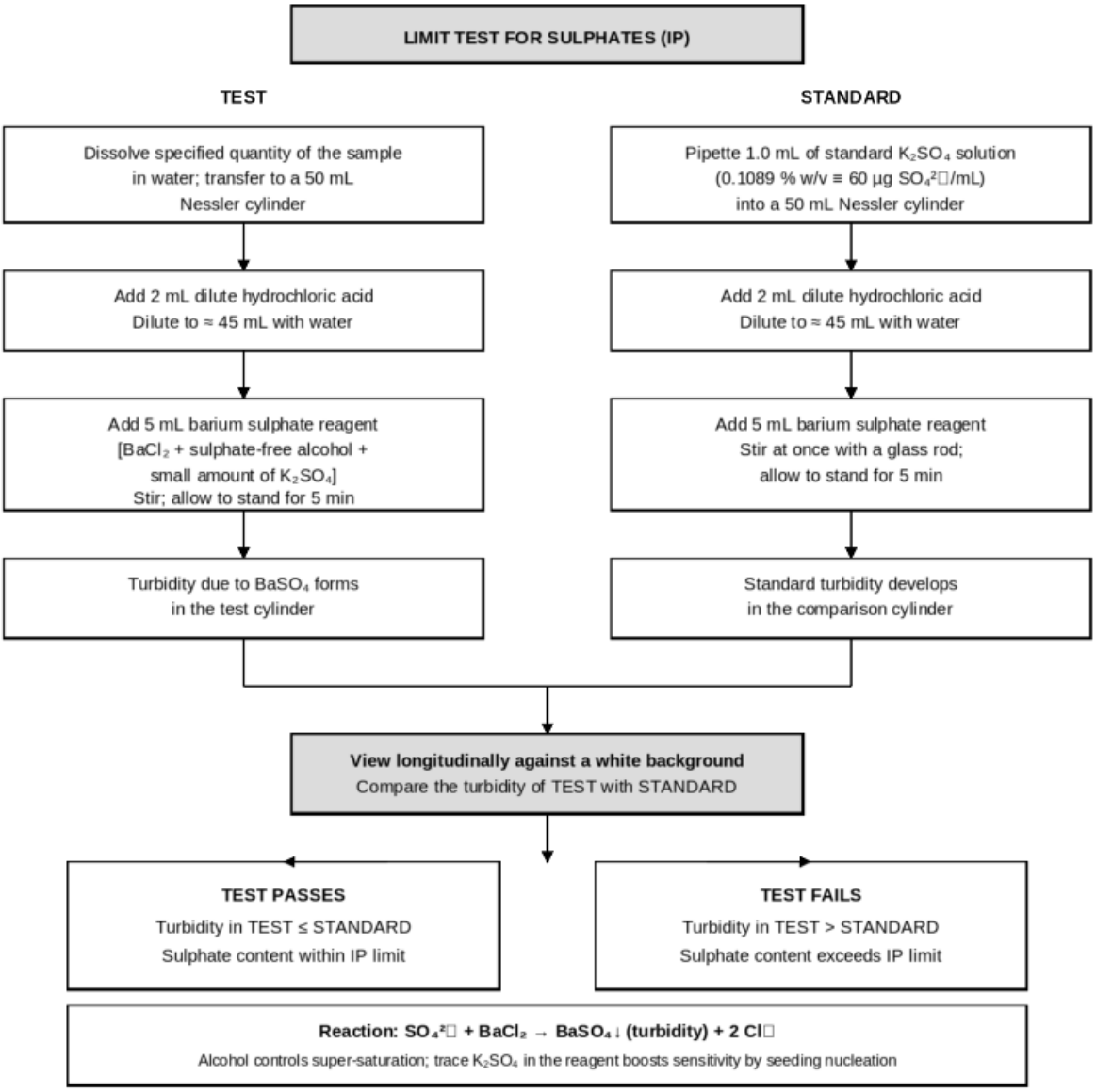

Fig. 1.5 Procedural flowchart for the limit test for sulphates.

1.14.3 Limit Test for Iron

Principle. Ferric iron in the sample is reduced to ferrous iron by thioglycollic acid in ammoniacal medium; the ferrous ion forms a coloured complex with thioglycollate, varying from pale pink (low concentration) to deep reddish-purple (higher concentration). Citric acid is added to mask the iron, that is, to prevent its precipitation as ferric hydroxide in the ammoniacal medium. The colour developed in the test is compared with that of a parallel standard.

$$Fe^{3+} + \text{thioglycollate} \rightarrow Fe^{2+}(\text{thioglycollate})_2 \text{ (pink-purple, in ammoniacal medium)}$$

Stability note. The coloured complex is stable only in the absence of air. On exposure, the ferrous iron re-oxidises and the colour fades. The visual comparison must therefore be made promptly, within a few minutes of full colour development.

Reagents

- Standard iron solution: 0.1726 g of ferric ammonium sulphate dissolved in 10 mL of 0.1 N H_2SO_4 and made up to 1000 mL with water. 1 mL ≡ 20 µg Fe.
- 0.1 N sulphuric acid (4.904 g H_2SO_4 in 1000 mL water);
- Iron-free citric acid 20 % w/v;
- Thioglycollic acid;
- Iron-free ammonia solution.

Procedure

25. Test: dissolve the prescribed quantity of substance in about 40 mL of water; transfer to the Test cylinder.
26. Standard: dilute 2 mL of standard iron solution (≡ 40 µg Fe) with 40 mL of water in the Standard cylinder.
27. Add 2 mL of 20 % w/v iron-free citric acid solution to each and mix.
28. Add 0.1 mL of thioglycollic acid to each and mix.
29. Make each alkaline with iron-free ammonia solution.
30. Dilute each to 50 mL with water and allow to stand for 5 minutes.
31. Compare the colours longitudinally against a white background, without delay.

Interpretation. A colour in the Test no deeper than that of the Standard indicates compliance.

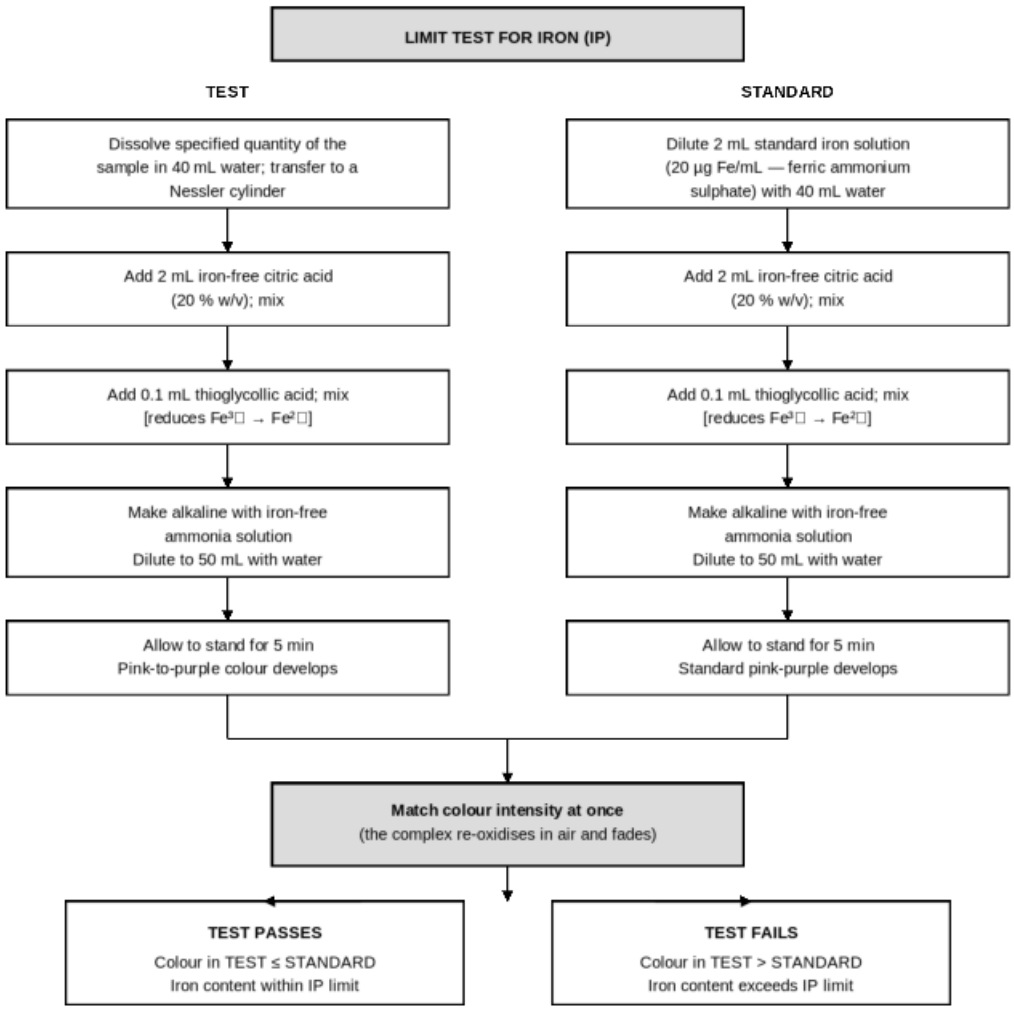

Fig. 1.6 Procedural flowchart for the limit test for iron.

1.14.4 Limit Test for Heavy Metals

The expression "heavy metals" in pharmacopoeial usage covers metals that precipitate as sulphides in the conditions of the test, chiefly Pb, Bi, Sb, Sn, Cd, Hg, Cu, Mo, Ag and As. The test is reported on the basis of an equivalent lead concentration, since lead is the most toxicologically significant of the group and is taken as the reference impurity.

The IP recognises four official methods for this test, distinguished by the way the sample is brought into solution and by the precipitating reagent (Figure 1.10).

Method A. For substances that are freely soluble in water. The sample is dissolved in water; the buffered solution is treated with hydrogen sulphide solution; the brown-black colloid of metal sulphides is compared with a parallel standard prepared from lead nitrate.

Method B. For substances insoluble in water, but free of organic matter. The sample is first ignited with concentrated sulphuric acid to give the sulphated ash; the residue is dissolved, buffered and treated with H_2S.

Method C. For acid-sensitive substances. The sample is dissolved in sodium hydroxide solution and the resulting alkaline solution is treated with sodium sulphide. The colour of the dark-brown sulphide is compared visually.

Method D (the "modified limit test"). The sample is buffered to pH 3.5 with acetate buffer and treated with a freshly prepared thioacetamide reagent. Thioacetamide, CH_3CSNH_2, hydrolyses in acidic medium to release H_2S in situ, which then precipitates the heavy-metal sulphides. The method dispenses with the toxic and malodorous H_2S gas and is the preferred procedure in modern laboratories. It is described in greater detail in Section 1.14.5.

Standard lead solution

A stock solution is prepared by dissolving 0.1598 g of lead nitrate in 100 mL of water, adding 1 mL of concentrated HNO_3 and making up to 1000 mL with water. A working standard is prepared by diluting 10 mL of the stock to 100 mL with water; the working standard contains 20 µg Pb per mL (≡ 20 ppm Pb^{2+}).

Procedure for Method A (the most commonly cited)

32. Test: dissolve the prescribed quantity of substance in 25 mL of water; transfer to a Nessler cylinder.
33. Adjust the pH to 3–4 with dilute acetic acid or dilute ammonia.
34. Dilute to 35 mL with water.
35. Add 10 mL of freshly prepared hydrogen sulphide solution.
36. Dilute to 50 mL with water, mix and allow to stand for 5 minutes.
37. Standard: take 2 mL of standard lead solution in a Nessler cylinder, dilute to 25 mL with water, adjust the pH to 3–4, dilute to 35 mL, add 10 mL of fresh H_2S solution and dilute to 50 mL. Allow to stand for 5 minutes.
38. Compare the colours longitudinally against a white background.

$$Pb^{2+} + H_2S \rightarrow PbS\downarrow \text{ (brown-black)} + 2\,H^+$$

Interpretation. A colour or turbidity in the Test no more pronounced than that of the Standard indicates compliance.

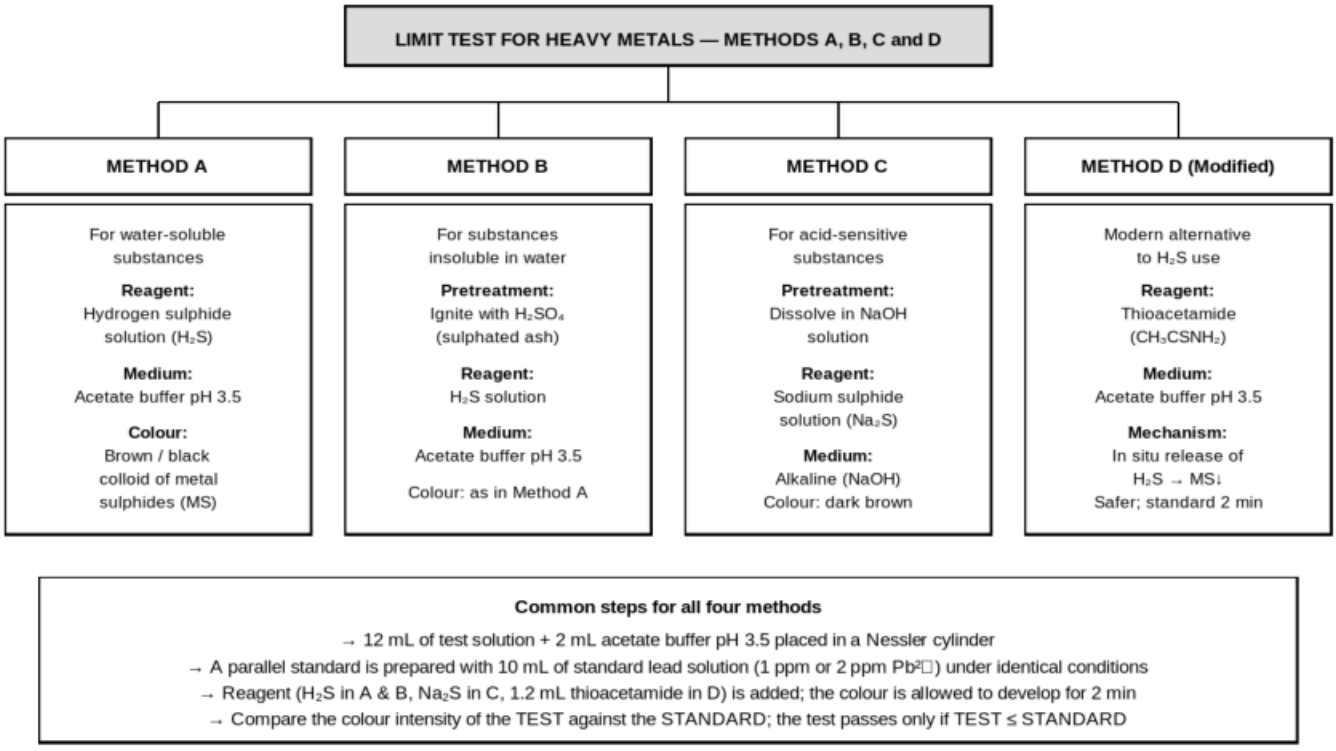

Fig. 1.10, Comparison of the four pharmacopoeial methods for the limit test of heavy metals; Method D (thioacetamide) is the modified limit test.

1.14.5 Modified Limit Test for Heavy Metals (Thioacetamide / Method D)

The modified limit test was introduced into the pharmacopoeias to replace the use of gaseous hydrogen sulphide, a substance that is malodorous, acutely toxic (PEL 20 ppm in air) and which produces inconsistent results if the gas is not freshly generated. Thioacetamide (CH_3CSNH_2) is a solid, water-soluble compound that hydrolyses slowly in aqueous solution to release H_2S in situ:

$$CH_3CSNH_2 + H_2O \rightarrow CH_3CONH_2 + H_2S$$

The H_2S so liberated reacts at once with any heavy-metal ions present in the buffered solution to give the corresponding sulphide:

$$M^{2+} + H_2S \rightarrow MS\downarrow + 2\,H^+ \quad (M = Pb, Cu, Bi, Sn, Cd, Hg, \ldots)$$

Reagents

- Thioacetamide reagent: 1 mL of thioacetamide solution (4 % w/v) + 5 mL of an alkaline glycerol mixture (15 mL of 1 N NaOH + 5 mL of water + 20 mL of glycerin), heated for 20 s in a water bath at 90 °C and used at once;
- Acetate buffer pH 3.5;
- Standard lead solution 1 ppm or 2 ppm Pb^{2+} (as in Section 1.14.4).

Procedure

39. Take 12 mL of test solution (prepared as in the monograph) in a Nessler cylinder.
40. In a second matched cylinder, place 10 mL of standard lead solution and 2 mL of test solution (so that the matrix of the standard matches that of the test).
41. Add 2 mL of acetate buffer pH 3.5 to each cylinder and mix.
42. Add 1.2 mL of the freshly prepared thioacetamide reagent to each.
43. Allow each to stand for exactly 2 minutes.
44. View longitudinally against a white background and compare the colour.

Interpretation. The colour in the Test must not be more intense than that in the Standard.

Advantages of the modified test. The reagent is a stable solid and a fixed amount is delivered each time; H_2S is released in a closed, buffered medium and does not escape into the atmosphere; the test is sensitive down to about 1 ppm Pb^{2+} and is reproducible between operators. The procedure is now the default heavy-metals test in the European, British and Indian pharmacopoeias.

1.14.6 Limit Test for Arsenic (Gutzeit's Test)

Principle. Arsenic in the sample, whether in the As(III) or As(V) form, is reduced by nascent hydrogen, generated by the action of stannated hydrochloric acid on granulated zinc, to arsine gas (AsH_3). The gas is allowed to rise through the apparatus and to react with a strip of paper that has been impregnated with mercuric chloride. A yellow-to-brown stain is produced, and its intensity is compared with the stain produced by a parallel standard prepared from a known amount of arsenic.

$$Zn + 2\ HCl \rightarrow ZnCl_2 + 2\ [H]$$

$$As^{3+}\ (or\ As^{5+}) + 6\ [H] \rightarrow AsH_3\uparrow + 3\ H^+\ (or\ 5\ H^+)$$

$$AsH_3 + HgCl_2 \rightarrow AsH(HgCl)_2 + 2\ HCl\ \ (yellow\ stain)$$

$$AsH_3 + 3\ HgCl_2 \rightarrow As(HgCl)_3 + 3\ HCl\ \ (brown\ stain)$$

Role of stannated HCl. Stannous chloride is added to the hydrochloric acid (the resulting mixture is called "stannated HCl AsT") for two reasons. First, stannous ion reduces any antimony in the sample to stibine, which would otherwise react with the mercuric chloride paper and give a false positive. Second, stannous ion accelerates the reduction of As(V) to As(III), which is the species that gives the colour with the test paper.

Role of the lead-acetate cotton pad. The pad sits between the reaction flask and the $HgCl_2$ paper. Its purpose is to absorb hydrogen sulphide (formed from sulphide impurities in the zinc), which would otherwise react with the mercuric chloride paper and give a black stain that interferes with the arsenic colour.

Apparatus - the Gutzeit bottle

The Gutzeit apparatus consists of a 120 mL wide-mouthed glass bottle with a mouth 2.5 cm in diameter. The mouth is closed by a rubber or ground-glass stopper that carries a glass tube approximately 20 cm long (external diameter 0.8 cm, internal diameter 0.65 cm). The lower end of the tube carries the lead-acetate cotton pad, and the upper end carries a small glass cap, the central orifice of which (about 15 × 15 mm) holds a square of mercuric chloride paper between two ground-glass flats. The complete assembly is shown in Figure 1.7.

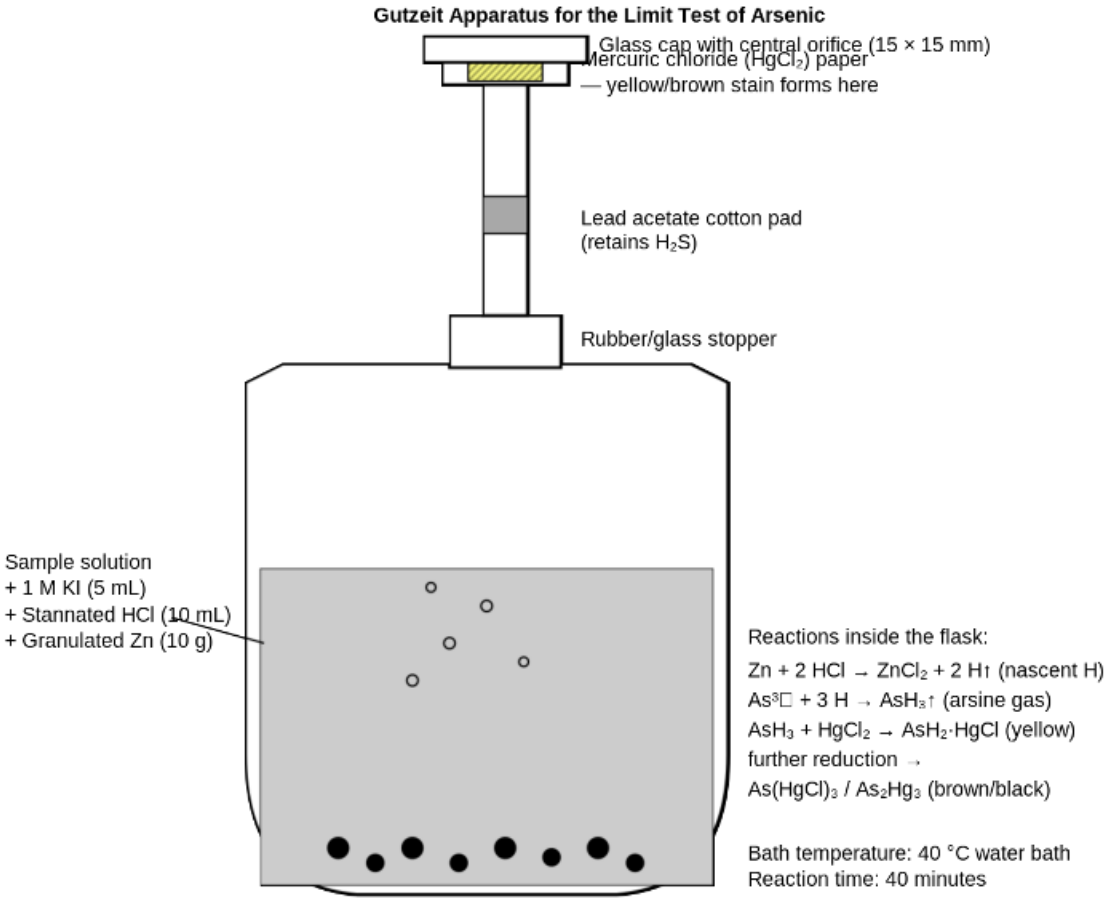

Fig. 1.7 Gutzeit apparatus for the limit test of arsenic.

Reagents

- Stannated hydrochloric acid AsT: AR-grade concentrated HCl with 0.1 % w/v stannous chloride; the reagent must itself comply with the arsenic limit;
- Granulated zinc AsT: arsenic-tested, of pellet size approximately 1 mm;
- Mercuric chloride paper: filter paper soaked in saturated mercuric chloride solution and dried in a desiccator;
- Standard arsenic solution AsT: 10 µg As per mL (1 mL ≡ 10 µg As);

- 1 M potassium iodide solution (arsenic-free).

Procedure

45. Test: take the quantity of substance prescribed by the monograph in the wide-mouthed bottle; dissolve or suspend in 50 mL of water (or the prescribed solvent).
46. Add 5 mL of 1 M potassium iodide (arsenic-free).
47. Add 10 mL of stannated hydrochloric acid AsT.
48. Add 10 g of granulated zinc AsT.
49. Immediately close the bottle with the assembly carrying the lead-acetate pad and the $HgCl_2$ paper at the orifice.
50. Place the bottle in a water bath maintained at 40 °C; allow steady evolution of arsine for 40 minutes.
51. Standard: in a second identical Gutzeit apparatus, repeat the procedure with 1 mL of standard arsenic solution AsT in place of the sample (≡ 10 µg As).
52. Compare the intensity of the yellow / brown stain on the two $HgCl_2$ papers, side by side and in good daylight.

Interpretation. A stain in the Test no deeper than the stain produced in the Standard indicates compliance.

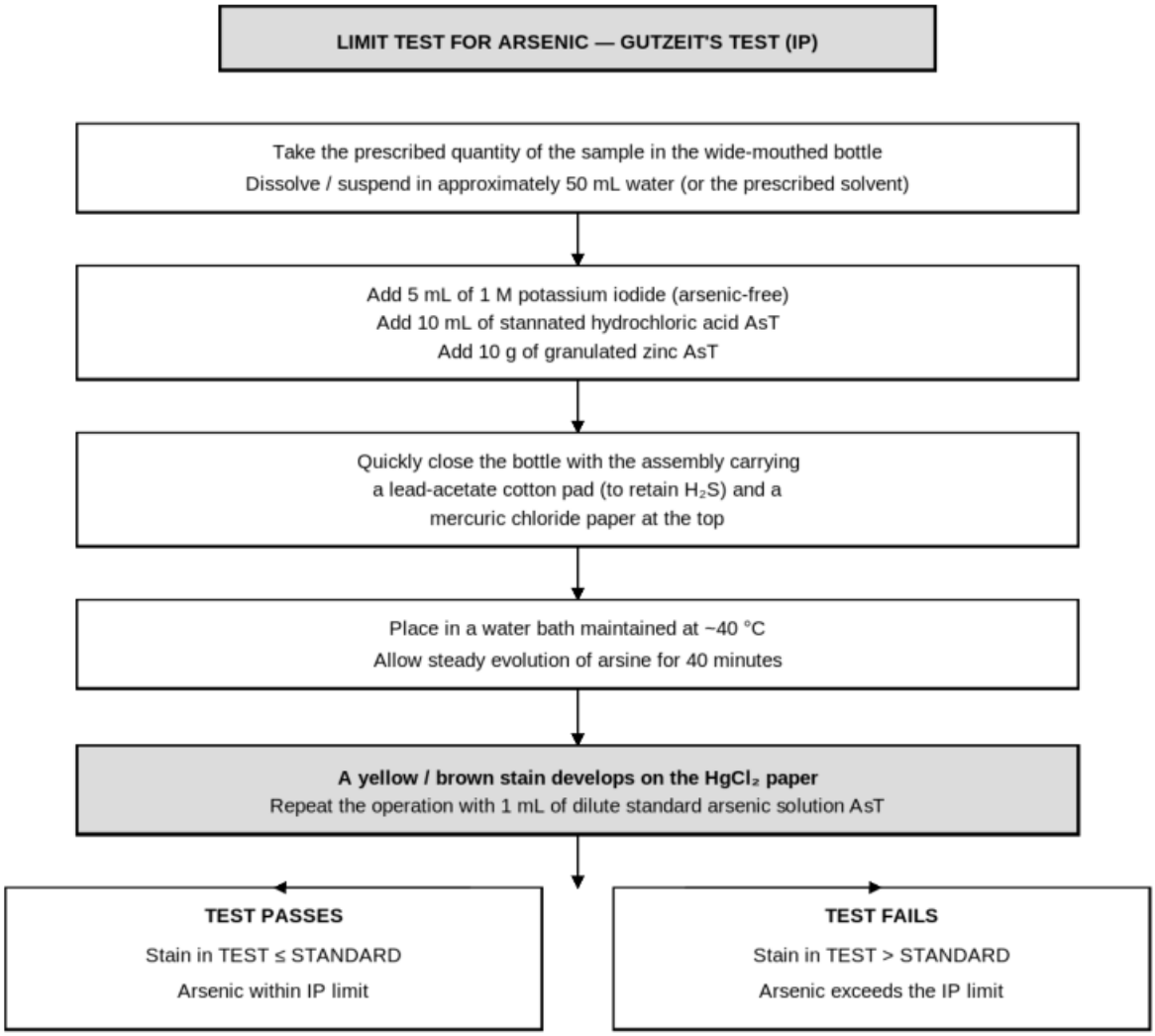

Fig. 1.8 Procedural flowchart for the limit test for arsenic.

1.14.7 Limit Test for Lead (Dithizone Method)

Principle. Lead ion in the buffered, masked sample is extracted into chloroform as its dithizone complex; the green dithizone in chloroform is converted to a red-violet lead-dithizonate, and the intensity of the colour is compared with that of a parallel standard prepared from a known amount of lead nitrate.

$$Pb^{2+} + 2\ H_2Dz\ (\text{green, in } CHCl_3) \rightarrow Pb(HDz)_2\ (\text{red-violet, in } CHCl_3) + 2\ H^+$$

Dithizone (diphenylthiocarbazone) is the analytical reagent that gives the test its name. It is a black-violet solid that dissolves in chloroform to a green solution and reacts with metal ions in alkaline aqueous medium to give intensely coloured neutral complexes that partition almost completely into the chloroform layer.

