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A Five-Year Stability Study of Controlled-Release Diltiazem Hydrochloride Tablets Based on Poly(Ethylene Oxide)

Laila H. Emara, Ahmed A. El-Ashmawy, Nesrin F. Taha

Industrial Pharmacy Laboratory, Medical and Pharmaceutical Chemistry Department, Division of Pharmaceutical Industries, National Research Centre, 33 EL Bohouth st. (former EL Tahrir st.), Dokki, Giza, P.O.12622, Egypt.

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ABSTRACT

The aim of this study is to investigative the stability of poly(ethylene oxide) (PEO) matrix tablets containing diltiazem hydrochloride (DTZ) after five-year storage at room temperature. DTZ matrix tablets containing different molecular weights (M_W) of PEO and electrolytes (sodium carbonate anhydrous Na_2CO_3, potassium chloride KCl and pentasodium tripolyphosphate anhydrous PSTPP) were prepared. The fresh and stored tablets were evaluated by DTZ content, *in vitro* drug release rates and kinetics as well as DSC. All the PEO's matrix tablets showed no significant changes in release rate, kinetics and drug content. The release rates of DTZ following five-year storage were slightly increased as the M_W of PEO increased from 900,000 to 8,000,000. Also, it was clear that the addition of electrolyte drastically slowed the release rates of DTZ from fresh and stored tablets. DSC thermograms and similarity factor (f_2) depicted good system stability for all stored tablets. This is the first five-year long-term stability study reported concerning DTZ/PEO matrix tablets with different M_W, which proved its stability for several years. This study might throw light on the dramatic difference observed between this study and the reported data of accelerated stability testing under stress conditions found in the literature.

INTRODUCTION

Hydrophilic matrices are a principal technology used for extended release (ER) oral dosage forms and their development is currently one of the most important challenges in pharmaceutical research (Shojaee *et al.,* 2013). Polyethylene oxide (PEO) is among various hydrophilic polymers that, in the presence of water, form a hydrogel that could control the release of the active moiety either by swelling or by swelling/erosion. PEOs have been proposed as alternatives to cellulose or other ethylene glycol derivatives in the production of controlled release drug delivery systems (Emara *et al.,* 2012; Jeong *et al.,* 2002). The rate and kinetics of drug release from hydrophilic matrix is dependent on various factors such as types of polymer, solubility of drug, polymer content, particle size of drug and polymer as well as types and amounts of excipients used in the formulation (Emara *et al.,* 2012; Levina and Rajabi-Siahboomi, 2004; Bravo *et al.,* 2004).

* *Corresponding Author*
Email: ashmawya@yahoo.com

It is known that there can be thermal oxidation of PEOs in the solid state and that this is an autocatalytic free radical process (Shojaee *et al.,* 2013; Crowley *et al.,* 2007).

It is also recognized that butylated hydroxytoluene (BHT) is added to Polyox at < 0.1% to prevent oxidation (Shojaee *et al.,* 2013; Körner *et al.,* 2005). However, there is limited and sometimes potentially conflicting data available in the literature regarding the stability of these polymer systems (Shojaee *et al.,* 2013).

Shojaee et al. (Shojaee *et al.,* 2013) reported that there were significant reductions in the M_W of PEO 300,000, 900,000, 3,000,000 and 7,000,000 following storage of the DTZ matrix tablets at 40 °C and RH of 30 % from controlled-release PEO-based matrix tablets. The changes in M_W led to dramatic increases in the release rate of the water-soluble drug DTZ from the matrix tablets. The similarity factor (f_2) indicated that even after only two weeks of storage the majority of release profiles were already significantly faster than the corresponding control at time zero. After eight weeks of storage all the release profiles including those for the higher PEO M_W 7,000,000 clearly exhibited an immediate release profile (Shojaee *et al.,* 2013).

