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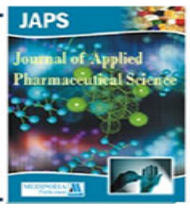

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Short Communication

Review of in vitro drug release test method's statistical evaluation to compare dissolution profile of semisolid dosage forms – Part I

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ABSTRACT

The aim of this mini-review study is to give an overview about *in vitro* drug release test methods statistical evaluation comparing dissolution profile of semisolids.

The FDA released guidance in May 1997 entitled Scale-up and Post Approval Changes for Nonsterile Semisolid Dosage Forms (SUPAC-SS). The guidance focuses on creams, gels, lotionts and ointments. The guideline desribes *in vitro* dissolution tetsing as an useful final quality control (QC) tool. The aim of it is to assure batch-to-batch quality of the product. Changes are separated in 4 categories in 3 Levels (Level 1,2,3). Level 2 recommends in vitro release (IVR) testing. Although there are several *in vitro* drug release test methods of semisolid dosage forms, their statistical evaluation is not clarified up to this day.

Our second challenge was to describe similarity and difference of these pharmaceutical dosage forms with use of similarity (f2) and difference (f1) factors. The FDA has issued these factors for solid dosage forms.

Our present work deals with calling attention on the lack of statistical validated method for semisolid dosage forms.

Keywords: semisolid dosage forms, dissolution, in vitro**.**

INTRODUCTION

In May, 1997 the FDA issued a guidance entitled Scale-up and Post Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Release Testing and In Vivo Bioequivalence Documentation for Nonsterile Semisolid Dosage Forms (SUPAC-SS). The guidance focuses on creams, gels, lotions and ointments. It describes changes in 4 categories: components and composition; manufacturing equipment and process; scale (batch size); site of manufacture. Changes are categorized in 3 Levels: Level 1,2,3. Level 1 means changes that are unlikely to have any detectable impact on formulation quality and performance of the product in contrast with Level 2, which could have this impact. For Level 2 changes the guideline recommends in vitro release (IVR) testing in addition to application and compendial specifications. Level 3 is which have a significant impact on formulation quality and performance of the product. This level contains of IVR test for a site change or in vivo bioequivalence where application and compendial specifications are met.

The IVR test can characterize the performance of the product. The guideline describes several critical parameters of the method; diffusion cell system, synthetic membrane, receptor medium, number of samples, sample applications, sampling time, sample analysis, IVR rate, design of the rate comparison study. (FDA Guidance for Industry, 1997; Shah et al., 1998).

Among several mathematical methods investigated for dissolution profile, f1 and f2 by Moore and Flanner are the most common used and simplest (Moore and Flanner, 1996).

METHODS

In Vitro Release (IVR) Test Comparison

The IVR test should be carried out as a two-stage study. At the first stage, 2 runs of (six cells) *in vitro* apparatus should be carried out, yielding 6 slopes for the prechange lot (R) and 6 slopes for the postchange lot (T). IVR should be expressed in percentage. If, at the first stage, the 90% confidence interval falls within the limits of 75% to 133.33%, no further *in vitro* test is necessary. If the test is not passed at the first stage, 4 additional runs of the apparatus should be carried out, yielding 12 additional slopes or 18 in all. The first step in the statistical evaluation is to form the 36=6x6 individual T/R ratios from the post- and prechange slope data. The second step is to order the 36 rations from lowest to highest. In the third step, the eigth and twenty-ninth ordered individual ratios are the lower and upper limits. The product can pass or fail at the first stage. If the product had not passed at the first stage, an additional 4 runs would have been carried out, yielding 12 additional slopes per lot, for a total of 18 slopes. All 324=18x18 would be obtained. At the second stage, the 110th and the 215th ordered individual ratios are the lower and upper limits. The product can pass or fail at the second stage.

In case of there is only 30=5x6 individual T/R ratios, the sixth and twenty-fifth ordered T/R ratio are the limits.

Similarity (f2) and difference factors (f1)

Moore and Flanner described 2 equations – a difference factor (f1) (1) and the similarity factor (f2) (2). Both of them are acceptable methods by FDA for dissolution profile comparison, although f2 is preferred (O'Hara et al., 1998).

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \times 100 \quad \dots (1)$$

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad \dots (2)$$

where n is the number of dissolution sample times, R*t* and T*t* the mean percent drug released at each time point: *t* for the reference and the test dissolution profiles.

The difference factor calculates the percent difference between the 2 curves at each time point and is a relative error between the 2 curves.

The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a similarity on percentage between the 2 curves.

Curves to be considered similar, f1 values should be close to zero – between 0 and 15 and f2 values should be close to 100 – between 50 and 100 (Shah et al., 1998).

CONCLUSION

FDA has focused on a dissolution profile comparison in the pre- and post approval changes and bioequivalence. A dissolution profile can characterize the product better than a single point dissolution test. It helps to assure product performance and bioequivalence.

Our aim is to evaluate the IVR test and the similarity and difference factors with our developed products – ointments, creams and gels – in the future. We would like to discuss the deficiences of this field and validate the in vitro, in vivo and also the statistical evaluation of semisolid dosage forms.

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