Role of the masking reagents. Most heavy metals (Cu, Zn, Co, Ni, Cd, Hg) also react with dithizone and would interfere with the determination of lead. They are kept in the aqueous phase by complexation: potassium cyanide masks Cu, Zn, Co and Ni as their cyanide complexes; ammonium citrate prevents the

precipitation of iron and other hydroxides in the alkaline medium; hydroxylamine hydrochloride reduces any oxidants that would destroy dithizone.

Reagents

- Dithizone extraction solution: 25 mg of dithizone dissolved in 1 L of chloroform; stored in a brown bottle and protected from light;
- Standard dithizone solution: 10 mL of the extraction solution diluted to 100 mL with chloroform;
- Ammonium citrate solution 20 % w/v;
- Hydroxylamine hydrochloride solution 20 % w/v;
- Potassium cyanide solution 10 % w/v;
- Strong ammonia solution;
- Phenol red indicator solution 0.1 %;
- Standard lead solution 20 µg Pb per mL (as in Section 1.14.4).

Procedure

53. Prepare the test solution as directed in the monograph; transfer to a 250 mL separating funnel.
54. Add 6 mL of ammonium citrate solution and 2 mL of hydroxylamine hydrochloride solution.
55. Add two drops of phenol red indicator and make the solution alkaline (red colour) with strong ammonia.
56. Add 2 mL of potassium cyanide solution.
57. Extract by shaking with successive 5 mL portions of dithizone-extraction solution, draining each chloroform extract into a second separating funnel, until the last chloroform layer remains green (i.e. all the lead has been extracted).
58. Shake the combined chloroform extracts for 30 s with 30 mL of 1 % v/v nitric acid; discard the chloroform layer and retain the acid layer (lead is now in the acid layer as Pb^{2+}).
59. To the acid layer add exactly 5 mL of standard dithizone solution; shake for 30 s.
60. Observe the colour of the chloroform layer.
61. In a parallel determination, repeat the procedure on a standard lead solution prepared to contain the maximum permitted amount of lead.

Interpretation. The colour in the Test must not be more intense than that of the Standard. A pure green chloroform layer in the Test indicates that all the dithizone is still in the unreacted form, that is, the lead content of the substance is below the maximum permissible amount.

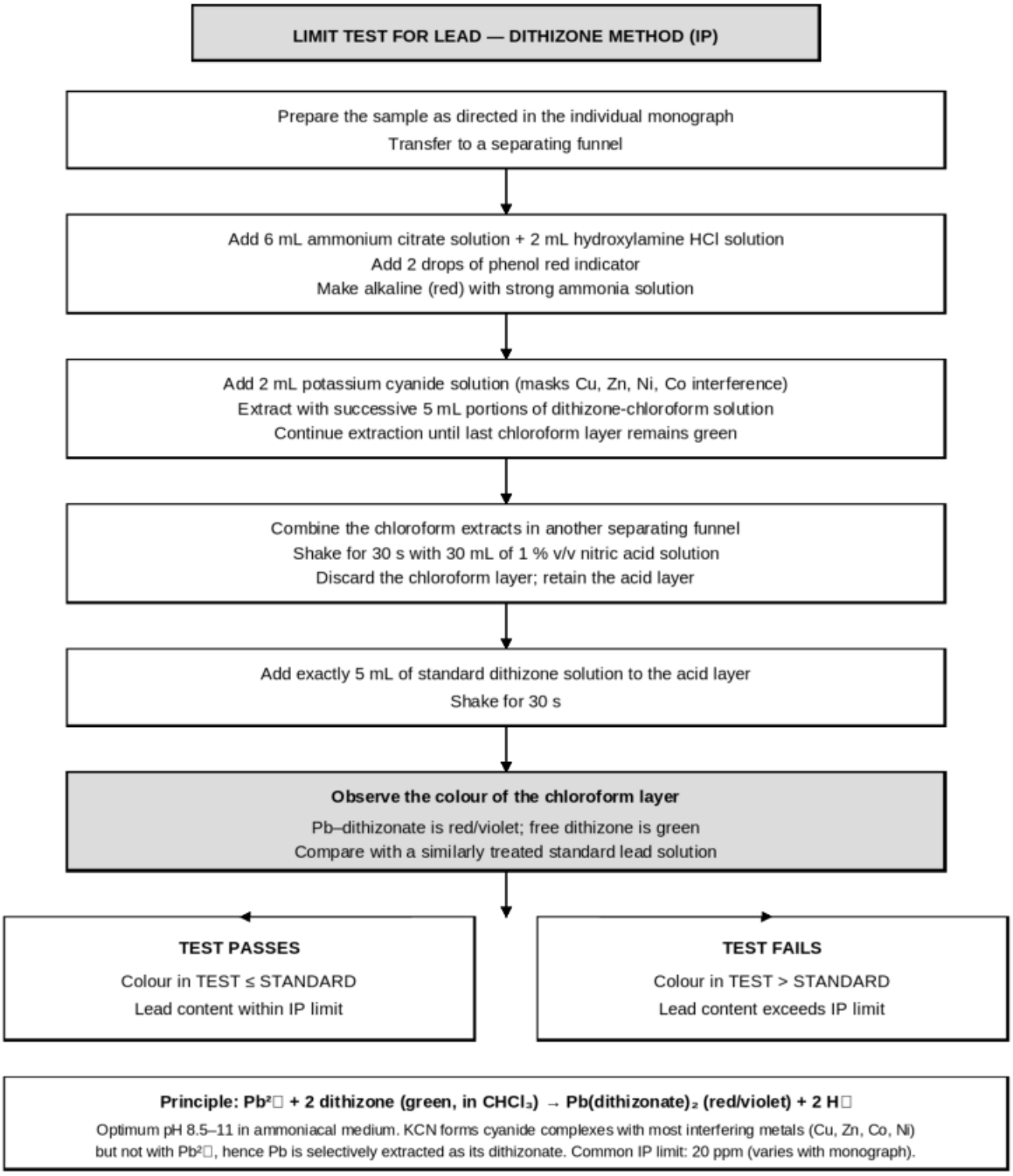

Fig. 1.9 Procedural flowchart for the limit test for lead (dithizone method).

1.15 Summary of the Limit Tests

The features of the six limit tests covered in this unit are summarised in Table 1.7. Typical IP limits for the same impurity vary between monographs, since each substance has its own toxicological profile and synthetic history; the values listed are the most commonly cited ones in the IP 2022 and IP 2026 monographs for inorganic substances.

Table 1.7 Summary of the six pharmacopoeial limit tests

Impurity	Reagent / detection principle	Visible signal	Typical IP limit (varies with monograph)
Chloride (Cl^-)	$AgNO_3$ in dil. HNO_3; AgCl opalescence	White opalescence	125–330 ppm
Sulphate (SO_4^{2-})	$BaCl_2$ in dil. HCl; $BaSO_4$ turbidity (alcohol controls super-saturation)	White turbidity	150–600 ppm
Iron (Fe)	Thioglycollic acid + NH_3; Fe(II) thioglycollate (citric acid masks Fe-OH precipitation)	Pink to reddish-purple colour	40–250 ppm
Heavy metals (as Pb)	H_2S / Na_2S / thioacetamide (Method D, modified test) in acetate buffer pH 3.5	Brown-black colloid of metal sulphides	10–40 ppm
Arsenic (As)	Gutzeit's test: Zn + stannated HCl → AsH_3 → $HgCl_2$ paper	Yellow to brown stain on the paper	1–8 ppm
Lead (Pb)	Dithizone in chloroform in ammoniacal medium with KCN masking	Red-violet chloroform layer	10–20 ppm

1.16 Marketed Inorganic Pharmaceuticals - IP Specifications

To anchor the material to clinical practice, Table 1.8 lists eight inorganic medicines that the student will encounter in retail and hospital pharmacy. For each substance, the table gives the official monograph in the IP 2026, an Indian brand example, the strength, and the most stringent impurity limits set by the IP.

Table 1.8 Marketed inorganic pharmaceuticals in India with their typical IP impurity specifications

Substance (IP monograph)	Indian brand example	Typical strength	Key impurity limits (IP 2026)
Ferrous sulphate	Fefol-Z, Livogen, Dexorange	200 mg dried salt = 65 mg Fe per tablet	Arsenic ≤ 2 ppm; Pb ≤ 10 ppm
Calcium gluconate injection	Calcium Sandoz IV	10 % w/v	Fe ≤ 5 ppm; heavy metals ≤ 20 ppm
Sodium chloride injection	NS / Normasol 0.9 %	0.9 % w/v	Heavy metals ≤ 5 ppm; arsenic ≤ 1 ppm
Potassium chloride injection	KCl 15 % IV	15 % w/v	Iron ≤ 40 ppm; lead ≤ 10 ppm
Magnesium sulphate	$MgSO_4$ IP / Epsom salt	0.5 g per sachet	Arsenic ≤ 2 ppm; heavy metals ≤ 10 ppm

Substance (IP monograph)	Indian brand example	Typical strength	Key impurity limits (IP 2026)
Zinc oxide	Calamine lotion BP	15 % w/v in calamine lotion	Arsenic ≤ 5 ppm; lead ≤ 50 ppm
Aluminium hydroxide gel	Digene, Gelusil-MPS	0.6 g of $Al(OH)_3$ equiv. per 10 mL	Heavy metals ≤ 20 ppm; arsenic ≤ 3 ppm
Sodium bicarbonate	Eno (with citric acid)	5 g per sachet	Chloride ≤ 0.015 % w/w; heavy metals ≤ 10 ppm

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UNIT II

Acid–Base Chemistry · Buffers · Buffered Isotonic Solutions · Body-Fluid Electrolytes

2.1 Acids and Bases

The concept of acidity and basicity is one of the oldest in chemistry, and one of the most useful in pharmacy. Acid–base equilibria determine the rate at which a drug substance dissolves in the gastric fluid, the fraction of the drug that crosses the intestinal membrane, the pH-dependent stability of an injectable formulation, the buffering of an eye-drop against tear pH, and the regulation of arterial blood pH within the narrow physiological window of 7.35–7.45. Five separate theoretical frameworks have been developed over the past hundred and forty years to describe what makes a substance an acid or a base, each of them fit for a different family of situations.

A practical starting point, common to all theories, is the operational description. Acids taste sour (citric acid in lemon, acetic acid in vinegar, ascorbic acid in amla), turn blue litmus red, react with active metals to liberate hydrogen, and have a pH below 7. Bases taste bitter (quinine, caffeine), feel soapy to the touch (sodium hydroxide solution, milk of magnesia), turn red litmus blue, and have a pH above 7. The operational description is sufficient for elementary qualitative work; the theoretical frameworks below provide the quantitative basis.

2.2 Theories of Acids and Bases

2.2.1 Arrhenius theory (1887)

Svante Arrhenius (Nobel Prize, Chemistry, 1903) proposed that, when a substance dissolves in water, it dissociates into its component ions. An acid is then any substance which on dissolution liberates hydrogen ions (H^+), and a base is any substance which on dissolution liberates hydroxide ions (OH^-).

$$HCl(aq) \rightarrow H^+(aq) + Cl^-(aq)$$

$$NaOH(aq) \rightarrow Na^+(aq) + OH^-(aq)$$

$$H^+ + OH^- \rightarrow H_2O \qquad (neutralisation)$$

The theory is intuitive and explains everyday observations in aqueous solution. Its weakness is that it is unable to handle four categories of acid–base behaviour:

- reactions in non-aqueous solvents (acetic acid in liquid ammonia, picric acid in pyridine);
- reactions in the gas phase, such as the combination of HCl(g) and NH_3(g) to give NH_4Cl(s);
- compounds that show basic character without an OH^- in their formula (NH_3, pyridine, amines);
- electron-pair-acceptor acidity (BF_3, $AlCl_3$) and complex-ion formation.

2.2.2 Brønsted–Lowry theory (1923)

Working independently, Johannes Nicolaus Brønsted in Copenhagen and Thomas Martin Lowry in London put forward, in the same year, a proton-transfer view of acid–base chemistry. An acid is a substance that can donate a proton (H^+), and a base is a substance that can accept one. Every acid, on giving up a proton, generates its conjugate base; every base, on accepting a proton, generates its conjugate acid. The pair (HA, A^-) is called a conjugate acid–base pair.

$$HA \rightleftharpoons H^+ + A^- \qquad \textit{(HA = acid, } A^- \textit{ = its conjugate base)}$$

$$B + H^+ \rightleftharpoons BH^+ \qquad \textit{(B = base, } BH^+ \textit{ = its conjugate acid)}$$

A proton transfer reaction therefore involves two conjugate pairs:

$$HCl + H_2O \rightleftharpoons H_3O^+ + Cl^-$$

Here HCl is the acid, Cl^- is its conjugate base, H_2O is the base, and H_3O^+ is its conjugate acid. Water shows amphiprotic behaviour, that is, it can act as either an acid or a base depending on the partner. The Brønsted–Lowry definition does not require water as the solvent, so it applies equally to non-aqueous systems used in pharmaceutical assays of weak bases (e.g. titration of caffeine in glacial acetic acid).

The strength of a Brønsted acid is quantified by its acid dissociation constant Ka, and that of a base by its base ionisation constant Kb. The two are linked through the auto-ionisation constant of the solvent. For aqueous solutions at 25 °C, $K_w = [H^+][OH^-] = 1.0 \times 10^{-14}$, so that pKa + pKb = pKw = 14.00.

2.2.3 Lewis theory (1923)

In the same year, Gilbert Newton Lewis at Berkeley proposed an even broader framework. Lewis recognised that proton transfer is a special case of a more general process, the formation of a coordinate covalent bond. A Lewis acid is therefore any electron-pair acceptor and a Lewis base is any electron-pair donor. The neutralisation reaction in this framework is the formation of an adduct held together by a coordinate covalent bond.

$$BF_3 + :NH_3 \rightarrow F_3B\text{-}NH_3 \qquad \textit{(}BF_3 \textit{ is the Lewis acid; } NH_3 \textit{ is the Lewis base)}$$

$$Ag^+ + 2\ :NH_3 \rightarrow [H_3N \rightarrow Ag \leftarrow NH_3]^+$$

Three categories of substance qualify as Lewis acids: positive ions (H^+, Ag^+, Fe^{3+}, Cu^{2+}), neutral molecules with an electron-pair-deficient atom (BF_3, BCl_3, $AlCl_3$) and molecules with an expandable valence shell (SiF_4, $SnCl_4$). Lewis bases are any species with a lone pair, amines, ethers, halides, anions of weak acids. The framework is indispensable in coordination chemistry (the IP monographs on iron-dextran, iron-sucrose, cisplatin and gold sodium thiomalate are all chelation chemistry), in catalysis (Friedel–Crafts acylations in the synthesis of paracetamol intermediates) and in drug–receptor binding (zinc coordination in angiotensin-converting-enzyme inhibitors).

2.2.4 Lux–Flood theory

Hermann Lux (1939) and Håkon Flood (1947) extended the acid–base concept into the oxide melts encountered in metallurgy. A Lux–Flood acid is an oxide-ion acceptor and a Lux–Flood base is an oxide-ion donor:

$$CaO + SiO_2 \rightarrow CaSiO_3 \qquad (CaO = \text{base} = O^{2-}\ \text{donor};\ SiO_2 = \text{acid} = O^{2-}\ \text{acceptor})$$

The framework is mainly of historical interest in undergraduate pharmacy, but it is relevant to the chemistry of silicate excipients, talc, kaolin and bentonite, and to the preparation of phosphate glasses used in controlled-release implants.

2.2.5 Solvent-system theory

The solvent-system theory generalises the Brønsted picture to any auto-ionising solvent. A solvent SH is allowed to auto-ionise according to $2\ SH \rightleftharpoons SH_2^+ + S^-$. Then any solute that increases the concentration of the cation SH_2^+ is an acid in that solvent, and any solute that increases the concentration of the anion S^- is a base. The theory becomes essential when the solvent is not water, for example, liquid ammonia, glacial acetic acid, sulfuric acid and dimethylformamide. Non-aqueous titrations of weak bases (alkaloids, amines, sodium salts of weak organic acids) take place in glacial acetic acid; non-aqueous titrations of weak acids (barbiturates, phenols) take place in dimethylformamide or pyridine. The theoretical basis is solvent-system theory, and it is developed in detail in Unit III.

2.2.6 pH and the ionic product of water

Pure water at 25 °C self-ionises to a very small extent:

$$H_2O + H_2O \rightleftharpoons H_3O^+ + OH^- \qquad K_w = [H_3O^+][OH^-] = 1.0 \times 10^{-14}$$

In pure water, $[H_3O^+] = [OH^-] = 1.0 \times 10^{-7}$ mol L^{-1}, so the $pH = -\log_{10}[H^+] = 7$. The pH scale, introduced by Søren Sørensen in 1909 at the Carlsberg Laboratory, runs from 0 to 14 at 25 °C; values below 7 are acidic, values above 7 are alkaline. Note that K_w is temperature-dependent, it rises with temperature, so the pH of pure water at body temperature (37 °C) is 6.81, not 7.00. The same correction must be remembered for high-precision pH measurements at non-standard temperatures.

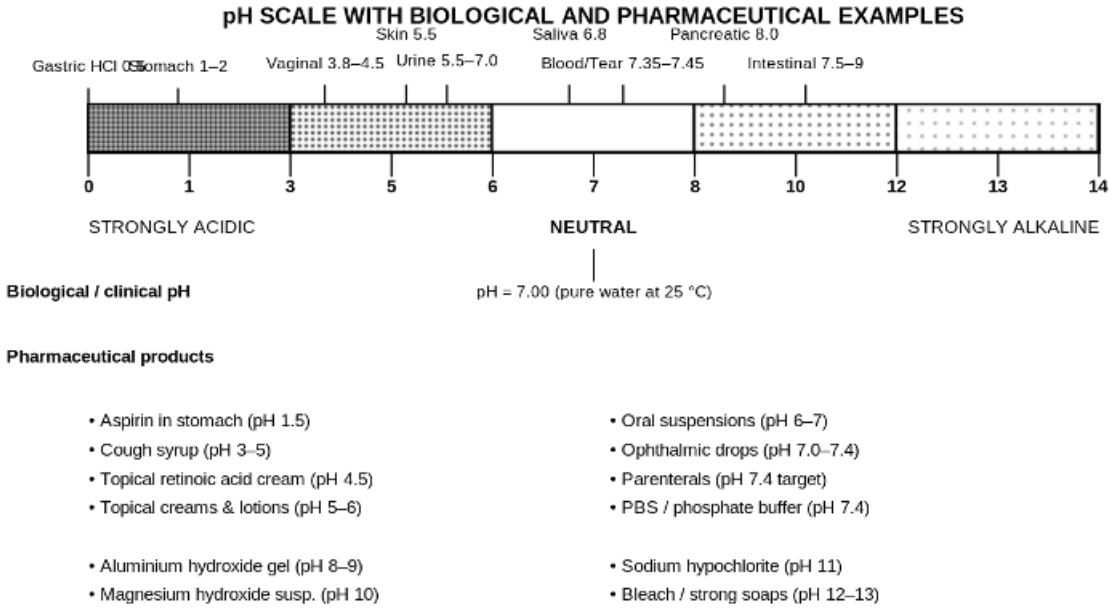

Fig. 2.1 pH scale with the principal biological and pharmaceutical pH ranges.

Table 2.1 Comparison of the three principal acid–base theories.

Feature	Arrhenius	Brønsted–Lowry	Lewis
Year	1887	1923	1923
Acid is …	A substance that gives H^+ in water	A proton donor	An electron-pair acceptor
Base is …	A substance that gives OH^- in water	A proton acceptor	An electron-pair donor
Solvent required?	Yes: water	No (any protic solvent)	No solvent needed
Strength measured by	Degree of dissociation (α)	Ka and Kb	Equilibrium constant of adduct formation
Typical pharmaceutical use	Basic teaching of pH	Most drug ionisation and ADME work	Coordination chemistry of metal-containing drugs (Fe-dextran, cisplatin)

2.3 Buffers

A buffer is a solution that resists changes in pH when a small amount of acid or base is added, or when it is diluted. The buffering capacity is provided by a conjugate acid–base pair in roughly comparable concentrations. Two classes are recognised.

Acidic buffer. A mixture of a weak acid and the salt of that acid with a strong base. The conjugate base of the weak acid is then present in a high concentration. The buffer maintains a pH below 7. The classical example is the acetic acid–sodium acetate buffer (pKa = 4.76, working range pH 3.76–5.76).

Basic buffer. A mixture of a weak base and the salt of that base with a strong acid. The conjugate acid of the weak base is present in a high concentration. The buffer maintains a pH above 7. The classical example is the ammonia–ammonium chloride buffer (pKb = 4.74; pKa of NH_4^+ = 9.25; working range pH 8.25–10.25).

2.4 Mechanism of Buffer Action

A buffer holds the pH steady by converting any added strong acid into the weak acid of the buffer pair, and by converting any added strong base into the weak base of the buffer pair.

Response of an acidic buffer

Consider 1 L of a buffer that contains 0.1 mol CH_3COOH and 0.1 mol $CH_3COO^-Na^+$. The pH is initially equal to the pKa, that is 4.76.

On adding a small amount of strong acid, say 0.01 mol HCl, the H^+ ions react with the conjugate base of the buffer:

$$CH_3COO^- + H^+ \rightarrow CH_3COOH$$

The strong acid HCl is therefore converted into the weak acid CH_3COOH. The free hydrogen-ion concentration of the solution rises only marginally, from 1.74×10^{-5} M to about 2.13×10^{-5} M, a pH change from 4.76 to 4.67.

On adding 0.01 mol NaOH, the OH^- ions are neutralised by the weak acid of the buffer:

$$CH_3COOH + OH^- \rightarrow CH_3COO^- + H_2O$$

NaOH is therefore converted into water plus an additional molecule of the conjugate base. The pH rises from 4.76 to about 4.85.

In an unbuffered solution, the addition of the same amount of NaOH would raise the pH from 7 to about 12. The buffer has limited the pH change by a factor of approximately fifty.

Response of a basic buffer

In a basic buffer (NH_3 / NH_4Cl), the weak base mops up added H^+ and the conjugate acid mops up added OH^-:

$$NH_3 + H^+ \rightarrow NH_4^+ \quad \textit{(added strong acid neutralised)}$$

$$NH_4^+ + OH^- \rightarrow NH_3 + H_2O \quad \textit{(added strong base neutralised)}$$

2.5 The Henderson–Hasselbalch Equation

The Henderson–Hasselbalch equation is the workhorse formula of buffer chemistry. It was derived independently by Lawrence Joseph Henderson (a biological chemist at Harvard, in 1908) and Karl Albert Hasselbalch (a physiologist at the Carlsberg Laboratory, in 1916), in connection with the bicarbonate buffer system of blood. The same algebra connects pH, pKa and the ratio of conjugate base to weak acid.

2.6 Derivation for a Weak Acid–Salt Buffer

Begin with the dissociation of a weak acid HA in water:

$$HA \rightleftharpoons H^+ + A^-$$

$$Ka = [H^+][A^-] / [HA]$$

Rearranging:

$$[H^+] = Ka \times ([HA] / [A^-])$$

Taking the negative logarithm of both sides:

$$-\log[H^+] = -\log Ka - \log ([HA] / [A^-])$$

That is:

$$pH = pKa + \log ([A^-] / [HA]) \quad \ldots \quad \text{(Henderson–Hasselbalch equation)}$$

In a buffer prepared by dissolving a weak acid and its salt with a strong base, the conjugate base concentration is essentially the salt concentration (since the salt is completely dissociated), and the weak-acid concentration is the un-ionised acid that remains. The equation is therefore often written as:

$$pH = pKa + \log ([salt] / [acid])$$

2.7 Derivation for a Weak Base–Salt Buffer

For a weak base B with its salt BH^+Cl^- (formed with a strong acid):

$$B + H_2O \rightleftharpoons BH^+ + OH^-$$

$$Kb = [BH^+][OH^-] / [B]$$

By analogous algebra:

$$pOH = pKb + \log ([BH^+] / [B]) \qquad i.e. \qquad pOH = pKb + \log ([salt] / [base])$$

And since pH + pOH = 14 at 25 °C, the pH of a basic buffer is calculated by subtraction from 14.

2.8 Worked Examples

Example 2.1 - Acetate buffer

Calculate the pH of a buffer prepared by dissolving 0.20 mol of sodium acetate and 0.10 mol of acetic acid in 1 L of water. The pKa of acetic acid is 4.76.

Solution. Applying the Henderson–Hasselbalch equation:

$$pH = 4.76 + \log (0.20 / 0.10) = 4.76 + \log 2 = 4.76 + 0.301 = 5.06$$

Example 2.2 - Phosphate buffer of pH 7.40 for ophthalmic use

How should disodium hydrogen phosphate and sodium dihydrogen phosphate be combined to give a buffer of pH 7.40? The pKa of the $H_2PO_4^-$ / HPO_4^{2-} couple is 7.20.

Solution. The Henderson–Hasselbalch equation gives:

$$7.40 = 7.20 + \log ([HPO_4^{2-}] / [H_2PO_4^-])$$

$$\log ([HPO_4^{2-}] / [H_2PO_4^-]) = 0.20$$

$$[HPO_4^{2-}] / [H_2PO_4^-] = 1.585$$

A 1:1 mole ratio gives pH 7.20; a 1.585:1 ratio of dibasic to monobasic phosphate gives pH 7.40. This is essentially the Sørensen recipe used to prepare the ophthalmic standard phosphate-buffered saline (PBS).

Example 2.3 - Ammonium buffer for a basic application

Calculate the pH of a buffer prepared by dissolving 0.10 mol of NH_3 and 0.10 mol of NH_4Cl in 1 L of water. The pKb of ammonia is 4.74.

Solution. pOH = 4.74 + log (0.10 / 0.10) = 4.74. pH = 14.00 − 4.74 = 9.26.

2.9 Applications of the Henderson–Hasselbalch Equation

- Computing the pH of a buffer from its composition.
- Selecting the conjugate-base-to-acid ratio required to formulate a buffer at a desired pH (the inverse problem).
- Estimating the fraction of a weak acid or base that is ionised at a given physiological pH, a step central to the prediction of intestinal absorption, renal reabsorption and blood-brain barrier permeability of drugs.
- Determining the pKa of a drug by potentiometric titration and inversion of the equation.
- Predicting the pH-dependent solubility of weakly acidic or weakly basic drug substances (the modified Henderson–Hasselbalch solubility equation).
- Calculating the isoelectric point (pI) of an amphoteric drug or protein, where $pI = \tfrac{1}{2} (pK_{a1} + pK_{a2})$ for a simple amino acid.

2.10 Limitations of the Equation

- The equation assumes that the concentrations of HA and A^- at equilibrium are equal to the analytical concentrations of the acid and the salt that were weighed out. This is a reasonable approximation when both are between about 0.05 M and 1 M and the pH is within ±1 of the pKa, but it fails for very dilute buffers, for very strong acids or bases, and at extremes of pH where water self-ionisation contributes appreciably.
- The equation uses concentrations rather than activities. For solutions of moderate-to-high ionic strength, activity coefficients should replace concentrations.
- The equation does not account for ion-pairing in the buffer (e.g. $Na^+ \cdot CH_3COO^-$ pairs in acetate buffer above 0.5 M).
- Temperature affects both Ka and the activity coefficients; the equation in its undergraduate form is good only at the temperature for which the pKa is reported, typically 25 °C.

2.11 Buffer Capacity

Buffer capacity is the quantitative measure of a buffer's ability to resist a change in pH. It was defined by Donald D. Van Slyke in 1922 as the number of moles of strong acid or strong base that must be added to one litre of buffer to change its pH by one unit. Mathematically:

$$\beta = dn / dpH$$

where dn is the increment in moles per litre of added strong acid (taken as positive) or strong base, and dpH is the resulting change in pH. A buffer of capacity 0.1 mol L^{-1} pH^{-1} requires 0.1 mole of HCl or NaOH per litre to change the pH by one unit.

2.12 Factors Affecting Buffer Capacity

Buffer concentration. For a given pKa, the capacity rises linearly with the total buffer concentration. Doubling the buffer concentration doubles its capacity.

Ratio of the two components. The capacity is at a maximum when the ratio of the conjugate base to the weak acid is 1:1, that is, when pH = pKa. The capacity falls off rapidly as the pH moves away from the pKa, dropping to about a third of its maximum at pH = pKa ± 1, and to negligible values beyond pKa ± 2 (Figure 2.4). The useful working range of a buffer is therefore pKa ± 1.

Nature of the buffer pair. Different pairs have different pKa values and therefore work in different pH windows. Acetate (pKa 4.76) is unsuited to a near-neutral injectable; phosphate (pKa 7.20) is well suited.

Temperature. Both pKa and Kw vary with temperature. A buffer formulated at 25 °C will have a slightly different pH at body temperature 37 °C; the shift is small for phosphate and acetate but appreciable for tris-buffer (where $\Delta pKa \approx -0.028$ per °C).

Ionic strength. High ionic strength alters the activity coefficients of the buffer ions and reduces the working capacity.