On the other hand, Maggi et al. (Maggi *et al.,* 2000) reported that the stability test, after 1 year of storage at room temperature, did not evidence any problem related to possible oxidation of the PEO chain (PEO M_W 2,000,000 and 7,000,000). The dissolution profiles of PEO based DTZ tablets at time zero and after the one year storage were completely superimposable (Maggi *et al.,* 2000). Emara *et al.,* (Emara *et al.,* 2012) reported that amoxicillin trihydrate double layer floating tablets based on PEO of M_W 900,000 and 8,000,000 exhibited similar release rate profiles after 1 year storage at room temperature, which might indicate good system stability. On the other hand, metronidazole double layer floating tablets based on PEO of M_W 900,000 and 8,000,000 showed a pronounced increase in the drug release rate after 1 year storage. The similarity factor (f_2) value for the metronidazole tablets was 25.0, which was out of the FDA limit of acceptance (f_2 value should be $\geq$ 50 for similar dissolution profiles) (FDA, 1997). Therefore, metronidazole tablets was not considered stable under these storage conditions as indicated by the (f_2) values of comparing the release rate data before and after storage (Emara *et al.,* 2012). Other researchers had results of instability of metronidazole/PEO formulae of M_W 1,000,000 and 7,000,000 by storage (Kiss *et al.,* 2008). In case of lower M_W polymer (1,000,000), a significant increase in metronidazole release was observed after storing the samples under stress conditions for four weeks at 40 °C and RH of 75%. The reason behind this phenomenon was reported to be the result of structural changes of PEO, which lead to stronger polymer–polymer interaction, resulting in the decrease of the strength of the secondary bonds formed between the polymer chains and the active ingredient molecules. On the other hand, no such changes was seen in the case of the higher M_W form (7,000,000), although earlier studies by these group of researchers confirmed structural alterations similar to those of the low molecular weight polymer (Kiss *et al.,* 2008). This suggested that not only the modified physical properties of the polymer matrix determine the behavior of the dosage form in the course of storage but also the characteristics of the molecules. In addition, the authors reported that in the case of theophylline, drug release from high M_W PEO matrices increased to a greater extent, under stress conditions for four weeks at 40 °C and RH of 75% (Kiss *et al.,* 2008). While, Dandagi et al. (Dandagi *et al.,* 2014) reported that carbamazepine osmotic tablets containing PEO of M_W 2,000,000 was found to be stable for storage conditions at 40 °C and 75 % RH for 3 months in terms of drug content, hardness and *in vitro* release profile (Dandagi *et al.,* 2014). In our previous study (El-Ashmawy, 2009) on *in vitro* and in vivo evaluation of DTZ controlled-release gel-matrix tablets based on PEO, the study showed that some of the prepared matrix tablets gave similar release rate profiles compared to the reference product (Tildiem Retard 90-mg tablets, Sanofi Winthrop Industrie, France). In addition, the percentage relative bioavailability of a selected DTZ/PEO matrix tablets, compared to the reference product, using eight healthy male volunteers in a crossover design under fed condition, was found to be 133.71, 114.02, and 113.65 %, for C_{max}, AUC_{0-48}, and $AUC_{0-\infty}$, respectively. However, no stability studies were performed to support further in vivo study of this formulation. Therefore, and due to the limited and sometimes potentially conflicting data available in the literature regarding the stability of these PEOs systems (Shojaee *et al.,* 2013; Emara *et al.,* 2012; Maggi *et al.,* 2000; Kiss *et al.,* 2008; Dandagi *et al.,* 2014), it was of prime importance to study the long-term stability of different DTZ/PEO matrix tablets. The aim of this work was to study the stability of PEO matrix tablets containing DTZ after five-year storage at room temperature. The fresh and stored tablets were evaluated by studying the DTZ release rate and kinetics, DTZ content and differential scanning calorimetry (DSC).

