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Equivalence Test of Some Commercial Brands of Theophylline and Diltiazem Present on Saudi Arabia Market

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ABSTRACT

The aim of this study was to compare the dissolution profiles of some commercially available brands of diltiazem hydrochloride and theophylline present on Saudi Arabia market. Dissolution studies for 8 h in pH 6.8 phosphate buffers (900 ml) were carried out on six tablets of each product using USP dissolution paddle at 37 ± 0.5°C and the stirring speed was maintained at 50 rpm. Drug concentration was determined at 236 nm and 272 nm using UV/Vis Spectrophotometer for diltiazem hydrochloride and theophylline, respectively. The kinetics of dissolution for all products used in this study were studied using three different equations, namely, the zero - order, the first - order and the Weibull equations. Also, the lyoequivalency of all products used in this study was tested by dissolution profiles comparison using the similarity factor (f2) and the two one-sided tests (Equivalence test - TOST). Results showed that two out of three commercial products of diltiazem hydrochloride showed zero – order kinetic, while the two commercial products of theophylline B1 and B2 showed first - order kinetic. Results from Weibull equation showed that the shape of dissolution profiles was parabolic (b<1) (case 3) for products A1, A2, B1 and B2 and was sigmoid (b>1) (case 2) for A3. Results obtained from the similarity factor (f2) as well as from the two one-sided tests indicate that all products used in this study have different dissolution profiles, and they were not similar. From the results of this study we strongly recommend that patients using one of these commercial products are not advised to switch on to another commercial product before consultation of their physician, as it may not give the same expected therapeutic response.

Keywords: Dissolution kinetic, Equivalence test, Similarity factor, Theophylline, Diltiazem hydrochloride

INTRODUCTION

Controlled and sustained release dosage forms were designed to release the active pharmaceutical ingredient (API) at a predetermined rate thus reducing the frequency of drug administration and improving patient compliance [1-4]. The efficacy of oral modified release dosage forms is dependent on the dissolution of the drug before reaching into the systemic circulation; therefore, the rate of dissolution is critical. Dissolution tests are used during the development and stability testing as part of product specifications. Many factors affecting the rate of drug dissolution from a dosage form *in vitro* such as the physical and chemical properties of the drug, product formulation, the dosage form of drug, dissolution testing apparatus, dissolution medium and pH environment [5-18]. A change in the dissolution rate will produce a change in the dissolution profile of the formulation that can produce a significant difference in the bioavailability of the drug from different formulations present in the market. Previous studies mentioned a number of mathematical models that can be used to describe the release rate of drugs from different drug delivery systems such as zero order kinetics, first-order kinetics, Higuchi, Korsmeyer-Peppas, Hixson-Crowell, Weibull distribution, Baker-Lonsdale, Gompertz and Hopfenberg models. In general, the common methods used to choose the "best model" that fit to study the dissolution/release phenomena are the coefficient of determination (R2), the mean square error (MSE), the sum of squares of residues (SSR) and the F-ratio probability [19-28]. Also, to compare dissolution profiles for different formulations it is possible to use other

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models, such as dissimilarity factor (f1), similarity factor (f2), two one-sided tests (Equivalence test - TOST) and Rescigno index (j) [28-35].

Previous studies demonstrated that the similarity factor (f2) and dissimilarity factor (f1) are useful tools to confirm similarity between two dissolution profiles. However, both factors f1 and f2 does not allow point-to-point comparison. Due to this disadvantage, an alternative simple method was proposed called two one-sided tests (Equivalence test - TOST). TOST is an alternative method that can be used to compare dissolution profiles and to provide the time-points that show similarity as well as the time-points that did not show similarity for modified release dosage forms [35].

A change in release profiles from using different commercial dosage forms present on the market for the same drug, such as theophylline or diltiazem hydrochloride, may result in the release of a lower or a higher amount of the drug than the recommended and hence could produce lower therapeutic response or toxic effects [36-38].

The aim of this work was to study the dissolution kinetic and the lyoequivalency (similarity of dissolution profiles) of some commercially available brands of theophylline and diltiazem hydrochloride present on the Saudi Arabia market. The kinetics of dissolution for all products used in this study were studied using three different equations, namely, the zero – order, the first – order and the Weibull equations. Also, the lyoequivalency of all products used in this study was tested by dissolution profiles comparison using the similarity factor (f2) and the two one-sided test methods.

