Acta Poloniae Pharmaceutica – Drug Research, Vol. 67 No. 1 pp. 93–97, 2010 ISSN 0001-6837
Polish Pharmaceutical Society

PHARMACEUTICAL TECHNOLOGY

TESTING LYOEQUIVALENCY FOR THREE COMMERCIALLY SUSTAINED-RELEASE TABLETS CONTAINING DILTIAZEM HYDROCHLORIDE

HAMZAH A. MASWADEH[1]*, OTHMAN A. AL-HANBALI[1] , REEM A. KANAAN[2] , ASHOK K. SHAKYA[1] and ANWAR MARAQA[1]

[1]Department of Pharmacy, Faculty of Pharmacy and Medical Sciences, Al-Ahliyya Amman University, 19328 Amman, Jordan
[2]Faculty of Pharmacy, Al-Zaytoonah University, Amman, Jordan

Abstract: *In vitro* release kinetics of three commercially available sustained release tablets (SR) diltiazem hydrochloride were studied at pH 1.1 for 2 h and for another 6 h at pH 6.8 using the USP dissolution apparatus with the paddle assemble. The kinetics of the dissolution process was studied by analyzing the dissolution data using five kinetic equations: the zero-order equation, the first-order equation, the Higuchi square root equation, the Hixson-Crowell cube root law and the Peppas equation. Analyses of the dissolution kinetic data for diltiazem hydrochloride commercial SR tablets showed that both Dilzacard and Dilzem SR tablets released drug by Non-Fickian (Anomalous transport) release with release exponent (n) equal to 0.59 and 0.54, respectively, which indicate the summation of both diffusion and dissolution controlled drug release. Bi-Tildiem SR tablets released drug by super case II (n = 1.29) which indicate zero-order release due to the dissolution of polymeric matrix and relaxation of the polymer chain. This finding was also in agreement with results obtained from application of zero-order and Hixson-Crowell equations. A dissolution profile comparative study was done to test the lyoequivelancy of the three products by using the mean dissolution time (MDT), dissimilarity factor f_1 and similarity factor f_2. Results showed that the three products are different and not lyoequivalent.

Keywords: lyoequivelancy, diltiazem hydrochloride, Higuchi, Hixson-Crowell and Peppas equations

Diltiazem hydrochloride is a calcium ion, cellular influx inhibitor used in long-term treatment of coronary heart disease and in long-term therapy for arterial hypertension (1). Common side effects are nausea, fatigue, dizziness and pruritus with or without a rash. In higher doses, ankle or leg edema and in rare cases, bradycardia or a slight elevation in serum enzymes (SGOT, SGPT and LDH) have been observed. Therefore, close monitoring of patients with impaired hepatic function during therapy with diltiazem hydrochloride is recommended and dosage must be adjusted to each patient's needs (1, 2).

The development of oral controlled-release dosage forms has attracted much attention in recent years. These dosage forms were designed to deliver the drug at a controlled and predetermined rate thus maintaining a therapeutically effective concentration of the drug in the systemic circulation for a long period of time, also reducing the frequency of dosing and improving patient compliance (3, 4). Previous studies have shown that the diverse manufacturing techniques employed in the preparation of SR dosage forms give very different release patterns (5, 6).

A change in release patterns from using different dosage forms available on the market for the same drug, such as diltiazem hydrochloride, may result in the release of a larger amount of the drug than the recommended and hence could produce toxic effects.

The aim of this study was to analyze the dissolution kinetic data and to test the lyoequivalency of three commercially available SR tablets of diltiazem hydrochloride, namely; Dilzem retard, Bi-Teldiem and Dilzacard. To achieve this goal, an attempt was made to study the *in vitro* release characteristics and kinetics of three commercially available SR diltiazem hydrochloride tablet preparations. The kinetics of the dissolution process were studied applying five different kinetic equations to the dissolution data, namely, the zero-order, the first-order, the Higuchi square root, the Hixson-Crowell cube law and the Peppas equations.