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride (DTZ) was obtained as a gift sample from EIPICO (Egypt). Poly(ethylene oxide) (PEO) molecular weights (M_W) 900,000, 4,000,000, and 8,000,000 were purchased from Aldrich (Germany). Avicel PH-101 (microcrystalline cellulose, particle size~50 μm) was from Fluka (Switzerland). Sodium carbonate anhydrous (Na_2CO_3) were from Laboratory Rasayan (India). Pentasodium tripolyphosphate anhydrous (PSTPP) was purchased from Sigma (USA). Potassium chloride GRG (KCl) was obtained from Winlab (UK). Talc (Al-Gomhuria Co., Egypt) and magnesium stearate (Peter Greven Nederland, Germany) were used as received. Acetonitrile (HPLC grade) were from Prolabo (France). Ortho-phosphoric acid 85 %, extra-pure (Merck, Germany), potassium di-hydrogen phosphate KH_2PO_4 (Adwic, Egypt), and sodium hydroxide pellets (NaOH) (Laboratory Rasayan, India) were used. Milli-Q purified water (Millipore Corp., Billerica, MA, USA) was used to prepare both dissolution medium and HPLC mobile phase. All other reagents were of analytical grade.

Preparation and storage of matrix tablets

Formulation of DTZ (90 mg/tablet) in swellable matrix tablets was carried out. These tablets were formulated with the use of swellable polymer (PEO M_W 900,000, 4,000,000 or 8,000,000) with or without electrolyte (PSTPP, Na_2CO_3 or KCl) in different ratios. All ingredients (for each formula) in their specified ratios (Table 1) were sieved through 710 μm sieve (mesh number 25) except for magnesium stearate and talc which were sieved through 425 μm sieve (mesh number 40). Blending of all ingredients was carried out simultaneously using polyethylene bag (Emara *et al.,* 2012; Nama *et al.,* 2008), after which tablets were prepared from different blends by direct compression at 1.5-tons compression force (Single Punch Press Tablet Machine, Stokes-Merrill Model 511-7-A, USA). For such formulae, a round die (13 mm internal diameter) with the flat-faced punches was employed to give round flat-surface tablets. The tablets were stored in amber tightly closed glass bottles away from direct light at room temperature and samples were taken for testing after five-year storage.

Determination of DTZ content by HPLC

Twenty tablets of each formula were weighed, ground, and the weight equivalent to one tablet was transferred quantitatively into 100 ml glass-stoppered volumetric flask. The volume was then completed to the mark with 0.025 M potassium di-hydrogen phosphate adjusted to pH 5.5 by 1 M sodium hydroxide.

The volumetric flasks were shaken using "temperature-controlled shaking water-bath (Lab-Line, USA)" for 120 min in 37°C water bath. The solution was then filtered, and injected into the HPLC. Determination of DTZ was carried out by a modified HPLC method (El-Ashmawy, 2009). HPLC apparatus consists of Waters 600 E Multi Solvent Delivery System Controller equipped with Rheodyne injector P/N 7725i, and Waters 2487 Dual λ Absorbance Detector coupled to Millennium 32 computer program. The analytical column was Symmetry C18 (5 µm, 3.9X150, Waters Assoc., USA) protected by a guard pack precolumn module with Symmetry C18, 5 µm inserts (Waters Assoc., USA). The mobile phase consisted of 0.025 M potassium di-hydrogen phosphate adjusted to pH 5.5 by 1 M sodium hydroxide – acetonitrile (68 : 32). The mobile phase was filtered on Millipore membrane filter 0.45 µm and degassed. The flow rate was 1 ml/min, the column was kept at room temperature, and the detection wavelength was 237 nm.

