# USP Dissolution and In Vivo Relevance

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In vitro dissolution of immediate release oral drug products is one of the most relevant tools to ensure batch to batch quality and process performance. This test is an integral component of any new drug application worldwide. Nevertheless, the in vivo relevance of the Quality control dissolution tests depends on the biopharmaceutical properties of the drug and the formulation characteristics. Ideally, the dissolution test conditions should discriminate product changes that may affect product performance. However unless an IVIVR or and IVIVC exists for the product, variations in dissolution behavior may or may not reflect variations in performance. To determine if a dissolution method can discriminate the impact of product changes the method needs to be challenged against in vivo data. Two recent reports aimed to estimate the probability of proving BE (or the risk of obtaining Non-BE or BI results) for products containing drugs from all BCS classes and how well QC in vitro dissolution test could predict the bioequivalence outcome (Cristofoletti R et al *J. Pharm. Sci.* 102(9) 2013 and Ramirez E et al *Br. J. Clin. Pharmacol.* 70(5) 2010). In both surveys the probability of obtaining a BE result when the dissolution profiles were similar was around 90% for Class 1 and 3 drugs (Post-tes probability or positive predictive value PPV), whereas for Class 2 drugs the posttest BE probability after a similar dissolution profile was 61%. On the other hand, the probability of false positive results (i.e similar dissolution but Non-BE results) was almost 90% for class 2 drugs. These results point out the lack of in vivo predictive value of the pharmacopoeial dissolution tests used. In Ramirez et al survey, Class 1 (provisionally classified) drugs products failing the BE test (in Cmax) were identified: Pravastatin and Zolpidem. As these products were available it was possible to perform dissolution studies using those drug products. Dissolution studies with the reference and test formulations were performed in USP 2 apparatus (50 rpm) at pH 1.2, 4.5 and 6.8 to explore the outcome of a BCS-based in vitro dissolution test. Caco-2 cell permeability studies and in situ closed loop perfusion studies in rats were develop with the API and with the formulations to explore any excipient effect on drug permeability. Dissolution profiles of Zolpidem formulations showed to be similar in all conditions for the BE and the Non-BE formulation while differences were detected for Pravastatin but with the BE formulation whereas the non-BE presented similar dissolution profiles. Two Cloperastine formulations (BE and Non-BE) were also studied and the biowaiver dissolution conditions were not able to detect the non-BE drug product. In the case of the Zolpidem product a biowaiver would have been granted considering the low risk associated with a difference in Cmax. Pravastatin as class 3 would have not received the biowaiver due to the difference in excipients and Cloperastine as class 2 is not a candidate. Due to the concerns regarding biowaiver extensions to class 3 and class 2 drugs the last revised version of the WHO recommendations about in vitro BE studies have been changed. In the new version the solubility definition requires that the highest single dose (instead of higher strength) has to be soluble in 250 mL at 1.2, 4.5 and 6.8. The class 3 drug product candidates are required to have the same qualitative and quantitative very similar excipient composition and the class 2 weak acids are no longer recommended for biowaivers. Agitation rate and time for complete dissolution in BCS biowaiver are also under debate. Several slow dissolution product (BE and Non BE) from a Class I compound, Desketoprofen trometamol have been investigated to explore the impact of the agitation rate (50 vs 75 rpm) in USP 2 apparatus and in the GastroiIntestinal Simulator (GIS) in order to find a methodology able to predict the BE outcome. Preliminary results will be presented and discussed to highlight the potential of in vivo predictive dissolution methods.