



Cover story

Mechanisms controlling drug release from coated pellets



Since the use of PEG-coated pellets for the first oral sustained-release formulation in 1952, coated pellets have been used extensively to control the drug release kinetics. The term “pellet” has been used interchangeably with other terms, such as bead, sphere, granule, and particle. A large number of drug products have been available to patients. Despite extensive use of the coated pellets, the underlying mass transport mechanisms controlling the release of the active agent from the coated pellets are not always fully understood. Consequently, product optimization through a series of trial-and-error experiments can be cumbersome, time-consuming, and cost-intensive. This is simply due to the fact that the mechanisms controlling drug release from coated pellets are often complex. The drug release from the pellet core through polymer coating depends on the properties of the core and the film coating. These include the permeability of the film coating for water and the drug, water-solubility of the drug and drug loading in the core, the osmotic activity of the pellet core, and the density and mechanical stability of the film coating [1]. Drug molecules can be released by diffusion through an intact film and/or through newly formed aqueous cracks. The water-filled cracks can be formed by the hydrostatic pressure building up in the pellet core as water penetrates into the system [2,3]. In addition, drug release can be affected by time-dependent changes in the composition of the film coatings (e.g., by plasticizer leaching or swelling by water). The release mechanism of a particular type of coated pellets depends on the composition of the system as well as on its manufacturing procedure.

To elucidate the mechanisms controlling drug release from a given type of coated pellets, reliable physico-chemical characterization methods are of importance. One of the crucial questions to be answered is whether drug release occurs through the intact film coating and/or through water-filled cracks. The paper by Professor Siepmann and his team [4] presents the use of synchrotron X-ray computed microtomography (SR- μ CT) which allows for a direct, non-invasive monitoring of potential crack formation in the film coatings of coated pellets during drug release. Importantly, no sample preparation (e.g., drying) is required: the pellets are monitored while they are exposed to the release medium. In this study, sugar starter cores were layered with propranolol HCl and subsequently coated with Kollicoat SR 30D (an aqueous dispersion of poly(vinyl acetate) containing small amounts of polyvinylpyrrolidone and sodium lauryl sulfate) plasticized with 10% triethyl citrate.

Professor Siepmann and his co-workers made a few interesting observations from the study. Many small air-filled pores were seen throughout the sugar starter cores in the coated pellets. Once water penetrated into the system, however, the pellet cores became semi-

solid/liquid and the trapped air started fusing together into larger air bubbles. The mobility of the air bubbles increased with time. The imaging technique also allowed monitoring the creation of cracks in the film coatings during drug release in these systems. In addition to the drug, tiny sugar particles from the starter core were also expelled through these cracks by convection into the surrounding bulk fluid. Larger air bubbles were often observed in close vicinity of the cracks. These air bubbles may play a decisive role for crack formation in the film coatings of coated pellets. The changes happening inside the pellets have been so far largely ignored due to the lack of suitable non-invasive experimental techniques.

The use of SR- μ CT proposed by Professor Siepmann and his co-workers provides a new avenue of studying the structure of the inner core of pellets and its impact on drug release. The potential importance of air trapped within the pellet starter cores can be understood only by such non-invasive technologies. The importance of the SR- μ CT shown by the Siepmann group extends beyond the oral coated pellet formulations. The technique, for instance, might be used for studying microparticles. In particular, no clear understanding exists on how drug molecules are released from the microparticles made of poly(lactic-co-glycolic acid). Advances in new non-invasive techniques will allow for an improved understanding of how controlled drug delivery systems work.

References

- [1] J. Siepmann, F. Siepmann, Mathematical modeling of drug delivery, *Int. J. Pharm.* 364 (2008) 328–343.
- [2] E. Kaunisto, M. Marucci, P. Borgquist, A. Axelsson, Mechanistic modelling of drug release from polymer-coated and swelling and dissolving polymer matrix systems, *Int. J. Pharm.* 418 (2011) 54–77.
- [3] M. Marucci, G. Ragnarsson, U. Nyman, A. Axelsson, Mechanistic model for drug release during the lag phase from pellets coated with a semi-permeable membrane, *J. Control. Release* 127 (2008) 31–40.
- [4] J. Fahier, S. Muschert, B. Fayard, C. Velghe, G. Byrne, J. Doucet, F. Siepmann, J. Siepmann, Importance of air bubbles in the core of coated pellets: Synchrotron X-ray microtomography allows for new insights, *J. Control. Release* 237 (2016) 125–137.

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