Comparison of dissolution profile of extended-release oral dosage forms — Two one-sided equivalence test

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The aim of this work is to present the two one-sided test (TOST) as an alternative approach to compare dissolution profiles of extended-release dosage forms. The dissolution profiles of oxycodone extended-release tablets containing 10 mg, 20 mg and 40 mg (reference and generic) were evaluated according to the requirements described in United States Pharmacopeia. These dissolution profiles were compared using the conventional similarity factor (f2) and the proposed TOST as an equivalence test. TOST is a simple and alternative approach to compare dissolution profiles of extended-release dosage forms. It allows us to identify the time-point (or time-points) that did not show similarity. We concluded that the two one-sided test performed at a significance level of 5% and defined as $\Delta = 10$ showed results comparable to those obtained by the conventional similarity factor (f2).

Uniterms: Dissolution profile. Extended-release tablets. Similarity factor. Two one-sided test. Equivalence test.

O objetivo deste trabalho é apresentar o teste uni-caudal duplo (TOST) como uma abordagem alternativa na comparação do perfil de dissolução de formas farmacêuticas de liberação prolongada. Os perfis de dissolução de comprimidos de liberação prolongada de oxicodona contendo 10 mg, 20 mg e 40 mg (genérico e referência) foram avaliados de acordo com os requisitos descritos na Farmacopeia Americana. Estes perfis de dissolução foram comparados empregando-se o fator de semelhança convencional (f2) e o método TOST como teste de equivalência. TOST é uma abordagem simples e alternativa para a comparação de perfis de dissolução de formas farmacêuticas de liberação prolongada. Este permite identificar o ponto (ou pontos) que não apresentou semelhança. Considerando-se $\Delta = 10$, concluímos que o teste uni-caudal duplo num nível de significância de 5% apresenta resultados comparáveis àqueles obtidos com o fator de semelhança convencional (f2).

Unitermos: Perfil de dissolução. Comprimidos de liberação prolongada. Fator de semelhança. Test uni-caudal duplo. Teste de equivalência.

INTRODUCTION

The absorption of a solid dosage form after oral administration depends on three factors: the release of the substance taken, the dissolution of the drug under physiological conditions and the permeability across the gastrointestinal tract. Due to the critical nature of the first two of these steps, an in vitro dissolution may be relevant to the prediction of an in vivo performance (Amidon *et al.*, 1995; FDA, 1997; Siewert *et al.*; 2003).

Dissolution studies can, among other useful purposes, be used as tools in the control of quality to demonstrate consistency in manufacture as well as similarity between different products/formulations. The dissolution profile comparison may be carried out using model independent or model dependent methods (EMEA, 2001).

An extended-release dosage form requires at least three test time points to characterize the in vitro drug release profile. An early time point, usually consisting of 1 to 2 hours, is used to show that there is little probability of dose dumping; an intermediate time point is chosen

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to define the in vitro release profile of the dosage form; a final time point is related to the complete release of the drug. Test times and specifications are usually established taking the evaluation of drug release profile data as a basis (USP 35, 2012a).

A simple model independent approach used a difference factor (f1) and a similarity factor (f2) to compare dissolution profiles (Moore, Flanner, 1996). The difference factor (f1) calculates the percentage (%) of difference between the two curves at each time point, there being a measurement of relative error between the two curves. The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and works as a measurement of the similarity in the dissolution percentage between the two curves (FDA, 1997).

This model independent method becomes the most suitable for dissolution profile comparison when the following recommendations are taken into account: (a) five or more dissolution time points must be available; (b) dissolution measurements of the test and reference batches must be made under the same conditions; (c) only one measurement must be considered after an 85% dissolution of both products; (d) the use of a mean will only be possible if the relative standard deviation (RSD) at the earlier time points is not superior to 20% and to 10% at other time points (FDA, 1997; O'Hara *et al.*, 1998; Shah *et al.*, 1998). An f2 value between 50 and 100 generally suggests similarity between the two dissolution profiles.

Studies carried out by several researchers demonstrated that the similarity factor (f2) is a useful tool to confirm similarity between two dissolution profiles. However, according to our practical experience, similarity factor f2 does not allow point-to-point comparison, occasionally not showing which time-point (or time-points) is not similar. These limitations are critical, particularly regarding extended-release dosage forms.