MATERIALS AND METHODS

Materials

Pure diltiazem hydrochloride and anhydrous theophylline were obtained from Sigma Chemical Co. England. Three brands of diltiazem hydrochloride 90 mg (A1, A2 and A3) and two brands of theophylline 300 mg (B1 and B2) commercially available were purchased from the Kingdom of Saudi Arabia market. All the products were analyzed spectrophotometrically and were found to contain their corresponding label claim.

In vitro dissolution study

In vitro dissolution studies for 8 h in pH 6.8 phosphate buffer (900 ml) were carried out on six tablets of each product using USP dissolution paddle (Hanson Research Co., USA). The temperature of dissolution medium was controlled at 37 ± 0.5°C and the stirring speed was maintained at 50 rpm. Samples were withdrawn at predetermined time intervals and immediately replaced with equal volumes of phosphate buffer. Samples were filtered and then their concentrations were determined at 236 nm and 272 nm using UV/Vis Spectrophotometer for diltiazem hydrochloride and theophylline, respectively.

STATISTICAL ANALYSIS

For dissolution profiles comparison of all commercial products in this study, we used the two one-sided tests (equivalence test - TOST) as an equivalence test (XLSTAT equivalence test). The dissolution profiles similarity (equivalence) was evaluated by the determination of 90% confidence intervals according to the standard deviations of each time-point of the dissolution profiles. In this equivalence test - TOST (α=0.05), we exclude the null hypothesis and considered the dissolution profiles equivalent when the 90% confidence intervals for the difference were completely included in the predefined range that was considered to be insignificant ($\pm \Delta$) [35].

RESULTS AND DISCUSSION

To characterize the dissolution kinetics of diltiazem hydrochloride and theophylline from commercial products present on the Kingdom of Saudi Arabia market three equations were used, namely, zero – order, first – order and Weibull equations. The first order equation and the zero order equation describe if the release of drug from the formulation is concentration dependent or independent. The Weible equation can be applied for all types of dissolution studies and provide very important and useful information about the overall process of dissolution such as the shape of the dissolution profile, the dissolution time and the lag time.

As shown in **Table 1** and **Figure 1**, two out of the three commercial products of diltiazem hydrochloride showed zero – order kinetic with r2 values equal to 0.98 and 0.99 for A2 and A3, respectively. While the two commercial products of theophylline used in this study showed first – order kinetic with r2 equal to 0.99 and 0.98 for B1 and B2 respectively **(Table 1** and **Figure 2)**. It is evidence that A2 and A3 products containing different types of excipients as shown in **Table 2**, however, the dissolution profiles of the two products followed zero – order kinetics.

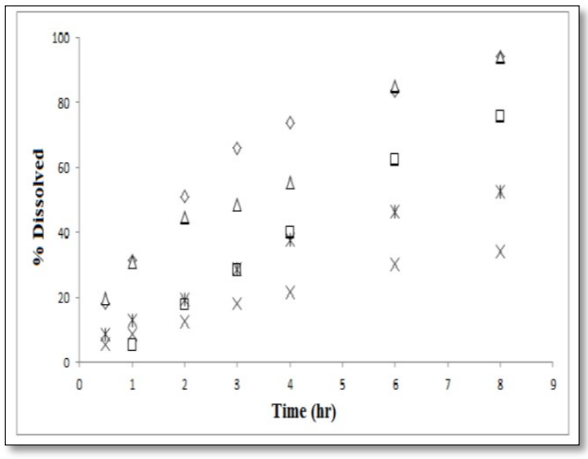

Figure 1. A linear plots of dissolution data in accordance with the zero-order equation for all products.
B1 (X), B2 (ж), A3 (□), A2 (Δ) and A1 (◊)

Table 1. Dissolution rate constant and r^2 values for all products obtained from the application of zero – order, first – order and Weibull equations.

Product	Weiblle distribution function				Zero order rate constant (K_0)	First order rate constant (K_1)
	Intercept	Shape scale (b)	Time scale (a)	Dissolution Time (t_d) per hour (h)		
A1	-0.423	0.925	2.66	2,88	9.41 r^2=0.89	0.352 r^2=0.98
A2	-0.464	0.860	2.91	3.46	9.68 r^2= 0.98	0.341 r^2=0.92
A3	-1.351	1.75	22.45	5.91	10.2 r^2=0.99	0.192 r^2=0.97
B1	-1.049	0.739	11.21	26.34	3.90 r^2=0.97	0.055 r^2=0.99
B2	-0.847	0.80	7.04	11.44	6.10 r^2=0.97	0.094 r^2=0.98