***In vitro* release studies**

These studies were carried out using the closed-loop system of the flow-through cell (FTC), USP Apparatus 4, which is composed of Dissotest CE-6 equipped with a CY 7-50 piston pump (Sotax, Switzerland). Each tablet was placed into the large dissolution cell (22.6 mm diameter) according to the cell design shown in Figure 1. Built - in filtration system (0.7 µm Whatmann GF/F and GF/D glass micro-fiber filters, and glass wool) was used throughout the study. The dissolution medium was distilled water (USP 30 (Convention, 2007)), which was filtered (on 0.45 µm filter), degassed, and then pumped at a turbulent flow rate of 8.0 ± 0.2 ml/min. Temperature of the dissolution medium was kept constant at 37 ± 0.5 °C. At predetermined time intervals, volume fractions were collected and then analyzed spectrophotometrically (UV-Visible spectrophotometer, Beckman, DU-650, USA) for DTZ content by measuring the absorbance at the predetermined λ_{max} of DTZ (235 nm) against distilled water as blank. Each formula was tested in triplicate for up to 8.0 h and the mean value was calculated.

Similarity factor (f_2) calculation

The similarity factor (f_2, Eq.1), as proposed by Moore and Flanner (Moore and Flanner, 1996) was calculated from the mean release data and used to evaluate the effect of storage on the release profile. (f_2) is defined as:

$$f_2 = 50 \text{ x log } \{[1+ (1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \text{ x } 100\}$$ Eq. 1 (Moore and Flanner, 1996)

where, n is number of data time points collected during the *in vitro* release test, R_t and T_t are the cumulative release percentages released at the selected (n) time point of the fresh and stored tablets, respectively. The (f_2) value is a measure of the similarity between two dissolution curves and its value ranges from 0 and 100. A high (f_2) value indicates high similarity between two release rate profiles. FDA suggests that two dissolution profiles are considered similar if the similarity factor (f_2) is between 50 and 100 (FDA, 1997; Shah *et al.*, 1998).

Kinetic study of the drug release data

The release kinetics was computed by fitting the release rate data to various mathematical equations: the zero-order rate (Eq. 2), the first-order equation (Eq. 3), the second-order equation (Eq. 4), the Higuchi square root of time model (Eq. 5), and the Hixson–Crowell cube root model (Eq. 6).

$Q_t = k_0.t$ Eq. 2 (Wright, 2004)

$ln (100 - Q_t) = ln\ 100 - k_1.t$ Eq. 3 (Wright, 2004)

$1 / (100 - Q_t) = k_2.t$ Eq. 4 (Wright, 2004)

$Q_t = k_H.t^{1/2}$ Eq. 5 (Sood and Panchagnula, 1998; Karasulu *et al.*, 2003)

$(100 - Q_t)^{1/3} = (100)^{1/3} - k_{HC}.t$ Eq. 6 (Sood and Panchagnula, 1998; Karasulu *et al.*, 2003)

where, Q_t is the percent drug release at time t; k_0, k_1, k_2, k_H, and k_{HC} are release rate constants for zero-order, first-order, second-order, Higuchi square root of time model, and Hixson–Crowell cube root model equations, respectively. *The criteria for selecting the most appropriate model was based on* the best goodness of fit and the smallest sum of squared residuals (SSR) (Ostle, 1960; Sood and Panchagnula, 1998; Philip and Pathak, 2006). The data obtained from the *in vitro* drug release studies were analyzed by means of personal computer using regression analysis by Microsoft Excel software.

Differential scanning calorimetry (DSC) studies

DSC was performed for pure DTZ, pure polymers and for ground tablets of each formulation to detect any possible chemical interactions between the drug and polymers employed in tablet formulations. DSC was carried out at zero time and after five-years of tablet storage. DSC thermograms were performed using an automatic thermal analyzer (DSC-50, Shimadzu, Japan). Sealed and holed aluminum pans heated in an atmosphere of nitrogen were used in the experiments for all samples and an empty pan, prepared in the same way was used as a reference. Samples of pure Drug and powdered tablets of 5 mg each were weighed directly into the aluminum pans and the thermal analysis was carried out using heating ramp from 25 to 300 °C at 10 °C/min scale up rate. A nitrogen purge (20 ml/min) was maintained throughout the run.