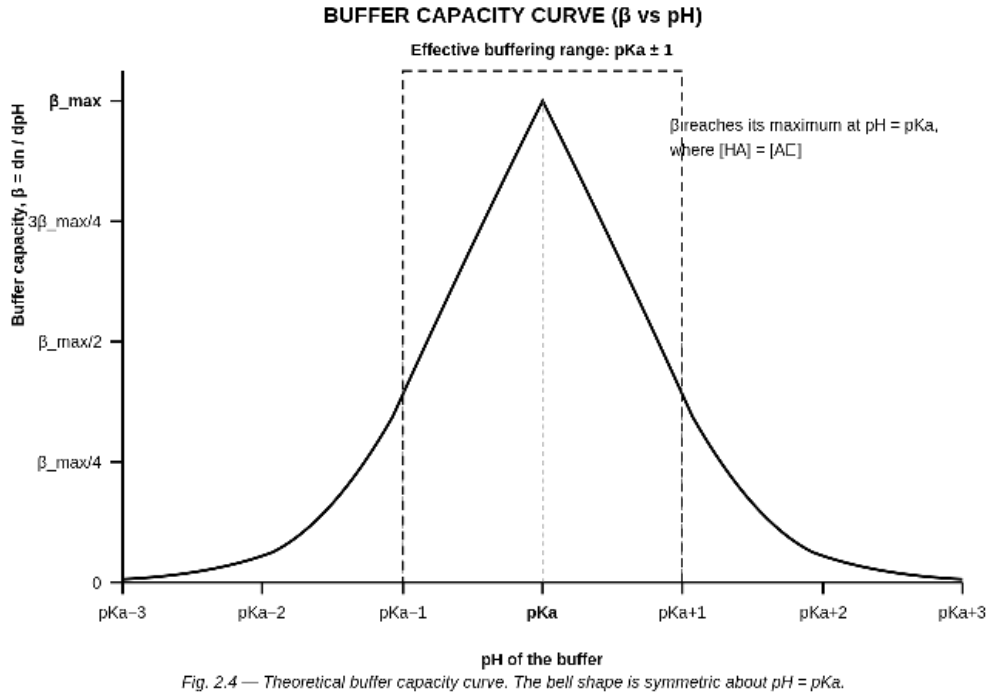

Fig. 2.2 Buffer capacity (β) plotted against pH. The bell-shaped curve is symmetric about pH = pKa.

2.13 Common Pharmaceutical Buffer Systems

Table 2.2 Pharmaceutical buffer systems commonly listed in the IP and the USP.

Buffer pair	pKa(s) at 25 °C	Effective pH window	Typical use in pharmacy
Citric acid / sodium citrate	3.13, 4.76, 6.40	2.1–7.4 (three plateaus)	Oral liquids, parenterals, oral rehydration salt; also used as a chelator in injectables.
Acetic acid / sodium acetate	4.76	3.76–5.76	Parenteral (e.g. acetate-buffered penicillin G), topical, ophthalmic for low-pH actives.
Lactic acid / sodium lactate	3.86	2.86–4.86 (and as carbonate precursor in Ringer's)	Ringer's lactate (Hartmann's solution): physiological replacement fluid.
Sodium dihydrogen phosphate / Disodium hydrogen phosphate (Sørensen)	7.20	6.20–8.20	Ophthalmic, parenteral, PBS for biological work; standard buffer of choice for pH 7.4.

Buffer pair	pKa(s) at 25 °C	Effective pH window	Typical use in pharmacy
Carbonate / bicarbonate	6.10 (effective, blood) / 10.33	5.10–7.10 (with CO_2); 9.33–11.33	Sodium bicarbonate injection 7.5 %; bicarbonate-buffered dialysis fluids.
Boric acid / borax	9.24	8.24–10.24	Eye washes, contact-lens fluids, dermatological preparations.
Tris (hydroxymethyl) aminomethane	8.06	7.06–9.06	Buffered protein and DNA preparations; some biological injectables.
Glycine / sodium glycinate	2.34 and 9.60	1.34–3.34 and 8.60–10.60	Antacid effervescent powders; specific pharmaceutical actives.

2.14 Sørensen Phosphate Buffer - Composition Table

The Sørensen phosphate buffer is the workhorse of ophthalmic and biological pH 5.8–8.0 work. A 0.1 M buffer is prepared by mixing the volumes shown in Table 2.3 of 0.2 M disodium hydrogen phosphate ($Na_2HPO_4 \cdot 12\ H_2O$, M.W. 358.14, 71.64 g L^{-1}) and 0.2 M sodium dihydrogen phosphate ($NaH_2PO_4 \cdot H_2O$, M.W. 138.01, 27.60 g L^{-1}), and diluting the mixture to 100 mL with distilled water.

Table 2.3 Composition of 0.1 M Sørensen phosphate buffer at 25 °C, pH 5.8 to 8.0.

Target pH	mL of 0.2 M Na_2HPO_4	mL of 0.2 M NaH_2PO_4	Diluted to
5.8	4.0	46.0	100 mL
6.0	6.15	43.85	100 mL
6.2	9.25	40.75	100 mL
6.4	13.25	36.75	100 mL
6.6	18.75	31.25	100 mL
6.8	24.50	25.50	100 mL
7.0	30.50	19.50	100 mL
7.2	36.00	14.00	100 mL
7.4	40.50	9.50	100 mL
7.6	43.50	6.50	100 mL
7.8	45.75	4.25	100 mL

Target pH	mL of 0.2 M Na_2HPO_4	mL of 0.2 M NaH_2PO_4	Diluted to
8.0	47.35	2.65	100 mL

2.15 Role of Buffers in Pharmaceutical Systems

Pharmaceutical formulations live inside narrow pH windows. The buffer is the formulator's tool for keeping the formulation inside that window through manufacture, storage and administration. Eight situations call for a buffer.

1. Stability of the active ingredient. Many drugs hydrolyse, oxidise or rearrange at a rate that depends strongly on the pH of the medium. Aspirin (acetylsalicylic acid) hydrolyses to salicylic acid and acetic acid at a rate that is minimum near pH 2.4. Chloramphenicol has its stability maximum at pH 6. Adrenaline injection is buffered between pH 2.8 and 3.6 to limit oxidation to the inactive adrenochrome.

2. Drug solubility. Weakly acidic drugs (ibuprofen, naproxen, indomethacin) dissolve better at pH above their pKa, where the ionised form predominates; weakly basic drugs (lignocaine, chlorpromazine, ciprofloxacin) dissolve better at pH below their pKa. The buffer is used to bring the formulation pH to a value at which the drug stays in solution.

3. Drug absorption. Lipid-soluble unionised forms cross intestinal and ophthalmic membranes more readily than ionised forms. The pH-partition hypothesis of Brodie, Hogben and Schanker links the absorbed fraction of a drug to its pKa and to the pH of the absorbing surface, pH 1.5 in the stomach, 6.5 in the duodenum, 7.0 in the jejunum, 7.4 in the ileum. Enteric-coated tablets, gastro-retentive systems and pH-triggered colonic-release formulations all exploit this gradient.

4. Ophthalmic formulations. The eye tolerates eye drops within the pH range 6.5–8.5, with optimum comfort at the tear-film pH of 7.4. A pH outside this window causes lacrimation, foreign-body sensation and blinking, all of which wash out the formulation. Ophthalmic buffers (phosphate, borate, citrate) are routinely formulated at pH 6.8–7.4 with osmolarity matched to tears.

5. Parenteral formulations. A pH that is too far from physiological 7.4 produces pain on injection (sub-cutaneous and intra-muscular), thrombophlebitis (intravenous) and tissue necrosis (peripheral extravasation). The IP and USP set a default tolerance of pH 6.0–8.5 for unbuffered IV solutions, with tighter limits for individual monographs.

6. Topical formulations. Skin has a normal pH of 5.4–5.9, the so-called acid mantle. Cosmetic and pharmaceutical creams are buffered around pH 5.5 to avoid disturbing the acid mantle, which has bacteriostatic and barrier functions.

7. Biopharmaceutical formulations. Proteins, peptides, monoclonal antibodies, vaccines and enzymes are intolerant of pH change. Insulin is formulated in phosphate buffer at pH 7.0–7.8; vaccines are formulated in phosphate buffer at pH 6.5–7.5; therapeutic monoclonal antibodies are usually formulated in histidine buffer at pH 6.0.

8. Controlled-release systems. In matrix tablets and reservoir devices, an embedded buffer maintains a constant pH inside the diffusion layer adjacent to the drug, which keeps the dissolution profile constant and predictable over the labelled release period.

2.16 Buffer Selection for a Pharmaceutical Product

A buffer is selected on the basis of four interlocking criteria.

1. pKa close to the desired pH (within one unit).
2. Capacity sufficient to hold the pH against acid or base produced during storage, but not so high that it overpowers physiological buffers on administration.
3. Compatibility with the active and the excipients: for example, phosphate ions form insoluble precipitates with calcium and barium ions; borate ions form complexes with cis-diols including ribose and glucose; citrate ions chelate iron and so should not be used in iron-containing parenterals.
4. Tolerance: the buffer must not produce irritation or other adverse effects at the site of application. Tris-buffer at concentrations above 0.05 M is irritant by the intramuscular route and is therefore avoided in IM injections.

2.17 Preparation of a Pharmaceutical Buffer

5. Identify the target pH from the stability and tolerance profile of the active.
6. Pick a buffer pair whose pKa is within ±1 pH unit of the target.
7. Use the Henderson–Hasselbalch equation to calculate the ratio of the conjugate base to the weak acid required.
8. Set the total buffer concentration. For pharmaceutical use this is usually between 0.01 M (low capacity, low ionic strength) and 0.10 M (moderate capacity, physiologically tolerated). Higher concentrations are used only when the formulation generates titratable acid or base on storage.
9. Weigh out and dissolve the acid and salt components in distilled water in a calibrated volumetric flask.
10. Measure the pH with a calibrated pH meter; adjust if necessary with small additions of 0.1 N HCl or 0.1 N NaOH (the dropwise addition does not change the buffer ratio appreciably).
11. Make up to final volume with distilled water and sterilise as appropriate to the route (membrane filtration through 0.22 μm for thermolabile products; autoclaving at 121 °C for 15 min for thermostable parenterals).

2.18 Buffered Isotonic Solutions

Two requirements must be met simultaneously by any aqueous formulation that is to be brought into contact with body fluids, the pH must be physiological, and the osmotic pressure must be physiological. A buffered

isotonic solution is one that meets both requirements at once. The pH is controlled by an appropriate buffer system; the osmotic pressure is brought to that of blood plasma, namely 285–310 mOsm/L (a freezing-point depression of −0.52 °C), by the addition of an inert solute such as sodium chloride, dextrose or mannitol.

Three categories are defined on the basis of osmotic pressure.

Isotonic. Osmotic pressure equal to that of blood plasma (285–310 mOsm/L). Cells neither shrink nor swell on contact with the solution. Examples, 0.9 % w/v NaCl (Normal Saline), 5 % w/v dextrose, Ringer's lactate, 1.9 % w/v urea.

Hypotonic. Osmotic pressure lower than that of plasma. Water flows into cells, which swell. Red blood cells in hypotonic solution lyse (haemolyse), releasing oxyhaemoglobin.

Hypertonic. Osmotic pressure higher than that of plasma. Water flows out of cells, which shrink (crenate). Hypertonic infusions are used therapeutically, 3 % NaCl in severe hyponatraemia; 25 % mannitol for raised intracranial pressure.

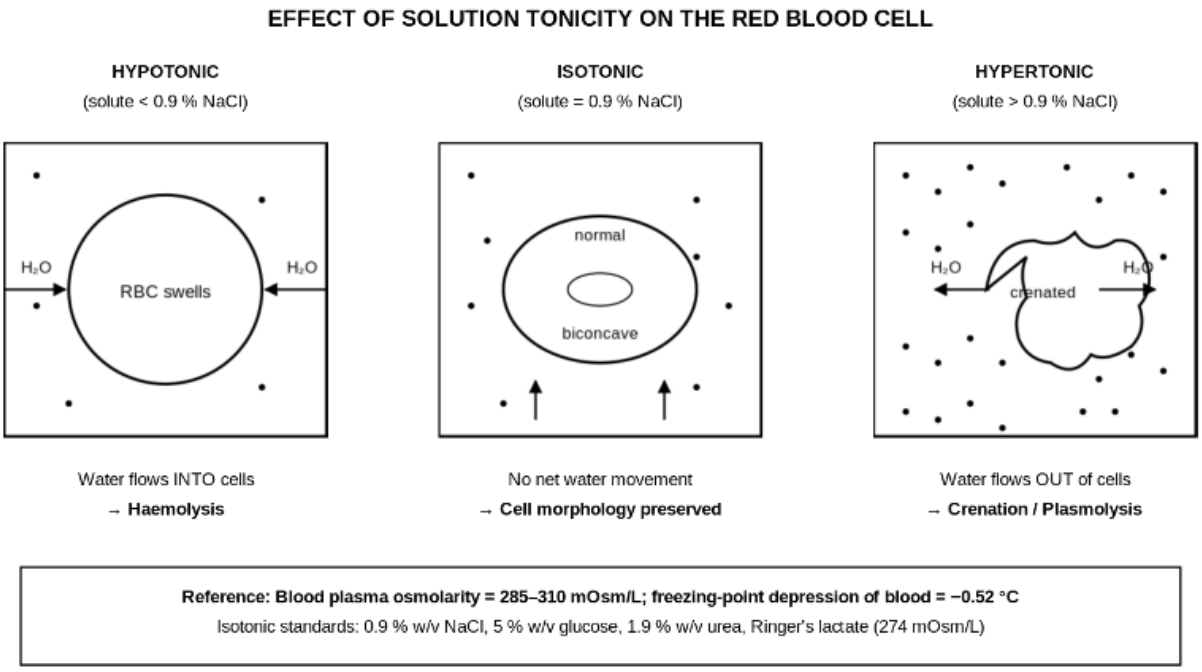

Fig. 2.3 Effect of solution tonicity on the red blood cell.

2.19 Measurement of Tonicity

2.19.1 Hemolytic method

Krogh, Husa and Husa (1934) developed a method based on direct observation of red blood cells. The solution under test is incubated with a 2 % suspension of washed human or bovine erythrocytes for 45 minutes. If the cells haemolyse and release oxyhaemoglobin, the solution is hypotonic. If the cells crenate, the solution is hypertonic. If the cells retain their biconcave shape, the solution is isotonic. The method has

been refined by Husa and by Hammarlund (1958) to give the so-called Hammarlund-Pedersen Vbar values, but is now used mainly for verifying calculated tonicity.

2.19.2 Cryoscopic (freezing-point depression) method

Tonicity is a colligative property: it depends on the number of solute particles in solution and not on their nature. The freezing point of pure water is 0 °C; the freezing point of blood and lacrimal fluid is −0.52 °C. A drug solution that freezes at −0.52 °C is therefore isotonic with body fluids. The freezing-point depression of a 1 % w/v solution of a drug is tabulated in the USP and BP as the Liso (T1 %) value. The cryoscopic method is the basis of three of the four methods of adjusting tonicity that follow.

2.20 Methods of Adjusting Tonicity

2.20.1 Class I methods (add an inert solute)

A. Sodium chloride equivalent method. Introduced by Mellen and Seltzer in 1936, this method is the most widely used in dispensing pharmacy. The sodium chloride equivalent (E) of a drug is the weight in grams of sodium chloride that produces the same osmotic effect as 1 g of the drug. Values are tabulated in the USP for most pharmacopoeial actives. The procedure is:

12. Calculate the amount of sodium chloride represented by the drug: weight of drug × E.
13. Calculate the amount of sodium chloride needed to make the prescribed volume of solution isotonic: volume (mL) × 0.009 g/mL.
14. Subtract the first from the second to obtain the amount of sodium chloride that must be added.

B. Cryoscopic method (Class I). When the freezing-point depression of a 1 % w/v solution of the drug (Tf,drug) and that of NaCl (0.576 °C for 1 %) are known, the amount of NaCl needed to adjust tonicity is calculated from the equation:

$$W = 0.52 - (a \times b) / 0.576 \quad [\text{g of NaCl per 100 mL}]$$

where a is the percent concentration of the drug and b is the freezing-point depression of a 1 % w/v solution of the drug.

2.20.2 Class II methods (add water and then bring to volume with isotonic vehicle)

C. White–Vincent method (1947). The volume of water (V, in mL) required to dissolve the prescribed amount of drug so that the resulting solution is isotonic is calculated as:

$$V = W \times E \times (111.1)$$

where W is the weight of the drug in grams and E is its sodium chloride equivalent. The factor 111.1 is the number of mL of an isotonic solution prepared from 1 g of NaCl (since 0.9 % w/v isotonic NaCl contains 0.9 g per 100 mL, that is, 1 g per 111.1 mL). The drug is dissolved in V mL of water, sufficient water is added to make the prescribed volume, and then the solution is brought to that volume with an isotonic vehicle such as normal saline.

D. Sprowls method (1949). A variant of the White–Vincent method in which the weight of the drug is held constant at 0.3 g and the volume of water (V) is tabulated for each drug. This avoids fresh calculation for each prescription.

Worked example (sodium chloride equivalent method)

Calculate the amount of sodium chloride needed to render 100 mL of a 1 % w/v atropine sulphate solution isotonic. The sodium chloride equivalent of atropine sulphate is 0.13.

Solution.

$$NaCl \text{ represented by atropine sulphate} = 1.0\ g \times 0.13 = 0.13\ g$$

$$NaCl \text{ needed for isotonicity in } 100\ mL = 100 \times 0.009 = 0.90\ g$$

$$NaCl \text{ to be added} = 0.90 - 0.13 = 0.77\ g$$

Table 2.4 Sodium-chloride-equivalent values of selected pharmaceutical substances (USP General Chapter ⟨1160⟩).

Drug	NaCl equivalent (E)	Drug	NaCl equivalent (E)
Atropine sulphate	0.13	Penicillin G potassium	0.18
Procaine HCl	0.21	Pilocarpine HCl	0.24
Ephedrine HCl	0.30	Phenobarbital sodium	0.24
Boric acid	0.50	Lignocaine HCl	0.22
Glucose (anhydrous)	0.18	Tetracaine HCl	0.18
Chloramphenicol	0.10	Sulfacetamide sodium	0.23
Gentamicin sulphate	0.05	Benzalkonium chloride	0.16
Streptomycin sulphate	0.07	Neomycin sulphate	0.11

2.21 Commonly Used Buffered Isotonic Vehicles

Table 2.5 Common buffered or pharmacopoeial isotonic vehicles.

Solution	Composition	Osmolarity (mOsm/L)	pH	Clinical use
0.9 % w/v Sodium chloride (Normal Saline)	NaCl 9 g/L (Na^+ 154, Cl^- 154 mEq/L)	308	~5.0 (unbuffered)	IV fluid replacement; vehicle for many parenterals.
5 % w/v Dextrose (D5W)	Dextrose monohydrate 50 g/L	278	4.0–5.0	Carbohydrate energy source and free water provider.
Ringer's lactate (Hartmann's)	Na^+ 130, K^+ 4, Ca^{2+} 3, Cl^- 109, Lactate 28 mEq/L	274	6.0–7.5	Balanced electrolyte replacement; first-line trauma resuscitation fluid.
Phosphate-buffered saline (PBS)	NaCl 8.0, KCl 0.2, Na_2HPO_4 1.44, KH_2PO_4 0.24 g/L	~285	7.4	Biological work, cell culture, ophthalmic vehicle.
Sterile water for injection (WFI)	Pyrogen-free water	0	5.0–7.0	Reconstitution of lyophilised injectables (never given IV undiluted).
Sodium bicarbonate 7.5 %	$NaHCO_3$ 75 g/L	1786 (hypertonic)	7.5–8.5	Severe metabolic acidosis; cardiac arrest.

2.22 Distribution of Body Water

Total body water (TBW) accounts for about 60 % of the body weight of a healthy young adult man (~42 L in a 70 kg adult) and about 55 % in a woman. The percentage falls with age, to about 50 % in a 70-year-old, because lean body mass shrinks. Total body water is partitioned between the intracellular and the extracellular compartments in a roughly 2:1 ratio.

Intracellular fluid (ICF) about 28 L, that is 40 % of body weight, or two-thirds of TBW. It is the fluid inside the body's 30 trillion cells and is dominated by potassium as the cation and by organic phosphate and protein as the anion.

Extracellular fluid (ECF) about 14 L (20 % of body weight, one-third of TBW). It is further sub-divided into three compartments: (a) plasma (the fluid component of blood), about 3.5 L (5 % of body weight); (b) interstitial fluid (between cells, bathing them), about 10.5 L (15 % of body weight); and (c) transcellular fluid (cerebrospinal, intra-ocular, pleural, pericardial, peritoneal, synovial fluids and glandular secretions), about 1–2 L. Sodium and chloride dominate the ECF.

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2.23 Electrolyte Composition of ICF and ECF

The sum of cations must equal the sum of anions in any fluid compartment (electroneutrality). The dominant cation and anion differ markedly between the two compartments. Sodium is high in ECF and low in ICF; potassium is the reverse. The gradient is set up actively by the Na^+/K^+-ATPase, which pumps three Na^+ ions out of the cell in exchange for two K^+ ions and consumes one ATP per cycle. The mismatch in valencies underlies the resting membrane potential of −70 mV (inside negative) on which nerve and muscle conduction depend.

Table 2.6 Electrolyte composition of plasma (ECF) versus intracellular fluid (ICF) in healthy adults. Values are typical adult ranges; individual monographs and clinical references should be consulted for definitive limits.

Ion	Plasma (ECF): mEq/L	Intracellular (ICF): mEq/L	Notes
Sodium (Na^+)	135–145	10–15	Chief ECF cation; governs ECF osmolarity and volume.
Potassium (K^+)	3.5–5.0	140–160	Chief ICF cation; governs ICF volume and membrane excitability.
Calcium (Ca^{2+})	4.5–5.5 (total 8.5–10.5 mg/dL)	< 1 (cytosolic free)	Bone storage; muscle contraction and clotting.
Magnesium (Mg^{2+})	1.5–2.5	40	Cofactor for 300+ enzymes; ATP requires Mg^{2+}.
Chloride (Cl^-)	95–108	~ 4	Chief ECF anion; balances Na^+.
Bicarbonate (HCO_3^-)	22–28	10	Major extracellular buffer.
Phosphate (HPO_4^{2-} / $H_2PO_4^-$)	~ 2 (inorganic)	~ 100 (mostly organic ATP, ADP)	Major intracellular anion; energy currency.
Sulphate (SO_4^{2-})	~ 1	20	Sulphation of bile acids and drug metabolites.
Proteins (anion)	~ 16	~ 55	Albumin, globulins in plasma; enzymes and structural proteins in cells.

2.24 Sodium - Functions and Disorders

Sodium is the dominant cation of the extracellular fluid. Its functions are to maintain the osmotic pressure of plasma and interstitial fluid, to determine the volume of the extracellular compartment, to participate in the generation and conduction of nerve impulses (the depolarising current of the action potential is carried by Na^+ moving into the axon), to combine with chloride and bicarbonate in the regulation of acid-base balance, and to drive the secondary active transport of glucose, amino acids and water across the intestinal and renal-tubular epithelia. Total body sodium is around 60 mEq/kg body weight, of which about half is exchangeable; the rest is sequestered in bone. The kidney is the principal regulatory organ, controlled by the renin–angiotensin–aldosterone axis, atrial natriuretic peptide and antidiuretic hormone.

Normal serum sodium. 135–145 mEq/L (i.e. 135–145 mmol/L).

2.24.1 Hyponatraemia (serum Na^+ < 135 mEq/L)

Caused by either an absolute deficit of sodium or a relative excess of water. Common causes include prolonged use of thiazide and loop diuretics, severe diarrhoea, vomiting, profuse sweating, hypotonic intravenous fluids in the post-operative period, syndrome of inappropriate ADH secretion (SIADH), Addison's disease, congestive cardiac failure with fluid retention, cirrhosis, and primary polydipsia. Clinical features run from headache, lethargy, nausea, muscle cramps and confusion at mild levels (130–135 mEq/L) to seizures, coma, brainstem herniation and death below 115 mEq/L.

Management is by fluid restriction (in dilutional hyponatraemia), oral or intravenous sodium chloride 0.9 % for isovolaemic patients, and 3 % hypertonic saline for severe symptomatic hyponatraemia. Correction must be slow, no faster than 8–10 mEq/L in 24 hours, to avoid central pontine myelinolysis.

2.24.2 Hypernatraemia (serum Na^+ > 145 mEq/L)

Caused by excess sodium intake (rare; salt poisoning, hypertonic-saline error) or by free-water deficit (much more common). Common causes include profuse insensible loss (high fever, burns, hyperventilation), diabetes insipidus, osmotic diuresis (uncontrolled diabetes mellitus), inability to access water (elderly, comatose, intubated patients), and hypertonic feeding in infants. Clinical features include intense thirst, dry mucous membranes, low urine output, tachycardia, restlessness, irritability, hyperreflexia, seizures and coma.

Management is by gradual rehydration with 5 % dextrose or hypotonic saline, the rate of correction being limited to 0.5 mEq/L per hour to avoid cerebral oedema.

2.25 Potassium - Functions and Disorders

Potassium is the dominant cation of the intracellular fluid; 97 % of total body potassium is intracellular, mostly in skeletal muscle. Its functions are: maintenance of resting membrane potential, propagation of the action potential (the repolarising current is carried by K^+ moving out of the axon), excitation-contraction coupling in cardiac and skeletal muscle, regulation of intracellular osmolarity and cell volume, control of acid–base balance through K^+/H^+ exchange at the renal tubule, and activation of intracellular enzymes (e.g.

pyruvate kinase). The kidney is again the principal regulator, with aldosterone driving renal K^+ excretion. About 90 % of dietary potassium is excreted in the urine.

Normal serum potassium. 3.5–5.0 mEq/L. Serum K^+ below 2.5 or above 7.0 mEq/L is life-threatening because of cardiac arrhythmia.

2.25.1 Hypokalaemia (serum K^+ < 3.5 mEq/L)

Caused by inadequate intake (anorexia, prolonged parenteral nutrition without K^+), gastrointestinal loss (vomiting, diarrhoea, laxative abuse, nasogastric suction), renal loss (loop and thiazide diuretics, Cushing's syndrome, primary hyperaldosteronism, renal tubular acidosis), and intracellular shift (insulin overdose, β-agonist therapy, alkalosis, refeeding syndrome). Clinical features include muscle weakness, leg cramps, fatigue, paralytic ileus, polyuria, orthostatic hypotension, ECG changes (flattening of the T wave, U wave, ST depression) and ventricular ectopy.

Management is by oral potassium chloride (10–40 mEq/day) in mild cases, intravenous potassium chloride (no faster than 10 mEq/h peripherally; 20 mEq/h centrally with cardiac monitoring) in severe cases. Indian marketed examples include K-Sav, Pot-Klor and Kaprex (oral); Ster-K and KCl IP (injection).

2.25.2 Hyperkalaemia (serum K^+ > 5.0 mEq/L)

Caused by impaired renal excretion (acute and chronic kidney disease, mineralocorticoid deficiency, potassium-sparing diuretics, ACE inhibitors and angiotensin-receptor blockers), cellular release (rhabdomyolysis, tumour lysis syndrome, massive transfusion of old stored blood, severe acidosis), and exogenous load (salt substitutes, IV potassium overdose). Clinical features include muscle weakness, paraesthesiae, abdominal cramps, bradycardia, and the typical sequence of ECG changes, peaked T waves, prolonged PR, widening of QRS, loss of P waves, sine-wave appearance, and finally asystole.

Management of severe hyperkalaemia is staged: intravenous calcium gluconate 10 % (to stabilise the cardiac membrane), insulin–dextrose infusion or salbutamol nebulisation (to shift K^+ into cells), sodium polystyrene sulfonate / patiromer (to remove K^+ via the gut), and haemodialysis in renal failure.

2.26 Chloride - Functions and Disorders

Chloride is the dominant anion of the extracellular fluid. Its functions are to maintain electroneutrality alongside sodium, to participate in the regulation of acid-base balance through the chloride-bicarbonate shift in erythrocytes, to act as the principal anion of gastric hydrochloric acid (parietal-cell H^+/K^+-ATPase secretes H^+ in exchange for Cl^- taken up by the same cell), and to serve as the inhibitory current carrier in neurons (GABA-A receptor opens Cl^- channels). Chloride is filtered freely at the glomerulus and reabsorbed actively, mostly in the thick ascending limb of the loop of Henle (where it is the target of furosemide).

Normal serum chloride. 95–108 mEq/L.

2.26.1 Hypochloraemia and Hyperchloraemia

Hypochloraemia (serum Cl^- < 95 mEq/L) commonly accompanies the vomiting of gastric contents (loss of HCl), metabolic alkalosis, diuretic therapy, salt-losing nephropathy and SIADH. Hyperchloraemia (serum Cl^- > 108 mEq/L) accompanies dehydration, renal tubular acidosis, ureterosigmoidostomy, large-volume normal-saline resuscitation (which can produce hyperchloraemic metabolic acidosis), and excessive oral salt intake. Both are managed by treating the underlying cause; severe hyperchloraemic acidosis is corrected with isotonic sodium bicarbonate or balanced crystalloid (e.g. Ringer's lactate, Plasma-Lyte).

