# EPR AND NMR IMAGING IN MONITORING THE RELEASE MECHANISMS FROM EGALET® DOSAGE UNITS


Martin Luther University Halle-Wittenberg

**H. Metz[1], D. Bar-Shalom[2], P. Høyrup Hemmingsen[2], G. Fischer[2], K. Mäder[1]**

[1] Institute of Pharmaceutics and Biopharmaceutics, Martin Luther University Halle-Wittenberg, D-06120 Halle/Saale
[2] Egalet a/s , Værløse, Denmark
Corresponding author: karsten.maeder@pharmazie.uni-halle.de

## Abstract

The drug release from Egalet® dosage units involves the processes of water penetration, polymer dissolution and erosion. The kinetics of these processes can be observed continuously and noninvasive by EPR and NMR Imaging techniques. These methods are capable of giving a detailed picture of the release mechanism. Polarity gradients can be detected and quantified by both methods.


## Introduction

The Egalet® dosage unit is one in a series of controlled release products developed by Egalet® a/s. Egalet® products have already been successfully tested in vitro and in vivo with a variety of active ingredients including peptides, water-insoluble and unstable molecules. The technology offers new possibilities in controlled release drug delivery for both well-known and new chemical entities.

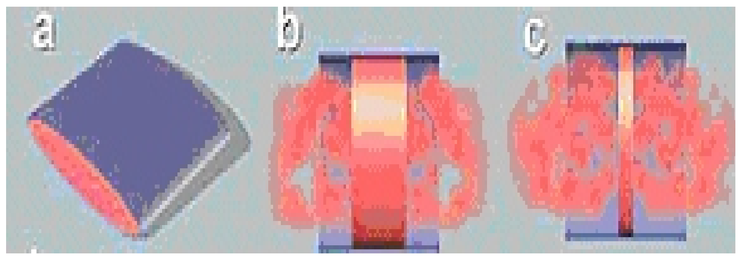


Fig. 1: Egalet® principle. An erodible core is surrounded by an impermeable polymer. The core erodes by dissolution and the incorporated drugs are released.

The drug release mechanism is supposed to be surface erosion, effected through water diffusion, polymer hydration, disentanglement and dissolution. The aim of this study was to shed more light on the release mechanism, i.e. to follow the water penetration and to monitor the change of the microenvironment within the tablet. The non-invasive Imaging techniques of NMR and EPR were used to characterize the drug delivery system [1, 2].

## Materials and Experimental methods

### Egalet® dosage units

7*11*5 mm Egalet® dosage units were obtained from Egalet a/s. For EPR studies, the dosage units contained the nitroxide TEMPOL (4-Hydroxy-TEMPO2,2,6,6-Tetramethyl-4-hydroxy- piperidin-1-oxyl) spin probe. The core contained high molecular PEO mw. 200000 (Polyox N-80NF, Dow Chemicals) and Poloxamer 8400 (Lutrol F68, BASF).

### EPR Spectroscopy and Imaging

EPR spectroscopy and Imaging was performed on an L-band system from Magnettech, Berlin.

### NMR Imaging

A 20 MHz Oxford benchtop NMR spectrometer "MARAN DRX2" with imaging capability was used for the NMR studies.

## Results and discussion

The electron paramagnetic resonance (EPR) detect the splitting of the energy levels of unpaired electrons due to magnetic moments in the surrounding area in an external magnetic field (similar to the Frauenhofer lines in the solar spectrum).

The EPR spectrum (Fig.2) indicates high mobility of the nitroxide despite the solid state of the Egalet® dosage unit core. This phenomenon is commonly observed for PEG [1]. The nitroxide is released from the dosage unit with almost zero order kinetics over several hours.(Fig. 3).

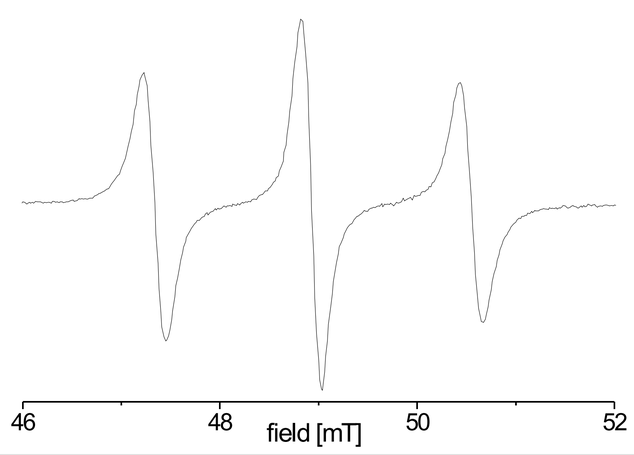


Fig. 2: EPR spectrum of Tempol in dry Egalet® dosage units.

