Pharmaceutical Applications of EPR

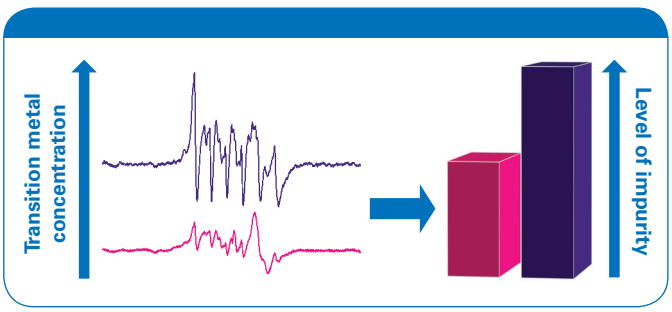
V. Paramagnetic Impurity Profiling

All drugs contain impurities that can arise from the drug substances (APIs) or inert materials (excipients). They are also introduced into the drug product during the formulation processes, packaging, and storage. Impurities have many unwanted effects, such as:

- Decreasing the therapeutic effect
- Lowering the product shelf-life
- Inducing toxicity

Identification, quantification, and control of impurities in API and the drug product are critical in drug development. Organic impurities are often free radicals from by-products, intermediates, or degradation products. Inorganic impurities include transition metals, reagents, and ligands.

Electron Paramagnetic Resonance (EPR) spectroscopy is the only technique for the direct and non-invasive detection, identification and quantification of paramagnetic impurities (organic free radicals and transition metals). EPR is able to detect traces of impurities down to parts per billion levels.



Metal concentration correlates with the EPR signal

Challenge

Identifying and monitoring impurities during drug development, manufacturing process as well as storage is critical to fulfill the regulatory requirements.

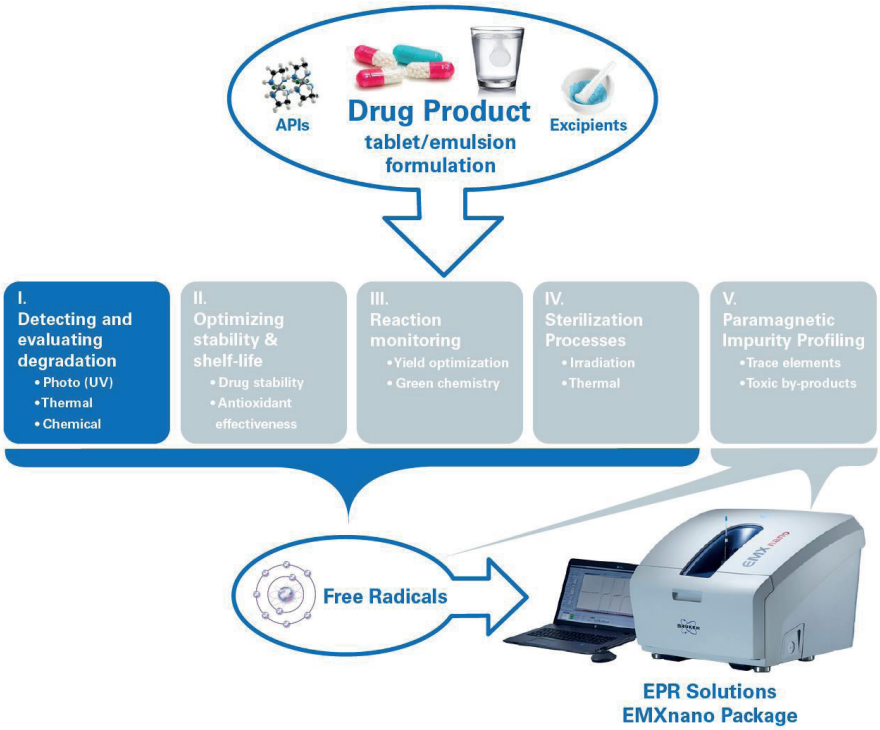
Solution

The Bruker EMXnano benchtop EPR spectrometer package

- Detects and identifying traces of transition metals
- Monitors drug degradation processes that produce and involve free radicals
- Observes the production of free radicals catalyzed by transition metals or other impurities

EMXnano key features:

- No prior EPR experience needed
- Video how-to-guide and startup kit
- Accurate results
- Superior sensitivity
- Ease of use
- Full workflow for measuring, analyzing and quantifying free radicals
- Compact foot print
- Low cost of ownership

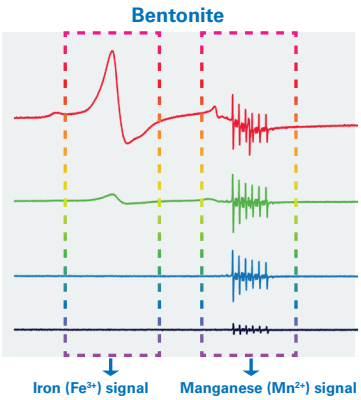


Summary

Detection, characterization, as well as monitoring of impurities and their impact on drug stability is essential and mandatory. The EMXnano package is your solution to the challenges of reactive impurities in pharmaceutical APIs, excipients, and formulations. With EPR one gains insight into the stability 'soft spots' of the drug which is important for developing a robust product.

References

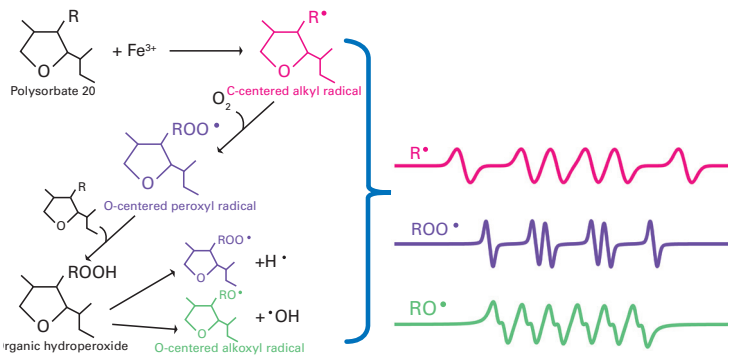
1. Lam X.E. et al.(Genentech Inc.), Site-specific tryptophan oxidation induced by autocatalytic reaction of polysorbate 20 in protein formulation, Pharm. Res. (2011) 28 2543
2. Wu Y. et al. (Bristol-Myers Squibb Co.), Understanding drug-excipient compatibility: Oxidation of compound A in a solid dosage form, Pharm. Dev. Technol. (2009) 14 556
3. Williams H. (AstraZeneca), Claybourn M., The power of electron paramagnetic resonance spectroscopy in pharmaceutical analysis , Spectroscopy Europe (2006) 18(1)



Trace Analysis: Impurity Identification & Control

- Manganese (Mn^{2+}) and iron (Fe^{3+}) are present at trace levels in the excipient bentonite, commonly used as a filler in tablets.
- With the EMXnano impurity concentrations can be determined.
- Increasing amounts of metals accelerate the degradation of APIs and excipients.

- Polysorbate 20 used in drug formulation as a stabilizer undergoes autoxidation.
- Autoxidation is catalyzed by transition metals and results in side-chain cleavage and free radical formation.
- The EMXnano can detect, identify and quantify the free radical impurities.



Bruker BioSpin
epr@bruker.com
www.bruker.com/EMXnano