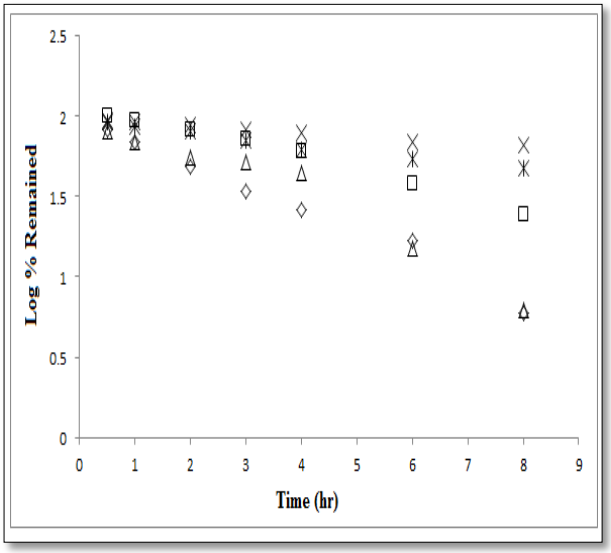

Figure 2. A linear plots of dissolution data in accordance with the first-order equation for all products.
A1 (◊), A2 (□), A3 (Δ), B1 (X) and B2 (ж)

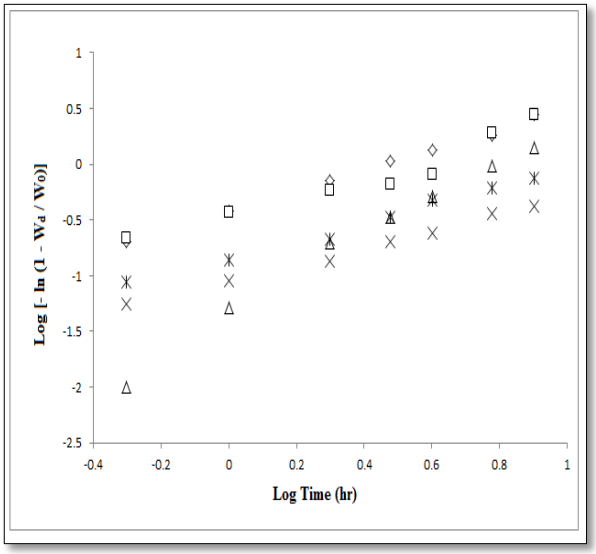

Figure 3. A linear plots of dissolution data in accordance with the Weibull distribution function model for all products.
A1 (◊), A2 (□), A3 (Δ), B1 (X) and B2 (ж)

The dissolution data of all products were plotted in accordance with the Weibull equation as shown in **Figure 3**. Results from **Table 1** showed that the values of the shape scale for products A1, A2, B1 and B2 were 0.92, 0.86, 0.74 and 0.80, respectively, indicates that the shape of dissolution profiles was parabolic (b<1) (case 3). The shape of dissolution profile for A3 was sigmoid with shape scale value equal to 1.75 (b>1) (case 2).

Also by using the Weibull parameters a and b, the time required for 63.2% of the drug present in the five products known as dissolution time, Td (Td=(a)1/b) was calculated. The dissolution time was significantly different between the products of the same drug (A1, A2 and A3) as well as for the products with different drugs (A and B) as shown in **Table 1**. The lowest value of dissolution time was for A1 with 2.8

h and the highest value of dissolution time was for B1 with 26.3 h. It is important to mention that both drugs (Diltiazem hydrochloride and theophylline) are classified as class I in the Biopharmaceutics Classification System (BCS) which mean that both drugs are highly soluble and highly permeable [39-42]. However, there was a significant difference between them in the dissolution kinetics as well as in the dissolution time and in the shape of dissolution profile. These differences may be due to the method of manufacturing and differences in the type of excipients used in each product as shown in **Table 2**.

Table 2. List of excipients present in each product as reported from the manufacturer.

Product	Excipients
A1	Not listed
A2	Lactosum monohydricum, Talcum, Ricini oleum hydrogenatum, Acidum stearinicum, Carboxymethylcellulosum natricum, Magnesii stearas, Methylhydroxypropylcellulosum, Titanii dioxidum, Polyaethylenglycolum 6000, Simeticonum
A3	Monosodium citrate, Sucrose, Povidone, Magnesium stearate, Macrogol 6000. Coating: Sucrose modified PVC, Acetyl tributyl citrate, Sodium bicarbonate, Ethylvanillin, Titanium dioxide (E 171)
B1	Not listed
B2	Hydroxyethylcellulose, Povidone (K25), Cetostearyl Alcohol, Macrogol 6000, Talc, Magnesium stearate

To test similarity between the products of the same drug we used two different methods, namely, the similarity factors (f2) and the two one-sided tests (equivalence test - TOST).