RESULTS AND DISCUSSION

Estimation of DTZ content

The HPLC method (El-Ashmawy, 2009) adopted to estimate DTZ content in fresh and five-year stored PEO matrix tablets was found to be linear in the concentration range of 0.3–3.0 µg/ml. The regression coefficient (R^2) of the constructed calibration curve was found to be 0.9997 with the percentage recovery ranged from 97.13 % to 104.99 %. The DTZ content in different tablets was not less than 87.89 % (F1) and did not exceed 105.12 % (F3) of the labeled claim. This result indicated that all the prepared tablets were found to be within the accepted drug content limits of US-Pharmacopoeia, i.e., the average percentage of drug content of all formulae was found to be within the range of 85% and 115% of the label claim (Convention, 2007). The average of DTZ content in fresh and five-year stored PEO matrix tablets was shown in Table 2.

In vitro evaluation of DTZ release rate from fresh and stored tablets

In this study, seven formulations covering different M_W of PEO (i.e. 900,000, 4,000,000 and 8,000,000) were prepared. In addition, DTZ matrix tablets based on PEO M_W 900,000 were evaluated in the presence of electrolytes (PSTPP, Na_2CO_3 or KCl) and also in a different drug to polymer/electrolyte ratio (Table 1).

Effect of different M_W of PEO

Figure 2 showed the DTZ release rate profiles from the matrix tablets containing PEO with different M_W at zero-time (fresh samples) and after five-year storage at room temperature. It was found that the release rate of DTZ from fresh matrix tablets decreased and the duration of release was prolonged as the PEO M_W increased from 900,000 to 8,000,000 (F1 to F3, respectively). On the other hand, the difference in release rate of DTZ tablets between fresh and five-year stored samples was increased as the PEO M_W increased from 900,000 to 8,000,000. It was obvious that increasing PEO M_W decreased the superimposition of the release profiles after storage for five years. This might be due to the reduction of the high PEO *Mw* upon storage under stress conditions as reported earlier by Shojaee et al. (Shojaee *et al.*, 2013).

This reduction in molecular weight led to dramatic increase in the release rate of DTZ from the PEO matrix tablets following storage for only a few weeks, resulting in immediate release profiles after eight weeks, even for the highest molecular weight grade (Shojaee *et al.*, 2013). However, it should be taken into consideration that these changes of PEO *Mw* reported was observed after storage under stress conditions. Another study of Maggi *et al.* (Maggi *et al.*, 2000), indicated that DTZ in a matrix tablet containing PEO was stable after one year storage at room temperature.

Figure 3 depicted that all tablets were found to be stable after five-year storage as indicated by the value of (f_2) ($\geq$ 50) (FDA, 1997; Shah *et al.*, 1998). Meanwhile, the similarity factor (f_2) values between the fresh and the stored tablets were decreased as PEO M_W increased (f_2 = 96, 70 and 56 for F1, F2 and F3, respectively, Figure 3), indicating a sign for the decrease in system stability as PEO M_W increased. However, similar release rate profiles indicated that these systems were stable after this long storage period (five years).

Effect of electrolytes

This part of the study investigated the effect of addition of three different electrolytes to the DTZ matrix tablet based on PEO of M_W 900,000 as illustrated in Table 1 (F4 – F6). Incorporation of electrolytes was used to interact with polymeric carriers by causing a partial dehydration and salting out of the polymer molecules (Levy and Schwarz, 1958; Durig and Fassihi, 2002).

The inclusion of inorganic salts in hydroxypropylmethylcellulose (HPMC) and PEO matrices might show a zero-order release of water-soluble drugs (Durig and Fassihi, 2002; Chen and Chiao, 1995; Pillay and Fassihi, 1999). The ability of water-soluble electrolytes to compete for water of hydration, thereby causing the dehydration of hydrophilic colloids leading to salting out, precipitation or gelling, was also well documented (Levy and Schwarz, 1958; Durig and Fassihi, 2002; Sarkar, 1979). The ability of electrolytes to affect such changes is generally dependent on the extent to which the anions and cations can be hydrated and could be predicted from the Hofmeister (lyotropic) series (Durig and Fassihi, 2002; Jakubowski, 2006; Zhang and Cremer, 2006).

