Quality Assurance

A dosage form must possess acceptable in vivo bioavailability or bioequivalence performance characteristics. After pivotal in vivo studies, in vitro dissolution testing methodology and acceptance criteria are devised based on dissolution testing of these biolots as well as upon the current knowledge of drug solubility, permeability, dissolution, and pharmacokinetics. This in vitro dissolution testing is then performed on future production lots and is used to assess the lot-to-lot performance characteristics of the drug product and provide continued assurance of product integrity/similarity.

Product Stability

In vitro dissolution is also used to assess drug product quality with respect to stability and shelf-life. As products age, physicochemical changes to the dosage form may alter the dissolution characteristics of the drug product over time. For example, as the moisture level increases or decreases over time, this can result in altered tablet hardness and subsequent possible changes in dissolution characteristics. For some products, polymorph transformations to more stable and hence less soluble crystalline forms may result in reduced dissolution rates. As mentioned previously, for gelatin-encapsulated drug products, aldehyde-amino cross-linking over time may result in pellicle formation that also slows the dissolution rate [48]. As in vitro dissolution testing is performed for products throughout their shelf-life, this type of testing provides assurance of adequate product performance throughout the expiry period.

Comparability Assessment

In vitro dissolution is also useful for assessing the impact of preapproval or postapproval changes to the drug product, such as changes to the formulation or manufacturing process. Various "SUPAC Guidances," depending on the nature and extent of these changes, recommend either a single-point dissolution or dissolution profile comparison(s) to evaluate the effect of these changes. This type of in vitro comparability assessment is critical to ensure continued performance equivalency and product "similarity."

Waivers of In Vivo Bioequivalence Requirements

In vitro dissolution testing or drug release testing may be used for seeking waiver of the requirement to conduct in vivo bioavailability or bioequivalence studies in conjunction with the following.

Formulation Proportionality

In situations where an in vivo bioavailability and bioequivalence study is conducted on the highest strength of the drug product, in vivo bioavailability and bioequivalence testing on the lower strength(s) of the same dosage form may be waived, provided that the lower strength(s) are proportionally similar in their active and inactive ingredients and that their dissolution profiles have sufficient similarity [3,49].