2.27 Calcium, Magnesium, Phosphate and Bicarbonate

2.27.1 Calcium

Calcium is the most abundant divalent cation in the body. About 99 % is stored in bone as hydroxyapatite; only 1 % is in soft tissue and body fluids. In plasma, calcium circulates in three forms, ionised (50 %, the physiologically active form), protein-bound (40 %, mainly to albumin) and complexed (10 %, with citrate, phosphate, bicarbonate). Calcium is essential for bone and tooth mineralisation, blood coagulation (factor IV), neuromuscular excitability, excitation-contraction coupling in skeletal, cardiac and smooth muscle, secretion of insulin, parathyroid hormone, gastrin and other peptide hormones, and intracellular signal transduction (calmodulin, troponin C). Calcium homeostasis is controlled by parathyroid hormone, calcitonin and 1,25-dihydroxy-vitamin D_3.

Normal serum calcium. Total: 8.5–10.5 mg/dL (2.2–2.6 mmol/L); ionised: 4.5–5.5 mg/dL (1.1–1.3 mmol/L).

Hypocalcaemia (causes: hypoparathyroidism, vitamin D deficiency, chronic kidney disease, acute pancreatitis, hypoalbuminaemia, massive transfusion of citrated blood) produces neuromuscular irritability, Chvostek's sign, Trousseau's sign, perioral tingling, carpopedal spasm, laryngospasm, seizures. Hypercalcaemia (causes: primary hyperparathyroidism, malignancy with bone metastases, vitamin D toxicity, sarcoidosis, thiazide diuretics) produces the classical pentad, stones (renal), bones (pain), abdominal groans (constipation, pancreatitis), psychic moans (confusion, depression), and fatigue overtones. Marketed Indian calcium preparations include Calcium Sandoz (IV calcium gluconate 10 %), Calcimax-P forte (oral calcium citrate + vitamin D), Shelcal-500 (calcium carbonate + vitamin D_3) and Ostocalcium-B12 syrup.

2.27.2 Magnesium

Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation after potassium. It is a cofactor for over three hundred enzymes (including all ATP-using enzymes, ATP is biologically active only as the Mg-ATP complex), is essential for DNA and RNA synthesis, and modulates the function of calcium channels and the NMDA receptor. Normal serum magnesium is 1.5–2.5 mEq/L. Hypomagnesaemia (causes: alcoholism, diuretic use, proton-pump inhibitor therapy, malabsorption)

produces neuromuscular hyperexcitability and ventricular arrhythmia and is often the unrecognised cause of refractory hypokalaemia and hypocalcaemia. Hypermagnesaemia (cause: renal failure with magnesium-containing antacid or laxative use, or magnesium sulphate overdose in eclampsia) produces hyporeflexia, hypotension and respiratory paralysis at very high levels.

2.27.3 Phosphate

Phosphate is the principal intracellular anion. Eighty-five per cent is in bone as hydroxyapatite; the rest is intracellular as inorganic phosphate and as a component of every nucleic acid, every nucleotide, every nucleotide coenzyme (ATP, NAD^+, FAD) and every phospholipid of every cell membrane. In plasma, inorganic phosphate exists in two forms, $H_2PO_4^-$ (≈ 20 %) and HPO_4^{2-} (≈ 80 %), and is normally 2.5–4.5 mg/dL (0.8–1.5 mmol/L) in adults. The two phosphate species form one of the body's three major buffer systems (the others being bicarbonate and protein). When the pH of the extracellular fluid drops, $H_2PO_4^-$ rises and HPO_4^{2-} falls; the kidney excretes the excess hydrogen as $H_2PO_4^-$ (titratable acidity), regenerating bicarbonate.

2.27.4 Bicarbonate

Bicarbonate is the second most abundant anion of the ECF and the most important extracellular buffer. Normal arterial bicarbonate is 22–28 mEq/L. About 4 320 mEq of bicarbonate is filtered by the kidneys every day; all of it is reabsorbed in the proximal tubule under normal conditions. In acidosis, the kidney reabsorbs all filtered bicarbonate and generates fresh bicarbonate by ammoniagenesis; in alkalosis, the kidney excretes the surplus. The bicarbonate buffer is uniquely open, both components can be altered independently by the lungs (CO_2) and the kidneys (HCO_3^-) - which makes it the most rapidly adjusted buffer in the body.

2.28 Physiological Acid–Base Balance

Three lines of defence keep arterial pH within 7.35–7.45. The first is the buffer line: bicarbonate (extracellular), phosphate (intracellular and in urine) and protein (haemoglobin in red cells, albumin in plasma). They act within milliseconds. The second is the respiratory line: a fall in pH stimulates chemoreceptors and increases ventilation, blowing off CO_2 and raising pH; a rise in pH suppresses ventilation, retaining CO_2. The respiratory adjustment takes minutes. The third is the renal line: the kidney reabsorbs or excretes bicarbonate, and excretes acid as titratable acidity ($H_2PO_4^-$) and as ammonium (NH_4^+). The renal adjustment takes hours to days. Disorders of acid-base balance are classified as metabolic or respiratory, and as acidosis or alkalosis, on the basis of which arm is primary; their detailed analysis (the Henderson–Hasselbalch arterial-blood-gas interpretation) is developed in clinical biochemistry courses.

2.29 Electrolyte Preparations for Replacement Therapy

Four electrolyte preparations are listed in the IP for replacement of fluid and acid–base losses.

2.29.1 Sodium chloride

Empirical formula NaCl, molecular weight 58.44. The IP monograph requires the substance to contain not less than 99.0 % of NaCl on the dried basis. Pharmaceutical sodium chloride is sourced from solar evaporation of sea water or by purification of rock-salt brine, with limit tests for arsenic (≤ 1 ppm), heavy metals (≤ 5 ppm), barium, calcium, magnesium, sulphate, ferrocyanide and bromide. Sodium chloride is formulated as: (a) Sodium chloride injection IP 0.9 % w/v (Normal Saline), the universal vehicle for fluid replacement and drug reconstitution; (b) Sodium chloride and dextrose injection IP (0.45 % NaCl + 5 % dextrose); (c) hypertonic NaCl injection 3 % and 5 % for severe hyponatraemia; and (d) oral sodium chloride tablets for sodium deficit.

2.29.2 Potassium chloride

Empirical formula KCl, molecular weight 74.55. The IP monograph requires not less than 99.0 % w/w of KCl on the dried basis. Indian marketed examples include Pot-Klor Liquid (20 mEq per 15 mL, oral), K-Sav syrup, Kaylixir, and KCl 15 % w/v injection 10 mL ampoules (20 mEq K^+). Intravenous potassium chloride is never given as a bolus, it must be diluted to a maximum of 40 mEq per litre, infused at no more than 10 mEq/h through a peripheral vein and 20 mEq/h through a central vein, and with continuous cardiac monitoring above 10 mEq/h.

2.29.3 Calcium gluconate

Empirical formula $C_{12}H_{22}CaO_{14} \cdot H_2O$, molecular weight 448.40. The IP monograph requires the substance to contain not less than 98.5 % of calcium D-gluconate monohydrate on the dried basis. Each gram of calcium gluconate provides 89 mg (4.45 mEq) of elemental calcium. The injection is supplied as a 10 % w/v solution (10 mL ampoule; 1 g of calcium gluconate; 4.45 mEq Ca^{2+}); the brand name Calcium Sandoz IV has been the market leader in India since 1929. Calcium gluconate is preferred to calcium chloride for the intravenous route because it is less irritating to the vein; it is the first-line agent in symptomatic hypocalcaemia, hyperkalaemic membrane stabilisation, magnesium-sulphate toxicity, and hydrofluoric-acid burns.

2.29.4 Oral rehydration salt (ORS) - the WHO low-osmolarity formula

Oral rehydration salt is the most important pharmaceutical product of the twentieth century, UNICEF has estimated that it has saved more than fifty million children since its introduction in 1968. The current formulation, recommended by WHO and UNICEF in 2003, has a total osmolarity of ≤ 245 mOsm/L. Compared with the original 311 mOsm/L formula, this reduced-osmolarity ORS has been shown in randomised trials to reduce stool output by 20 %, vomiting by 30 %, and the need for unscheduled intravenous fluid therapy by 33 %.

Composition of a single sachet, reconstituted in 1 litre of water:

- Sodium chloride: 2.6 g (provides 75 mmol/L Na^+ and 65 mmol/L Cl^-);

- Potassium chloride: 1.5 g (provides 20 mmol/L K^+ and a further 20 mmol/L Cl^-);
- Trisodium citrate dihydrate: 2.9 g (provides 10 mmol/L citrate, which is metabolised to bicarbonate in the liver, replacing the bicarbonate lost in diarrhoea);
- Anhydrous glucose: 13.5 g (provides 75 mmol/L glucose; the 1:1 glucose:Na^+ molar ratio is what drives the SGLT-1 co-transporter at the brush border of the small intestine, pulling Na^+ and water into the enterocyte).

Indian marketed examples include Electral (FDC Ltd), Walyte, Enerzal, Pedialyte (Abbott), Prolyte and Dolosalt. All carry the IP monograph "Oral rehydration salts" with the WHO low-osmolarity composition.

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UNIT III

Volumetric and Gravimetric Methods of Pharmaceutical Analysis

3.1 Introduction to Volumetric Analysis

Volumetric analysis, also called titrimetric analysis, is the family of quantitative methods in which the amount of an analyte is determined from the volume of a standard solution (the titrant) that reacts stoichiometrically with it. The technique was perfected by Karl Friedrich Mohr in Germany in the middle of the nineteenth century and remains the workhorse of pharmaceutical assay. Compared with instrumental methods it is inexpensive, robust, requires no electrical power, and gives an accuracy of 0.1–0.3 % on a milligram sample. The pharmacopoeias still prescribe volumetric assays for most inorganic actives and many low-molecular-weight organic actives, even when an HPLC method is available.

Volumetric methods are classified by the type of reaction involved:

- Acid–base (neutralisation) titrations: both aqueous and non-aqueous.
- Precipitation titrations: argentometry (Mohr, Volhard, Fajans).
- Complexometric titrations: chiefly with EDTA.
- Redox titrations: permanganometry, iodometry, iodimetry, ceriometry, dichromatometry (developed in Unit IV).
- Diazotisation titrations: for primary aromatic amines.

Gravimetric analysis runs in parallel: the analyte is precipitated, filtered, dried (or ignited) and weighed; from the mass of the precipitate and the gravimetric factor the amount of analyte is calculated.

3.2 Acid–Base Titrations

In an acid–base titration the analyte is a base titrated with a standardised acid, or an acid titrated with a standardised base. The endpoint is detected with a chemical indicator or by potentiometry. The Henderson–Hasselbalch equation derived in Unit II is the algebraic backbone of the titration curve.

3.2.1 Theory of Acid–Base Indicators

An acid–base indicator is a weakly acidic or weakly basic organic dye whose un-ionised form has one colour and ionised form a sharply different colour. The Ostwald theory (Wilhelm Ostwald, 1894) explains the colour change in terms of acid-base equilibrium of the indicator itself.

For an acidic indicator written symbolically as HIn:

$$HIn \rightleftharpoons H^+ + In^- \quad (HIn = \text{colour 1}, In^- = \text{colour 2})$$

$$Ka(HIn) = [H^+][In^-] / [HIn]$$

Taking the negative logarithm of both sides gives the indicator form of the Henderson–Hasselbalch equation:

$$pH = pKa(HIn) + \log\left([In^-] / [HIn]\right)$$

The eye perceives the colour of an indicator as the colour of the predominant species. When $[In^-]$ is about ten times [HIn], the eye sees only the In^- colour; when [HIn] is about ten times $[In^-]$, the eye sees only the HIn colour. The transition region is therefore about pKa ± 1, that is, two pH units wide.

A second framework, the chromophore (quinonoid) theory, explains the colour change in terms of a tautomeric rearrangement: the un-ionised form has the benzoid chromophore, the ionised form has the quinonoid chromophore. Phenolphthalein is the classical example, in which the lactone form (colourless) opens up in alkali to the quinonoid carboxylate (pink).

3.2.2 Common Acid–Base Indicators

Table 3.1 Common acid–base indicators with their pKa values and pH transition ranges.

Indicator	pKa(HIn) at 25 °C	pH transition range	Colour (acid → base)
Methyl violet	0.8	0.0 – 1.6	Yellow → blue
Thymol blue (acid range)	1.7	1.2 – 2.8	Red → yellow
Methyl orange	3.7	3.1 – 4.4	Red → yellow
Bromphenol blue	4.0	3.0 – 4.6	Yellow → blue
Methyl red	5.1	4.4 – 6.2	Red → yellow
Bromcresol purple	6.1	5.2 – 6.8	Yellow → purple
Bromthymol blue	7.1	6.0 – 7.6	Yellow → blue
Phenol red	7.4	6.4 – 8.0	Yellow → red
Cresol red	8.3	7.2 – 8.8	Yellow → red
Phenolphthalein	9.4	8.2 – 10.0	Colourless → pink
Thymolphthalein	9.7	9.3 – 10.5	Colourless → blue
Alizarin yellow R	11.0	10.1 – 12.0	Yellow → red

3.2.3 Selection of Indicator

The correct indicator is one whose pKa falls within the steep portion of the titration curve at the equivalence point. The choice depends on which of the four classical cases the titration represents.

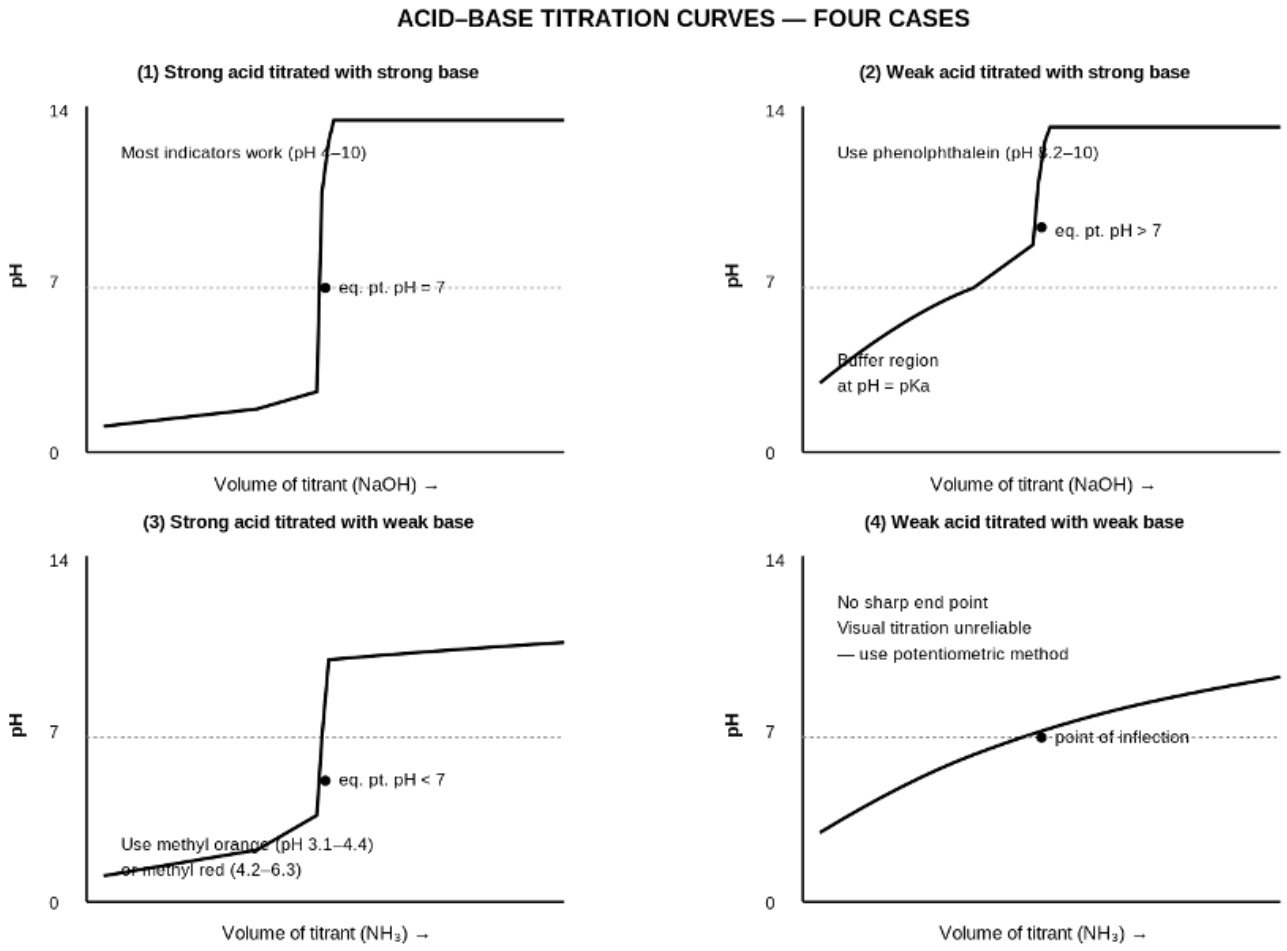

Fig. 3.1 Four classical acid–base titration curves: (1) strong acid–strong base, (2) weak acid–strong base, (3) strong acid–weak base, (4) weak acid–weak base.

Case 1 - Strong acid versus strong base. The pH at the equivalence point is 7.00. The pH jump near the equivalence point is large (about 4 to 10 pH units for a 0.1 N reagent) and so almost any indicator with a transition between pH 4 and 10, methyl orange, methyl red, bromcresol purple, phenol red or phenolphthalein, gives a sharp endpoint. Example: titration of HCl with NaOH.

Case 2 - Weak acid versus strong base. The pH at the equivalence point is above 7 (typically 8.3 for the acetic acid / NaOH system) because the salt formed is hydrolysed slightly to give a basic solution. The jump is narrower, from about pH 7 to pH 11. Phenolphthalein (pH 8.2–10) is the indicator of choice. Methyl orange would change colour well before the true equivalence point. Example: assay of acetic acid in vinegar; assay of boric acid (in presence of glycerol) with sodium hydroxide.

Case 3 - Strong acid versus weak base. The pH at the equivalence point is below 7 (about 5.3 for the HCl / NH_3 system) because the cation of the weak base is hydrolysed to give an acidic solution. Methyl orange (pH 3.1–4.4) or methyl red (pH 4.4–6.2) is the indicator of choice. Phenolphthalein would have already changed colour. Example: assay of sodium carbonate by titration with HCl using methyl orange.

Case 4 - Weak acid versus weak base. No sharp jump in pH at the equivalence point: the titration curve has only a point of inflexion. Visual indication is unreliable; potentiometric (pH-meter) titration must be used. Example: titration of acetic acid with ammonia.

A useful empirical rule (Ostwald-Bjerrum) is that an indicator can be used only when the pH at the equivalence point lies within ±1 pH unit of the indicator pKa.

3.3 Non-Aqueous Titrations

Many pharmaceutical actives are too weakly acidic or too weakly basic to give a sharp endpoint when titrated in water. Water itself is amphiprotic, its self-ionisation generates H_3O^+ and OH^-, both of which compete with the analyte for the titrant. This levelling effect of water masks the inherent acid–base strength of the analyte and gives a poor, drifting endpoint. Non-aqueous titration replaces water with a solvent chosen to suppress the levelling effect and enhance the apparent strength of the analyte. The technique was systematised by Conant and Hall (1927) and brought into routine pharmaceutical use by Pifer, Wollish and Schmall in the 1950s.

3.3.1 Advantages of Non-Aqueous Titration

- Direct, sharp titration of very weak acids and very weak bases that cannot be titrated in water.
- Mixtures of two or more acids (or bases) of comparable strength in water can be resolved into separate endpoints by appropriate solvent choice.
- Organic actives that are insoluble in water (alkaloids, organic acids, halide salts of bases) are dissolved in the non-aqueous solvent.
- The procedure is simple, accurate, and well suited to pharmacopoeial routine analysis. The IP, BP and USP all prescribe non-aqueous titration as the assay of choice for tens of weakly acidic and weakly basic actives, barbiturates, sulphonamides, amines, halide salts of alkaloids.

3.3.2 Classification of Non-Aqueous Solvents

A non-aqueous solvent is classified on the basis of its protic behaviour into four categories.

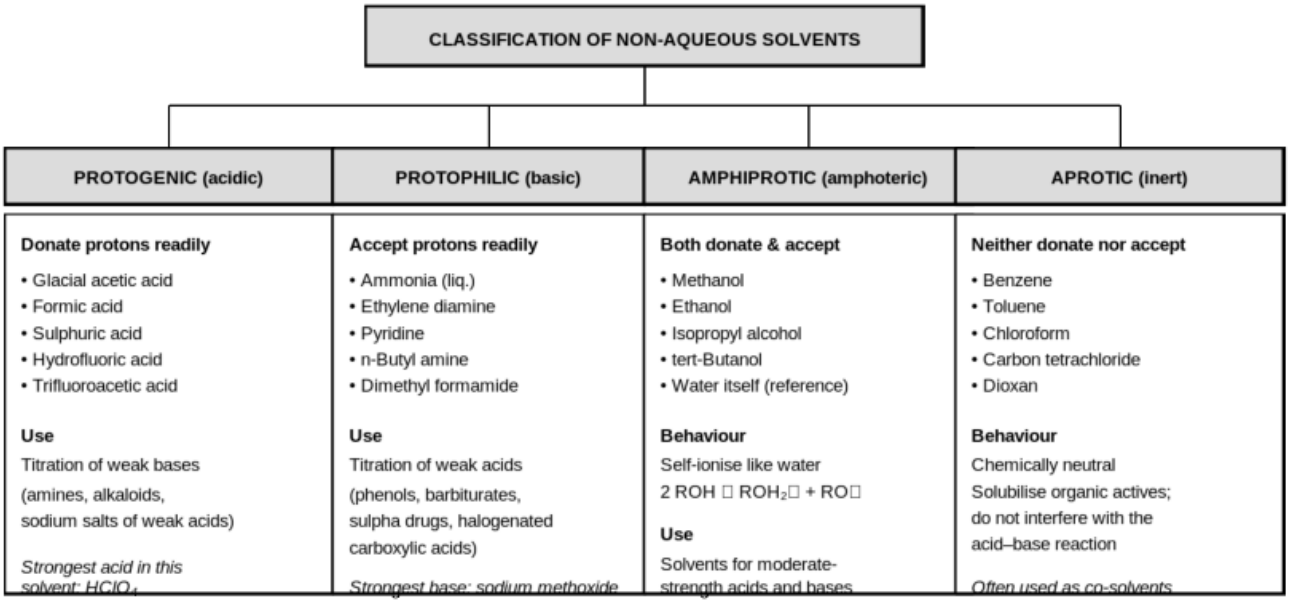

Fig. 3.2 Classification of non-aqueous solvents (protogenic, protophilic, amphiprotic, aprotic).

Protogenic (acidic) solvents. Donate protons readily. Examples: glacial acetic acid, formic acid, sulphuric acid, hydrofluoric acid, trifluoroacetic acid. They suppress the basic character of a weak base, that is, in such a solvent every base is "weaker" than it would be in water, but they enhance the contrast between bases of nearly equal strength, allowing their resolved titration. Glacial acetic acid is the workhorse solvent for the titration of weak bases. The strongest acid that can exist in glacial acetic acid is $HClO_4$ (perchloric acid in glacial acetic acid is the strongest titrant in routine pharmaceutical practice).

Protophilic (basic) solvents. Accept protons readily. Examples: liquid ammonia, ethylenediamine, n-butylamine, pyridine, morpholine, dimethylformamide. They enhance the apparent strength of weak acids and are used to titrate phenols, barbiturates, sulpha drugs, and other very weak organic acids. The strongest base that can exist in these solvents is sodium methoxide (CH_3ONa) or tetrabutylammonium hydroxide.

Amphiprotic (amphoteric) solvents. Both donate and accept protons. Examples: methanol, ethanol, isopropanol, tert-butanol. They self-ionise like water ($2\ ROH \rightleftharpoons ROH_2^+ + RO^-$) and behave as moderate levelling agents. Used as solvents for moderate-strength acids and bases.

Aprotic (inert) solvents. Neither donate nor accept protons. Examples: benzene, toluene, chloroform, carbon tetrachloride, dioxan. They do not interfere with the acid-base reaction itself but improve the solubility of organic actives. They are often used as co-solvents in mixed-solvent systems (for example, benzene + glacial acetic acid, or chloroform + glacial acetic acid).

3.3.3 Titrants and Indicators in Non-Aqueous Titration

Acidimetry (titration of weak bases)

The titrant is acetous perchloric acid (perchloric acid in glacial acetic acid), 0.1 M. It is prepared by mixing 8.5 mL of 70 % $HClO_4$ with 500 mL of glacial acetic acid and 21 mL of acetic anhydride (to mop up the

water introduced with the perchloric acid); the solution is allowed to stand for 24 hours and is standardised against primary-standard potassium hydrogen phthalate dried at 105 °C for 2 hours. The dissolution of 700 mg of KHP in 50 mL of glacial acetic acid is titrated with the $HClO_4$ solution to a sharp colour change of crystal violet from blue-violet to emerald green.

Caution: undiluted $HClO_4$ reacts violently with acetic anhydride; the perchloric acid must always be diluted with glacial acetic acid first. The titrant must be protected from moisture and is unstable above 30 °C.

Alkalimetry (titration of weak acids)

Common titrants are sodium methoxide (CH_3ONa, 0.1 M in methanol–benzene 1:9), tetrabutylammonium hydroxide (in benzene–methanol) and potassium methoxide. They are standardised against primary-standard benzoic acid dissolved in dimethylformamide, with thymol blue or azo-violet as the indicator.

Indicators for non-aqueous titration

Table 3.2 Indicators used in non-aqueous titrations.

Indicator	Use	Colour change (acid → base)
Crystal violet (0.5 % in glacial acetic acid)	Titration of bases with $HClO_4$	Violet → blue-green → emerald-green → blue-green → blue
Oracet blue B (0.5 % in glacial acetic acid)	Titration of bases with $HClO_4$	Pink → purple → blue
Methyl red (0.5 % in dioxan)	Titration of weak bases (mild)	Red → yellow
α-Naphtholbenzein	Titration of weak bases	Yellow → green → blue
Quinaldine red	Titration of bases	Magenta → colourless
Thymol blue (0.3 % in DMF or methanol)	Titration of weak acids	Yellow → blue
Azo violet	Titration of very weak acids	Red → blue-violet

3.3.4 Assay of Sodium Benzoate (Non-aqueous Acidimetry)

Sodium benzoate (C_6H_5COONa, M.W. 144.10) is the sodium salt of a weak acid; in glacial acetic acid the benzoate ion functions as a base and can be titrated with perchloric acid:

$$C_6H_5COO^- Na^+ + HClO_4 \rightarrow C_6H_5COOH + NaClO_4$$

Procedure (IP 2026 monograph): weigh accurately about 0.25 g of sodium benzoate dried at 105 °C for 1 hour; dissolve in 20 mL of anhydrous glacial acetic acid, warming to 50 °C if necessary, and cool. Add 2 drops of crystal violet TS and titrate with 0.1 M acetous perchloric acid until the violet colour changes to emerald green. Carry out a blank titration on the solvent system and subtract.

Calculation: each mL of 0.1 M $HClO_4$ ≡ 14.41 mg of sodium benzoate. The IP monograph requires the substance to contain not less than 99.0 % and not more than 100.5 % of C_6H_5COONa on the dried basis. Indian marketed examples - sodium benzoate is used as a preservative (0.1–0.5 % w/v) in oral cough syrups (Benadryl, Corex, Codistar) and as the active in oral therapy for hyperammonaemia (Sodium Benzoate USP 5 g sachet).

3.3.5 Assay of Ephedrine Hydrochloride (Non-aqueous Acidimetry)

Ephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$, M.W. 201.69) is the hydrochloride salt of a weak base. The free amine cannot be titrated directly in glacial acetic acid because the chloride ion of the hydrochloride is too weak a base to give a sharp endpoint with perchloric acid. Mercuric acetate is therefore added to displace the chloride as the undissociated, weakly ionised mercuric chloride; the acetate so liberated then acts as a strong base in glacial acetic acid:

$$2\ R{\cdot}NH_2{\cdot}HCl + Hg(CH_3COO)_2 \rightarrow 2\ R{\cdot}NH_2{\cdot}CH_3COOH + HgCl_2$$

$$R{\cdot}NH_2{\cdot}CH_3COOH + HClO_4 \rightarrow R{\cdot}NH_2{\cdot}HClO_4 + CH_3COOH$$

Procedure (IP 2026 monograph): weigh accurately about 0.5 g of ephedrine hydrochloride; dissolve in 25 mL of glacial acetic acid; add 10 mL of mercuric acetate solution (6.0 % w/v in glacial acetic acid); mix and titrate with 0.1 M acetous perchloric acid using 2 drops of crystal violet TS, until the colour changes from blue-violet to bluish green. Carry out a blank titration and subtract.