Figure 4 showed the effect of addition of different electrolytes (PSTPP, Na_2CO_3 and KCl, cf. Table 1) on the release rate of DTZ from PEO 900,000 based matrix tablets (F4, F5 and F6, respectively). It was found that addition of electrolytes drastically affected the release rate patterns in case of PSTPP and Na_2CO_3 (Figure 4 "A & B", respectively). Where in case of PSTPP (F4) and Na_2CO_3 (F5), the DTZ release rates were decreased compared to the tablet without electrolyte (F1, Figure 2 A) for both fresh and five-year stored tablets. While addition of KCl gave a slight decrease in the amount of DTZ released from fresh samples (Figures 2 A and 4 C). Further illustration of the electrolytes effects on DTZ release rate from fresh and five-year stored samples was displayed in Figure 5A, which showed that DTZ release rates were slightly increased after five-year storage from all samples.

Figure 5 B depicted the systems stability as indicated by the high (f_2) values. However, the similarity factor values (f_2) obtained from fresh and stored F6 tablets, was decreased from 96 (F1) to 60 (F6) (Figure 5 B). Importantly, the superimposition of the release rate profiles of DTZ at zero time and after storage for five years was decreased by the addition of the three electrolytes as shown by the lower values of similarity factor f_2 when present in this particular PEO of M_W 900,000 matrix as shown in Figures 2A, 4 and 5 B.

Table 1: Compositions of DTZ matrix tablets (90 mg/tablet).

Tablet code	Tablet composition (mg) [a]						Ratio of Drug: Polymer: Electrolyte (D : P : E)
	PEO molecular weight			Electrolyte			
	900,000	4,000,000	8,000,000	PSTPP	Na_2CO_3	KCl	
F1	180	0	0	0	0	0	1 : 2 : 0
F2	0	180	0	0	0	0	1 : 2 : 0
F3	0	0	180	0	0	0	1 : 2 : 0
F4	180	0	0	90	0	0	1 : 2 : 1
F5	180	0	0	0	90	0	1 : 2 : 1
F6	180	0	0	0	0	90	1 : 2 : 1
F7	90	0	0	0	0	45	1 : 1 : 0.5

[a] 150-mg avicel, 1% magnesium stearate and 1% talc were used as filler, lubricant and glidant, respectively.

Table 2: DTZ content of the matrix tablets (90 mg/tablet).

Tablets*	Average DTZ content (%) ± S.D. (n=3)	
	Fresh	After five-year storage
F1	88.95 ± 1.45	87.89 ± 1.82
F2	96.37 ± 0.98	95.67 ± 1.23
F3	102.62 ± 1.72	105.12 ± 1.54
F4	97.87 ± 0.83	95.91 ± 1.37
F5	95.37 ± 1.24	92.37 ± 1.59
F6	102.31 ± 1.19	100.03 ± 1.43
F7	103.93 ± 1.25	103.45 ± 1.39

* For tablet composition see Table 1.