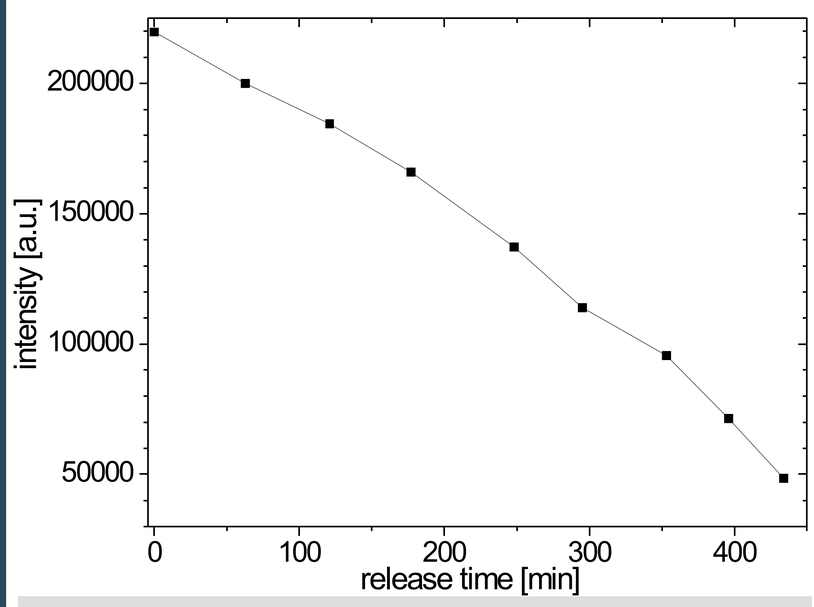


Fig. 3: Kinetics of the EPR signal intensity remaining in the dosage unit.

The results of the spectral-spatial EPR-Imaging study indicate water penetration over several hours from outside into the core (Fig 4, 5). Because the hyperfine splitting is sensitive to the polarity of the environment, EPR makes it possible to obtain a map of polarity distribution within the Egalet® dosage units. In dry dosage units, the polarity was equally distributed. Sharp gradients of polarity were evident after 1 and 3 hours (Fig. 4, 5). With time, the polarity increased throughout the tablet and the polarity gradients decreased. (Fig. 5)The analysis of the spatial dimension of the images yielded a decrease of the spatial dimensions, indicative of erosion of the core (Fig. 6).

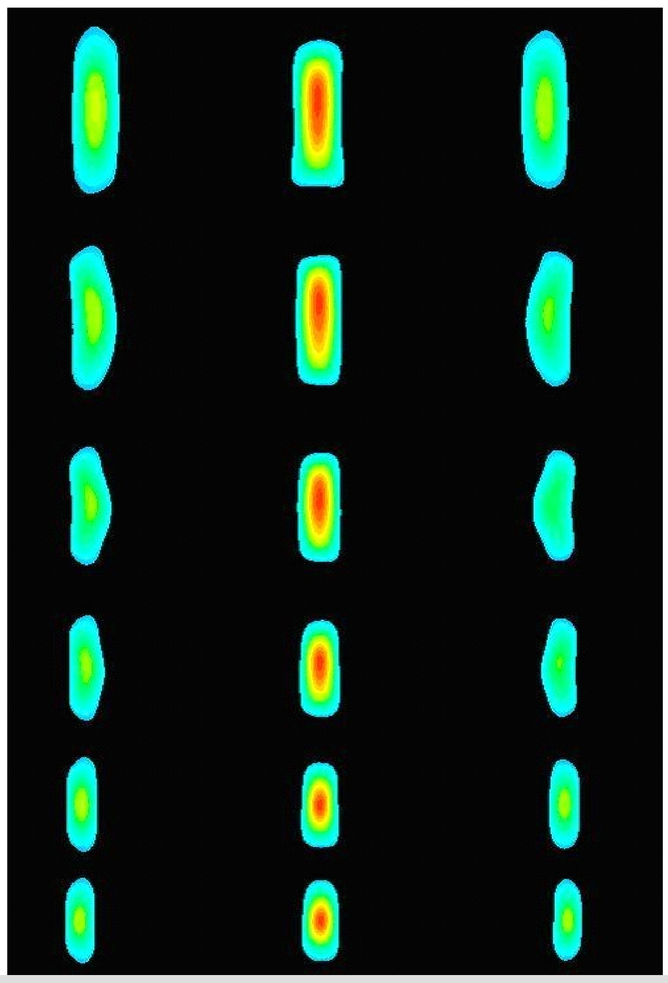


Fig. 4: ESR spectral-spatial images after different exposure time to the buffer.