Calculation: each mL of 0.1 M $HClO_4$ ≡ 20.17 mg of ephedrine hydrochloride. Indian marketed examples - Asthalin Expectorant, Wikoryl, Ephedrine HCl IP 30 mg tablets, Ephedrine HCl injection 30 mg/mL (off-licence vasopressor in operating theatres).

3.4 Precipitation Titrations

Precipitation titrations are based on the formation of a sparingly soluble precipitate during the titration. The most important sub-family is argentometry, titrations using silver nitrate as the titrant for halide, pseudohalide and silver-precipitable species. Three classical methods are listed in every pharmacopoeia, supplemented by the modified Volhard procedure.

3.4.1 Mohr's Method (Direct Argentometry)

Karl Friedrich Mohr published this method in Annalen der Chemie in 1856, the first practical titration of halide ions. The principle is direct: the chloride ion in the sample is titrated with standardised silver nitrate; the endpoint is signalled by the formation of red-brown silver chromate in the presence of potassium chromate as an internal indicator.

The chemistry is built on the differential solubilities of the two silver salts. Silver chloride is much less soluble ($K_{sp} = 1.8 \times 10^{-10}$) than silver chromate ($K_{sp} = 1.1 \times 10^{-12}$) - but because the chromate is divalent, the actual concentration of silver ion required to start precipitating silver chromate is higher than that for

silver chloride. Therefore AgCl precipitates first; only when essentially all chloride has been removed does silver ion accumulate to a concentration sufficient to precipitate the red-brown Ag_2CrO_4, signalling the endpoint.

$$Ag^+ + Cl^- \rightarrow AgCl \downarrow \text{(white)} \qquad \text{- precipitation phase}$$

$$2\,Ag^+ + CrO_4^{2-} \rightarrow Ag_2CrO_4 \downarrow \text{(red-brown)} \qquad \text{- endpoint indicator}$$

pH window

The titration must be carried out at pH 6.5–9.0. Below pH 6.5 the chromate ion is protonated ($CrO_4^{2-} + H^+ \rightleftharpoons HCrO_4^- \rightleftharpoons Cr_2O_7^{2-}$), and the indicator concentration falls. Above pH 9.0 silver ion precipitates as silver hydroxide or silver oxide, giving a premature, false endpoint. The titration is therefore performed in neutral or weakly basic medium. If the sample is acidic, it is neutralised with calcium carbonate or sodium bicarbonate before titration.

Procedure for the assay of sodium chloride

1. Weigh accurately about 0.10 g of sodium chloride; dissolve in 50 mL of distilled water in a conical flask.
2. Add 2 mL of 5 % w/v potassium chromate solution as indicator.
3. Titrate with 0.1 M silver nitrate solution from the burette, swirling continuously.
4. The white turbidity of silver chloride grows during the titration. The endpoint is the persistent appearance of a red-brown tinge of silver chromate.
5. Calculate: each mL of 0.1 M $AgNO_3$ ≡ 5.844 mg of NaCl. The IP requires sodium chloride to contain not less than 99.0 % of NaCl on the dried basis.

3.4.2 Volhard's Method (Indirect Argentometry)

Jacob Volhard published the second classical method in 1874. It is a back-titration designed for halides (Cl^-, Br^-, I^-, SCN^-) and is carried out in acidic medium, a major advantage over Mohr's method which fails in acid.

The principle: an excess of standardised silver nitrate is added to the halide sample in acidic medium (dilute nitric acid). The silver halide precipitates and the excess silver is then back-titrated with standardised potassium thiocyanate using ferric ammonium sulphate as the indicator. At the endpoint, the first drop of thiocyanate that has no silver to react with produces the deep red-brown ferric thiocyanate complex $[Fe(SCN)]^{2+}$.

$$Cl^- + Ag^+ \text{ (excess, known)} \rightarrow AgCl \downarrow + Ag^+ \text{ (residue)}$$

$$Ag^+ \text{ (residue)} + SCN^- \text{ (titrant)} \rightarrow AgSCN \downarrow \text{(white)}$$

$$Fe^{3+} + SCN^- \rightarrow [Fe(SCN)]^{2+} \text{ (red-brown)} \qquad \text{- endpoint}$$

Indicator and medium

The indicator is ferric ammonium sulphate $FeNH_4(SO_4)_2 \cdot 12\ H_2O$, 5 % w/v in dilute HNO_3. The acidic medium serves two purposes, it suppresses the hydrolysis of Fe^{3+} to coloured hydroxides, and it prevents the precipitation of silver chromate, silver hydroxide and silver phosphate that would otherwise interfere with the assay of chloride in alkaline media.

Modified Volhard's method

For the assay of chloride, AgCl is more soluble than AgSCN. During the back-titration, the silver chloride in the precipitate exchanges chloride for thiocyanate from the titrant, leading to over-consumption of thiocyanate and a low value for the chloride. The Caldwell–Moyer modification (1935) solves the problem by coating the AgCl precipitate with about 1 mL of nitrobenzene, which forms a hydrophobic film around the silver chloride and prevents thiocyanate from reaching it. The back-titration then proceeds in the usual way with accurate results.

Volhard's method is the IP method for the assay of bromides (Sodium bromide IP), iodides (Potassium iodide IP), silver nitrate (silver nitrate ophthalmic solution 1 %), and chlorides in samples that cannot tolerate neutral-to-alkaline medium. The IP also prescribes the method for the assay of organomercury preservatives such as thiomersal.

3.4.3 Fajans Method (Adsorption-Indicator Titration)

Kazimierz Fajans, working in Munich in the 1920s, recognised that the surface of a freshly precipitated colloidal silver halide carries either a net negative charge (when halide is in excess in solution) or a net positive charge (when silver is in excess), in accordance with the Paneth-Fajans-Hahn adsorption rule. An organic dye whose anion can be electrostatically attracted to the positive surface, but which is otherwise in the bulk of the solution, can be used as a precipitation-onset indicator.

The classical indicator is dichlorofluorescein (a fluorescein derivative). Before the equivalence point, the AgCl particles carry surface-adsorbed Cl^- and bulk solution is yellow-green from the free dichlorofluorescein anion. At the equivalence point, the surface charge reverses to positive (because Ag^+ is now in slight excess); the negative dichlorofluorescein anion is adsorbed onto the positively charged surface, forming a pink-violet ion-pair on the precipitate that is visible against the rest of the solution.

Other adsorption indicators

Dichlorofluorescein. For Cl^-, pH 4–10. Yellow-green → pink-violet.

Fluorescein. For Cl^-, pH 6.5–10.0. Yellow-green → pink.

Eosin (tetrabromofluorescein). For Br^-, I^-, SCN^-. Pink → red-violet.

Bromphenol blue. For Cl^- in acidic medium pH 2–3.5. Yellow → blue.

Bromcresol green. For Br^- at pH 4–5.

Limitations of Fajans method

- Useful mainly for halides and a few pseudohalides; not extendable to most cations.
- The colloidal precipitate must remain in suspension (no flocculation). A protective colloid such as dextrin (5 mg per 100 mL) is sometimes added.
- Strong light bleaches some adsorption indicators; titrations are best performed in subdued light.
- Strict pH control is required for each indicator.

3.4.4 Comparison of the Three Precipitation Methods

Table 3.3 Mohr, Volhard and Fajans methods compared.

Feature	Mohr (1856)	Volhard (1874)	Fajans (1924)
Type	Direct titration	Indirect (back-titration)	Direct titration with adsorption indicator
Titrant	$AgNO_3$	$AgNO_3$ (excess) and KSCN	$AgNO_3$
Indicator	K_2CrO_4 (5 %)	Fe^{3+} (ferric ammonium sulphate)	Dichlorofluorescein, eosin, etc.
pH range	6.5 – 9.0	Acidic (HNO_3)	4 – 10 (depends on indicator)
Endpoint	Red-brown Ag_2CrO_4	Red-brown $[Fe(SCN)]^{2+}$	Coloured film on precipitate
Best for	Cl^- and Br^- in neutral solution	Cl^-, Br^-, I^-, SCN^- in acidic solution	Halides at moderate pH
Pharmacopoeial use	NaCl, KCl	NaBr, KI, $AgNO_3$, thiomersal	Halides where Mohr and Volhard fail

3.5 Complexometric Titrations

Complexometric titrations are based on the formation of a soluble, undissociated complex between the analyte (a metal ion) and the titrant (a chelating agent). The dominant titrant is ethylenediaminetetraacetic acid (EDTA), introduced by Gerold Schwarzenbach at the University of Zürich in 1945. EDTA forms a 1:1 chelate with virtually every metal ion in the periodic table except the alkali metals, and the chelate is colourless, both features ideally suited to a clean titration.

3.5.1 EDTA - Structure and Chemistry

EDTA (full name: 2,2′,2″,2‴-[(ethane-1,2-diyl)bis(nitrilo)]tetraacetic acid; molecular formula $C_{10}H_{16}N_2O_8$; M.W. 292.24 for the free acid, 372.24 for the disodium salt dihydrate $Na_2H_2Y \cdot 2\ H_2O$) carries six donor sites, four carboxylate oxygen atoms and two amine nitrogen atoms. In its 1:1 chelate with a divalent metal

ion, all six donor atoms coordinate to the metal in an octahedral geometry, forming five five-membered chelate rings (Figure 3.7). The high stability of the chelate arises from this chelation effect.

EDTA is a tetraprotic acid with stepwise pKa values 2.00, 2.67, 6.16 and 10.26. The fully deprotonated form Y^{4-} is the most effective chelator, but it predominates only above pH 12. At lower pH the partially protonated forms HY^{3-}, H_2Y^{2-} and H_3Y^{-} are present, and the apparent stability of the metal-EDTA chelate (the conditional formation constant Kf') varies with pH. The pH must therefore be controlled at the optimum for each metal.

$$M^{2+} + H_2Y^{2-} \rightarrow MY^{2-} + 2\ H^{+} \qquad \textit{(1:1 stoichiometry; releases 2 } H^{+}\textit{)}$$

Table 3.4 Optimum pH and buffer for the EDTA titration of common metal ions.

Metal	log Kf (MY)	Optimum pH	Recommended buffer
Ca^{2+}	10.7	10.0	NH_3 / NH_4Cl
Mg^{2+}	8.7	10.0	NH_3 / NH_4Cl
Zn^{2+}	16.5	10.0	NH_3 / NH_4Cl
Fe^{2+}	14.3	5.0	Acetate
Fe^{3+}	25.1	2 – 3	HNO_3
Cu^{2+}	18.8	6.0	Acetate or hexamine
Pb^{2+}	18.0	5 – 6	Acetate
Bi^{3+}	27.9	1 – 2	$HClO_4$
Al^{3+}	16.1	4 – 5 (back-titration with Zn^{2+})	Acetate

3.5.2 Classification of Complexometric Titrations

Direct titration. The metal ion is titrated directly with EDTA at an appropriate pH using a suitable metal-ion indicator. Most pharmacopoeial assays, calcium gluconate, magnesium sulphate, zinc oxide, are direct titrations.

Back-titration. An excess of EDTA is added to the metal ion and the unreacted EDTA is back-titrated with a standardised solution of a metal salt (zinc, magnesium, manganese). Used when the metal ion forms its chelate slowly (Al^{3+}, Cr^{3+}) or when no good metal-ion indicator is available.

Replacement (displacement) titration. The analyte metal displaces a less strongly bound metal from its EDTA chelate; the displaced metal is then titrated. The classical example is the assay of Ca^{2+} via its displacement of Mg^{2+} from Mg-EDTA.

Indirect (alkalimetric) titration. The metal-EDTA reaction releases 2 H^{+} per metal ion; the released H^{+} is titrated with a standardised base. Used for non-titratable cations.

3.5.3 Metal-Ion (Metallochromic) Indicators

The endpoint of a direct EDTA titration is signalled by a metal-ion indicator (also called a metallochromic indicator). The indicator is a chelating dye that forms a coloured complex with the metal ion. The colour of the metal-indicator complex must differ sharply from the colour of the free indicator. The stability of the metal-indicator complex must be lower than that of the metal-EDTA chelate, so that EDTA can displace the indicator at the endpoint.

M-In (colour A) + EDTA → M-EDTA (colourless) + In (colour B)

Table 3.5 Common metallochromic indicators used in EDTA titrations.

Indicator	Metals titrated	Optimum pH	Colour change (M-In → free In)
Eriochrome Black T (EBT, Solochrome Black T)	Mg^{2+}, Zn^{2+}, Mn^{2+}, Pb^{2+}	10	Wine red → blue
Murexide (ammonium purpurate)	Ca^{2+}, Cu^{2+}, Ni^{2+}, Co^{2+}	> 11	Red → blue-violet
Xylenol orange	Pb^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Bi^{3+}	5 – 6	Red → yellow
Patton & Reeder's indicator	Ca^{2+} in presence of Mg^{2+}	12 – 13	Wine red → blue
Calmagite	Ca^{2+} / Mg^{2+} (hardness)	9 – 11	Red → blue
PAN (1-(2-pyridylazo)-2-naphthol)	Cu^{2+}, Zn^{2+}, Ni^{2+}	2 – 11	Red → yellow

3.5.4 Masking and Demasking Agents

When several metal ions are present in the same sample, an interferent must be either removed by precipitation or "masked", that is, kept tied up in a complex more stable than its EDTA chelate, so that it does not consume titrant. Selective demasking can then liberate the masked metal for sequential titration.

Table 3.6 Common masking and demasking agents in complexometric titration.

Masking agent	Masks (forms a complex with)	Notes
Potassium cyanide (KCN)	Cu^{2+}, Cd^{2+}, Hg^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Ag^{+}	Most widely used. Cannot mask Ca^{2+} or Mg^{2+}.
Triethanolamine	Fe^{3+}, Al^{3+}, Mn^{2+}	Used in the assay of Ca^{2+} in the presence of iron and aluminium.
Ammonium fluoride	Al^{3+}, Ti^{4+}, Sn^{4+}	Forms stable fluoride complexes.
Thiourea	Cu^{2+}, Hg^{2+}, Bi^{3+}	Used in EDTA assay of Zn^{2+} in zinc-copper systems.
2,3-Dimercapto-1-propanol (BAL)	Heavy metals (Hg, Pb, Bi, Cd)	Also a chelation antidote in clinical toxicology.

Masking agent	Masks (forms a complex with)	Notes
Demasking: formaldehyde	Releases CN^- from cyanide complexes	For sequential titration after KCN masking.
Demasking: chloral hydrate	Releases metal from cyanide complex	Alternative to formaldehyde.

3.5.5 Assay of Magnesium Sulphate

Magnesium sulphate heptahydrate ($MgSO_4 \cdot 7\ H_2O$, M.W. 246.47, Epsom salt) is the official IP monograph form. The assay is a direct EDTA titration at pH 10 with Eriochrome Black T as the indicator.

Procedure (IP 2026 monograph)

6. Weigh accurately about 0.20 g of magnesium sulphate; dissolve in 50 mL of distilled water.
7. Add 10 mL of ammonia-ammonium chloride buffer (pH 10) and a small quantity (about 50 mg) of EBT indicator triturated with NaCl.
8. The solution turns wine-red, indicating the formation of the Mg-EBT complex.
9. Titrate with 0.05 M disodium edetate (EDTA) until the colour changes from wine-red to clear blue.
10. Each mL of 0.05 M EDTA ≡ 12.32 mg of $MgSO_4 \cdot 7\ H_2O$.

The IP requires the substance to contain not less than 99.0 % and not more than 100.5 % on the dried basis. Indian marketed examples include $MgSO_4$ IP (Epsom salt) sachet 5 g, magnesium sulphate injection 50 % w/v (4 mEq Mg^{2+} per mL, used in eclampsia by the Pritchard or Zuspan regimen), and oral magnesium hydroxide suspension (Milk of Magnesia, Polycrol-MPS).

3.5.6 Assay of Calcium Gluconate

Calcium gluconate ($C_{12}H_{22}CaO_{14} \cdot H_2O$, M.W. 448.40) is assayed by direct EDTA titration at high pH using Patton & Reeder's indicator or hydroxynaphthol blue. The assay must be done at pH > 12 because, at pH 10, calcium and magnesium are titrated together (both react with EBT). Above pH 12, magnesium is precipitated as $Mg(OH)_2$ and only calcium remains in solution.

Procedure (IP 2026 monograph)

11. Weigh accurately about 0.5 g of calcium gluconate; dissolve in 100 mL of warm water.
12. Add 4 mL of 2 N NaOH to raise the pH above 12 (any magnesium is precipitated as $Mg(OH)_2$).
13. Add about 50 mg of Patton & Reeder's indicator triturated with NaCl. The solution turns wine-red.
14. Titrate with 0.05 M EDTA until the colour changes from wine-red to clear blue.
15. Each mL of 0.05 M EDTA ≡ 22.42 mg of calcium gluconate monohydrate.

The IP requires the substance to contain not less than 98.5 % and not more than 102.0 % of calcium D-gluconate monohydrate on the dried basis. Indian marketed examples include Calcium Sandoz IV (1 g per

10 mL ampoule, the Indian market leader since 1929), Calcium Gluconate IP tablets 500 mg, and pediatric calcium gluconate syrups.

3.6 Gravimetric Analysis

Gravimetric analysis is the oldest quantitative method of analytical chemistry and is still the absolute method against which other techniques are calibrated. The analyte is separated from the sample as a sparingly soluble precipitate (the precipitating form), the precipitate is then dried or ignited to a definite, stoichiometric weighing form, and the mass of analyte in the sample is calculated from the mass of the weighing form and the gravimetric factor.

3.6.1 Requirements of a Good Gravimetric Precipitate

- Low solubility in the precipitation medium: the loss of analyte to the supernatant must be negligible (less than 0.1 mg per 100 mL is the rule of thumb).
- Free of co-precipitated impurities: the precipitate should be readily purified by re-precipitation.
- Easy to filter and wash: coarse crystalline precipitates rather than gelatinous or colloidal forms are preferred.
- Convertible to a definite, stoichiometric weighing form by drying at 105–110 °C or by ignition at 800–1000 °C.
- High purity and high formula weight: a high formula weight reduces the relative error.

3.6.2 Eight Steps in Gravimetric Analysis

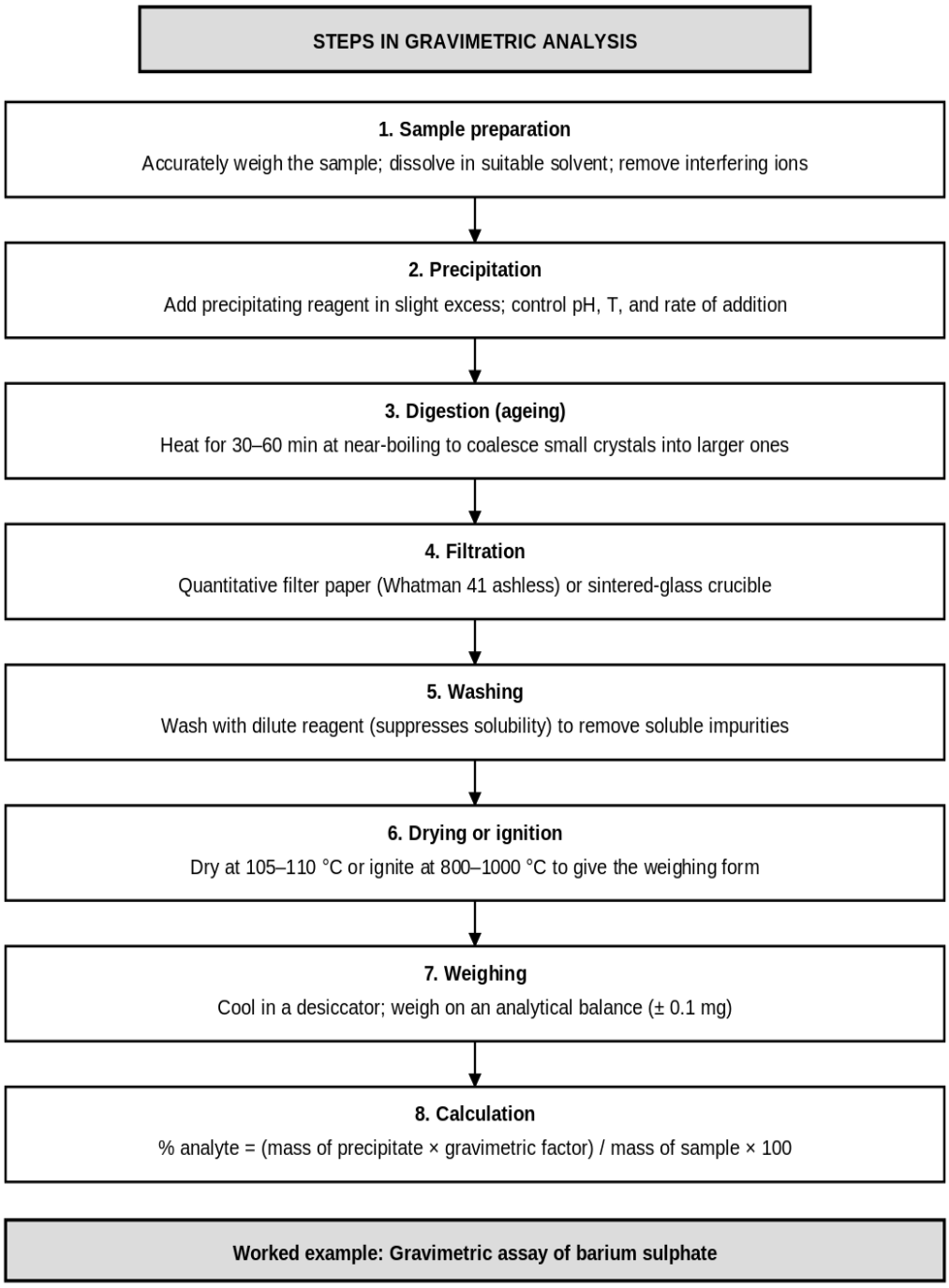

Fig. 3.3 Eight steps of a gravimetric analysis.

The procedure is divided into eight discrete steps, each of which can introduce error if performed carelessly.

Sample preparation. An accurately weighed sample is dissolved in a suitable solvent and interfering ions are removed by precipitation or masking.

Precipitation. The precipitating reagent is added slowly and with stirring, in slight excess. Temperature is controlled (usually near the boiling point of the solvent) and pH is adjusted to the optimum for the precipitate.

Digestion (ageing). The precipitate is left to stand near the precipitation temperature for 30–60 minutes. The small initial crystals dissolve and re-deposit on the larger ones (Ostwald ripening), producing a coarser, more easily filterable precipitate of higher purity.

Filtration. The aged precipitate is collected on a Whatman quantitative filter paper (ashless, grade 41 for fine, 42 for very fine, 540 for medium) or on a sintered-glass crucible if the precipitate is not to be ignited.

Washing. The precipitate is washed several times on the filter with a dilute aqueous solution that contains a common ion of the precipitate (to suppress its solubility through the common-ion effect). Peptisation is avoided.

Drying or ignition. For precipitates that are stable below 200 °C the precipitate is dried in an oven at 105–110 °C. For precipitates that need to be ignited to a stoichiometric oxide or sulphate, the filter paper and precipitate are placed in a porcelain crucible, the paper is charred and burned off, and the residue is ignited at 800–1000 °C in a muffle furnace to constant weight.

Weighing. The crucible plus precipitate is cooled to room temperature in a desiccator and weighed on an analytical balance reading to ±0.1 mg. Successive ignitions and weighings are performed until two consecutive weights agree within 0.3 mg ("constant weight").

Calculation. The mass of analyte is calculated using the gravimetric factor: % analyte in sample = (mass of precipitate × G.F.) / mass of sample × 100, where G.F. = (formula weight of analyte / formula weight of precipitate) corrected for stoichiometry.

3.6.3 Co-precipitation and Post-precipitation

Two errors of impurity are recognised. Co-precipitation is the incorporation of a foreign ion into the precipitate at the moment of precipitation; it cannot be removed by washing. Post-precipitation is the formation of a second, slow-forming precipitate on the surface of the first; it can be limited by short contact time.

Co-precipitation occurs by four mechanisms: surface adsorption (the precipitate adsorbs ions on its surface during growth), isomorphous inclusion (a foreign ion replaces a lattice ion of the precipitate), mechanical occlusion (mother liquor is trapped in pockets within the crystal as it grows), and post-deposition of a second precipitate on the surface. Errors due to co-precipitation are minimised by precipitating from dilute solution, adding the reagent slowly with stirring, ageing the precipitate at the precipitation temperature, and (where unavoidable) re-precipitating the analyte from a fresh acid solution after dissolution of the first precipitate.

Post-precipitation is the slow appearance of a second precipitate (often a co-existing analyte) on the surface of the first precipitate while it stands in contact with the mother liquor. Classical example:

precipitation of Ca^{2+} as calcium oxalate in a sample that also contains Mg^{2+}, magnesium oxalate is more soluble and precipitates much more slowly, so it crystallises on the surface of the calcium oxalate over hours. Solution: filter quickly after digestion is complete.

3.6.4 Gravimetric Assay of Barium Sulphate

The gravimetric assay of barium sulphate is the IP method for verifying the purity of pharmaceutical-grade barium sulphate used as an X-ray contrast medium (Indian brands: Micropaque, Baritop, Polibar). The principle: barium ions in the sample are precipitated with a slight excess of sulphuric acid; the barium sulphate is filtered, washed, ignited and weighed.

$$Ba^{2+} + SO_4^{2-} \rightarrow BaSO_4 \downarrow \text{ (white, very low solubility, } Ksp = 1.1 \times 10^{-10})$$

Procedure

16. Weigh accurately about 0.50 g of barium sulphate; dissolve in 20 mL of concentrated HCl by warming.
17. Dilute to 200 mL with water and heat to near boiling.
18. Add 2 mL of 10 % w/v sulphuric acid solution dropwise, with stirring, into the hot solution.
19. Continue stirring; the white precipitate of barium sulphate forms.
20. Age the precipitate by allowing it to stand on a hot plate (≈ 80 °C) for 1 hour.
21. Filter through Whatman 42 ashless filter paper.
22. Wash the precipitate with hot water until the wash water is free from chloride (test with $AgNO_3$).
23. Place the filter paper and precipitate in a porcelain crucible of known weight; char the paper without flaming on a low flame; ignite at 800 °C in a muffle furnace to constant weight.
24. Cool in a desiccator, weigh, and calculate.

Calculation: % $BaSO_4$ in sample = (mass of ignited $BaSO_4$ × 100) / mass of sample. The gravimetric factor for $BaSO_4$ as itself is 1.0000. The IP specifies that pharmaceutical barium sulphate must contain not less than 97.5 % of $BaSO_4$ and that soluble barium salts (which would be toxic) must not exceed 1 ppm.

3.7 Diazotisation Titrations

Diazotisation titration is the quantitative form of the diazotisation reaction first described by Peter Griess in 1858, the conversion of a primary aromatic amine to a diazonium salt by the action of nitrous acid in cold acidic solution. The reaction is stoichiometric, fast at 0–5 °C and goes to completion in dilute acid; it is therefore well suited to the assay of any drug that contains a primary aromatic amine group. The titrant is sodium nitrite ($NaNO_2$) solution. The technique is sometimes called sodium nitrite titration.

3.7.1 Principle

In acidic solution (excess HCl) the titrant $NaNO_2$ generates nitrous acid in situ. Nitrous acid is the electrophile that diazotises the primary aromatic amine:

$$NaNO_2 + HCl \rightarrow HNO_2 + NaCl \quad \textit{(generation of } HNO_2\textit{)}$$

$$Ar\text{-}NH_2 + HNO_2 + HCl \rightarrow Ar\text{-}N^{+}{\equiv}N \cdot Cl^{-} + 2\,H_2O \quad \textit{(diazotisation)}$$

The diazonium chloride formed is stable only at 0–5 °C; above this temperature it decomposes to a phenol with loss of nitrogen. After every molecule of the amine has reacted, the next drop of $NaNO_2$ leaves free HNO_2 in the flask, which is detected by an external indicator.

3.7.2 Critical Experimental Parameters

- Temperature: 0–5 °C in an ice bath. Above 10 °C the diazonium salt decomposes; below 0 °C the reaction is too slow.
- Strong acid concentration: 2–4 mol of HCl per mol of amine. The excess HCl stabilises the diazonium salt and prevents formation of the diazoamino coupling product.
- Reaction rate: vigorous stirring is essential because the titrant solution is added under the surface of the cold acidic amine solution to ensure quick contact.
- Titration speed: slow addition is required, with a 1–2 minute pause near the endpoint, to allow the reaction to come to completion before the next drop is added.

3.7.3 End-Point Detection

External indicator (classical). Starch-iodide paper. The first excess drop of $NaNO_2$ generates free HNO_2 in the flask. A drop of the reaction mixture is taken on a glass rod and brought into contact with a strip of starch-iodide paper. The HNO_2 oxidises I^- to I_2, which complexes with starch to give an intense blue-black colour. A blue-black ring around the touched spot signals the endpoint.

$$2\,KI + 2\,HNO_2 + 2\,HCl \rightarrow I_2 + 2\,NO + 2\,H_2O + 2\,KCl$$

$$I_2 + \textit{starch} \rightarrow \textit{blue-black complex}$$

Internal indicator (modern). A mixed indicator of tropaeolin OO and methylene blue (1:1) gives a sharp colour change at the endpoint from red-violet to blue. This avoids the inconvenience of repeated transfer to an external paper.