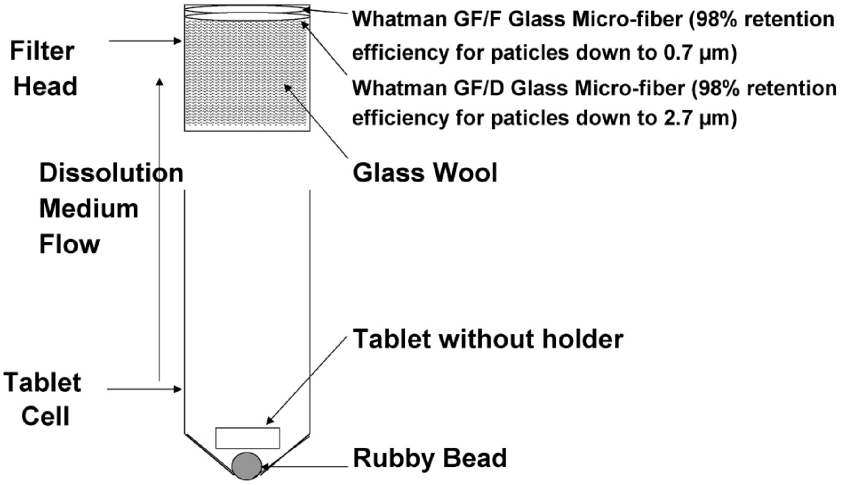

Fig. 1: Dissolution cell design of the FTC used for release evaluation of the prepared matrix tablets: turbulent flow with free tablet position.

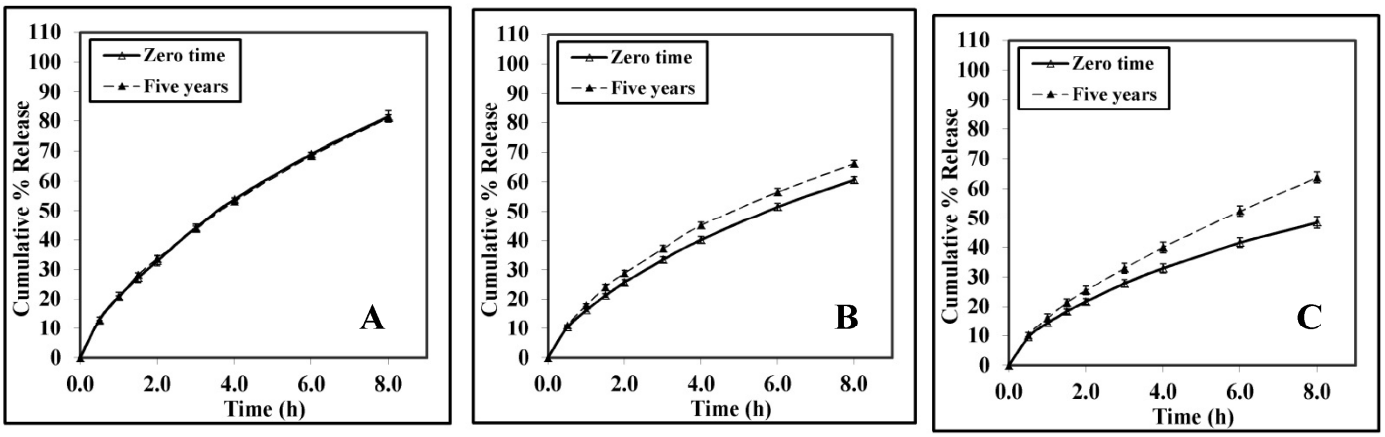

Fig. 2: DTZ release rate profiles, at zero time and after storage for five years, from the matrix tablets containing PEO with different MW: A: F1 (PEO 900,000); B: F2 (PEO 4,000,000); and C: F3 (PEO 8,000,000). Ratio of drug: polymer is 1:2 (Mean ± S.D., n = 3).

Table 3: Regression analysis, sum of squared residuals "SSR" and coefficient of determination "r^2" values for the different kinetic models for the release data of DTZ from F1 - F3 matrix tablets.

