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Assessment of Dissolution Profile of Marketed Aceclofenac Formulations

Soni T, Chotai N[1]

Department of Pharmaceutics, Anand Pharmacy College, Sardar Patel University, Anand, Gujarat,
[1]AR College of Pharmacy, Sardar Patel University, Vallabh-Vidyanagar, Gujarat, India

Address for correspondence: *Dr. Narendra Chotai; E-mail: pharmacist_chotai2002@yahoo.co.in*

ABSTRACT

Statistical comparison of dissolution profiles under a variety of conditions relating to formulation characteristics, lot-to-lot, and brand-to-brand variation attracts interest of pharmaceutical scientist. The objective of this work is to apply several profile comparison approaches to the dissolution data of five-marketed aceclofenac tablet formulations. Model-independent approaches including ANOVA-based procedures, ratio test procedure, and pair wise procedure. The ratio test includes percentage, area under the curve, mean dissolution time, while the pair wise procedure includes difference factor (f_1), similarity factor (f_2), and Rescigno index. In the model-dependent approach, zero order, first order, Hixson-Crowell, Higuchi, and Weibull models were applied to the utilization of fit factors. All the approaches were applicable and useful. ANOVA with multiple comparison tests was found to be sensitive and discriminating for comparing the profiles. Weibull parameters were more sensitive to the difference between two release kinetic data in terms of curve shape and level.

Key words: Aceclofenac, pair wise procedures, ratio test procedures, Weibull parameters

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INTRODUCTION

In 1995, FDA issued a guidance Immediate Release Solid Oral Dosage Forms; Scale-up and Post approval Changes: Chemistry, Manufacturing, and Controls; *in vitro* Dissolution Testing; *in vivo* Bioequivalence Documentation (SUPAC-IR). The *SUPAC-IR* provides recommendations to sponsors of new drug applications (NDA's), abbreviated new drug applications (ANDA's), and abbreviated antibiotic applications (AADA's) who intend, during the post-approval period, to change (i) the components or compositions; (ii) the site of manufacture; (iii) the scale-up/scale-down of manufacture; and/or (iv) the manufacturing (process and equipment) of an immediate release oral formulation. For each type of change, the *SUPAC-IR* also defines (i) levels of changes; (ii) recommended chemistry, manufacturing, and controls tests for each level of change; (iii) *in vitro* dissolution and/or *in vivo* bioequivalence tests for each level of change; and (iv) documentation that should support the change.[1-3]

If dissolution profile similarity is demonstrated for the formulations before and after the changes, then expensive *in vivo* bioequivalence testing can be waived. Various procedures have been proposed for statistical assessment of dissolution profile similarity. These methods include application of either a nested model or an autoregressive time series model to the correlations between cumulative percents dissolved at different time points, and consideration of Mahalanobis distance as a criterion for the assessment of similarity in dissolution profiles between two formulations. Comparison of profiles representing a cumulative event over time is not unique to the pharmaceutical sciences. For

equivalence dissolution profile, especially to assure similarity in product performance, regulatory interest is in knowing how similar the two curves are, and to have a measure that is more sensitive to large differences at any particular time point.[4-11]

Aceclofenac is a poorly water-soluble NSAIDS drug according to the BCS system (class II) and its dissolution is rate-limiting step for its absorption.[12-14] Drug absorption from solid dosage forms after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. Because of the critical nature of the first two of these steps, *in vitro* dissolution may be relevant to the prediction of *in vivo* performance.

In order to evaluate equivalence in dissolution profile among branded and generic formulations of poorly soluble drug, aceclofenac, observations were taken on a given experimental unit over time and Mathematical equations were applied to analyze discrimination in profile and to demonstrate curve shape and level of the profile.

EXPERIMENTAL DETAILS

Materials

Aceclofenac (ACE) was gifted from Mepro Pharmaceutical Pvt. Ltd. potassium dihydrogen orthophosphate (Qualigen, Mumbai), sodium bicarbonate (Qualigens, Mumbai) NaOH (Merck) and distill water were used throughout the study. Branded and generic formulations of 100 mg aceclofenac were purchased form a commercial market.

Methods

In vitro dissolution study

Dissolution was performed on five formulations of 100 mg aceclofenac tablets, one branded (Reference) coded S1 formulation and four generic T1, T2, T3, T4 formulations. Dissolution was carried out on six units of each formulation using USP apparatus-II (Paddle) at 37 ± 0.5°C in 900 ml phosphate buffer medium of pH 6.8 at 50 rpm. After appropriate time interval, a sufficient volume of sample was withdrawn and filtered through Whatman filter No. 41. Immediately, same volume of the fresh dissolution medium was transferred to the dissolution flask. Samples were collected at suitable time interval and analyzed spectrophotometrically at 275 nm.

Statistical evaluation

ANOVA-based procedures

One-way ANOVA plus *post hoc* Tukey testing of percentage-dissolved data were applied using Microsoft excel 2007.

Model-independent methods

Ratio test procedures

Three types of ratio test procedures were performed: Ratio test of percentage dissolved, ratio test of area under the curve, and ratio test of mean dissolution time. Each of these procedures compares the dissolution profile of two formulations at a particular time point. Descriptive statistic form data analysis tool on three types ratio test were performed to analyze standard error and a 90% confidence level for the mean value of ratio of percentage dissolved, AUC, and mean dissolution time.

Pairwise procedures

These include difference factor f_1 and similarity factor f_2 (equations 1 and 2) and two indices of rescigno. Rescigno proposed a bioequivalence index (equation 3) to measure the dissimilarity between a reference and a test product-based on plasma concentration as a function of time. This index can also be used for drug dissolution data. Like the ratio test procedure, pairwise procedures compare the dissolution profile of a pair of products and employ a 90% confidence approach. The main advantage of the f_1 and f_2 equations is to provide a simple way to describe the comparison of the data. The f_1 factor measures the percent error between two curves over all the points.

$$f_1 = \left[\sum_{i=n}^{in}|R-T|\right] / \left[\sum_{i=1}^{p}R\right]\times 100 \quad (1)$$

$$f_2 = 1/\sqrt{50\log\left[1+(1/p)\sum_{i=1}^{p}(R-T)^2\right]}\times 100 \quad (2)$$

In both equations, R and T represent the dissolution measurements at P time points of the reference and test, respectively:

$$\xi i = \left\{\frac{\int_0^{\infty}\left|d_R(t)-d_T(t)\right|^i\,dt}{\int_0^{\infty}\left|d_R(t)+d_T(t)\right|^i\,dt}\right\}^{1/i} \quad (3)$$

where $d_R(t)$ is the reference product dissolved amount and $d_T(t)$ is the test product dissolved amount at each sample time point. i is any positive integer number. This, a dimensional, index always presents values between 0 are 1 inclusive, and measures the differences between two dissolution profiles. This index is 0 when the two release profiles are identical and 1 when the drug from either the test or the reference formulation is not released at all.

Model-dependent methods

Model-dependent approaches including zero order, first order, Hixson-Crowell, Higuchi, and Weibull models as described