* Corresponding author: e-mail:.maswadehhamza@hotmail.com

A comparative study of the dissolution profiles was done, to test the lyoequivalency of the three formulations using the mean dissolution time (MDT), the dissimilarity factor (f_1) and the similarity factor (f_2).

EXPERIMENTAL

Materials and Methods

The products tested were Bi-Teldiem (sustained-release coated tablets, Sanofi-Synthelabo, Paris, France), Dilzem retard (sustained action tablets, Parke-Davis, Godecke AG, Germany), and Dilzacard (sustained action tablets, Dar Al Dawa, Amman, Jordan). The drug content in each product was 90 mg of diltiazem hydrochloride. Pure diltiazem hydrochloride was obtained from Dar Al Dawa, Amman, Jordan. All the products were analyzed spectrophotometrically at 236 nm and were found to contain their corresponding label claim.

Dissolution studies

In vitro dissolution studies were carried out on six tablets of each product using USP dissolution paddle (Hanson Research Co., USA) for 2 h in pH 1.1 (0.1 M HCl, 900 mL, simulated gastric fluid without enzyme). Then, the dissolution medium was replaced with pH 6.8 phosphate buffer (900 mL, simulated gastric fluid without enzyme) and tested for drug release for another 6 h. The temperature of dissolution medium was controlled at 37 ± 0.5°C and stirring speed was maintained at 50 rpm. Samples (5 mL) were withdrawn at predetermined time intervals and immediately replaced with equal volumes of dissolution medium. Samples were filtered (0.45 Millipore filter) and then their concentrations were determined using UV/Vis Spectrophotometer (Varian, Australia) at 236 nm.

RESULTS AND DISCUSSION

In order to describe the kinetics of the release process of diltiazem hydrochloride in the 3 products (commercial SR tablets), various equations were used such as the zero-order rate equation, which describes the systems where the release rate is independent of the concentration of the dissolved species (5). The first-order equation describes the release from systems where dissolution rate is dependent on the concentration of the dissolving species (6). The Higuchi square root equation, describes the release from systems where the solid drug is dispersed in an insoluble matrix and the rate of drug release is related to the rate of drug diffusion (7, 8). The Hixson-Crowell cube root law describes the release from system where there is a change in surface area and diameter of the particles or tablets (9, 10). The applicability of all of these equations was tested and results were compared with data obtained from Peppas equation, which is often used to describe the drug release from polymeric system.

The dissolution data obtained for all products at pH 1.1 for 2 h and at pH 6.8 for another 6 h were plotted in accordance with the zero-order equation, i.e., percent dissolved as a function of time (Fig. 1). The results showed that percent of drug dissolved from Dilzem Retard, Bi-Teldiem and Dilzacard in 0.1 M HCl with pH = 1.1, within 2 h were 44 %, 17 % and 50 %, respectively, while percent of drug dissolved after 8 h dissolution (2 h in 0.1 M HCl with pH = 1.1 and 6 h in phosphate buffer with pH = 6.8) were 93 %, 75 % and 93 %, respectively. It is evident from Figure 1 and Table 1 that the zero-order equation can best describe the kinetics of the dissolution process of diltiazem hydrochloride from Dilzem retard and Bi-Teldiem, with r^2 values 0.970 and 0.992, respectively.

The dissolution data of the three products were plotted in accordance with the first order equation, i.e. the logarithm of the percent remaining as a function of time (Fig. 2). It is evident from Figure 2 and Table 1 that the first-order equation described the kinetics of the dissolution process of diltiazem hydrochloride from Dilzacard best, with r^2 value 0.985.

The dissolution results were plotted in accordance with the Higuchi square root equation, i.e., percent dissolved as a function of the square root of time (Fig. 3). A linear relationship was obtained after an initial lag time had lapsed in all cases. The linearity of the plots indicates that the release process is diffusion-controlled.

