

Draft Guidance on Diltiazem Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Diltiazem hydrochloride

Dosage Form; Route: Extended-release capsule; Oral

Recommended Studies: Two studies

1. Type of study: Fasting
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 120 mg
Subjects: Males and non-pregnant, non-lactating females, general population excluding subjects with impaired ventricular function and cardiac conduction abnormalities
Additional comments: None

2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 120 mg
Subjects: Males and non-pregnant, non-lactating females, general population excluding subjects with impaired ventricular function and cardiac conduction abnormalities
Additional comments: None

Analytes to measure: Diltiazem and the active metabolites desacetyldiltiazem and desmethyl diltiazem in plasma

Submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolites, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}.

Bioequivalence based on (90% CI): Diltiazem

Additional strengths: Bioequivalence of 60 mg, 90 mg, and 180 mg strengths to the corresponding reference product strengths may be demonstrated based on principles laid out in the FDA guidance on "Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA¹."

¹ <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm>

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

In addition to the method above, for modified-release products, dissolution profiles on 12 dosage units each of test and reference products generated using United States Pharmacopeia (USP) Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

Due to concerns of dose dumping from this drug product when taken with alcohol, conduct additional dissolution testing on all strengths using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 500 mL, 0.1 N HCl, USP apparatus 2 (paddle) at 50 rpm, with or without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours.

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours.

Both test and Reference Standard (RS) products should be tested accordingly, and data should be provided on individual unit, means, range and %CV.