molecular pharmaceutics

editorial

Oral Bioperformance and 21st Century Dissolution

The ability to predict the oral bioperformance of a formulation from a laboratory based dissolution test is a long-term goal of the pharmaceutical scientist. This special issue is entitled "Oral Bioperformance and 21st Century Dissolution", and it demonstrates how far the science has progressed and yet how far it has to go to achieve this goal. Three keys to successful oral formulation design are stability, manufacturability, and in vivo performance. Current industry standards allow the pharmaceutical scientist to accurately predict the shelf life of a formulation under accelerated conditions. Similarly, recent advances even allow the manufacturability of formulations to be assessed using small amounts of material and lab sized equipment. The oral bioperformance of formulations, however, still remains a partially empirical art or mystery with dissolution testing at its core. USP Apparatus I was formally standardized and published in 1970 with Apparatus 2 appearing in 1980. While there have been some additional advances in regulatory type dissolution testing, progress has been slow compared to other areas of science. USP dissolution has been very successful and has allowed dissolution testing to be standardized and used as an analytical and quality control tool. It is perhaps an outgrowth of the 20th century vision of applying analytical tools to control product development and manufacture, to minimize changes and, in a way, to test quality into a product. However, only in certain circumstances, or after a large collection of empirical data, does this type of dissolution test allow a scientist to accurately predict the performance of a dosage form or even predict the in vivo impact of changes in a dosage form. USP dissolution tests even led to an entire branch of research defining in vitro/in vivo correlations between USP dissolution results and pharmacokinetic information.

We believe the 21st century is starting off differently. The human genome has been mapped for most of this decade. Systems biology is advancing and emphasizing an integrated view and understanding of biological systems. A more thorough and integrated view of the dosage form and how it interacts with our biological system (the gastrointestinal tract in this case) is consistent with this vision. In this liminal period, we are seeing a shift in regulatory emphasis from control to quality by design (QbD) which emphasizes material, process and product understanding and their influence on critical product attributes that impact performance. These changes are driving the movement toward an improved predictive capability of pharmaceutical science leading to improved oral bioperformance, but it necessitates a better understanding of the in vivo environment.

In this special issue of *Molecular Pharmaceutics*, several areas of research are highlighted that relate to oral bioperformance prediction. There are several innovative and nontraditional approaches to characterizing and understanding dissolution. Other topics address the simple, fundamental question of solubility, how to measure solubility in a way that is physiologically relevant, what is physiologically relevant media, and what are the proper methods for doing these studies. The question of supersaturation in vivo and modeling the impact of dynamic effects of solubility instead of using thermodynamic equilibrium solubility measurements is also discussed. The solid form is frequently key to all this. If the solid form and its solubility are understood, dissolution can be modeled successfully.

One must also consider the impact of the formulation on the dissolution and solubility as well as their time dependence. As pointed out in this issue, current models do not handle these factors very well and additional work is needed to bring the models up to snuff. If we are able to employ the right techniques, this will allow us to choose the proper solid forms and formulations and to correctly and accurately predict how they will behave in an in vivo system. This will lead to more robust formulation performance as seen in improved fraction absorbed, reduced food effects and reduced variability. As pharmaceutical scientists, our job is frequently to control how the compound is delivered to the intestine and the intestinal membrane. If we do this well, we have done our job.

The papers collected in this special issue show how much progress has been made recently in this area. But they also show how much more work is needed to achieve the vision of a lab based predictive system for oral bioperformance through better dissolution testing and modeling. Importantly, in this issue, there is a focus on models to try to convert laboratory data into pharmacokinetic profiles that enhance our understanding of what is actually happening in vivo. In QbD terminology: "process understanding"!

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