INTRODUCTION
Assessing therapeutic equivalence (TE) through dissolution studies (Biowaiver), is nowadays one of the experimental designs to prove interchangeability of pharmaceutical products. Some regulatory agencies accept these studies for Class 1 drugs (high solubility-high permeability) according to the Biopharmaceutical Classification System (BCS), when the drug is formulated in a rapidly dissolving solid oral dosage form, excluding drugs with a narrow therapeutic window. To demonstrate interchangeability, similarity in dissolution profiles between reference and test products has to be assessed (1,2,3). Experimental conditions of dissolution profiles for biowaiver are different from those of compendial methods like USP. The latter considers only one dissolution condition; in the case of citalopram tablets, dissolution medium is a pH 1.5 buffer (4). In contrary, for a biowaiver application, at least 3 different pH have to be tested, in the range of the gastrointestinal pH. Several guidances suggest the following pH values: 1.2 – 4.5 and 6.8, trying to represent pH ranging from the stomach to the middle part of the jejunum. Citalopram can be classified as a Class 1 drug according to BCS. Is used as solid dosage forms, 20 mg of dose. Its therapeutic window is 20-200 ug/L. According to these characteristics, citalopram tablets would be classified as a rapid dissolving product (5). The aim of this study was to evaluate the feasibility of a biowaiver protocol to assess TE for citalopram tablets, comparing the results obtained in an in vivo bioequivalence study with those of an in vitro dissolution study, in order to evaluate the concordance of the TE conclusions obtained from both protocols.

MATERIALS AND METHODS
Citalopram tablets, 20 mg dose, Reference (R) and Test (T) products.
In vivo study: crossover 2x2, n = 24 healthy volunteers. The protocol of the study was approved by the Ethical Review Board of the Clinical Hospital of the University of Chile, where the clinical part of the study was performed. A validated LC-MS-MS method was used for plasma citalopram assay. AUC, Cpeak, tpeak and K were obtained from plasma profiles. Comparison between T and R was assessed using the confidence bioequivalence interval of 80-125%. Absorption profiles were obtained assuming a one compartment model. In vitro study: dissolution profiles (n=12) were obtained with USP Apparatus 2 (paddle), 75 rpm, 37ºC, 900 mL of: HCl 0,1 N – acetate buffer pH 4.5 and phosphate buffer pH 6.8. Profiles obtained for R and T products in the 3 media were compared through the similarity factor f2.

RESULTS
T and R formulations were pharmaceutical equivalents. Formulations were bioequivalent when AUC and Cmax, both log transformed, were compared. 90% Confidence intervals were [99.8% - 101.2%] and [97.8% - 101.7%] respectively. Dissolution profiles showed no differences between R and T when pH 1.2 medium was used. At pH 4.5 and 6.8 differences were found at the first sampling times, specifically during the first 10 minutes. However, this differences don’t have a physiological meaning considering that at 15 minutes practically all the drug was released in the 3 media. Considering 20 minutes as the average gastric emptying times, the results of the study showed that R and T are completely dissolved when they are still at the stomach. From this point of view, T and R could be classified as a very rapid dissolving products (over 85% dissolved in 15 minutes at the pH range of the GI tract) and application of f2 for dissolution profiles comparison was not necessary (1,2).

CONCLUSIONS
Besides, due to this rapid dissolution behavior, no mathematical correlation could be found between dissolution and absorption profiles. According to the results of the dissolution study, both formulations can be considered as therapeutically equivalent and, therefore, interchangeable
Through the *in vivo* and *in vitro* studies the same conclusion regarding therapeutic equivalence was obtained. Bio waiver is a feasible model to evaluate therapeutic equivalence for citalopram tablets.

**REFERENCES**

2. Resolución Exenta Nº 727/05. Norma que define los criterios destinados a establecer equivalencia terapéutica a productos farmacéuticos en Chile. Publicada en el diario oficial el 29.11.05.
4. USP30/NF25, Rockville, United States Pharmacopeial Convention, Inc 2006

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