The aim of this work is to present the two one-sided test (TOST) as an alternative approach to compare dissolution profiles of extended-release dosage forms. Similarity factor f2 and two one-sided test (TOST) were compared, taking the results of dissolution profiles of oxycodone extended-release tablets as a basis. The two one-sided test has been employed in the assessment of pharmaceutical equivalence (Lourenço, Pinto, 2012).

MATERIAL AND METHODS

Extended-Release Tablets and Reference Standard

Oxycodone extended-release tablets of 10 mg, 20 mg and 40 mg (reference and generic) were purchased from Brazilian suppliers. Oxycodone hydrochloride reference standard (Batch: KOG276, Potency: 99.6%) was provided by United States Pharmacopeia.

Instrumentation

The dissolution tests were conducted using a VanKel system (VanKel VK 7010)−comprising a bath with six vessels−and meeting the physical and mechanical specifications required by the USP chapter <711> (USP 35, 2012b). The instrument was mechanically calibrated using a paddle and baskets, according to the USP requirements. An Agilent liquid chromatograph (Agilent 1200 Series) equipped with a binary pump, auto-sampler and UV variable wavelength detector was employed in the quantifications of dissolved oxycodone.

Dissolution test

The tests were conducted using 900 mL of simulated gastric fluid (without enzymes) maintained at 37.0 ± 0.5 ºC, using USP baskets at a rotation speed of 100 rpm. Aliquots of dissolution medium were withdrawn after 1, 2, 4, 8 and 12 hours of dissolution. Samples were filtered using 0.45 µm syringe filters, being their oxycodone content then analyzed by liquid chromatography.

The liquid chromatograph was equipped with a 230 nm detector and a 3.9 mm x 30 cm column containing 10 µm packing L1. It was maintained at a temperature of 60 ºC with a flow rate of about 1.0 mL per minute. Aliquots of 50 µL of oxycodone reference standard and sample solutions were injected into the chromatograph, having the amounts of dissolved oxycodone been calculated taking the areas obtained in the chromatograms as a basis (USP 35, 2012c).

Statistical analysis

The two one-sided test was employed as an equivalence test to compare the results of the dissolution profiles of reference generic products. Equivalence was tested by the determination of 90% confidence intervals (90% CI) based on the standard deviations obtained from the results of each time-point of the dissolution profiles. In this two one-sided test, we considered $\alpha = 0.05$. We rejected the null hypothesis and declared the dissolution profiles similar (or equivalent) when the 90% CI for the difference was completely contained in the defined range that was considered to be scientifically trivial ($\pm\Delta$). We considered that an appropriate range to equivalence testing should be defined taking the specifications of the

TABLE I - Dissolution results of oxycodone extended-release tablets

Dose (mg)	Time (h)	Acceptance Criteria (%)	Generic Mean (%) (RSD %)	Reference Mean (%) (RSD %)
40	1	37-57	45.5 (2.8)	45.6 (3.3)
	2	---	60.1 (2.9)	59.8 (3.1)
	4	68-88	77.1 (3.2)	76.2 (2.6)
	8	---	94.6 (3.5)	92.9 (1.7)
	12	NLT 85	101.0 (3.4)	98.7 (1.3)
20	1	33-53	44.1 (1.4)	45.8 (1.7)
	2	---	57.8 (1.5)	59.7 (1.5)
	4	63-83	74.4 (1.6)	76.7 (1.5)
	8	---	93.4 (2.0)	94.8 (1.2)
	12	NLT 85	102.9 (2.6)	101.0 (1.1)
10	1	29-49	39.5 (1.1%)	38.7 (1.5)
	2	---	51.6 (1.4)	50.8 (1.7)
	4	58-78	66.4 (1.4)	65.6 (1.8)
	8	---	84.0 (1.1)	83.1 (1.4)
	12	NLT 85	93.4 (1.2)	91.7 (1.8)

NLT: Not less than

dissolution test of extended-release dosage forms as a basis.

RESULTS AND DISCUSSION

The dissolution profile of oxycodone extended-release tablets containing 40 mg, 20 mg and 10 mg is shown in Figure 1. All the evaluated products comply with the acceptance criteria−shown in Table I−described in the United States Pharmacopeia (USP 35).