Similarity factor (f2) was calculated for all products used in this study **(Table 3)**. The similarity factor (f2) for A1 versus A2, A1 versus A3, A2 versus A3 and B1 versus B2 was 46.1, 25.2, 30.6 and 45.7, respectively. The values obtained from the similarity factor (f2) indicate that all products used in this study were not similar (if f2<50, dissolution profiles are defined as non-similar). These results were in agreement with the equivalence test - TOST performed for the same products that showed that all products were not similar as shown in **Table 3**. In addition to the information about the similarity of two dissolution profiles, the TOST helps us to identify the time-points that show similarity as well as the time-points that did not show similarity. This information can't be provided from the dissimilarity factor (f1) and similarity factor (f2) approach. According to the comparison results shown in **Figure 4**, the equivalence test - TOST showed that for many points – times there is no similarity. In the comparison between A1 versus A2 and A2 versus A3, we found that the dissolution profiles were not similar in all time points **(Figures 4A and 4C)**. While the results obtained from the application of the two one-sided tests for the comparison between A1 and A3 showed that the dissolution profiles were not similar in 3 and 4 h **(Figure 4B)**. Differences in the point – times were also observed in 3, 4, 6 and 8 h for the comparison between B1 and B2 as shown in **Figure 4D**.

Table 3. Similarity factor and the Two – One Sided Test (equivalence test – TOST) for all products.

Comparisons	Similarity factor (f_2)	Two one – sided test (TOST-equivalence test)
A1 & A2	46.1	Not Similar
A1 & A3	25.2	Not Similar
A2 & A3	30.6	Not Similar
B1 & B2	45.7	Not Similar

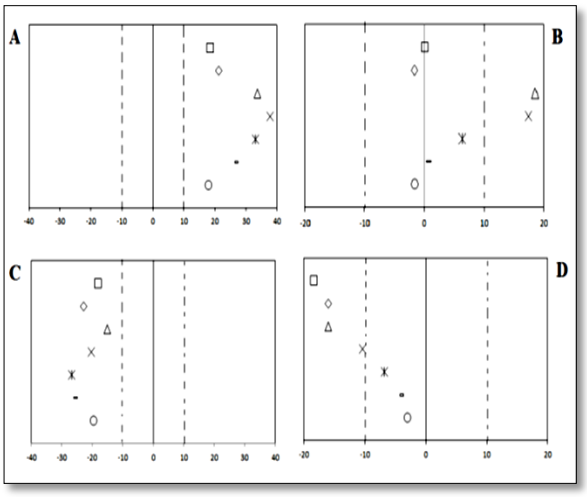

Figure 4. Two one-sided test (TOST – Equivalence test) for dissolution profiles of A1 versus A2 (A), A1 versus A3 (B), A2 versus A3 (C) and B1 versus B2 (D). Dissolution time-points of 0.5 (o), 1 (-), 2 (ж), 3 (X), 4 (Δ), 6 (◊) and 8 h (□).

CONCLUSION

Analyses of the dissolution kinetic data for diltiazem hydrochloride and theophylline commercial products present on Saudi Arabia market showed that two of three commercial products of diltiazem hydrochloride followed zero – order dissolution kinetic, while the two products of theophylline followed first order dissolution kinetic. Differences between products were also observed in the shape of dissolution profiles and dissolution time due to the method of manufacturing and type of excipients present in each product.

Results obtained from the similarity factor (f2) and from the equivalence test – TOST showed that the three commercial products of diltiazem hydrochloride as well as the two commercial products of theophylline available in the Saudi Arabia market are variant and not similar. It is important to note that products with different dissolution rate will change significantly the rate of absorption into the gastrointestinal tract as well as the level of drug concentration in the plasma and hence could produce a lower therapeutic response or toxic effects. From this study, it can be concluded that patients using either one of these commercial products of diltiazem hydrochloride or theophylline available in the Saudi Arabia market are not advised to switch on to another commercial product of the same drug before consultation of their physician, as it may not give the same expected therapeutic response.

CONFLICT OF INTEREST

The authors do not have any conflict of interest.

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