



## Cover story

## Magnetic resonance imaging for developing intramuscular formulations



Parenteral administration of dosage forms is widely used in clinical practice. Parenteral applications of long acting formulations have many advantages, including higher bioavailability, improved patients' compliance, and reduced side effects resulting from reduced fluctuation of plasma levels. However, *in vivo* processes following intramuscular injection are not fully understood to date. Drug absorption from the injected formulation is known to be affected by the blood perfusion rate of the muscle tissue, local reactions at the site of injection, and the site of injection itself (intradeltoidal/intragluteal) [1–3]. Furthermore, the rate of absorption of an intramuscularly applied drug may also be influenced by the shape of the depot, its distribution within the muscle tissue, and the time needed for depot removal. Thus, the evaluation of the temporal development of a depot and its influence on drug absorption requires non-invasive imaging methods in combination with pharmacokinetic data.

The paper by Professor Werner Weitschies and his team in this issue presents a method combining magnetic resonance imaging (MRI)-based visualization of intramuscular depots in rats together with the determination of the resulting blood concentration profile of the administered drugs [4]. Aqueous solutions and oily suspensions of paracetamol, diclofenac and prednisolone were administered into the muscle tissue of the hind leg of rats. Afterwards MRI measurements were performed simultaneously to blood withdrawal from the tail vein. The drug concentrations in the withdrawn blood samples were determined by LC-MS/MS-measurements. Interesting observations were obtained in the presented pilot study. A freehand injection often leads to the administration into subcutaneous areas or inter-fascial spaces in the rats. Thus, it is suggested to perform MRI-guided injections in rats and other small experimental animals. The location of the injection within the muscle tissue influences the distribution and absorption behavior of the depot considerably. Nevertheless, these differences did not affect the rate of absorption of the drug into the systemic circulation. The study by the Weitschies team showed, against common belief, that the administered drugs were not absorbed together with the aqueous or oily depots. In the case of the aqueous solutions and oily suspensions investigated within this pilot study, no correlation was found between the shape of the depot or the time for depot removal and the extent and velocity of the absorption of the drugs. All tested formulations had in common that the maximum measured plasma concentration ( $C_{max}$ ) was reached long before the formulations had been removed from the muscle tissue. This observation indicates that the common

assumption that a drug dissolved in aqueous fluid is absorbed together with the formulation is not necessarily valid. The study by the Weitschies group also revealed the benefit of MRI in detecting local reactions in the muscle tissue. The aqueous and the oily formulations of diclofenac led to an accumulation of interstitial fluid which is considered a sign for an inflammatory process. Histopathological investigations confirmed a correlation between the extent of accumulating water and the severity of the local reactions. MRI may be a very valuable tool in the preclinical assessment of drug safety.

Although more work needs to be carried out in the investigation of absorption processes of intramuscularly injected depots, the work by Professor Weitschies and his colleagues may help to obtain fresh insights in physiological and formulation parameters affecting drug absorption after intramuscular administration. Furthermore, the pilot study demonstrates the potential of MRI, especially in preclinical stages, to estimate the functionality and local tolerability of newly developed intramuscular dosage forms. Currently, there are only a dozen of parenteral depot formulations in clinical use. This small number of clinical products indicates the difficulty of developing long-term injectable depot formulations. The work presented by the Weitschies team helps in understanding the drug release and subsequent absorption for development of more clinical useful injectable formulations.

## References

- [1] N. Darville, M. van Heerden, A. Vynckier, M. De Meulder, P. Sterkens, P. Annaert, G. Van den Mooter, Intramuscular administration of paliperidone palmitate extended-release injectable microsuspension induces a subclinical inflammatory reaction modulating the pharmacokinetics in rats, *J. Pharm. Sci.* 103 (2014) 2072–2087.
- [2] S.D. Soni, D. Wiles, A. Schiff, J. Bamrah, Plasma levels of fluphenazine decanoate. Effects of site of injection, massage and muscle activity, *Br. J. Psychiatry* 153 (1988) 382–384.
- [3] P. Ylitalo, Effect of exercise on pharmacokinetics, *Ann. Med.* 23 (1991) 289–294.
- [4] M. Probst, J.-P. Kühn, E. Scheuch, A. Seidlitz, S. Hadlich, K. Evert, S. Oswald, W. Siegmund, W. Weitschies, Simultaneous magnetic resonance imaging and pharmacokinetic analysis of intramuscular depots, *J. Control. Release* 227 (2016) 1–12.

Kinam Park  
Purdue University  
Departments of Biomedical Engineering and Pharmaceutics  
West Lafayette, IN 47907, USA  
E-mail address: [kpark@purdue.edu](mailto:kpark@purdue.edu)