

NMR & ESR

NMR Spectroscopy (Nuclear Magnetic Resonance)

Introduction

- Atomic Absorption Spectrometry (AAS) is a quantitative analytical technique used to determine the concentration of metal elements in samples by measuring the absorption of light (usually UV or visible) by free atoms in the gaseous state.
- In pharmaceutical analysis, AAS is primarily employed for:**
 - Elemental impurity testing
 - Quality control of raw materials and drug products
 - Trace metal analysis in APIs and excipients
- AAS is particularly effective for detecting toxic metals such as lead (Pb), cadmium (Cd), arsenic (As), and mercury (Hg) at trace levels (ppm to ppb).

Theoretical Aspects

Basic Principle:

- NMR is based on the fact that certain nuclei possess spin and a corresponding magnetic moment.
- When placed in an external magnetic field, these nuclei can absorb radiofrequency energy and transition between different energy levels.

Key Concepts:

1. Nuclear Spin (I):

- Only nuclei with non-zero spin ($I \neq 0$) exhibit NMR.
- Common NMR-active nuclei: ^1H , ^{13}C , ^{19}F , ^{31}P , etc.
- The most commonly studied nucleus in pharmaceuticals is proton (^1H).

2. Magnetic Field (B_0):

- When placed in an external magnetic field, nuclear magnetic moments align either with (lower energy) or against (higher energy) the field.
- The energy difference between these states is small but detectable.

3. Resonance Condition:

- When the sample is irradiated with radiofrequency radiation matching the energy difference between the spin states, absorption occurs.
- This is called resonance, and the frequency at which this occurs depends on the magnetic field strength and chemical environment.

4. Chemical Shift (δ):

- The resonance frequency of a nucleus is affected by its electronic environment.
- Chemical shifts are reported in parts per million (ppm) and provide information about the type of functional group or chemical bonding.

5. Spin-Spin Coupling:

- Interaction between neighboring nuclear spins splits NMR signals into multiplets (doublets, triplets, etc.), giving insights into the number of adjacent atoms.

Applications of NMR

A. Structural Elucidation:

- Determination of the molecular structure of APIs and excipients.
- Identification of stereochemistry, isomerism, and functional groups.

B. Purity and Impurity Profiling:

- Detection of residual solvents, degradation products, and synthetic by-products.
- Ensures compliance with regulatory standards.

C. Quantitative NMR (qNMR):

- Accurately measures the concentration of compounds without needing a reference standard.

D. Polymorphism and Solid-State Analysis:

- Solid-state NMR is used to distinguish between different polymorphs, crystal forms, and amorphous states.

E. Drug-Receptor Interaction Studies:

- Investigates binding sites and molecular interactions using ligand-based or receptor-based NMR techniques.

F. Metabolite Identification:

- Tracks biotransformation of drugs in biological systems.

ESR Spectroscopy (Electron Spin Resonance)

(Also known as EPR – Electron Paramagnetic Resonance)

Introduction

- Electron Spin Resonance (ESR) is a spectroscopic technique used to detect species with unpaired electrons, such as free radicals, transition metal complexes, and paramagnetic centers.
- In pharmaceutical analysis, ESR is primarily used for:

- Studying free radicals in drugs and excipients.
- Stability testing under stress conditions.
- Investigating irradiation effects and oxidative degradation.

Theoretical Aspects

Basic Principle:

- Electrons, like nuclei, have spin and an associated magnetic moment.
- In an external magnetic field, unpaired electrons exhibit two energy levels corresponding to their spin states (+½ and -½).
- ESR measures the absorption of microwave radiation (typically 9–10 GHz) when an unpaired electron transitions between these spin states.

Zeeman Effect:

- In the presence of a magnetic field, the energy levels of electron spins split.
- The **energy difference** depends on the strength of the magnetic field and the **g-factor**, which is characteristic of the electron's environment.

Resonance Condition:

$$\Delta E = h\nu = g\beta B_0$$

- **Where:**
 - ΔE = energy difference
 - h = Planck's constant
 - ν = microwave frequency
 - g = g-factor (electron environment-dependent)
 - β = Bohr magneton
 - B_0 = magnetic field strength

Hyperfine Splitting:

- If the unpaired electron is in proximity to **magnetic nuclei (e.g., ^1H , ^{14}N)**, it interacts with their nuclear spins.
- This leads to **hyperfine splitting**, resulting in multiple ESR signals instead of one.
- The number and intensity of lines follow specific rules (based on nuclear spin I and number of equivalent nuclei).
- **For example:**
 - 1 proton ($I = \frac{1}{2}$) will split the ESR signal into **2 lines (doublet)**.
 - 2 equivalent protons cause a **triplet** (3 lines), and so on.

Applications of ESR

1. Detection of Free Radicals:

- Identifies free radicals formed during drug degradation, irradiation, or oxidative stress.
- Important for assessing shelf life and stability of formulations.

2. Radiation Dosimetry:

- ESR is used to measure radiation exposure in pharmaceutical materials (e.g., gamma-irradiated excipients or packaging).

3. Stability Testing:

- ESR can monitor the formation of radicals over time or under stress conditions such as heat, light, or oxygen exposure.

4. Oxidation Studies:

- Determines the extent and mechanism of oxidative degradation of sensitive drugs, particularly those with aromatic or unsaturated groups.

5. Analysis of Transition Metal Complexes:

- Used to study paramagnetic metal-containing drugs or catalysts.



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