studies for this product can be waived [49]. BCS is thus a useful approach for which the FDA has issued a guidance [50]. As of July 2012, 37 drug substances have been found to be eligible for BCS I classification, allowing their oral products to be considered for biostudy waivers. Attempts have also been made [51] to ascertain the maximum absorbable dose using information such as solubility, transintestinal absorption rate constant, small intestine water volume, and transit time.

In Vitro/In Vivo Correlations

After a formulation is developed, meaningful in vitro dissolution in conjunction with techniques such as deconvolution can be used to establish an in vitro/in vivo relationship that is able to predict in vivo dissolution and absorption. These relationships between in vitro drug release and in vivo absorption (level "A," "B," or "C" correlation) are generally more likely for drugs exhibiting low solubility and high permeability (BCS Class II) and for ER products. When these IVIVCs have been established, in vivo bioavailability or bioequivalence studies, which are normally required, may be waived [4]. Polli [52] recently suggested development of an objective criterion to identify models a priori to IVIVC analysis.

LIMITATIONS OF IN VITRO DISSOLUTION

This chapter has focused on the general utility of dissolution testing. Nonetheless, the limitations of this methodology cannot be overlooked. The precision and accuracy of dissolution testing is often dependent on several subtle operational controls, including stirring element eccentricity, agitation alignment, torsional vibration, dosage form position, sampling position, dissolved gases, flow patterns, and heat transfer, among other factors, which if overlooked, may have a large effect upon the dissolution measurement. This is exemplified by a recent study demonstrating dramatically different dissolution rates arising from changes in tablet position, which are attributed to the segregation of solution hydrodynamics in the dissolution testing apparatus [53]. Therefore, strict observance of these many subtle factors are essential to assure reliable and reproducible test results.

Another limitation is that, in the absence of a suitable IVIVC, dissolution testing may not be particularly relevant to drug product performance. In the case of IR products containing BCS Class I and Class III drugs, dissolution testing may be "overdiscriminating" because its oral absorption is likely to be limited by gastric emptying or intestinal permeation. On the other hand, in the case of IR products containing BCS Class II and IV drugs, single-point dissolution testing may be "nondiscriminating" and hence may not be able to detect lots having poor in vivo performance. In addition, even when an IVIVC has been developed, this will likely be of limited value as such correlations are often "product specific."

Despite these apparent limitations, dissolution testing remains one of the most important and useful in vitro tests for assuring product quality. It is only by recognizing these limitations that one can make judicious conclusions regarding the significance or insignificance of a dissolution test result as it pertains to product performance. Recognizing these limitations will also enable the development of more meaningful and useful dissolution testing methodology.