Potentiometric end-point. A platinum indicator electrode versus a saturated calomel reference electrode shows a sharp potential break at the endpoint; this is the most accurate method and is used in pharmaceutical quality-control laboratories.

3.7.4 Standardisation of the Sodium Nitrite Solution

A 0.1 M sodium nitrite solution is prepared by dissolving 7.5 g of $NaNO_2$ AR in water and making up to 1 L. The solution is standardised against primary-standard sulphanilamide: 0.5 g of sulphanilamide dried at 105 °C is dissolved in 50 mL of water + 20 mL of concentrated HCl, cooled to 15 °C, and titrated with the $NaNO_2$ solution to the starch-iodide endpoint. Each mL of 0.1 M $NaNO_2$ ≡ 17.22 mg of sulphanilamide.

3.7.5 Pharmaceutical Applications

All drugs containing a free primary aromatic amine group can be assayed by diazotisation. The principal categories are:

Table 3.7 Pharmaceutical primary aromatic amines assayed by diazotisation.

Drug	Class / use	Brand examples (India)
Sulphanilamide	Original sulpha; primary standard	Sulpha tablets IP (limited use today)
Sulphadiazine	Antimicrobial (silver sulphadiazine cream)	Silverex, Argicrem, Burnol-S
Sulphamethoxazole	Antimicrobial (in co-trimoxazole)	Bactrim, Septran (with trimethoprim)
Sulphacetamide	Topical ophthalmic antibacterial	Sulfacetamide eye drops 10 %, 20 %, 30 %
Dapsone (DDS)	Antileprosy, antimalarial	Dapsone IP 100 mg
Procainamide	Class IA antiarrhythmic	Pronestyl, Procanbid
Benzocaine	Topical local anaesthetic	Mucopain gel, Orajel
p-Aminobenzoic acid (PABA)	Sunscreen, B-vitamin precursor	Padimate-O cosmetics
p-Aminosalicylic acid (PAS)	Anti-tubercular	PASER, Sodium PAS IP

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UNIT IV

Gastro-intestinal Agents · Topical Agents · Dental Products · Inhalants · Antidotes · Radiopharmaceuticals

4.1 Gastro-Intestinal Agents

The gastrointestinal tract is a 9-m long muscular tube whose chemistry is at the heart of pharmaceutical practice. The pH of the gastric lumen varies from 1.5 in the fasting state to about 5 after a meal; the duodenum sits at pH 6, the jejunum at 6.5 and the colon at 7.0–7.4. Disorders of acid secretion, motility and water balance generate the indications for the three classes of inorganic gastrointestinal medicines covered in this section, acidifiers, antacids and cathartics.

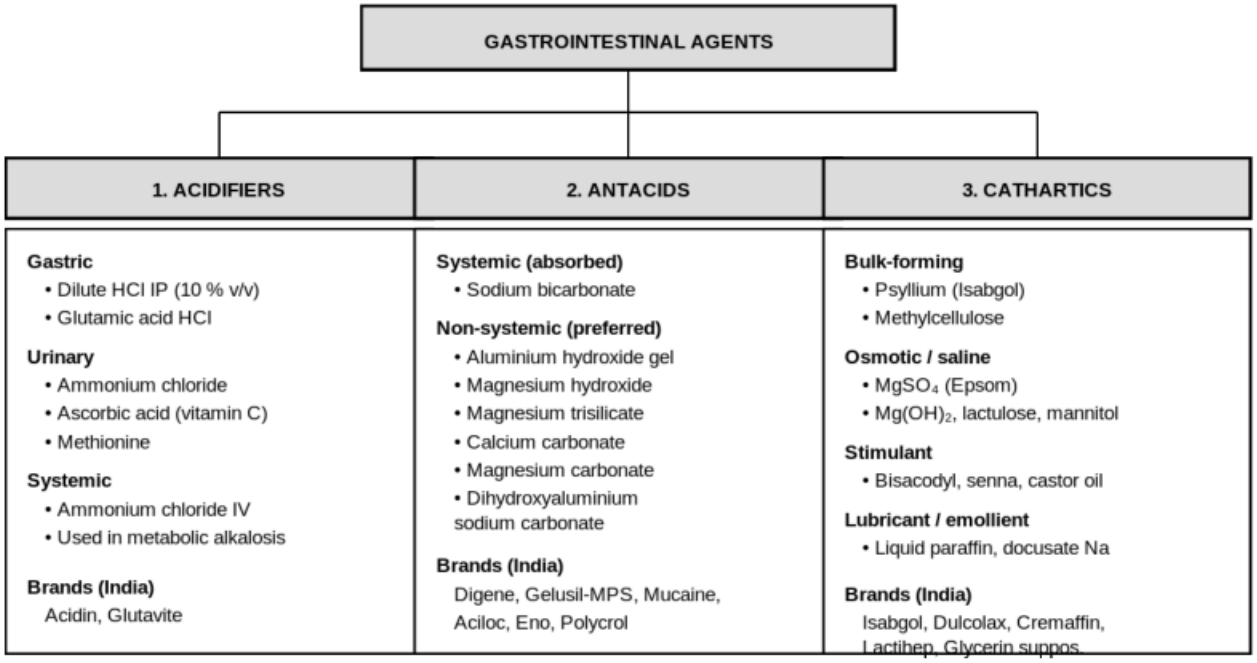

Fig. 4.1 Classification of gastro-intestinal agents.

4.2 Acidifiers

Acidifiers are agents that lower the pH of either the stomach, the urine or the systemic circulation. Three sub-types are recognised.

Gastric acidifiers. Used in the rare condition of achlorhydria (deficient secretion of gastric HCl, seen in pernicious anaemia and atrophic gastritis). Dilute hydrochloric acid IP (10 % v/v, given as 2–4 mL diluted in 50 mL of water through a glass straw to protect tooth enamel) and glutamic acid hydrochloride are the official preparations.

Urinary acidifiers. Lower the urinary pH to 5.0–5.5. They are used to dissolve and excrete certain drugs (the basic drugs such as amphetamines and quinidine become ionised at acidic urinary pH and so are not reabsorbed), to enhance the antibacterial action of methenamine (which decomposes to formaldehyde only in acid urine), to dissolve calcium phosphate or carbonate renal stones, and to acidify urine for urinary-antiseptic action. Examples, ammonium chloride 0.5–1 g four times daily, ascorbic acid 1–2 g/day, and methionine 0.5 g three times daily.

Systemic acidifiers. Reduce the alkali reserve of the body and correct metabolic alkalosis. The principal example is ammonium chloride given intravenously as a 2.14 % w/v isotonic solution. In the liver, ammonium ion is converted to urea, releasing a proton that combines with bicarbonate to produce CO_2 and water. The net effect is the removal of bicarbonate from the body and a fall in plasma pH.

$$2\ NH_4Cl + 2\ NaHCO_3 \rightarrow 2\ NaCl + (NH_2)_2CO + CO_2 + 3\ H_2O \quad \textit{(hepatic urea cycle)}$$

Indian marketed examples - Acidin tablets (glutamic acid HCl 250 mg), Glutavite, ammonium chloride USP injection.

4.3 Antacids

An antacid is a substance that neutralises gastric acid in the lumen of the stomach. Antacids are first-line therapy for transient dyspepsia, heartburn and mild reflux, and second-line therapy (alongside H_2 blockers and proton-pump inhibitors) for peptic ulcer disease and erosive oesophagitis. The ideal antacid should, (a) act quickly and last reasonably long; (b) buffer gastric pH to 4–6 rather than overshoot to alkaline values; (c) not be appreciably absorbed (so that systemic alkalosis is avoided); (d) not produce gas (CO_2 from carbonate or bicarbonate sources stretches the stomach and causes belching and even rebound acid hypersecretion); (e) not cause constipation or diarrhoea on chronic use; (f) be palatable and inexpensive. No single antacid meets every one of these criteria, so combinations are widely marketed.

4.3.1 Systemic vs Non-Systemic Antacids

Systemic antacids are absorbed into the bloodstream and can shift systemic acid-base balance. The classical example is sodium bicarbonate, which is rapid, palatable and inexpensive but causes belching from CO_2, transient systemic alkalosis on chronic high-dose use, sodium loading (50 mEq Na^+ in each 4.2 g of $NaHCO_3$ - a problem in heart failure, hypertension and renal disease), and acid rebound (the wave of HCl secreted from the parietal cell when the pH of the antrum rises). Sodium bicarbonate is still used for short-term symptomatic relief and as an effervescent component of preparations such as Eno ($NaHCO_3$ + citric acid + sodium carbonate).

Non-systemic antacids are not absorbed into the bloodstream in significant amounts. They are preferred for long-term use. The four classical members are aluminium hydroxide, magnesium hydroxide, magnesium trisilicate and calcium carbonate. Combination products, most often $Al(OH)_3$ + $Mg(OH)_2$, neutralise the constipation of the aluminium salt with the laxative effect of the magnesium salt.

4.3.2 Individual Antacids

Sodium bicarbonate ($NaHCO_3$)

A white crystalline powder, soluble 1 in 11 of water, IP M.W. 84.01. Manufactured by the Solvay (ammonia-soda) process, a hot ammoniacal brine is saturated with carbon dioxide:

$$NH_3 + CO_2 + H_2O + NaCl \rightarrow NaHCO_3 \downarrow + NH_4Cl$$

Tested for purity by liberation of CO_2 on acidification and by alkaline reaction (5 % w/v solution gives pale pink with phenolphthalein, turning deep red on heating). IP requires 99.0–100.5 % of $NaHCO_3$. Pharmaceutical uses - antacid; component of effervescent salts (Eno, Pudin Hara Pearls); intravenous correction of severe metabolic acidosis (7.5 % w/v injection); reconstitution of antineoplastic infusions that require alkaline pH; mouth-wash for stomatitis; dialysis fluid. Dose 0.3–2 g orally.

Aluminium hydroxide gel

A viscous white aqueous suspension containing 3.6–4.4 % w/w of $Al(OH)_3$ as the IP monograph form. The substance is amphoteric, it reacts with both acids and bases, and is a slow-onset antacid because the reaction with HCl is rate-limited by the dissolution of the gel particles. It binds dietary phosphate in the gut and is used as a phosphate binder in chronic kidney disease (although calcium acetate and sevelamer have largely replaced it). Side effects on chronic use include constipation, hypophosphataemia, and aluminium accumulation (encephalopathy and osteomalacia in patients with renal failure). Dose 5–10 mL of gel.

Magnesium hydroxide and magnesium carbonate

Magnesium hydroxide IP appears as a white aqueous suspension of 7–8.5 % w/w $Mg(OH)_2$ in the form known to the consumer as Milk of Magnesia. Onset is rapid; the magnesium ion produced is poorly absorbed and acts as an osmotic laxative, a useful pairing with aluminium hydroxide. Magnesium carbonate is similar; in the stomach, it generates magnesium chloride and CO_2. Dose 5–10 mL.

Calcium carbonate

A white tasteless powder of high acid-neutralising capacity (1 g neutralises about 20 mEq HCl in vitro). Risks on chronic use, hypercalcaemia, alkalosis and the milk-alkali syndrome (the classical Burnett's triad of hypercalcaemia, alkalosis and renal impairment seen in the 1920s in patients who took $NaHCO_3$ for ulcer pain together with large amounts of milk). Acid rebound (CO_2 liberation and reflex gastrin release) makes it less popular than the Al / Mg salts. Dose 0.5–1.5 g.

Magnesium trisilicate ($2\ MgO \cdot 3\ SiO_2 \cdot n\ H_2O$)

Used at 0.5–1 g per dose. In the stomach it reacts slowly with HCl, releasing colloidal silica that adheres to ulcerated mucosa and provides a mechanical barrier. The reaction yields magnesium chloride and silica:

$$2\ MgO \cdot 3\ SiO_2 + 4\ HCl \rightarrow 2\ MgCl_2 + 3\ SiO_2\downarrow + n\ H_2O$$

Dihydroxyaluminium sodium carbonate, $NaAl(OH)_2CO_3$

A combination salt designed to give both aluminium and sodium-bicarbonate-style action, with the constipating tendency of aluminium balanced by the rapid CO_2 release of the carbonate moiety.

Table 4.1 Comparison of the principal antacids used in pharmaceutical practice.

Antacid	Onset	Side effect	Indian brand examples
Sodium bicarbonate	Very fast	Belching, alkalosis, Na^+ load	Eno, Pudin Hara, $NaHCO_3$ IP injection
Calcium carbonate	Fast	Acid rebound, hypercalcaemia, constipation	Tums (international), Shelcal-500, Calcium IP
Magnesium hydroxide	Fast	Diarrhoea, hypermagnesaemia in renal failure	Milk of Magnesia, Polycrol-MPS
Aluminium hydroxide gel	Slow	Constipation, hypophosphataemia	Aludrox, Digene, Gelusil-MPS, Mucaine
Magnesium trisilicate	Slow	Renal silicate stones rarely	Trisil, Gelusil tab
Magaldrate	Fast	Mild diarrhoea	Mucaine, Riflux
Al + Mg combination	Balanced	Bowel-neutral	Digene gel, Gelusil-MPS, Acidogel

4.4 Cathartics (Laxatives)

Cathartics are agents that promote the evacuation of the bowels. They are indicated in functional constipation, in pre-operative or pre-procedural bowel preparation (colonoscopy, abdominal X-ray), in poisoning where prevention of further absorption is desired, and as adjuncts to anthelmintics. They are contraindicated in undiagnosed abdominal pain, suspected intestinal obstruction and acute abdominal inflammation. Four mechanistic classes are recognised (Figure 4.3).

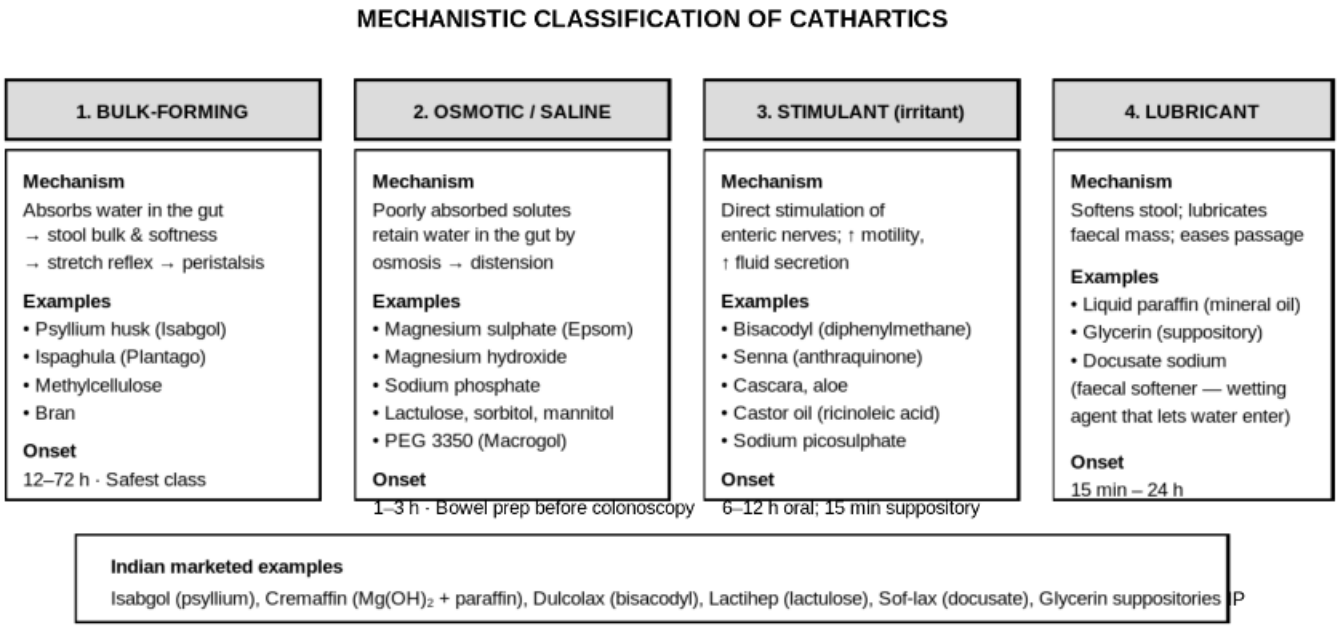

Fig. 4.2 Mechanistic classification of cathartics.

Bulk-forming laxatives. Hydrophilic colloids that absorb water in the intestinal lumen, swell to a viscous gel, and stretch the bowel wall, the stretch reflex elicits peristalsis. Onset 12–72 h. They are the safest class for long-term use and the first choice in chronic constipation. Examples, psyllium husk (Indian brand Isabgol, taken as 1–2 teaspoonfuls in a glass of water at bedtime), ispaghula (Plantago ovata), methylcellulose, sterculia, and wheat bran.

Osmotic / saline laxatives. Poorly absorbed solutes that hold water in the gut lumen by osmosis, distending the bowel and triggering peristalsis. Onset 1–3 h orally; minutes for the rectal route. Examples, magnesium sulphate (Epsom salt, 5–10 g in a glass of water on an empty stomach), magnesium hydroxide, sodium phosphate, lactulose (a non-absorbable disaccharide, also used to treat hepatic encephalopathy), sorbitol, mannitol, and polyethylene glycol 3350 (PEG, used for pre-colonoscopy bowel preparation as Macrogol or Peglec).

Stimulant (irritant) laxatives. Act directly on the enteric nervous system to increase peristalsis and reduce net water absorption. Onset 6–12 h orally; 15 min as a suppository. Members of the class include bisacodyl (Dulcolax 5 mg tablet or 10 mg suppository), the anthraquinones (senna in Senokot, cascara, aloe), castor oil (in which ricinoleic acid generated by lipase action is the active species), and sodium picosulphate. Long-term use leads to dependence ("cathartic colon") and electrolyte loss, and is discouraged.

Lubricant and emollient laxatives. Soften the stool and ease its passage. Liquid paraffin (mineral oil) is the classical lubricant; docusate sodium (an anionic wetting agent) lets water penetrate the faecal mass; glycerin suppositories provide both osmotic and lubricant effects and act within minutes. Liquid paraffin is now used much less than formerly because of the risk of lipoid pneumonia from aspiration and of interference with the absorption of fat-soluble vitamins.

4.5 Topical Agents

Topical agents are pharmaceutical preparations applied to the skin or to accessible mucous membranes. The inorganic topical agents in BP104T fall into four functional groups, protectives and adsorbents, astringents, antimicrobials, and antifungals / scabicides

4.6 Protectives and Adsorbents

Protectives form a physical barrier on the skin or mucosa and shield the underlying tissue from chemical, mechanical or microbial insult; adsorbents take up irritants, exudates and toxins by surface attraction.

Zinc oxide (ZnO) is the workhorse - a white amorphous powder used at 10–25 % w/w in calamine lotion BP, in zinc oxide ointment (15 %), in nappy-rash creams, in calamine + zinc oxide lotions for chickenpox, prickly heat and insect bites. Calamine itself is a mixture of zinc oxide and a small amount of ferric oxide (0.5 %); the iron contributes the characteristic pink colour and additional astringent action. Indian marketed examples - Calamine lotion BP, Sudocrem, Skin-Lite.

Talc (hydrated magnesium silicate, $Mg_3Si_4O_{10}(OH)_2$) is a fine inert powder used as a dusting powder (talc IP), as a lubricant in tablet making, and as a filter aid. It must be tested for the absence of asbestos. Talcum powder (talc + boric acid + zinc stearate + perfume) was at one time the universal infant nursery powder.

Kaolin (natural aluminium silicate, $Al_2Si_2O_5(OH)_4$) is used internally as an adsorbent in non-specific diarrhoea (Kaolin and pectin mixture, brand name Kaomycin) and externally as a dermatological dusting powder.

Titanium dioxide (TiO_2) is the high-refractive-index white pigment that gives sunscreens and zinc-titanium creams their physical sun-blocking property; it reflects and scatters UVA and UVB. Used at 5–25 %.

Petroleum jelly (soft white paraffin) is a semi-solid mixture of long-chain alkanes that forms an occlusive lipid film. Used in lip balms, nappy creams, ointment bases, and as a vehicle for active drugs. Indian brands, Vaseline (Hindustan Unilever), Boroline.

4.7 Astringents

Astringents precipitate the surface proteins of skin and mucosa, drawing the tissue together and reducing capillary permeability. The result is a temporary local toughening of the surface, vasoconstriction and reduction of exudate. They are used to stop minor capillary bleeding (shaving cuts), to treat haemorrhoids and pruritus, and to control profuse sweating.

Alum (potash alum, $KAl(SO_4)_2 \cdot 12\ H_2O$). White crystalline solid; used as a styptic stick for shaving cuts and as a mouth-wash for ulcerated gums. Mode of action, the aluminium ion crosslinks tissue proteins. The alum block (fitkari) is a popular traditional barbershop styptic in India.

Zinc sulphate (0.25 % solution as eye wash; 1 % lotion). Used in chronic conjunctivitis to reduce mucus production and in mild dermatological exudation.

Aluminium chloride (20 % w/v in alcohol). The most potent topical anti-perspirant; blocks the eccrine sweat ducts. Used for axillary hyperhidrosis.

Calamine (see Section 4.6, protective + astringent combined). The smell-and-feel template for all childhood skin lotions.

Tannic acid (0.5–2 % solution; used historically in burn dressings; now restricted because of hepatotoxicity from absorption).

Silver nitrate (0.5–1 % solution as a wet dressing; 10 % stick to cauterise excess granulation tissue and hypertrophic scars).

4.8 Topical Antimicrobials

Topical antimicrobials are non-selective surface germicides used as antiseptics (on living tissue) and as disinfectants (on inanimate surfaces). Five inorganic classes are pharmacopoeial.

Oxidising agents. Hydrogen peroxide (3 % w/v solution, the classical wound-cleansing antiseptic, releases oxygen on contact with catalase in tissue, producing the familiar fizz; the freed oxygen kills anaerobic bacteria and mechanically dislodges debris). Potassium permanganate (1 in 10,000 solution as Condy's lotion for the wet dressing of weeping eczema, fungal foot infections, perianal cleansing in haemorrhoids; releases nascent oxygen that oxidises bacterial cell walls). Sodium peroxide and barium peroxide are precursor industrial reagents but not used directly in pharmacy.

Halogens and halogen compounds. Elemental iodine, dissolved in 50 % alcohol with potassium iodide to keep it in solution, gives the time-honoured tincture of iodine (2 % I_2 + 2.4 % KI in 50 % v/v alcohol) - pre-operative skin preparation, minor wound disinfection. Povidone-iodine is a complex of iodine with polyvinylpyrrolidone that releases free iodine slowly on contact with tissue; 5 % and 10 % solutions are used in surgical scrubbing (Betadine, Wokadine, Pyodine). Sodium hypochlorite (Dakin's solution, 0.5 % NaOCl) is a wound-cleansing irrigant used in chronic infected wounds. Calcium hypochlorite is the bleaching powder used in water disinfection. Chlorhexidine gluconate (4 % aqueous solution as Hibiscrub or Savlon) is the surgical scrub of choice in modern operating theatres.

Heavy-metal compounds. Silver nitrate (1 % w/v ophthalmic: the historical Crede prophylaxis against gonococcal ophthalmia of the newborn; less used now because of chemical conjunctivitis). Silver sulphadiazine (Silverex, Burnol-S) is the standard topical antibacterial cream for burn wounds at 1 % w/w in a hydrophilic base. Colloidal silver, silver picrate, and metallic silver dressings (Acticoat) are used in chronic wound care. Mercurochrome (merbromine 2 %) and thiomersal (Merthiolate) were the universal childhood antiseptics of the twentieth century; both are now largely discontinued because of mercury toxicity. Yellow mercuric oxide (1 % ophthalmic ointment) is still listed in the IP for blepharitis.

Boric acid. ($B(OH)_3$, M.W. 61.83). A weakly acidic substance used at 4 % w/v in eye wash, at 3 % as a dusting powder, and at 5 % as boric acid ointment for fungal otitis externa. Reacts with skin proteins to form a soft protective film. Toxic by ingestion, so the eye wash must be clearly labelled.

Aniline dyes (historical, restricted use). Gentian violet 1 % solution for skin candidiasis; brilliant green 1 % for impetigo. Both stain skin and clothing and are now mainly of historical interest.

4.9 Antifungals, Scabicides and Pediculicides

Whitfield's ointment. 6 % benzoic acid + 3 % salicylic acid in an emulsifying ointment base. The salicylic acid is keratolytic; the benzoic acid is fungistatic. Used for tinea pedis, tinea cruris and intertrigo. Historical but still listed in the IP.

Sulphur ointment. Sulphur 10 % in white soft paraffin. Used for scabies in pregnancy and infancy, in whom permethrin and lindane are best avoided.

Sodium thiosulphate ($Na_2S_2O_3 \cdot 5\ H_2O$). 20 % w/v solution applied with a 4 % dilute hydrochloric acid follow-up, for tinea versicolor (Pityriasis versicolor). The free sulphur liberated in situ kills the Malassezia organism.

Selenium sulphide. 2.5 % shampoo (Selsun, Head & Shoulders Clinical Strength) for seborrhoeic dermatitis and tinea versicolor.

Benzyl benzoate (25 % emulsion, Ascabiol). Topical scabicide and pediculicide; applied to the whole body for 24 hours.

Permethrin (5 % cream, Permite, Scabper) and lindane (1 %, now restricted because of CNS toxicity in infants), modern scabicides; permethrin is preferred.

4.10 Dental Products

Dental products fall into three pharmacopoeial groups: anti-caries agents (fluorides), polishing agents (mild abrasives in toothpaste), and dentifrices (the formulated toothpaste itself).

4.11 Anti-Caries Agents - Fluorides

Dental caries is the demineralisation of tooth enamel by acids produced by plaque bacteria (chiefly Streptococcus mutans) from dietary carbohydrates. Fluoride, introduced systematically into dentistry by Frederick McKay (1908) and H. Trendley Dean (1942), is the single most effective agent against caries, public-water fluoridation reduces childhood caries by about 40 %. Its action is by three concurrent mechanisms.

First, fluoride drives remineralisation: in the presence of salivary Ca^{2+} and PO_4^{3-}, fluoride ions are incorporated into the growing apatite lattice, forming fluorapatite $Ca_{10}(PO_4)_6F_2$ in place of the native hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$. Second, the fluorapatite formed is less soluble, it begins to dissolve only

below pH 4.5, compared with pH 5.5 for hydroxyapatite, so enamel survives the post-prandial acid challenge for longer. Third, fluoride inhibits the glycolytic enzymes of plaque bacteria (enolase and the H^+-ATPase), reducing the amount of acid that the bacteria produce.

Fluoride compounds used in dental products

Table 4.2 Fluoride compounds used in dental products.

Compound	Formula	Concentration in product	Use
Sodium fluoride	NaF	1000–1500 ppm F^- in toothpaste; 2 % topical gel; 0.05 % mouthwash	Daily toothpaste; topical gel; mouthwash
Stannous fluoride	SnF_2	0.4 % in toothpaste (1000 ppm F^-); 8 % gel	Toothpaste; Sn^{2+} also antibacterial
Sodium monofluorophosphate (MFP)	Na_2PO_3F	0.76 % (≈ 1000 ppm F^-); up to 1500 ppm	Toothpaste; MFP releases F^- slowly on contact with phosphatase in saliva
Acidulated phosphate fluoride (APF)	1.23 % F^- in 0.1 N H_3PO_4	Professional fluoride gel (twice yearly)	Topical application in dentist's chair
Fluoride varnish	5 % NaF in resin	22 600 ppm F^-	Painted on teeth at 6-monthly visit
Silver diamine fluoride	$Ag(NH_3)_2F$	38 % w/v solution	Arrests caries in children

Risk of dental fluorosis. Ingestion of fluoride exceeding 0.05 mg F per kg body weight per day before the age of six can cause dental fluorosis, visible mottling of erupting permanent teeth. Pea-sized portion of pediatric toothpaste (≈ 0.25 g) and parental supervision of brushing are the WHO recommendations. In Indian regions with endemic fluorosis (Rajasthan, Andhra Pradesh, Telangana, parts of Karnataka, where ground-water fluoride exceeds the WHO 1.5 ppm limit), the use of fluoride toothpaste in children is restricted.

4.12 Dentifrices and Polishing Agents

A dentifrice is a substance used with a toothbrush to clean the teeth. The modern toothpaste contains six functional ingredients:

Polishing agent (abrasive, 30–50 % w/w). Mild abrasion removes plaque, food residue and surface stain without scratching enamel. Common abrasives, calcium carbonate (precipitated chalk), dicalcium phosphate dihydrate ($CaHPO_4 \cdot 2\,H_2O$), sodium bicarbonate, hydrated silica, aluminium hydroxide. RDA (radioactive dentin abrasion) below 250 is considered safe.

Fluoride source (see Section 4.11).

Detergent / foaming agent (1–2 %). Sodium lauryl sulphate is the standard.