The two one-sided equivalence test showed that in all time-points evaluated the generic and reference

FIGURE 1 - Dissolution profiles for generic 10 mg (●), generic 20 mg (■), generic 40 mg (▲), reference 10 mg (○), reference 20 mg (□) and reference 40 mg (△) products.

products were found similar (Figure 2). According to the comparison results among doses, the two one-sided test showed that for some point-times there is not similarity (Figure 3). In the comparison between 10 mg and 40 mg generics we verified that the dissolution rates were not similar in 4 and 8hours. The same happened in the point-times of 8 and 12 hours when comparing 10 mg and 20 mg generics. These results are in accordance with the similarity factor (f2) obtained in each comparison, as shown in Table II.

The similarity factors (f2) obtained for the comparisons between generic 10 mg and generic 20 mg and between generic 10 mg and generic 40 mg reached a score above 52.6 and 55.3, respectively. In spite of this, these values were significantly lower than those obtained in the other comparisons, what might be a hint that the two one-sided test (TOST) is more rigorous (conservative) than the similarity factor (f2).

The two one-sided test (TOST) allowed us to identify the time-point (or time-points) that did not show similarity, what may help in the development of new products. This information is mistaken in the conventional similarity factor (f2) approach. One of the most important issues regarding the two one-sided test (TOST) is the definition of Δ. This acceptance criteria (±Δ) is the limit beyond which the difference in mean values should be considered scientifically significant. Its definition requires prior knowledge as well as its intended application. We
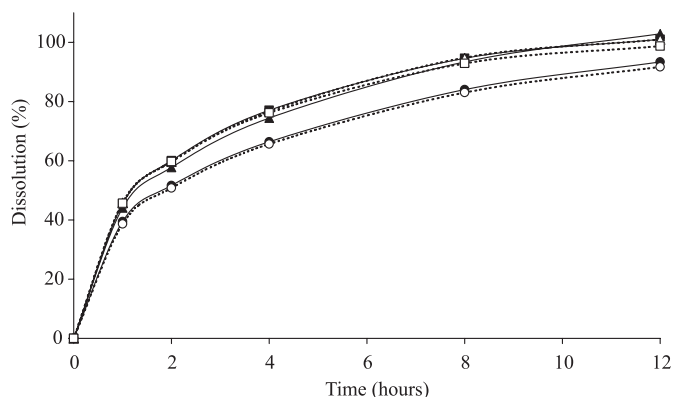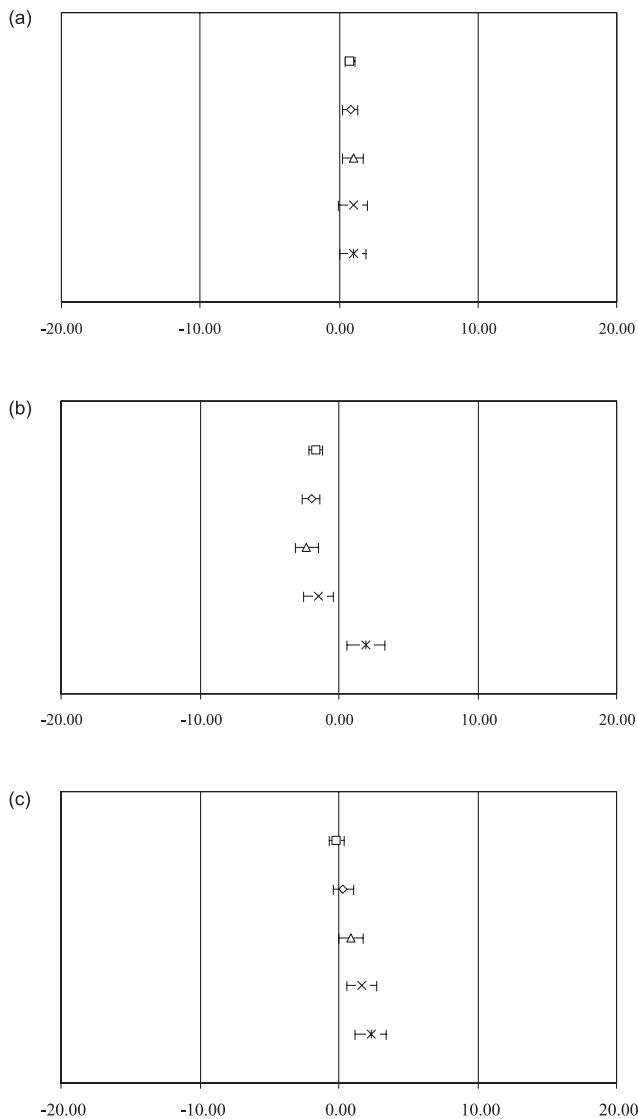
(a)

