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Comparative in vitro bioequivalence evaluation of atenolol tablets available in Sri Lanka

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Abstract: The availability of multiple brands for a single drug places health professionals and patients in a dilemma of drug substitution. Hence, evaluating bioequivalence of different brands compared to respective innovator drug is a timely need. This study was performed to compare the in vitro bioequivalence of commercially available brands of atenolol 50 mg tablets in the Sri Lankan market. Four different brands of atenolol 50 mg tablets (A1 – A4) and the innovator drug (A5) were selected for the study. All the tablets were tested for organoleptic properties, uniformity of weight, thickness and diameter, hardness, friability, assay percentage and dissolution. To evaluate in vitro bioequivalence of the selected drugs, their dissolution profiles were compared with the innovator drug using calculated fit factors (difference and similarity factors) and dissolution efficiencies of respective brands. The results of organoleptic properties of all the tested tablets showed no sign of defects. Tablets' thickness, diameter and hardness complied with the general standards. All the tested tablets complied with the British Pharmacopoeial (BP) standards for uniformity of weight, friability, assay percentage and dissolution. Tablets; A1-A4 had similarity factors above 50 and the difference factors below 15 revealing that their dissolution profiles are similar to the innovator product. According to the dissolution efficiency calculations, only A1, A2, and A3 of the selected brands of atenolol 50 mg tablets were similar with the innovator. Hence, the brands; A1, A2 and A3 could be regarded as bioequivalent thus expected to produce similar therapeutic effects.

Keywords: Bioequivalence, Atenolol, Tablets, in vitro

Introduction

Availability of several brands of a drug places health practitioners and patients in problematic situations like which one to be selected or is it possible to substitute with another brand.(Tamader, Y. E.; Mosbah, A. E. M.; Redab, 2016) New brands of the same drug from multiple sources are coming to the market time to time. Additionally, a number of undesirable clinical responses have also been reported as a result of batch-batch inconsistencies.(Thambavita et al., 2018) So, it is essential to monitor the quality of pharmaceutical products regularly.

Antihypertensive drugs are one of the drug categories that large extent of different brands are available in the market with significant price variations.(Kumar et al., 2015) Therefore, it is essential to compare and evaluate the bioequivalence of such drugs. Based on the wide usage, availability of several brands and price variations, atenolol tablets were selected for this study.

In vivo bioequivalence studies are time consuming, difficult and very expensive. Therefore, in vitro bioequivalence studies are established to check the bioequivalence among generics and brands. According to the Biopharmaceutics Classification System

(BCS), atenolol can be categorized as a class III drug substance.(Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms, 1997) In class III, in vitro – in vivo correlation can be expected only for rapidly dissolving drug substances. Atenolol is regarded as a rapidly dissolving drug, therefore in vitro bioequivalence studies through dissolution profiles can be applied in order to waive in vivo bioequivalence studies.

Materials and Methodology

The five brands of atenolol 50 mg tablets (coded as A1, A2, A3, A4 and A5) were used for the study. A5 was the reference drug.

Following tests were performed for all the tablets,

- visual observations for organoleptic properties
- test for thickness and diameter
- test for uniformity of weight
- hardness test
- friability test
- assay percentages
- dissolution test

Dissolution profiles were compared using fit factors (f1 & f2) and dissolution efficiency (DE) to evaluate in vitro bioequivalence of the selected drugs. Equations for f2, f1 and DE calculations are given below (Equation 1, 2 and 3)

Equation 1

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

Equation 2

$$f_1 = \left\{\frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t}\right\} \times 100$$

Equation 3

$$DE = \frac{\int_{t_1}^{t_2} y.dt}{y_{100} \times (t_2 - t_1)} \times 100$$

Results and Discussion

The visual inspection for colour, shape and surface texture of all the atenolol 50 mg tablets showed no sign of defects.

The physicochemical parameters of the tested atenolol 50 mg tablets are listed in Table 1.

Table 1: Evaluated physicochemical parameters of atenolol 50 mg tablets

Tested brands	Mean DE (%) with CIS	DE	CIS
A_1	77.74 (81.44 – 74.04)	-4.95	1.37
A_2	72.90 (75.27 – 70.53)	-0.11	4.88
A_3	76.51 (82.28 – 70.75)	-3.72	4.66
A_4	70.88 (80.80 – 60.96)	1.91	14.45
A_5	72.79 (75.41 – 70.17)	0.0	0

Mean DE is the mean value of dissolution efficiencies calculated for each of the 6 vessels of the dissolution apparatus.

DE = DE of innovator – DE of test brand

CIS = 95% Confidence Intervals

CIS = maximum possible mean DE value of innovator - minimum possible mean

DE value of test brand

This study shows that the price variation of the tablets tested may not be due to the quality of the product. However, the quality of ingredients, excipients and packaging materials in all these tablet formulas may not be the same. Therefore, stability and side effect profiles may vary. Even though some drugs comply with all routine quality control

tests and BP specifications, they may fail in bioequivalence studies.

Conclusion

The conventional quality control tests performed in this study indicated that all the selected brands of atenolol 50 mg tablets are chemically and pharmaceutically equivalent to the innovator brand. However, according to the in vitro bioequivalence studies, only A1, A2 and A3 are similar with its innovator drug; therefore bioequivalent.

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