Humectant (20–30 %). Glycerine, sorbitol or propylene glycol keeps the paste moist.

Thickener / binder (1–2 %). Sodium carboxymethyl cellulose, xanthan gum, carrageenan.

Flavour, sweetener, preservative. Peppermint or spearmint oil; saccharin sodium; methylparaben.

Indian marketed examples - Colgate Strong Teeth, Pepsodent, Closeup, Sensodyne (potassium nitrate added for tooth sensitivity), Vicco Vajradanti (herbal), Dabur Red, Patanjali Dant Kanti. The IP monograph for toothpaste prescribes maximum heavy-metal content (lead ≤ 5 ppm, arsenic ≤ 1 ppm) and microbiological limits.

4.13 Inhalants

Inhalants are pharmaceutical agents administered through the respiratory route. The inorganic inhalants of pharmaceutical importance are oxygen, carbon dioxide, nitrous oxide and the noble gas helium; the inhalational anaesthetics (halothane, isoflurane, sevoflurane, desflurane) are organic actives and are dealt with under pharmacology.

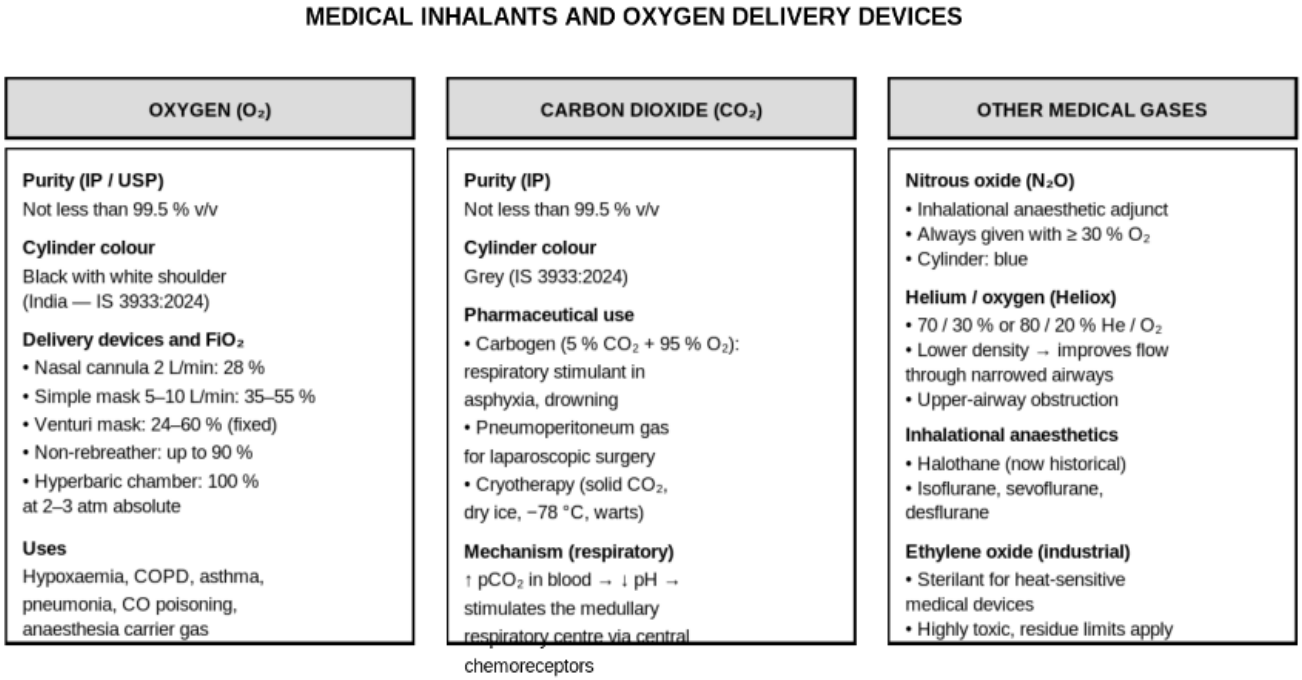

Fig. 4.3 Medical gases - composition, cylinder colour, delivery and use.

4.14 Oxygen

Oxygen is the most important medicinal gas. Therapeutic oxygen is supplied at not less than 99.5 % v/v purity (IP / USP) in a cylinder painted black with a white shoulder (the colour scheme of IS 3933:2024). The 1 L of compressed oxygen at 137 bar (cylinder pressure) expands to about 140 L at atmospheric pressure; cylinder size E (the small 4.7 L cylinder) thus carries about 660 L of usable gas.

Indications for oxygen therapy

- acute hypoxaemia (pneumonia, ARDS, asthma exacerbation, COPD exacerbation, pulmonary embolism);
- cardiac arrest and post-resuscitation care;
- carbon-monoxide poisoning (high-flow O_2 at 1 atm or hyperbaric O_2 at 2.4 atm);
- cluster headache (high-flow O_2 at 12 L/min for 15 min);
- general and regional anaesthesia (as carrier gas);
- neonatal resuscitation (with caution because of the risk of retinopathy of prematurity).

Oxygen delivery devices and their delivered fraction (FiO_2)

Table 4.3 Oxygen-delivery devices and their delivered fraction of inspired oxygen.

Device	Flow rate (L/min)	Delivered FiO_2	Notes
Nasal cannula	1–6	24–44 %	Comfortable; patient can eat and talk
Simple face mask	5–10	35–55 %	Needs ≥ 5 L/min to flush exhaled CO_2
Venturi mask (fixed-FiO_2)	4–15 (set by jet)	24, 28, 35, 40, 50, 60 %	Precise FiO_2; first choice in COPD
Non-rebreather (reservoir bag)	10–15	60–90 %	For severe hypoxia; one-way valves
Bag-valve-mask (Ambu)	12–15	Up to 100 % with reservoir	Resuscitation
Hyperbaric chamber	100 %	100 % at 2–3 ATA	CO poisoning, decompression sickness, gas gangrene

4.15 Carbon Dioxide and Carbogen

Medical-grade carbon dioxide (CO_2 IP, not less than 99.5 % v/v, grey cylinder) is used as a respiratory stimulant in carbogen (5 % CO_2 + 95 % O_2), as the insufflation gas for laparoscopic surgery, and in cryotherapy as solid CO_2 (dry ice, −78 °C, for warts, molluscum contagiosum, and skin tags). The respiratory-stimulant action arises from acidification of the cerebrospinal fluid, which excites the chemoreceptors of the medullary respiratory centre and increases both the depth and rate of breathing.

4.16 Nitrous Oxide and Helium

Nitrous oxide (N_2O, "laughing gas", blue cylinder) is an inhalational analgesic and anaesthetic-adjunct. A 50:50 mixture with oxygen (Entonox) is widely used for labour analgesia and minor surgical procedures.

Nitrous oxide must always be given with at least 30 % oxygen to prevent hypoxic injury. Chronic abuse depletes vitamin B_{12} and produces a peripheral neuropathy.

Helium is supplied as a 70:30 or 80:20 He:O_2 mixture (Heliox) for severe upper-airway obstruction; the lower density of the gas mixture reduces turbulent resistance to flow through narrowed airways.

4.17 Respiratory Stimulants

Respiratory stimulants (analeptics) are drugs that increase the depth and rate of breathing. The three categories are physical, inhalational and pharmacological.

Inhalational - Carbogen. 5 % CO_2 in 95 % O_2. The earliest analeptic, used in carbon-monoxide poisoning, gas asphyxia and post-anaesthetic respiratory depression. Carbogen has been displaced by intravenous doxapram in most modern settings.

Inhalational - Ammonia inhalation. Aromatic ammonia spirit IP (10 % w/v ammonia in 90 % alcohol, perfumed with lemon oil), the smelling-salts of nineteenth-century pharmacy. A few drops on a handkerchief held near the nostrils produce reflex stimulation of breathing through irritation of nasal sensory endings. Used for syncope.

Pharmacological - Doxapram. A synthetic central analeptic given by intravenous infusion (1–4 mg/kg/h) for acute respiratory failure that does not warrant ventilation. Mechanism, direct stimulation of the medullary respiratory centre at low doses, with stimulation of peripheral carotid-body chemoreceptors at high doses.

Pharmacological - Caffeine (citrated). Used in apnoea of prematurity; 20 mg/kg IV loading dose followed by 5–10 mg/kg/day maintenance.

Pharmacological - Ammonium carbonate. $(NH_4)_2CO_3$; mildly emetic and reflexly respiratory-stimulant; used in the early twentieth century in cough syrups but now of mainly historical interest.

4.18 Antidotes

An antidote is a substance that opposes the effects of a poison either by chemical, physiological, pharmacological or physical action. Antidotes are classified into six functional groups; a single poison may have more than one antidote available, and a single antidote may be useful against more than one poison.

4.19 Chelating Agents (Heavy-Metal Antidotes)

Dimercaprol (British Anti-Lewisite, BAL; 2,3-dimercapto-1-propanol). Developed at Oxford during World War II as an antidote to the arsenical chemical weapon Lewisite. It is now used for acute arsenic, mercury, gold and lead poisoning. The two sulfhydryl groups bind the heavy metal in a stable five-membered chelate ring that is excreted in the urine. Dose, 3 mg/kg deep intramuscular (the only practical route, since the substance is oil-soluble) every 4 hours for 2 days, then every 6 hours.

Calcium disodium edetate ($CaNa_2$-EDTA). The first-line antidote for symptomatic acute lead poisoning. Given intravenously at 1500 mg/m²/day; the calcium ion of the chelator is displaced by the lead ion, and the lead-edetate complex is excreted unchanged in the urine. Not used orally (poor absorption; mucosal toxicity).

Succimer (DMSA; meso-2,3-dimercaptosuccinic acid). An oral chelator approved by the FDA in 1991 for childhood lead poisoning. Dose, 10 mg/kg every 8 hours for 5 days, then 10 mg/kg every 12 hours for 14 days. Less toxic than dimercaprol; effective against lead, arsenic, mercury and cadmium.

Penicillamine (D-penicillamine). An oral copper chelator and the long-term treatment of Wilson's disease (hepato-lenticular degeneration). Dose 1–1.5 g/day. Indian brand: Distamine.

Deferoxamine and deferiprone. Iron chelators. Deferoxamine is given by IV or SC infusion for acute iron poisoning and chronic transfusional iron overload (thalassaemia major); deferiprone is given orally. Iron forms a stable octahedral complex with deferoxamine that is excreted as the rust-coloured ferrioxamine in the urine. Indian brands, Desferal (deferoxamine), Kelfer (deferiprone).

4.20 Universal and Symptomatic Antidotes

Universal antidote (historical). A mixture of activated charcoal 2 parts + magnesium oxide 1 part + tannic acid 1 part. The charcoal was meant to adsorb organic poisons, the magnesium oxide to neutralise acids and the tannic acid to precipitate alkaloids. Numerous studies in the 1960s showed that the magnesium oxide and tannic acid actually interfere with each other and with the adsorption of poisons on activated charcoal. The mixture is now obsolete, activated charcoal alone is used.

Activated charcoal. The first-line oral antidote in most acute poisonings within 1 hour of ingestion. The standard dose is 50–100 g for an adult and 1 g/kg (10–25 g) for a child, given as a slurry in 200 mL of water. The high surface area of activated charcoal (800–1200 m² per g) non-specifically adsorbs almost every drug or toxin into its pore system. Multiple-dose activated charcoal (25 g every 4 hours) is useful for drugs with enterohepatic recirculation, phenobarbital, carbamazepine, dapsone, quinine and theophylline. Activated charcoal does NOT bind iron, lithium, alcohols, acids, alkalis, hydrocarbons or cyanide.

Sodium nitrite and sodium thiosulphate (cyanide antidote kit). Cyanide ion blocks mitochondrial cytochrome oxidase. Sodium nitrite (300 mg IV slowly) converts a fraction of haemoglobin to methaemoglobin; the methaemoglobin then sequesters the cyanide as cyanmethaemoglobin. Sodium thiosulphate (12.5 g IV) then provides the sulphur substrate for hepatic rhodanese, which converts cyanide to the relatively non-toxic thiocyanate excreted in urine. Hydroxycobalamin (5 g IV, Cyanokit) is a modern alternative, vitamin B_{12}a binds cyanide to form cyanocobalamin (vitamin B_{12}), which is excreted in the urine.

Receptor antagonists. Naloxone (0.4–2 mg IV) for opioid overdose; flumazenil (0.2 mg IV, repeated to 1 mg) for benzodiazepine overdose; atropine (2 mg IV every 5 min) plus pralidoxime (1 g IV) for organophosphate poisoning; vitamin K_1 (10 mg IV) for warfarin overdose; protamine sulphate (1 mg per 100 IU of heparin) for heparin overdose.

Specific metabolic antidotes. N-acetylcysteine 150 mg/kg loading then maintenance for paracetamol; ethanol or fomepizole infusion for methanol and ethylene glycol; calcium gluconate IV for hydrofluoric-acid burns, calcium-channel-blocker overdose and severe hypocalcaemia.

Table 4.4 Selected poisons and their specific antidotes.

Poison	Specific antidote	Mechanism
Acetaminophen (paracetamol)	N-Acetylcysteine	Replenishes hepatic glutathione
Iron salts	Deferoxamine	Chelation; excreted in urine
Lead (acute)	$CaNa_2$-EDTA + dimercaprol	Chelation
Lead (chronic, children)	Succimer (DMSA, oral)	Chelation
Arsenic, mercury, gold	Dimercaprol (BAL, IM)	Chelation via –SH groups
Copper (Wilson disease)	D-Penicillamine	Chelation; oral
Cyanide	$NaNO_2$ + $Na_2S_2O_3$ (or hydroxycobalamin)	Forms metHb / thiocyanate / vitamin B_{12}
Methanol, ethylene glycol	Fomepizole or ethanol	Blocks alcohol dehydrogenase
Opioids	Naloxone	μ-receptor antagonist
Benzodiazepines	Flumazenil	GABA-A allosteric antagonist
Organophosphates	Atropine + pralidoxime	mAChR block + AChE reactivation
Warfarin	Vitamin K_1 ± FFP	Restores clotting-factor synthesis
β-blocker overdose	Glucagon	Activates cardiac adenylate cyclase
Digoxin	Digoxin-specific Fab (Digibind)	Antibody binding
Snake bite (Indian "big four")	Polyvalent ASV IP	Antibody binding of venom toxins

4.21 Radiopharmaceuticals

A radiopharmaceutical is a medicinal preparation containing a radionuclide, used either diagnostically (as a tracer to image organs and processes) or therapeutically (to deliver radiation to diseased tissue). Diagnostic radiopharmaceuticals account for about 95 % of nuclear-medicine procedures world-wide; the majority of these use the metastable isotope ^{99m}Tc, which is supplied to nuclear-medicine departments by the elegant ^{99}Mo/^{99m}Tc generator system.

4.22 Radioactivity - Brief Recap

Radioactivity, discovered by Becquerel in 1896 in the uranium salts of his Paris laboratory, is the spontaneous disintegration of an unstable nucleus with the emission of particulate or electromagnetic

radiation. Three categories of radiation, classified by Rutherford on the basis of their penetration through aluminium foil and their behaviour in electric and magnetic fields, are recognised.

Alpha (α) radiation. Helium-4 nuclei ($^{4}_{2}\mathrm{He}$) emitted by heavy radionuclides such as $^{238}\mathrm{U}$, $^{226}\mathrm{Ra}$, $^{210}\mathrm{Po}$. Travel a few centimetres in air; stopped by a sheet of paper or by the dead surface layer of skin. High linear energy transfer (LET), dangerous if ingested or inhaled (radon, polonium).

Beta (β) radiation. High-energy electrons (β^-) or positrons (β^+) emitted from the nucleus when a neutron converts to a proton (or vice versa). Travel several metres in air; penetrate skin to about 1 cm. Stopped by a few mm of aluminium.

Gamma (γ) radiation. Electromagnetic photons of high energy emitted by an excited nucleus on returning to its ground state. Highly penetrating; require centimetres of lead or metres of concrete for shielding. The diagnostic workhorse, almost all nuclear-medicine imaging uses γ emitters.

4.23 Units of Radioactivity

Five quantities are commonly measured, with both an SI unit and a traditional CGS unit for each.

Table 4.5 Quantities and units used in radioactivity measurement.

Quantity	Definition	SI unit	Traditional unit	Conversion
Activity	Disintegrations per second	Becquerel (Bq) = 1 dps	Curie (Ci)	1 Ci = 3.7×10^{10} Bq = 37 GBq
Exposure	Ionisation produced in air by X- or γ-rays	Coulomb per kg of air	Röntgen (R)	1 R = 2.58×10^{-4} C kg^{-1}
Absorbed dose	Energy deposited per kg of tissue	Gray (Gy) = 1 J kg^{-1}	rad	1 Gy = 100 rad
Equivalent dose	Absorbed dose × radiation weighting factor wR	Sievert (Sv)	rem	1 Sv = 100 rem; wR = 1 for X, γ, β; 20 for α
Half-life (T½)	Time for activity to fall to half	s, min, h, day, year		$A(t) = A_0 \cdot (½)^{(t/T½)}$

4.24 The ^{99}Mo / ^{99m}Tc Generator

The mainstay of routine nuclear-medicine imaging is $^{99m}\mathrm{Tc}$, the metastable isomer of technetium-99 with a 6.0066 hour half-life and a 140 keV γ emission that is ideally suited to the gamma camera. Its supply is solved elegantly by the so-called Mo/Tc cow, a small column of alumina (Al_2O_3) onto which the parent $^{99}MoO_4^{2-}$ is loaded. ^{99}Mo (T½ = 65.94 h) decays by β^- emission to ^{99m}Tc, which is daily eluted from the column as sodium pertechnetate $^{99m}TcO_4^-$ in sterile saline. The pertechnetate is then reduced (with stannous chloride) and combined with a ligand kit (MDP, MIBI, DTPA, MAG3, HMPAO) to produce the desired radiopharmaceutical.

4.25 Diagnostic Radiopharmaceuticals

Table 4.6 Common diagnostic radiopharmaceuticals.

Radionuclide	Half-life	Decay mode	Clinical use
^{99m}Tc-pertechnetate	6.01 h	γ 140 keV	Thyroid scan; Meckel's diverticulum
^{99m}Tc-MDP / HDP	6.01 h	γ 140 keV	Bone scan (skeletal metastases)
^{99m}Tc-MIBI (sestamibi)	6.01 h	γ 140 keV	Myocardial perfusion; parathyroid
^{99m}Tc-DTPA	6.01 h	γ 140 keV	Renal glomerular filtration
^{99m}Tc-MAG3	6.01 h	γ 140 keV	Renal tubular function
^{131}I-sodium iodide	8.02 d	β^- 0.61 MeV + γ 364 keV	Thyroid uptake scan; thyroid CA therapy
^{123}I-sodium iodide	13.2 h	γ 159 keV	Thyroid scan (preferred over ^{131}I)
^{18}F-FDG	109.8 min	β^+	PET - tumour, brain, cardiac viability
^{67}Ga-citrate	78 h	γ 93, 184, 300 keV	Inflammation, lymphoma imaging
^{201}Tl-chloride	73 h	γ 70–80 keV	Myocardial perfusion (older)

4.26 Therapeutic Radiopharmaceuticals

Table 4.7 Common therapeutic radiopharmaceuticals.

Radionuclide	Half-life	Indication	Mechanism
^{131}I-sodium iodide	8.02 d	Hyperthyroidism; differentiated thyroid carcinoma	β^- destroys thyroid tissue
^{32}P-sodium phosphate	14.3 d	Polycythaemia vera; CML	β^- destroys bone-marrow cells
^{89}Sr-chloride (Metastron)	50.5 d	Painful skeletal metastases	β^- in osteoblastic deposits
^{90}Y-microspheres (SIR-Spheres)	64.1 h	Liver tumours	Intra-arterial β^- brachytherapy
^{177}Lu-DOTATATE	6.65 d	Neuro-endocrine tumours	Peptide-receptor radionuclide therapy

Radionuclide	Half-life	Indication	Mechanism
^{223}Ra-dichloride (Xofigo)	11.4 d	Castration-resistant prostate cancer, bone mets	α-particle radiotherapy
^{125}I-seeds	59.4 d	Prostate brachytherapy	Permanent low-dose-rate implant
^{60}Co (teletherapy)	5.27 y	External-beam radiotherapy	γ 1.17 + 1.33 MeV
^{14}C	5730 y	Research tracer; ^{14}C-urea breath test for H. pylori	β^- low energy

4.27 Storage, Handling and Disposal

Radioactive materials are regulated in India by the Atomic Energy Regulatory Board (AERB), under the Atomic Energy Act, 1962. The principal precautions for the pharmacist are summarised below.

- Source is never handled with bare hands: long-handled tongs, forceps and remote manipulators are used.
- Sources are stored in shielded lead containers (γ emitters) or in thick-walled Perspex / aluminium containers (β emitters); α-emitters are sealed in glass or metal capsules.
- Each container carries the internationally recognised radiation trefoil and a radio-active label stating the radionuclide, activity, calibration date and form.
- The working area is fitted with stainless-steel benches, the floor is non-porous and easily decontaminated, and the air is exhausted through HEPA-filtered fume hoods.
- Personnel wear thermo-luminescent dosimeter (TLD) badges and a pocket dosimeter; eating, drinking, smoking and applying cosmetics inside the laboratory are strictly forbidden.
- Radioactive waste is segregated into short-lived (stored to decay) and long-lived (transferred to the centralised radioactive-waste facility of BRIT / NPCIL).
- Annual occupational dose limit is 20 mSv averaged over 5 years (ICRP, adopted by AERB); the limit for members of the public is 1 mSv per year.

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UNIT V

Expectorants · Emetics · Haematinics · Poisons & Antidotes · Electrolytes used in Replacement Therapy

5.1 Expectorants

Cough is a protective reflex that clears the lower respiratory tract of mucus, foreign material and irritants. The drugs prescribed for cough fall into two broad groups, antitussives, which suppress an unproductive cough by acting on the medullary cough centre or the peripheral receptors, and expectorants, which transform a dry, unproductive cough into a wet, productive one by altering the rheology and the volume of bronchial secretions. The pharmacopoeial expectorants are inorganic salts (potassium iodide, ammonium chloride, ammonium carbonate) and a small set of organic actives (terpin hydrate, guaifenesin, vasaka and other plant glycosides).

5.2 Mechanism of Expectorant Action

Reflex (gastric-vagal) expectorants. Drugs in this class irritate the gastric mucosa. The irritation generates afferent vagal impulses that reach the medullary vomiting centre; from the vomiting centre, efferent fibres travel through the vagus to the bronchial mucous glands, where they trigger an outpouring of a watery secretion. The result, the gel layer overlying the mucosa is diluted, the cilia of the columnar epithelium move it upwards more efficiently, and the patient can cough it up. Ammonium chloride and ammonium carbonate act by this mechanism.

Sedative / direct expectorants. Drugs in this class are absorbed in the small intestine, distributed in the body, and partially excreted by the bronchial mucous glands. The local action on the gland, and not the gastric reflex, is what stimulates secretion. Potassium iodide, guaifenesin and terpin hydrate act by this mechanism.

Mucolytics - adjuvants rather than expectorants. Mucolytic drugs do not increase secretion; they cleave the disulphide bonds of mucus glycoproteins, reducing viscosity. The classical agents are bromhexine, ambroxol (a metabolite of bromhexine) and N-acetylcysteine. They are listed here for completeness and are usually combined with expectorants in formulated cough syrups.

5.3 Principal Inorganic Expectorants

5.3.1 Potassium iodide (KI)

A white crystalline solid, freely soluble in water (1 in 0.7), M.W. 166.00. The IP monograph requires not less than 99.0 % of KI on the dried basis. Industrially prepared by reacting iodine with hot KOH followed by reduction of the iodate intermediate with charcoal (see Unit I, Section 1.11). Tested for free iodine, sulphate, thiosulphate, heavy metals and arsenic.

Pharmaceutical uses. (a) Expectorant - 300 mg three or four times daily in a flavoured aqueous solution (saturated solution of potassium iodide, SSKI, contains 1 g KI per mL); KI stimulates secretion of bronchial fluid directly. (b) Anti-thyroid - Lugol's iodine (5 % I_2 + 10 % KI) before thyroidectomy, to shrink the gland and reduce vascularity. (c) Anti-fungal - adjunct in cutaneous sporotrichosis. (d) Radioprotection - to saturate the thyroid against radioactive iodine in nuclear accidents (130 mg single dose for an adult). Indian marketed examples - KI is a component of cough syrups such as Coscopin Plus and Tedykoff.

5.3.2 Ammonium chloride (NH_4Cl)

White, crystalline, hygroscopic powder; freely soluble in water (1 in 3); M.W. 53.49. IP monograph requires not less than 99.5 % of NH_4Cl on the dried basis. Prepared by the Solvay process, the by-product NH_4Cl is collected from the ammoniacal brine after sodium bicarbonate precipitation.

Pharmaceutical uses. (a) Expectorant: 300–600 mg three or four times daily; mild gastric irritation reflexly stimulates the bronchial glands. (b) Urinary acidifier, 0.5–1 g three or four times daily. (c) Systemic acidifier, 2.14 % w/v isotonic injection in metabolic alkalosis. Indian cough-syrup brands containing ammonium chloride, Benadryl Expectorant (ammonium chloride 138 mg + diphenhydramine 14 mg + sodium citrate 57 mg per 5 mL), Ascoril Expectorant (NH_4Cl + guaifenesin + bromhexine + salbutamol), Glycodin Cough Syrup, Cofdex, Tossex.

5.3.3 Ammonium carbonate, $(NH_4)_2CO_3 \cdot NH_2CO_2NH_4$

White crystalline solid that releases ammonia on standing in air. Aromatic ammonia spirit (10 % ammonium carbonate in 90 % alcohol with aromatic oils) is the smelling-salts of the Victorian household. As an expectorant it has been displaced by guaifenesin in modern formulations.

5.3.4 Antimony potassium tartrate (tartar emetic), $K_2Sb_2(C_4H_2O_6)_2$

A white, crystalline, water-soluble solid. In a very small dose (1–8 mg, three times daily) it is a weak expectorant, it mildly irritates the gastric mucosa and gives rise to reflex bronchial secretion. At larger doses (30 mg or above) it is a powerful emetic, and at toxic doses (130 mg has been fatal) it produces cardiac arrhythmias and gastrointestinal haemorrhage. Tartar emetic has been almost entirely replaced in modern practice, it was used historically in the treatment of schistosomiasis and visceral leishmaniasis (kala-azar) before pentavalent antimonials and miltefosine took over.

Table 5.1 Expectorants used in pharmaceutical practice with Indian marketed examples.

Drug	Type	Adult dose	Indian brand examples
Ammonium chloride	Reflex (gastric)	300–600 mg × 3–4 / day	Benadryl Exp, Ascoril Exp, Cofdex, Glycodin
Ammonium carbonate	Reflex	300 mg × 3 / day	Liquor ammonia aromatic IP
Potassium iodide	Direct (bronchial)	300 mg × 3 / day; SSKI	Coscopin Plus, Tedykoff (component)

Drug	Type	Adult dose	Indian brand examples
Antimony potassium tartrate	Reflex (mild): emetic at higher doses	1–8 mg	Historical; Liquor antimonialis (IP)
Sodium citrate	Reflex	60 mg × 3 / day	In Benadryl Exp (alkaline pH supports KI / NH_4Cl action)
Terpin hydrate	Direct	85–200 mg × 3 / day	Terpin & Cydil; Tospro
Guaifenesin (modern)	Direct	100–400 mg × 3–4 / day	Asthalin Exp, Mucinex; in most Indian cough syrups
Bromhexine / ambroxol (mucolytic)	Direct mucolytic	8 mg × 3 / day; 30 mg × 3 / day	Mucolite, Mucinac (NAC)

5.4 Emetics

An emetic is a drug that induces vomiting. Emesis is a coordinated reflex involving the medullary vomiting centre (in the lateral reticular formation), the chemoreceptor trigger zone (CTZ, area postrema in the floor of the fourth ventricle, outside the blood-brain barrier and so accessible to humoral signals), the vestibular apparatus, and afferent inputs from the pharynx, stomach and intestines. The clinical role of emetic drugs has narrowed sharply since the 1990s; today, induction of vomiting is no longer first-line in poisoned patients, where activated charcoal, supportive care and specific antidotes are preferred. Emetic agents retain a role in veterinary practice and in selected human poisonings where the patient is alert and the ingested substance is recent and non-corrosive.

5.5 Classification of Emetics

Centrally acting emetics. Act on the chemoreceptor trigger zone (CTZ). The classical drug is apomorphine, a dopamine D_2-receptor agonist; injected subcutaneously at 6 mg, it produces vomiting within 5 minutes. Apomorphine itself is now rarely used in human poisoning because of CNS depression at higher doses; it has been largely replaced by activated charcoal. Cytotoxic drugs, opioids and digoxin produce emesis as an unwanted effect by the same central mechanism, and require central antiemetics for control.

