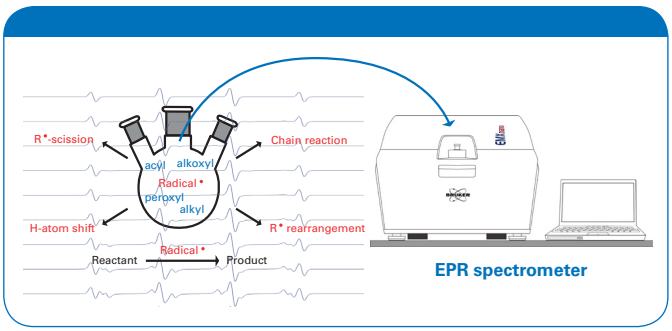
Pharmaceutical Applications of EPR

III. Reaction Monitoring

Reaction monitoring is critical for process understanding, optimization and scaling up, leading to cost savings and ensuring the quality of the final product. It often provides insights into the chemical reaction mechanisms. Kinetic information can be extracted from time course data to build kinetic models that will be used to predict conditions, enabling effective process optimization, risk assessment and control.

The quantitative nature of electron paramagnetic resonance (EPR) and the non-intrusive nature makes the technique extremely powerful for the identification and characterization of radical reaction intermediates, providing insights into the reaction mechanisms and kinetics of chemical reactions.

Free radical chemistry may offer many advantages over traditional synthetic approaches. Transition metal-containing catalysts are also widely used in pharmaceutical synthetic routes and EPR is the only technique for the direct and non-invasive detection of both free radicals and transition metals.



Reaction monitoring with EMXnano

Challenge

Chemistries involving radicals, transition metals and other unpaired electron species are integral components of maximizing product yield and minimizing the environmental footprint of synthetic reactions. Understanding these reactions is crucial for pharmaceutical drug development.

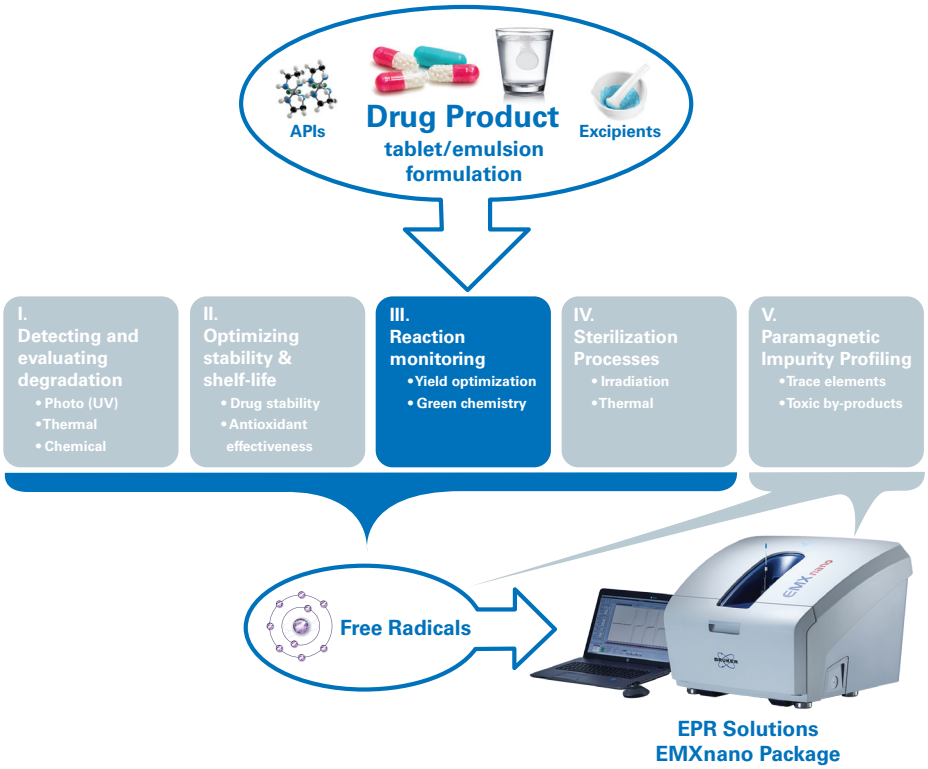
Solution

The Bruker EMXnano benchtop EPR spectrometer package

- Identifies reaction intermediates (free radical and transition metal) to obtain mechanistic information
- Answers key chemical questions: reaction yield and reaction kinetics
- Straightforwardly generates data to build kinetics model
- Quantifies paramagnetic intermediate species over the course of the reaction

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

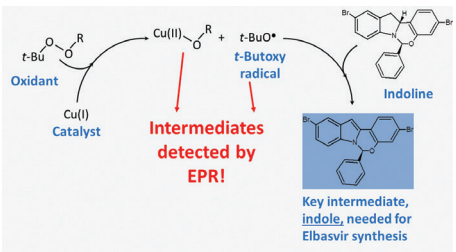
The EMXnano´s capability to monitor catalytic reactions and radical intermediates is crucial to obtain detailed knowledge of reaction mechanisms.

The EMXnano enables direct quantification of paramagnetic species without the need of empirical response factors.

Obtaining answers to key questions such as reaction yield and reaction kinetics enables strategic process chemistry decisions, ultimately leading to cost savings.

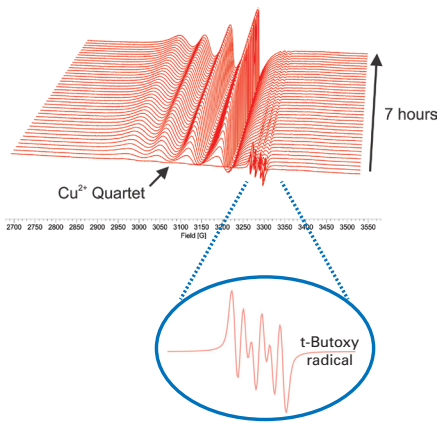
References

1. Peng F. et. al. (Merck), A mild Cu(I)-catalyzed oxidative aromatization of indolines to indoles, J. Org. Chem. (2016) 81 10009
2. Mangion I. et. al. (Merck), Using electron paramagnetic resonance spectroscopy to facilitate problem solving in pharmaceutical research and development. J. Org. Chem. (2016) 81 6937



Simplified proposed mechanism of indoline oxidation

- An indole intermediate is a synthetic challenge in the production of a new Hepatitis C drug (Elbasvir).
- A novel green chemistry synthesis with high efficiency (92% indole yield) is accomplished.
- A proposed mechanism suggests that the catalyst Cu(I) is oxidized to form Cu(II) and tert-butoxy radical.



- Monitoring the reaction confirms oxidation of the EPR silent Cu(I) to the EPR active Cu(II).
- Cu(II) signal reaches a plateau after ~ 3 hours indicating completion of the reaction.
- t-Butoxy radical is detected as well by EPR using a spin trap.
- Quantitative EPR analysis of both intermediates provides information about the synthesis efficiency.

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