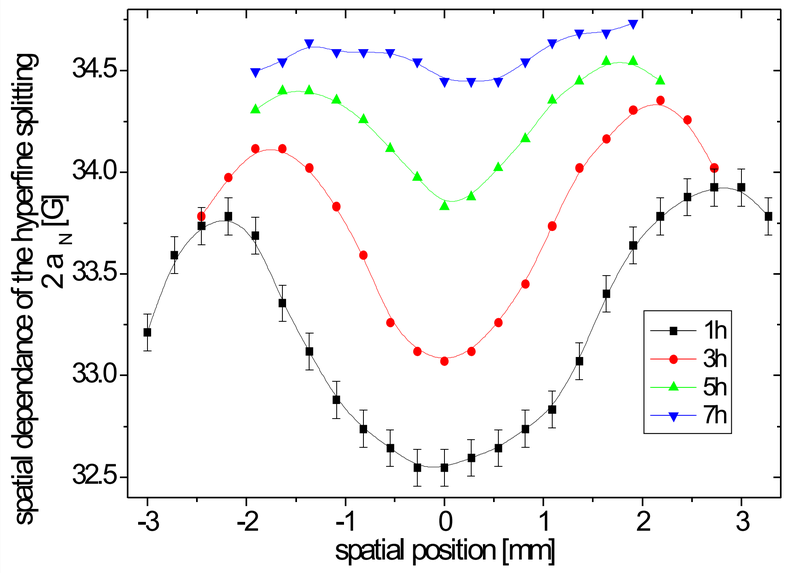


Fig. 5: Distribution of hyperfine splitting constants within the Egalet® dosage units at different times.

High values of hyperfine splitting indicate a high polarity. Note the presence and overall increase of polarity gradients.

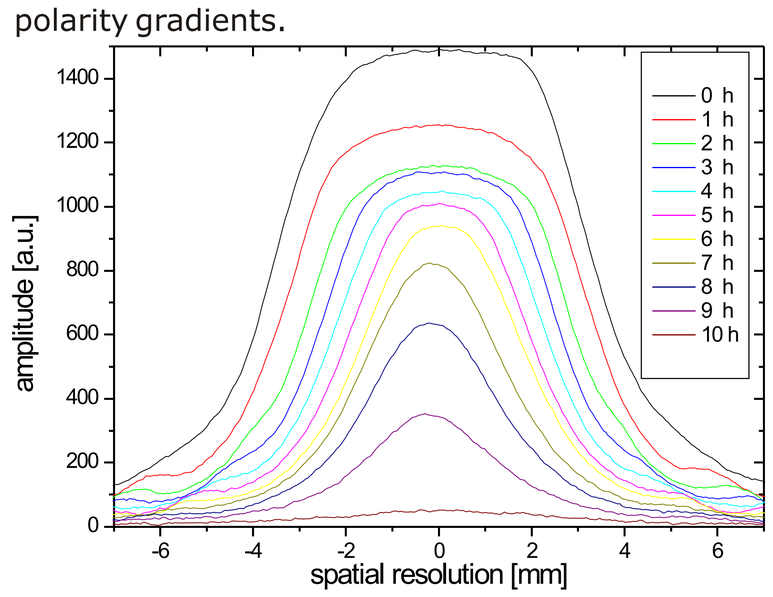


Fig. 6 Spatial cut through the ESR Images of nitroxide loaded Egalet® dosage units. Note the overall decrease of the signal intensity and the decreased spatial distribution which follows erosion.

The results of the NMR-Imaging studies further illustrated the water penetration into the core. In the images a thin layer of hydrating/dissolving layer is seen, water does not penetrate far into the core and a dry core is evident beyond this layer (except at the very end when the "fronts" meet)

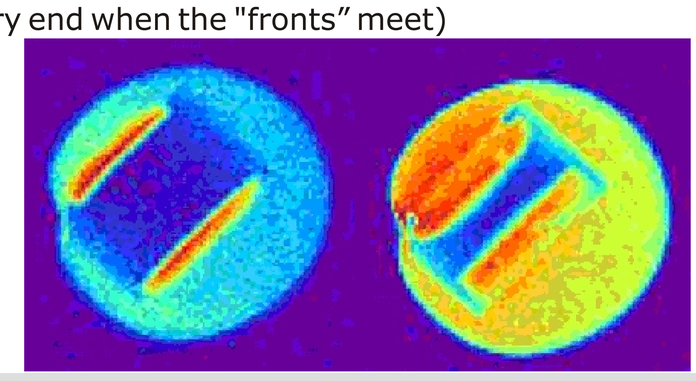

Fig. 7: NMR Image of Egalet® dosage units after 0.5 and 4 hours.

## Conclusion

The drug release from Egalet® involves the processes of water penetration, polymer dissolution and disentanglement, resulting in surface erosion. The kinetics of these processes can be characterized continuously and noninvasive by EPR and NMR Imaging techniques. Polarity gradients can be detected and quantified by both methods. Future studies will investigate the impact of drug load and

## References


[1] D.J. Lurie, K. Mäder; Adv. Drug Deliv. Rev. **57**, 1171-1190 (2005)).

[2] J.C. Richardson et al.; Adv. Drug Deliv. Rev. **57**, 1191-1209 (2005).