The dissolution data were also plotted in accordance with the Hixson-Crowell cube root law, i.e.,

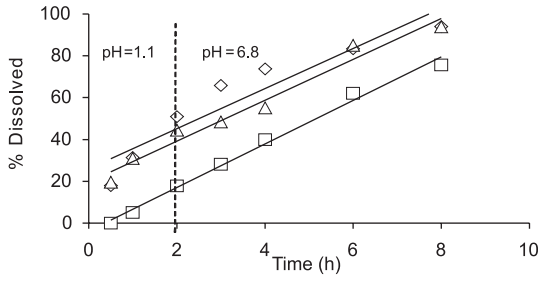

Figure 1. A linear plot of % dissolved versus time for the dissolution data in accordance with zero-order equation. Dilzacard (◊), Bi-Tildem (□) and Dilzem Ret. (Δ)

Table 1. Dissolution rate constants, r^2, n values and MDT for tested products obtained from application of different kinetic equations

Trade Name	Zero order rate constant (K_0)	First order rate constant (K_1)	Higuchi square root rate constant (K_2)	Hixson-Crowell rate constant (K_3)	Peppas rate constant (K_4)	Peppas constant (n)	MDT (min)
Dilzacard	9.586 $r^2 = 0.890$	0.329 $r^2 = 0.985$	35.861 $r^2 = 0.973$	0.416 $r^2 = 0.983$	0.305 $r^2 = 0.98$	0.596	164
Bi-Teldiem	10.390 $r^2 = 0.992$	0.189 $r^2 = 0.986$	37.017 $r^2 = 0.983$	0.288 $r^2 = 0.929$	0.061 $r^2 = 0.98$	1.292	293
Dilzem Ret.	9.775 $r^2 = 0.970$	0.334 $r^2 = 0.937$	34.906 $r^2 = 0.966$	0.392 $r^2 = 0.868$	0.291 $r^2 = 0.98$	0.547	203

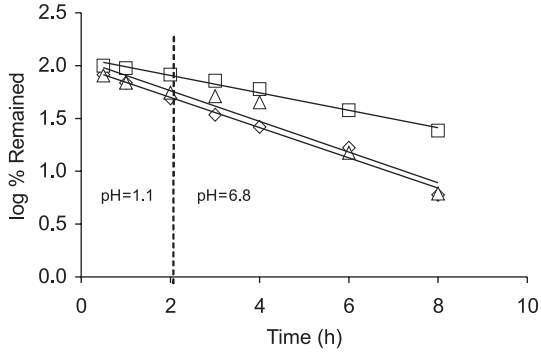

Figure 2. A linear plot of log (% remaining) versus time for the dissolution data in accordance with the first-order equation. Dilzacard (◊), Bi-Tildem (□) and Dilzem Ret. (Δ)

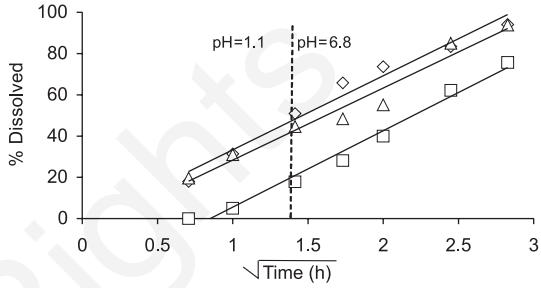

Figure 3. A linear plot of % dissolved versus square root of time for the dissolution data in accordance with the Higuchi square root equation. Dilzacard (◊), Bi-Tildem (□) and Dilzem Ret. (Δ)

