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: ^{1}H, ^{13}C, ^{19}F, ^{31}P, etc.
   - The most commonly studied nucleus in pharmaceuticals is proton (^{1}H).
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., ^{1}H, ^{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 = ½) 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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