(b)

(c)

FIGURE 2- Equivalence test (two one-sided test) for dissolution profiles of 10 mg generic *versus* reference 10 mg (a), 20 mg generic *versus* reference 20 mg (b) and 40 mg generic *versus* reference 40 mg (c). Dissolution time-point of 1 (□), 2 (◇), 4 (△), 8 (×) and 12 hours (∗).
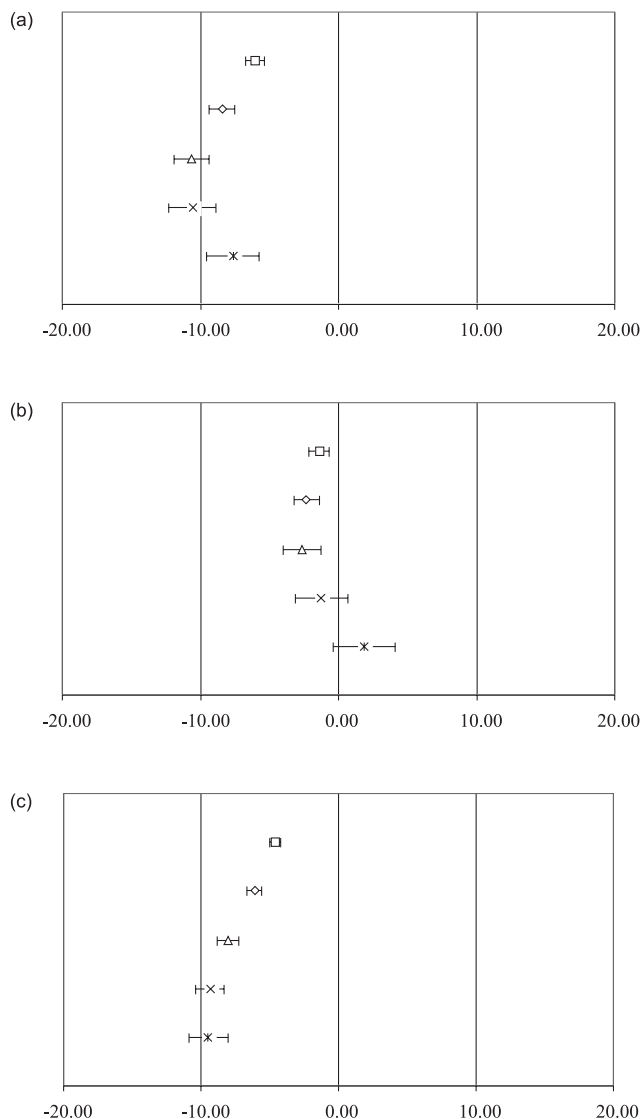
(a)

(b)

(c)

FIGURE 3 - Equivalence test (two one-sided test) for dissolution profiles of 10 mg generic *versus* 40 mg generic (a), 20 mg generic *versus* 40 mg generic (b) and 10 mg generic *versus* 20 mg generic (c). Dissolution time-point of 1 (□), 2 (◇), 4 (△), 8 (×) and 12 hours (∗).

TABLE II - Results of similarity factor (f2) and two one-sided test (TOST) for dissolution profile comparison of oxycodone extended-release tablets

Comparisons	Similarity factor (f2)	Two one-sided test (TOST)
Generic 10 mg *vs* Reference 10 mg	91.8	Similar
Generic 20 mg *vs* Reference 20 mg	83.5	Similar
Generic 40 mg *vs* Reference 40 mg	88.8	Similar
Generic 10 mg *vs* Generic 40 mg	52.6	Not similar*
Generic 20 mg *vs* Generic 40 mg	82.9	Similar
Generic 10 mg *vs* Generic 20 mg	55.3	Not similar**

*No similarity in 4 and 8 hours for Δ = 10. **No similarity in 8 and 12 hours for Δ = 10.

defined $\Delta = 10$ as an appropriate range to equivalence testing, based on the specifications of the dissolution test of extended-release dosage forms.

CONCLUSION

The two one - sided equivalency test (TOST) is a simple and alternative approach to compare dissolution profiles of extended-release dosage forms. It allows us to identify the time-point (or time-points) that did not show similarity. We concluded that the two one-sided test performed at a significance level of 5% and defined as $\Delta = 10$ presents results comparable to those obtained by the conventional similarity factor (f2).

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