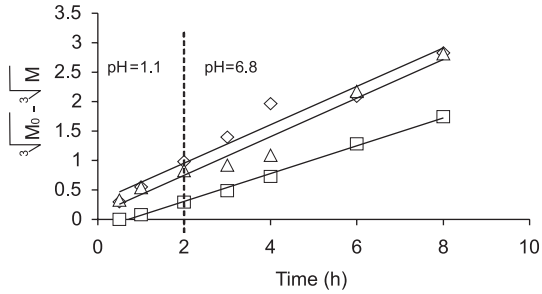

Figure 4. A linear plot of the cube root of the initial concentration minus the cube root of percent remaining versus time for the dissolution data in accordance with the Hixson-Crowell cube root law. Dilzacard (◊), Bi-Tildem (□) and Dilzem Ret. (Δ)

the cube root of the initial concentration minus the cube root of percent remaining, as a function of time. Figure 4 and Table 1 indicate that a linear relationship was obtained in all cases, with the r^2 value for Dilzacard being slightly higher than those for Dilzem retard and Bi-Teldiem. Erosion of the swollen polymer was higher in Dilzacard as visually inspected during dissolution testing, which explains the higher r^2 value for Dilzacard.

The best fit with higher correlation was found with the Higuchi's equation for all formulations. Two

Table 2. Dissimilarity factor f_1 and similarity factor f_2 obtained from dissolution profile comparative study

Group	f_1	f_2
Dilzacard & Dilzem	11.09	49.95
Dilzacard & Bi-Teldiem	45.16	27.68
Dilzem & Bi-Teldiem	39.39	33.25

factors, however, diminish the applicability of Higuchi's equation to matrix system. This model fails to allow for the influence of swelling of the matrix upon hydration and gradual erosion of the matrix. Therefore, the dissolution data were also fitted according to the Peppas equation, which is often used to describe the drug release from polymeric system (11, 12).

$$M_t/M_a = K\, t^n \quad (1)$$

where M_t/M_a is the fractional drug release at time t; K is a constant incorporating the properties of the macromolecular polymeric system and the drug and n is a kinetic constant which depends on and is used to describe the transport mechanism. The value of n for a tablet, n = 0.45 for Fickian (Case I) release, > 0.45 but < 0.89 for non Fickian (anomalous) release and 0.89 for case II (zero-order) release and > 0.89 for super case II type of release.

Equation one was used to calculate the n values and to identify the drug release mechanism of drug from the three SR tablets used in this study.

Table 1 showed that both Dilzacard and Dilzem SR tablets released the drug by non-Fickian (anomalous transport) release with release exponent (n) equal to 0.59 and 0.54, respectively, which indicate the summation of both diffusion and dissolution controlled drug release. While Bi-Tildiem SR tablets released drug by super case II (n = 1.29) which indicate zero-order release due to the dissolution of polymeric matrix and relaxation of the polymer chain. This finding was also in agreement with results obtained from application of zero-order and Hixson-Crowell equations.

Due to the differences in drug release kinetics, the Peppas constant K, though is one of the measures of release rate, should not be used for comparison. Therefore, to characterize the drug release rate in different formulations, mean dissolution time (MDT) was calculated from dissolution data according to Mockel and Lippold using the following equation (11, 12):

$$MDT = (n / n+1) \cdot K^{-1/n} \quad (2)$$

MDT value is used to characterize the drug release rate from the dosage form and the retarding efficacy of the polymer. A higher value of MDT indicates a higher drug retarding ability of the polymer and vice-versa. The MDT value was found to be 164 min, 202 min and 293 min for Dilzacard, Dilzem and Bi-Teldiem, respectively, indicating a higher drug retarding ability of the polymer used for Dilzacard compared to the polymer used for Dilzem and Bi-Teldiem tablets. As shown in Table 1, this differences in MDT value was found statistically significant (statistical significant difference was considered when $p < 0.05$ using unpaired *t*-test). It may be due to the different type of polymer used, which means different polymer properties such as hydrophilicity/lipophilicity, molecular weight and tortuosity or due to the relative ratio of drug and polymer used in the three formulations.

Also a dissolution profile comparison was done using dissimilarity factor f_1 and similarity factor f_2 to compare the dissolution profile of diltiazem hydrochloride for tested commercial SR tablets used in this study.