Peripherally acting emetics. Irritate the gastric or duodenal mucosa, generating vagal afferent signals to the vomiting centre. Examples, copper sulphate (300 mg in 30 mL of warm water), zinc sulphate (0.6–2 g), hypertonic sodium chloride (15 g in 200 mL water, risk of hypernatraemia, no longer recommended), mustard water (1 tablespoon of mustard powder in a glass of water, a household remedy). Onset is 10–15 minutes after ingestion.

Both centrally and peripherally acting (mixed) emetics. Ipecacuanha syrup IP is the classical example. It is prepared from the roots of Cephaelis ipecacuanha and contains the alkaloids emetine and cephaeline;

these act both on the CTZ (central) and on the gastric mucosa (peripheral). Dose 15 mL in 250 mL of warm water, followed by additional fluid; vomiting occurs in 15–30 minutes. Ipecac was the world-wide standard for home treatment of childhood poisoning from 1960s to 1990s; American Academy of Pediatrics withdrew the recommendation in 2003 after evidence accumulated that emesis did not improve outcome but did increase aspiration risk.

5.6 Indications and Contraindications of Induced Emesis

The indications for emetic use today are limited.

- A small subset of recently ingested oral poisonings in alert, conscious patients (within 30–60 minutes) when activated charcoal is unavailable.
- Veterinary practice - apomorphine in dogs and cats for plant poisoning, chocolate ingestion.
- Research - induction of emesis in pharmacological screening of new antiemetic agents.

The contraindications are absolute in modern practice.

- Corrosive (strong acid or alkali) ingestion: vomiting causes re-exposure of the oesophagus to the corrosive substance.
- Petroleum-distillate ingestion (kerosene, paint thinner, naphtha), risk of aspiration pneumonitis with severe lipoid pneumonia.
- Drowsy, comatose, convulsing or unconscious patient: risk of aspiration of vomit into the airway.
- Children below 6 months of age; pregnancy; severe cardiac disease.
- Patients on emetic-inducing drugs (cytotoxics): additive risk.

5.7 Haematinics

A haematinic is an agent that increases haemoglobin content or red-cell production. The three biological raw materials for erythropoiesis are iron (for haem), vitamin B_{12} and folic acid (for DNA synthesis during mitosis). Deficiency of any of these produces anaemia. Iron deficiency anaemia is the commonest nutritional deficiency in the world; the WHO and the Government of India National Family Health Survey (NFHS-5, 2019–21) recorded an anaemia prevalence of 67 % among Indian children under five and 57 % in non-pregnant women aged 15–49.

5.8 Iron Compounds

Iron supplements are subdivided by route of administration into oral and parenteral preparations.

5.8.1 Oral iron preparations

Oral iron is the first-line therapy of uncomplicated iron-deficiency anaemia. The therapeutic target is 100–200 mg of elemental iron per day in three divided doses, given on an empty stomach with a glass of water

and (where possible) with 200 mg of vitamin C to enhance absorption. Treatment is continued for 3–6 months after the haemoglobin has normalised, to replenish body iron stores. Side effects (nausea, epigastric pain, constipation, dark stools) are dose-related and improve when iron is taken with food (at the cost of reduced absorption).

Table 5.2 Oral iron preparations with their elemental iron content and Indian marketed examples.

Salt	Molecular formula	% elemental iron	Dose strength of tablet	Indian brand examples
Ferrous sulphate	$FeSO_4 \cdot 7\ H_2O$	20 %	200 mg salt = 65 mg Fe	Fefol-Z, Imferon, Feronia
Ferrous gluconate	$C_{12}H_{22}FeO_{14} \cdot 2\ H_2O$	12 %	300 mg salt = 35 mg Fe	Glucfer, Fergon
Ferrous fumarate	$C_4H_2FeO_4$	33 %	200 mg salt = 65 mg Fe	Livogen, Dexorange, Heptafur
Ferrous ascorbate		11 %	100 mg salt = 11 mg Fe	Orofer XT, Autrin
Ferric ammonium citrate	$C_6H_8FeNO_7 \cdot xNH_3$	16.5 %	Liquid: 80 mg Fe per 5 mL	Tonoferon, Hemfer-XT syrup
Carbonyl iron	Elemental Fe (1–5 μm)	98 %	50–100 mg Fe per tablet	Ferinject (oral), Tonact
Iron polymaltose (IPC)	Fe(III)-polymaltose	variable	100 mg Fe per tablet	Mumfer, Ferium-XT

Ferrous sulphate - IP monograph

Empirical formula $FeSO_4 \cdot 7\ H_2O$; M.W. 278.02. Bluish-green crystals; soluble 1 in 1.5 of water; freshly prepared aqueous solution gives the characteristic Fe^{2+} tests with potassium ferricyanide (blue colour) and with sulphate reagents (turbidity with $BaCl_2$). The IP requires the substance to contain not less than 98.0 % and not more than 105.0 % of $FeSO_4 \cdot 7\ H_2O$. Prepared industrially by the action of dilute sulphuric acid on iron filings or scrap iron:

$$Fe + H_2SO_4 \rightarrow FeSO_4 + H_2\uparrow$$

The solution is filtered, evaporated, and crystallised. Storage in a tightly closed container with low humidity is essential because the salt readily oxidises in air to a yellow-brown ferric basic sulphate that is not absorbed:

$$4\ FeSO_4 + O_2 + 2\ H_2O \rightarrow 2\ Fe_2(SO_4)_3 \cdot xH_2O + 2\ Fe(OH)_3$$

Ferrous gluconate - IP monograph

Empirical formula $C_{12}H_{22}FeO_{14} \cdot 2\ H_2O$; M.W. 482.17. Greenish-yellow powder; soluble in hot water; insoluble in alcohol. IP requires not less than 95.0 % and not more than 102.0 % of the dihydrate on the

dried basis. Better tolerated than ferrous sulphate because the gluconate anion is less astringent. Used at 300–600 mg three times daily, equivalent to 35–70 mg elemental Fe.

5.8.2 Parenteral iron preparations

Parenteral iron is indicated when oral iron has failed or is intolerable, in chronic kidney disease and in severe anaemia of late pregnancy. The total dose required to replenish the iron deficit is calculated by the Ganzoni equation:

$$\text{Total iron deficit (mg)} = \text{body weight (kg)} \times (\text{target Hb} - \text{actual Hb})\ (\text{g/dL}) \times 2.4 + 500$$

The +500 mg accounts for body iron stores in adults above 35 kg.

Table 5.3 Parenteral iron preparations.

Preparation	Strength	Route	Maximum single dose	Indian brands
Iron dextran	50 mg Fe per mL	Deep IM (Z-track) or slow IV	100 mg/day IM; total-dose IV	Imferon, Imferon-FA
Iron sucrose	20 mg Fe per mL	Slow IV (over 15 min) or infusion	200 mg per dose (× 2–3 / week)	Venofer, Orofer-S, Cosmofer
Ferric carboxymaltose (FCM)	50 mg Fe per mL	Slow IV (over 15 min)	1000 mg per single infusion	Encicarb, Ferinject, FCM-50
Iron isomaltoside	100 mg Fe per mL	Slow IV infusion	20 mg/kg per infusion	Monofer
Ferric gluconate	12.5 mg Fe per mL	Slow IV	125 mg per dose	Ferrlecit

Iron dextran carries a 1 % risk of anaphylaxis and requires a test dose of 25 mg over 5 minutes followed by 30 minutes of observation. Newer ferric carboxymaltose carries a much lower risk, allows 1000 mg to be given in a single 15-minute infusion, and is now the most widely used parenteral iron in Indian hospital practice.

5.8.3 Iron Absorption and Incorporation into Haemoglobin

Dietary iron exists in two forms - haem iron (from meat, fish, liver; absorbed 15–35 %) and non-haem iron (from cereals, pulses and leafy vegetables; absorbed 2–20 %). At the brush border of the duodenum, Fe^{3+} is reduced to Fe^{2+} by the membrane reductase duodenal cytochrome b (DcytB), then transported into the enterocyte by DMT1 (divalent metal transporter-1). Once inside the enterocyte, iron is either stored as ferritin (for excretion when the cell is shed) or exported across the basolateral membrane via ferroportin and oxidised to Fe^{3+} by hephaestin for binding to plasma transferrin. Hepcidin, the master regulator, binds ferroportin and triggers its degradation; high hepcidin (inflammation) → low iron absorption. Transferrin then delivers iron to the erythroid bone marrow via transferrin-receptor 1, where ferrochelatase inserts Fe^{2+} into the protoporphyrin IX ring to give haem. Four haem groups combine with four globin chains (two α and two β in adult Hb) to give the $\alpha_2\beta_2$ tetramer of haemoglobin A. The body of a 70 kg adult contains about 3.5 g of iron - 65 % in haemoglobin, 30 % in storage as ferritin and haemosiderin, 4 % in myoglobin, and less than 1 % in enzymes and transferrin.

5.9 Maturation Factors - Vitamin B_{12} and Folic Acid

Vitamin B_{12} (cobalamin) and folic acid are essential coenzymes for DNA synthesis. Deficiency leads to defective division of erythroid precursors, with enlarged red cells (macrocytes) in the bone marrow and the peripheral blood, megaloblastic anaemia. The B_{12} daily requirement (2.4 µg in adults, 2.8 µg in pregnancy) and folate daily requirement (400 µg, 600 µg in pregnancy) are easily met by ordinary diet but are commonly low in strict vegetarians, in the elderly, in pernicious anaemia (autoimmune destruction of gastric intrinsic factor that absorbs B_{12}), in tropical sprue, and in patients on long-term metformin or proton-pump inhibitors.

Vitamin B_{12} preparations. Cyanocobalamin (oral 50 µg; IM 1000 µg weekly × 8 then monthly); hydroxocobalamin (IM 1 mg every 2–3 months, longer-acting reservoir form, also used IV in cyanide poisoning); methylcobalamin (the active coenzyme, oral 500–1500 µg). Indian brands, Methycobal, Trinerve, Nervijen-Plus, Neurobion Forte, Auntiplate, Cyanokit (hydroxocobalamin for cyanide poisoning).

Folic acid preparations. Folic acid 5 mg tablet for treatment of megaloblastic anaemia; folic acid 0.4–1 mg for prevention (pregnancy and pre-conception, to prevent neural-tube defects). Folinic acid (calcium leucovorin) is used to rescue from methotrexate toxicity. Indian brands, Folvite, Folex, Tribose, Encicarb-FA (with iron), Iberet-Folic.

Table 5.4 Maturation factors and adjuvant vitamins in the management of anaemia.

Vitamin	Daily requirement (adult)	Deficiency disease	Treatment
B_{12} (cobalamin)	2.4 µg/day	Pernicious anaemia; subacute combined degeneration of cord	Cyanocobalamin or hydroxocobalamin 1

Vitamin	Daily requirement (adult)	Deficiency disease	Treatment
			mg IM, then monthly for life
B_9 (folic acid)	400 µg/day; 600 µg in pregnancy	Megaloblastic anaemia; neural-tube defects	Folic acid 5 mg/day orally for 4 months
B_6 (pyridoxine)	1.3 mg/day	Sideroblastic anaemia (rare)	Pyridoxine 50–200 mg/day
C (ascorbic acid)	40–90 mg/day	Scurvy	Vitamin C 100 mg × 4 / day

5.10 Erythropoiesis-Stimulating Agents

Recombinant human erythropoietin (rHuEPO), produced in CHO cells, and the longer-acting darbepoetin alfa, are used in anaemia of chronic kidney disease (target Hb 10–11 g/dL), in chemotherapy-induced anaemia (Hb < 10 g/dL), and as a peri-operative anaemia management tool. Iron supplementation must always accompany EPO treatment, since the new erythrocytes consume iron. Indian biosimilar brands, Eprex, Vintor, Epofit, Cresp (darbepoetin).

5.11 Poisons and Antidotes

A poison is any substance which on exposure causes injury or death in living organisms. The science of poisons is toxicology; the science of their identification, the legal-and-forensic specialty of forensic chemistry. The pharmacist meets poisons every day, in the safety profile of every drug, in accidental ingestion by children, in deliberate self-poisoning, in occupational and agricultural exposures, and in snake-bite, insect-bite and food poisoning. The general principles of management are the same regardless of the agent.

5.12 Five-Step General Management of Acute Poisoning

Step 1 - Resuscitation (ABCs). Airway, breathing and circulation come first. Clear the airway, intubate if the GCS is below 8 or the gag reflex is absent, give oxygen by mask, support breathing with assisted ventilation if depressed, secure intravenous access, infuse 0.9 % NaCl for hypotension, and start vasopressors if shock persists.

Step 2 - Focused history and physical examination. Identity of the substance, route, amount, time of ingestion, intent (accidental, suicidal, homicidal), co-ingestion (alcohol, medications) and prior history of substance abuse. Recognise the toxidromes, the cholinergic (DUMBELS) of organophosphate poisoning, the anticholinergic of atropine and TCAs, the opioid triad of pinpoint pupils, depressed respiration and depressed consciousness, the sympathomimetic of amphetamine and cocaine, and the sedative-hypnotic of benzodiazepines.

Step 3 - Decontamination. Skin: wash with copious water for 15–20 minutes; remove contaminated clothing. Eye, irrigate with isotonic saline for 15–20 minutes and check the pH of the conjunctival sac. Gut, give activated charcoal 50–100 g (1 g/kg in children) in 200 mL of water within 1 hour of ingestion; gastric lavage is now restricted to severe, life-threatening early ingestions of substances not bound by charcoal, with a protected airway. Whole-bowel irrigation with PEG is useful for sustained-release tablets and iron pills.

Step 4 - Specific antidote, if one is available. See Table 5.5 below.

Step 5 - Enhanced elimination and supportive care. Methods include forced diuresis (normal saline for lithium); urinary alkalinisation with sodium bicarbonate (for salicylates, phenobarbital, methotrexate); haemodialysis (for methanol, ethylene glycol, salicylates, lithium, valproate, theophylline, the mnemonic ISTUMBLE); haemoperfusion (for theophylline, carbamazepine).

Table 5.5 Common poisons encountered in Indian practice with their specific antidotes.

Poison	Specific antidote	Mechanism / route
Paracetamol (acetaminophen)	N-Acetylcysteine 150 mg/kg IV loading	Replenishes hepatic glutathione
Iron salts	Deferoxamine 15 mg/kg/h IV	Chelation; excreted as ferrioxamine
Lead (acute)	$CaNa_2$-EDTA 1500 mg/m²/day IV + BAL 3 mg/kg IM	Chelation
Lead (chronic, children)	Succimer (DMSA) 10 mg/kg q8h × 5 d, oral	Oral chelation
Arsenic, mercury, gold	BAL 3 mg/kg deep IM q4h × 2 d	Sulphydryl chelation
Copper	D-penicillamine 1–1.5 g/day oral	Chelation; Wilson disease
Cyanide	$NaNO_2$ 300 mg IV → $Na_2S_2O_3$ 12.5 g IV (or hydroxocobalamin 5 g IV)	Form metHb to bind CN^-; donate S to rhodanese
Methanol, ethylene glycol	Fomepizole 15 mg/kg IV (or ethanol)	Block alcohol dehydrogenase
Opioids	Naloxone 0.4–2 mg IV	μ-receptor antagonist
Benzodiazepines	Flumazenil 0.2–1 mg IV	GABA-A allosteric antagonist
Organophosphates and carbamates	Atropine 2 mg q5min IV + pralidoxime 1 g IV	mAChR block + AChE reactivation
Warfarin	Vitamin K_1 5–10 mg IV ± FFP	Restore clotting-factor synthesis
Heparin	Protamine sulphate 1 mg per 100 IU	Stoichiometric neutralisation
β-blockers (overdose)	Glucagon 5–10 mg IV bolus	Activates cardiac adenylate cyclase

Poison	Specific antidote	Mechanism / route
Calcium-channel blockers	Calcium gluconate 10 % IV	Restores Ca^{2+} influx
Digoxin	Digoxin-specific Fab (Digibind)	Antibody binding
Sulphonylureas	Octreotide 50 µg SC q8h + dextrose	Suppresses insulin release
Snake bite (Indian "big four")	Polyvalent anti-snake venom IP	Antibody binding of venom toxins

5.13 Cyanide Poisoning and its Antidote Kit

Cyanide poisoning is a textbook example of the principle of antidotal therapy and is the topic most frequently asked in the BP104T examination. The ingested or inhaled cyanide ion binds the ferric iron of mitochondrial cytochrome a/a_3 (complex IV of the electron-transport chain), preventing cells from using oxygen, the classical "internal asphyxia" syndrome with normal arterial PaO_2 and severe metabolic acidosis. The patient may exude the bitter-almond odour of HCN. Death from respiratory failure follows within minutes if untreated.

5.13.1 Sodium nitrite IP ($NaNO_2$)

White or pale-yellow granular solid; M.W. 69.00; soluble 1 in 1.5 of water. IP requires not less than 97.0 % of $NaNO_2$ on the dried basis. Prepared industrially by absorbing nitric oxide / nitrogen dioxide gas in sodium carbonate solution:

$$Na_2CO_3 + NO + NO_2 \rightarrow 2\ NaNO_2 + CO_2$$

Identification: reacts with dilute sulphuric acid to release brown nitrous gas; gives a violet colour with diphenylamine in sulphuric acid; reduces acidified potassium permanganate. The IP monograph requires limits for chloride, sulphate, heavy metals, and arsenic.

Cyanide-antidote dose: 300 mg (10 mL of a 3 % w/v solution) given slowly IV over 5 minutes. Mechanism, oxidises a fraction of haemoglobin (Fe^{2+}) to methaemoglobin (Fe^{3+}); the methaemoglobin then competes with cytochrome oxidase for cyanide and sequesters it as cyan-methaemoglobin. Target methaemoglobin level, 20–30 %. Caution, sodium nitrite produces vasodilatation and hypotension, and excessive methaemoglobinaemia (above 30 %) impairs tissue oxygen delivery; methylene blue or hyperbaric oxygen is the rescue therapy.

$$4\ HbFe^{2+} + 4\ NaNO_2 + 4\ H^+ \rightarrow 4\ MetHbFe^{3+} + 4\ NaOH + 4\ NO$$

$$MetHbFe^{3+} + CN^- \rightarrow Cyan\text{-}metHb\ \ (non\text{-}toxic)$$

5.13.2 Sodium thiosulphate IP ($Na_2S_2O_3 \cdot 5\ H_2O$)

Colourless transparent crystals; M.W. 248.18; freely soluble in water (1 in 0.5); efflorescent in dry air. IP requires not less than 99.0 % and not more than 101.0 % of $Na_2S_2O_3 \cdot 5\ H_2O$. Prepared by boiling a solution of sodium sulphite with elemental sulphur, followed by crystallisation:

$$Na_2SO_3 + S \rightarrow Na_2S_2O_3$$

On heating above 50 °C, the substance loses its five molecules of water of crystallisation; in dry acid it decomposes with formation of free sulphur, sulphur dioxide and water:

$$Na_2S_2O_3 + 2\ HCl \rightarrow 2\ NaCl + H_2SO_3 + S\downarrow$$

Pharmaceutical uses. (a) Cyanide antidote: 12.5 g (50 mL of a 25 % w/v sterile injection) IV over 10 minutes immediately after sodium nitrite. The substance donates a sulphur atom to the hepatic enzyme rhodanese (thiosulphate sulphurtransferase), which converts cyanide into the relatively non-toxic thiocyanate:

$$CN^- + Na_2S_2O_3 \text{ - rhodanese} \rightarrow SCN^- + Na_2SO_3$$

Thiocyanate is then excreted unchanged in the urine within 24 hours. (b) Antifungal, 20 % w/v topical solution for tinea versicolor (used with 4 % dilute HCl follow-up). (c) Reducing agent, primary titrant in iodimetric assay (e.g. assay of vitamin C, ascorbic acid). (d) Photographic fixer, historical use ("hypo"). (e) Dechlorinator for swimming pools.

5.13.3 Modern alternative - Hydroxocobalamin (Cyanokit)

Hydroxocobalamin (vitamin B_{12}a, 5 g IV infusion in 200 mL of 0.9 % NaCl over 15 minutes) binds cyanide directly, forming cyanocobalamin (vitamin B_{12}), which is excreted unchanged in the urine (turning it the characteristic deep red colour). It does not cause methaemoglobinaemia or hypotension, and is the preferred antidote in smoke-inhalation cyanide poisoning where the patient may also have carbon-monoxide-induced reduced oxygen-carrying capacity. Indian brand, Cyanokit by Merck/Cipla.

5.14 Electrolyte Preparations for Replacement and Acid–Base Therapy

The body of a 70 kg adult contains about 42 L of water distributed in two compartments (ICF 28 L, ECF 14 L) and an intricately regulated set of cations and anions. Disturbances of fluid and electrolyte balance, from diarrhoea, vomiting, fever, severe burns, diuretic overdose, renal disease and post-operative losses, are corrected with a small number of pharmacopoeial electrolyte preparations. The principal preparations are described below.

5.15 Sodium Salts

Sodium chloride injection 0.9 % w/v (Normal Saline, NS). The most widely used IV fluid. Contains 154 mEq Na^+ and 154 mEq Cl^- per L; osmolarity 308 mOsm/L; pH 5.0; isotonic with blood. Indications, fluid replacement in dehydration, hypovolaemic shock, hyponatraemia, vehicle for drug reconstitution. Limitation, large volumes can produce hyperchloraemic metabolic acidosis (the chloride load exceeds physiological 103 mEq/L).

Hypertonic sodium chloride 3 % and 5 % w/v. For severe symptomatic hyponatraemia ($Na^+ < 115$ mEq/L). Correction rate must not exceed 8–10 mEq/L in 24 hours to avoid central pontine myelinolysis.

Sodium bicarbonate injection 7.5 % w/v and 8.4 % w/v. Hypertonic solution (1786 mOsm/L for 7.5 %); 1 mEq Na^+ and 1 mEq HCO_3^- per mL of the 8.4 %. Indications - severe metabolic acidosis (pH < 7.1), cardiac arrest with hyperkalaemia, tricyclic antidepressant overdose with QRS prolongation, urinary alkalinisation in salicylate poisoning, intravesical alkalinisation in cyclophosphamide. Avoid intra-arterial administration and rapid bolus injection.

Sodium acetate. An alkaliniser in haemodialysis and continuous renal replacement therapy; converted in the liver to bicarbonate. Avoided in liver failure.

5.16 Potassium Salts

Potassium chloride injection 15 % w/v. 10 mL ampoule contains 20 mEq K^+ and 20 mEq Cl^-. NEVER given as bolus, must be diluted to a maximum of 40 mEq K^+ per L of IV fluid and infused at no more than 10 mEq K^+ per h through a peripheral vein, 20 mEq K^+ per h through a central vein, with continuous cardiac monitoring. The cardinal danger is cardiac arrest from hyperkalaemia.

Oral potassium chloride. Liquid (Pot-Klor 20 mEq per 15 mL; K-Sav syrup; Kaylixir; Potklor); slow-release tablets (Slow-K 600 mg = 8 mEq; K-Tabs). Used in mild and moderate hypokalaemia.

Potassium citrate / potassium bicarbonate. Urinary alkaliniser. Used in calcium oxalate / uric acid stone disease, salicylate poisoning, distal renal tubular acidosis. Indian brand, Cital syrup, Alkasol.

5.17 Calcium and Magnesium Salts

Calcium gluconate 10 % w/v IV. See Unit III, Section 3.5.6, for the IP monograph and assay. 1 g of calcium gluconate = 4.45 mEq elemental Ca^{2+} = 89 mg Ca. Used in (a) symptomatic hypocalcaemia (Trousseau / Chvostek positive); (b) hyperkalaemia (10 mL IV over 5 min stabilises the cardiac membrane); (c) HF burns (intra-arterial and topical); (d) magnesium sulphate toxicity; (e) calcium-channel-blocker overdose; (f) tetany after thyroidectomy.

Calcium chloride 10 % w/v IV. Provides three times the elemental calcium of equivalent volumes of calcium gluconate (27 mEq/g) but is more irritating to veins, strictly central-vein use. Reserved for cardiac arrest and severe hyperkalaemia.

Magnesium sulphate 50 % w/v IV / IM. 1 g = 4 mEq elemental Mg^{2+}. Used in (a) eclampsia and severe pre-eclampsia (Pritchard regimen, 4 g IV + 5 g IM each buttock, then 5 g IM every 4 h × 24 h after the last seizure; Zuspan regimen, 4 g IV + 1 g/h infusion); (b) torsades de pointes (2 g IV); (c) severe asthma exacerbation (2 g IV over 20 min); (d) digoxin-induced arrhythmias.

Zinc sulphate. Adjunct in oral rehydration therapy of childhood diarrhoea (20 mg/day for 10–14 days reduces stool output and duration). Indian brand, Zincovit, Zifi, ZinKid suspension.

5.18 Combination Fluids

Ringer's lactate (Hartmann's solution). See Unit II, Section 2.21. Na^+ 130, K^+ 4, Ca^{2+} 3, Cl^- 109, lactate 28 mEq/L; osmolarity 274 mOsm/L; pH 6.0–7.5. First-line in trauma resuscitation, surgical fluid replacement, paediatric fluid therapy; preferred to normal saline for large-volume resuscitation because it does not produce hyperchloraemic acidosis. Contains calcium, so it should not be given through the same line as blood transfusion (citrate-calcium clot risk) or with phosphate-containing antibiotics.

Dextrose-saline (D5NS, D5 1/2 NS). 5 % w/v dextrose + 0.9 % NaCl (or 0.45 % NaCl); provides Na^+, water and 170 kcal/L of energy. Used as maintenance fluid in patients with adequate sodium reserves.

Oral rehydration salt (WHO low-osmolarity formula). See Unit II, Section 2.29.4. NaCl 2.6 g + KCl 1.5 g + trisodium citrate dihydrate 2.9 g + anhydrous glucose 13.5 g per litre reconstituted; total osmolarity ≤ 245 mOsm/L. The cornerstone of childhood diarrhoea management - has saved more than 50 million lives since its introduction in 1968. Indian marketed examples - Electral, Walyte, Enerzal, Pedialyte, Prolyte, Dolosalt.

Plasma-Lyte A. A balanced crystalloid with Na^+ 140, K^+ 5, Mg^{2+} 3, Cl^- 98, acetate 27, gluconate 23 mEq/L; pH 7.4. Used in surgical and trauma resuscitation; advantages over normal saline include no hyperchloraemic acidosis and closer mimicking of plasma.

5.19 Sodium Citrate as a Combination Buffer

Trisodium citrate dihydrate ($Na_3C_6H_5O_7 \cdot 2\ H_2O$; M.W. 294.10) is a versatile pharmaceutical ingredient. (a) Buffer, pKa values 3.13, 4.76 and 6.40, so the salt buffers across pH 3–7. Used in oral liquids, syrups, parenteral solutions, ORS (citrate is metabolised to bicarbonate in the liver). (b) Anticoagulant, chelates Ca^{2+} in citrated blood for transfusion (ACD-A formulation: trisodium citrate + citric acid + dextrose). (c) Urinary alkaliniser, Cital syrup contains sodium citrate + potassium citrate + citric acid. (d) Mild expectorant, component of older cough syrups (Benadryl Expectorant carries 57 mg of sodium citrate per 5 mL).

5.20 Combination Therapy - Putting Principles Together

Many of the pharmaceutical preparations used in fluid and electrolyte management are formulated as fixed-dose combinations because the body manages its salts not as isolated species but as a complex ionic mixture. Four worked examples illustrate the principle.

Acute severe diarrhoea in a 5-year-old child. Net losses include water (10–15 % body weight), sodium (60–80 mEq/L of stool), potassium (15–25 mEq/L of stool), chloride and bicarbonate. Treatment, WHO low-osmolarity ORS 75–100 mL/kg over 4 hours (oral) for moderate dehydration; IV Ringer's lactate 100 mL/kg over 3–6 hours for severe dehydration. Zinc sulphate 20 mg orally for 14 days. The combination of glucose plus Na^+ in ORS exploits the SGLT-1 co-transporter (one Na^+ pulled into the enterocyte per glucose molecule pulled in) to pull water along.

Severe eclamptic seizure. Combination of magnesium sulphate (Pritchard regimen: 4 g IV bolus followed by 10 g IM, then 5 g IM every 4 hours), calcium gluconate ready at the bedside as the magnesium antidote, IV fluid restriction (Ringer's lactate at 80 mL/h), and antihypertensive (labetalol or hydralazine).

Severe hyperkalaemia (K^+ > 6.5 mEq/L with ECG changes). Four therapies in sequence: (1) calcium gluconate 10 mL of 10 % IV over 5 min to stabilise the cardiac membrane; (2) insulin 10 IU + dextrose 25 g IV to shift K^+ intracellularly; (3) salbutamol 10 mg nebulisation as an adjunct intracellular shift; (4) sodium polystyrene sulfonate (Kayexalate, 30 g oral) or patiromer to remove K^+ via the gut; (5) haemodialysis if renal function is severely impaired.

Severe metabolic acidosis with cardiac arrest. Sodium bicarbonate 1 mEq/kg IV every 10 minutes while compressions continue; insulin-dextrose-K^+ control if hyperkalaemic; calcium gluconate if hypocalcaemic; vasopressor support; ABG every 15 minutes.

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