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# Absorption of orally administered ultrafine drug particles

Ultrafine amorphous drug particles (UAPs) less than 1 μm in size have been used to overcome the formulation challenges for delivery of poorly water-soluble drugs. The high specific surface area of the small size leads to significantly improved apparent solubility and dissolution, facilitating desired oral absorption of poorly water-soluble drugs. Moreover, UAPs have a great potential for intravenous, transdermal, ocular and pulmonary drug delivery due to high drug loading, stability and the minimum use of excipients. Despite the success of several commercial formulations, development of UAP formulations has been difficult. This is mainly due to inadequate understanding of the *in vivo* fate of UAPs. It has been difficult to discriminate drug particles from dissolved drug molecules *in vivo* [1]. Currently, the *in vivo* behavior of UAPs is mainly deduced from the measurement of total drug concentration in biological samples. The data of pharmacokinetics and biodistribution may be different from the *in vivo* distribution of undissolved UAPs. Thus, it has been necessary to develop workable strategies to identify drug particles in biological samples from dissolved drugs. The hybrid nanocrystal technology, by embedding a trace amount of fluorophores into the lattice of drug crystals, provided a universal tool for bioimaging of drug particles [2]. In that study, albeit innovative, the free fluorophores also gave signals, making it difficult to distinguish dissolved drug molecules from drug particles.

The paper by Professor Yi Lu and his coworkers in this issue presents a clever approach of separating the dissolved drug from the drug particles by incorporating environment-responsive near-infrared fluorescent probes into UAPs [3]. The rationale mirrors their group's previous innovation of probing the *in vivo* fate of drug carriers using the same probes [4]. The probes, with a BODIPY or an aza-BODIPY parent structure, demonstrate distinctive water-quenching properties due to the aggregation-caused quenching (ACQ) effect via intermolecular π-π stacking upon contact with water [4]. The probes emit fluorescence when molecularly dispersed, such as dissolved in organic solvent or in a drug carrier matrix, but form aggregates and quench immediately and fully when they are exposed to water. The on/off fluorescence switching provides a workable solution to identify UAPs *in vivo*. The drug particles are illuminated by embedding the probes, whereas the released probes, due to the dissolution of particles, quench spontaneously in the aqueous media. In this study, the Lu team entrapped ACQ probes into cyclosporine A UAPs to study the *in vivo* fate post oral administration. Because of the high fluorescence quantum yield, only a trace amount of the probes (less than 0.05%) in the drug particles was enough to emit strong fluorescence for live imaging without affecting the physical status of the particles.

The study by the Lu team presents a few very interesting observations. First, the drug particles can be accurately identified by embedding ACQ probes. The fluorescence of the drug particles stays stable, excluding possible attenuation from water infiltration or probe leakage. However, the fluorescence of the drug particles quenched instantly upon dissolution, indicating high water-quenching sensitivity. This established a good correlation between the fluorescence intensity and the particulate mass. Second, orally administered cyclosporine A UAPs may be directly absorbed through epithelial membranes. It is generally understood that UAPs dissolve readily upon administration, and almost all drugs are absorbed in a dissolved state. Contrary to this common belief, the fluorescence of the cyclosporine A UAPs was observed in the gastrointestinal tract even after 18 h post administration, suggesting slow, instead of instant, dissolution of the UAPs in the body. Whole-body fluorescence imaging detected fluorescence in the liver and lungs, indicating a possibility of absorption of intact drug particles. It is also possible that the fluorescent probes assemble again after absorption as individual molecules, but it may be less likely to form clusters only in certain regions of the body. The sections of jejunum and ileum provided solid evidence supporting the direct absorption of the particles through epithelial membranes. Also, the transmembrane of UAPs was supported by *in vitro* membrane models. The mucus layer impeded the cellular uptake of the particles, while the larger particles were preferably transported by M cells.

The drug delivery field is at a crucial inflection point [5]. Disappointing outcomes of nanoformulations in clinical studies indicate that our overall approach of nanomedicine needs serious reevaluation. Deciphering the *in vivo* fate of various ultrafine drug particles is now at the center of research interest, promising potentially significant breakthroughs [6]. The paper by the Lu team is important, as it provides an innovative bioimaging tool to identify integral UAPs from bulk signals, as well as information concerning the *in vivo* performance of UAPs. The development strategy based on the *in vivo* distribution of UAPs provides a good opportunity of developing clinically useful formulations that have been elusive to date.

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