Dissimilarity factor f_1 was calculated from the following equation (12, 13):

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100 \quad (3)$$

Similarity factor was calculated from the following equation (12, 13):

$$f_2 = 50 \log \{[1 + 1/n \sum_{t=1}^{n} W_t (R_t - T_t)^2]^{-0.5} \times 100\} \quad (4)$$

where R_t is the reference assay at time point t, T_t is the test assay at time point t, n is the number of pull points and W_t is the optional weight factor.

Similarity factor f_2 was calculated for dissolution profile comparison of Dilzacard with Dilzem Retard, Dilzacard with Bi-Teldiem and Dilzem with Bi-Teldiem, f_2 were 49.9, 27.6 and 33.2, respectively (Table 2). This indicate that commercial products tested in this study are not similar, and they are not lyoequivelant ($f_2 > 50$, dissolution profiles are defined as similar) (13, 14).

Dissimilarity factor f_1 was calculated for dissolution profile comparison of Dilzacard with Dilzem Retard, Dilzacard with Bi-Teldiem and Dilzem with Bi-Teldiem, f_1 being 11, 45 and 39, respectively (Table 2). This indicate that commercial products tested in this study are different (% error increases as the dissimilarity between two profiles increases) (13, 14).

CONCLUSIONS

Analyses of the dissolution kinetic data for diltiazem hydrochloride commercial SR tablets showed that both Dilzacard and Dilzem SR tablets released drug by non-Fickian (anomalous transport) release, while Bi-Tildiem SR tablets released drug by super case II which indicates zero-order release. This finding was also in agreement with the results obtained from application of zero-order and Hixson-Crowell equations.

Based on the *in vitro* results obtained from this study, the calculated values for MDT, f_1 and f were found to be significantly different, this showed that the three commercially SR tablets available in the market are variant and not lyoequivalent. In order these three formulations to be bioequivalent they are expected to be firstly lyoequivalent. On the other hand, *in vitro* study is not enough to justify the bioequivalency of these three products. Currently, *in vivo* study is ongoing to test the bioequivalency of these formulations. This signifies the importance of this work, since patients using either one of these products are not advised to switch on to another product, as it may not give the same therapeutic response.

REFERENCES

1. Shan-Yang L., Tzu-Lag L.: Drug Dev. Ind. Pharm. 19, 1613 (1993).
2. Pabon CV., Frutos P., Lastres JL., Frutos G.: Drug Dev. Ind. Pharm. 18, 2163 (1992).
3. Khanvilkar KH., Huang Y., Moore A.D.: Drug Dev. Ind. Pharm. 28, 601 (2002).
4. uárez H., Rico G., Villafuerte L.: Int. J. Pharm. 216, 115 (2001).
5. Baveja SK., Range RKV., Singh A., Gombar VK.: Int. J. Pharm. 41, 55 (1988).
6. Najib N., and Suleiman M.: Drug Dev. Ind. Pharm., 11, 2162 (1985).
7. Obaidat AA., Obaidat RM.: Eur. J. Pharm. Biopharm. 52, 231 (2001).
8. Dortunc B., Gunal N.: Drug Dev. Ind. Pharm. 23, 1245 (1997).
9. Jalal I., Zmaily E., Najib N.: Int. J. Pharm. 52, 63 (1989).
10. Buckton G., Ganderton D., Shah R.: Int. J. Pharm. 42, 35 (1988).
11. Ritger PL., Peppas NA.: J. Control. Release 5 37 (1987).
12. Lopes CM., Lopes JF., Costas P., Pinto JF.: Drug Dev. Ind. Pharm. 32, 95 (2006).
13. Avachat A., Vikram K.: AAPS PharmSciTech. 8, 88 (2007).
14. Maswadeh H., Semreen M., Abdulhalim A.: Acta Pol. Pharm. Drug Res. 63, 63 (2006).

Received: 02. 06. 2009