Dissolution Testing of Diltiazem HCl Extended-Release Capsule Products *

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ABSTRACT

Purpose: Typically, dissolution criteria for an extended-release (ER) drug product are based on the average dissolution data from pivotal clinical batches using multiple-time-point criteria that cover the entire profile of drug release. However, the lack of bio-predictive power for the *in vitro* dissolution may pose a risk to patients for ER products, as it prevents linking the *in vitro* testing results to *in vivo* performance. In this study dissolution was performed on brand and generic Diltiazem HCl ER capsule products to compare dissolution profiles under various conditions. According to the FDA's Orange Book, there are almost 20 reference listed drugs (RLDs) and approved generic drug products for Diltiazem HCl ER capsule products in the U.S. market, making this an ideal candidate for this study.

Methods: U.S. Pharmacopeia monograph (USP 40, Page 3780-3784) contains 16 dissolution tests for Diltiazem HCl ER capsules. These dissolution tests recommend various testing conditions with individual acceptance criteria. RLD and generic diltiazem ER capsule products purchased from the U.S. market were used in dissolution testing based on USP methods. Since the USP dissolution methods are different for each studied product, these diltiazem ER products were also tested

under the same dissolution testing method with USP simulated intestinal fluid (SIF). Additionally, the *in vitro* drug dissolution of the tested drug products from multimedia (pH 1.2, 6.8 and 7.2) using USP apparatus 1 and 2 method was also studied.

Results: The RLD and generic diltiazem products tested in this study all met the USP monograph dissolution specifications at L1 level. The dissolution for the RLD and some generic products showed similar release profiles which fit a single Weibull function. By contrast, two generic products showed different dissolution profiles and released the drug in two phases fitting a double Weibull function. The drug release for one product with different release profile was found to be pH-dependent. The drug release from other tested RLD and generic products was not shown to be pH-dependent. For individual drug products, dissolution profiles obtained from Apparatus 1 and 2 didn't show observable differences.

Conclusions: The dissimilar dissolution profiles observed may indicate the different release mechanisms due to the differences in formulation design. Thus, the selection of the dissolution method for generic drug product development should consider the difference in formulation design from the RLD. Exploration of the clinical relevance of *in vitro* dissolution tests in pharmaceutical development would be very valuable for guiding formulation and process development as well as assessing quality risk and setting patient-focused quality specifications. Further work will focus on physiologically-based pharmacokinetics analysis to assess the biopredictive performance of *in vitro* dissolution test methods and evaluate the potential impact of drug release on pharmacokinetic performance of Diltiazem ER products.

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