Journal of Controlled Release 188 (2014) 101

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Cover story

Dissolution mechanisms of felodipine solid dispersions

Of the various drug delivery routes, oral administration has been the most widely used and accepted means to deliver drugs for its simplicity and convenience to patients. Delivery of poorly soluble drugs by the oral route, however, has been difficult due to the insufficient amount of a drug dissolved for absorption from the gastrointestinal tract. To overcome the difficulties associated with poor water solubility various formulations have been developed including nanocrystals, nanoemulsions, polymer micelles, and solid dispersion. Solid dispersion formulations can be prepared by mixing a poorly soluble drug with a carrier polymer through melting or dissolution in solvents. Despite its usefulness only a dozen of solid dispersion formulations have been available clinically. One of the reasons for this low number is the lack of clear understanding on the drug stability in the solid dispersion formulation.

The drug molecules have to be released from the formulation for subsequent absorption. Traditionally, the amount of drug released into a dissolution chamber is measured, and a kinetic model is used to fit the data and gain some insight into the drug release mechanism. This indirect method, however, does not provide any direct information on the transition of the drug molecules from insoluble to soluble state. Several research groups have made good progress towards obtaining chemically meaningful, spatially resolved data in real time on dissolving tablets in aqueous environments. Magnetic resonance imaging (MRI) has been used to study drug–polymer compacts, providing detailed 3-dimensional time-resolved information, albeit with limited chemical specificity [1]. Infra-red (IR) spectroscopy methods (near-IR and mid-IR) provide excellent detailed chemical information, and good progress has been made in overcoming the challenges inherent from the very strong background signal from water [2]. Raman spectroscopy is relatively insensitive to water, and therefore in principle could offer a useful alternative approach. Data capture, however, is typically prohibitively slow, limiting experiments to time-resolved spectroscopy, or ex-situ mapping. Conventional lab-based Raman systems have been used in an ex-situ manner to provide chemical maps at individual time points, while more complex CARS (coherent anti-Stokes Raman spectroscopy) measurements can provide excellent time resolution for in-situ measurements, albeit at the expense of limited chemical sensitivity [3].

In this issue, the paper by Dr. Burley and his colleagues employs lab-based Raman mapping spectroscopy in a new, in-situ time-resolved manner, to investigate felodipine solid-dispersion formulations. They made a curious observation that increasing the amount of drug in a tablet leads to a decrease in the amount released into solution [4]. The samples, comprising felodipine and copovidone, were formulated as amorphous solid dispersions. Previous work had suggested that crystallization of the drug in the dissolution medium at higher drug loadings was behind this reduction in release as drug loads increased. By using rapid acquisition of Raman spectra, and accounting for the time-resolved nature of the experiment, the Burley team were able to chemically image this crystallization as it happened, while the tablet was dissolving. The key technical part of the work involved analyzing all data at all time points together as a single entity, rather than dealing with each individual time point separately. The team also modified an existing dissolution technique of intrinsic dissolution rate measurement, which looks at drug release into solution, by coupling to an HPLC system. This allowed both drug and polymer release to be measured, and new information about whether this process is dominated by drug or polymer to be obtained.

The study by the Burley team is highly significant, because it opens up new and powerful methods for studying drug release from solid dosage forms. It also provides very detailed time resolved and spatially resolved information on this key step in drug delivery. Understanding the drug behavior at the molecular level in the solid dispersion, as well as in other formulations, allows formulation scientists to design better oral delivery systems for poorly soluble drugs.

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http://dx.doi.org/10.1016/j.jconrel.2014.07.036
0168-3659/© 2014 Published by Elsevier B.V.