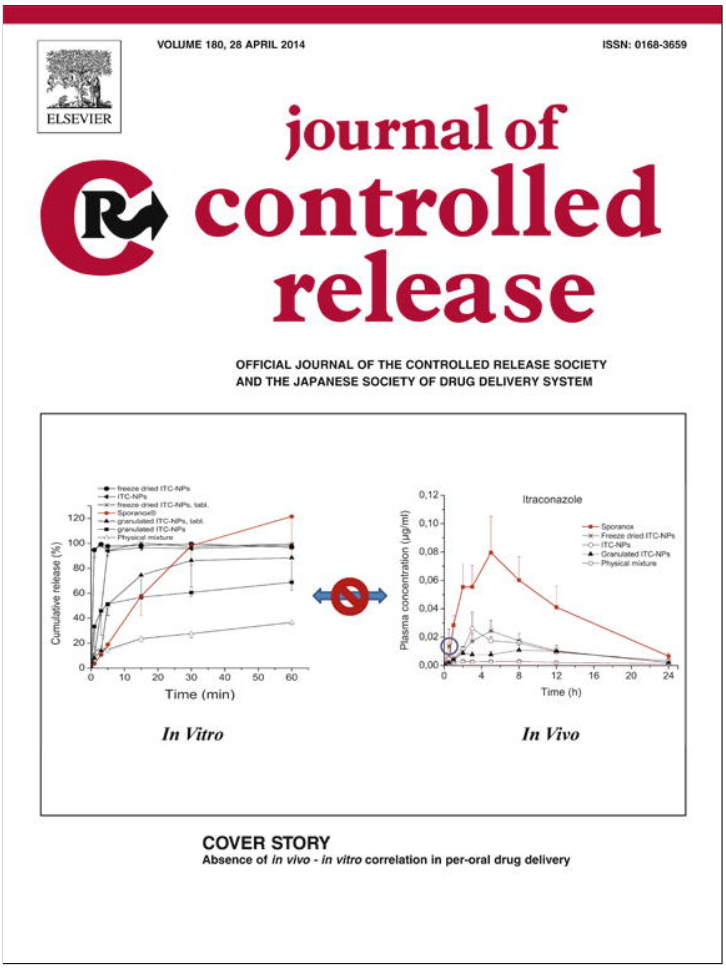

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Cover story

Absence of *in vivo–in vitro* correlation in per-oral drug delivery

The water-solubility of drugs is one of the important properties that affect the bioavailability. Many drugs are poorly soluble, and this creates formulation challenges. Of the many approaches used for improving drug solubility, the nanocrystal approach has been used successfully to develop several clinically available products. Nanocrystals, due to the presence of a huge surface area, improves dissolution properties often resulting in an increase in bioavailability. Although the nanocrystal approach has been useful, only several products have been successfully translated into commercial products. This number is miniscule considering the large number of poorly soluble drugs that require improved formulations. One assumption in improving the drug solubility is that improved dissolution results in improved bioavailability [1]. This is true in most cases, but this has not been tested extensively for the nanocrystal drugs. The fact that only several nanocrystal-based products are clinically available suggests a call for more careful studies. In fact, the *in vivo* characterization of different nanocrystal formulations has been largely missing. The *in vitro* and *in vivo* correlation (IVIVC) for nanocrystal formulations needs to be established for various drugs.

The paper by Sarnes et al. in this issue examines solid nanocrystal formulations as delivery systems of poorly soluble drugs [2]. Itraconazole (ITC) nanocrystal suspensions, prepared by media milling, were transformed into solid dosage forms by both freeze drying and granulation. The freeze dried ITC formulation proved to be equally advantageous as the suspension formulation both *in vitro* and *in vivo*. This is an important progress in itself. Even after a compaction process of both freeze-dried and granulated nanocrystal suspensions, the rapid *in vitro* dissolution characteristics were maintained. The ITC solid nanocrystal formulations were *in vitro* superior to Sporanox® capsules, a marketed itraconazole product which was used as a reference. When the *in vivo* bioavailability was compared, however, Sporanox® capsules significantly outperformed the nanocrystal formulations. This unexpected result indicates that the *in vitro* dissolution property alone may not be a good predictor of the *in vivo* bioavailability. In this particular case, the sugar beads in the Sporanox® formulation [3] may have increased its retention in the stomach where ITC is dissolved slowly and emptied into the intestine for enhanced absorption. On the other hand, the ITC nanocrystal formulations may have passed through the stomach rapidly like a liquid formulation due to increased dissolution. The solubility of ITC is lower in the intestine than in the stomach, and thus, the high concentration of ITC from nanocrystals may have precipitated in the small intestine. The peak drug concentration of the freeze dried formulation occurred in the first minutes, indicating rapid dissolution, followed by precipitation in the intestine. Because of this unique behavior of ITC in the gastrointestinal tract, its *in vivo* behavior could not be predicted on the basis of the *in vitro* analysis.

While more studies are necessary to clearly understand the lack of correlation between *in vitro* dissolution properties and *in vivo* drug absorption for ITC, the current study by Sarnes et al. presents a few important lessons. There may be many other drugs that show similar behavior as ITC. This may be one of the reasons why only a very small number of clinically used nanocrystal formulations have been developed. Each drug may have to be analyzed differently based on its pH-dependent solubility. If a drug is less soluble in the intestine, rapid dissolution in the stomach may not increase the bioavailability. The study is also a reminder of a long-felt need of developing effective gastric retention platforms. For the drugs like ITC having pH-dependent solubility and the drugs having a window for absorption, prolonged retention in the stomach may be as important as improving the drug solubility. It is vital to consider various formulation parameters carefully to develop clinically useful formulations, rather than relying on a single parameter such as water solubility alone.

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Kinam Park
Purdue University
Departments of Biomedical Engineering and Pharmaceutics
West Lafayette, Indiana, USA
E-mail address: kpark@purdue.edu

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