Release-Model		Matrix Tablets					
		F1		F2		F3	
		0 time	Five-year storage	0 time	Five-year storage	0 time	Five-year storage
Zero-Order	**SSR**	**80.894**	**83.679**	**45.621**	**75.236**	**31.687**	**27.899**
	r^2	0.9799	0.9787	0.9787	0.9706	0.9753	0.9883
	k ($mol.l^{-1}.h^{-1}$)	9.0667	8.9477	6.6095	7.1885	5.1039	6.9999
	$t_{1/2}$ (h)	5.51	5.59	7.56	6.96	9.80	7.14
First-Order	**SSR**	**23.093**	**20.508**	**3.635**	**6.903**	**9.419**	**3.477**
	r^2	0.9946	0.9941	0.9989	0.9984	0.9939	0.9983
	k (h^{-1})	0.2027	0.1983	0.1089	0.1271	0.0744	0.1184
	$t_{1/2}$ (h)	3.42	3.49	6.36	5.45	9.32	5.85
Second-Order	**SSR**	**2239.471**	**1904.217**	**26.621**	**52.328**	**1.334**	**92.305**
	r^2	0.9215	0.9214	0.9921	0.9889	0.9997	0.9746
	k ($mol^{-1}.l.h^{-1}$)	0.0053	0.0051	0.0019	0.0024	0.0011	0.0021
	$t_{1/2}$ (h)	1.89	1.96	5.26	4.17	9.09	4.76
Higuchi Square	**SSR**	**7.941**	**3.555**	**2.045**	**0.871**	**0.483**	**9.951**
	r^2	0.9980	0.9991	0.9990	0.9997	0.9996	0.9958
Root of Time	**k ($mol.l^{-1}.h^{-1/2}$)**	32.9480	32.5530	24.0460	26.2700	18.6060	25.3010
	$t_{1/2}$ (h)	3.56	3.59	5.74	4.86	8.49	5.52
Hixson and Crowell	**SSR**	**1.276**	**5.185**	**12.375**	**21.565**	**15.349**	**4.336**
Cube-Root	r^2	0.9997	0.9992	0.9952	0.9931	0.9891	0.9988
	k($mol^{1/3}.l^{-1/3}.h^{-1}$)	0.2358	0.2314	0.1419	0.1615	0.1012	0.1529
	$t_{1/2}$ (h)	3.61	3.64	5.77	4.97	8.03	5.52
Suggested Release Model (Smallest SSR)		Hixson and Crowell Cube-Root	Higuchi Square Root of Time	Higuchi Square Root of Time	Higuchi Square Root of Time	Higuchi Square Root of Time	First-Order

SSR is the sum of squared residuals; r^2 is the coefficient of determination; **k** is the release rate constant for the respective models; $t_{1/2}$ is the period of time required for the concentration or amount of drug in the tablet to be reduced to exactly one-half of the initial concentration or amount.

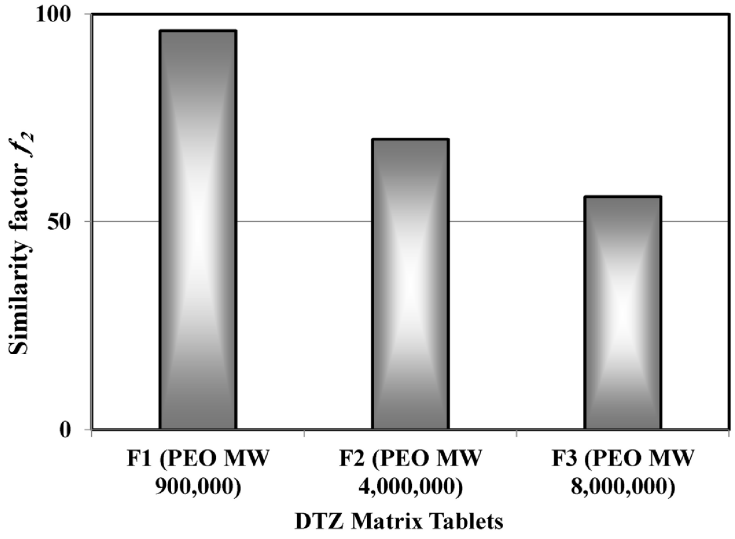

Fig. **3**: Similarity factor (f_2) values comparing the release rate profiles of DTZ matrix tablets before and after storage for five years.

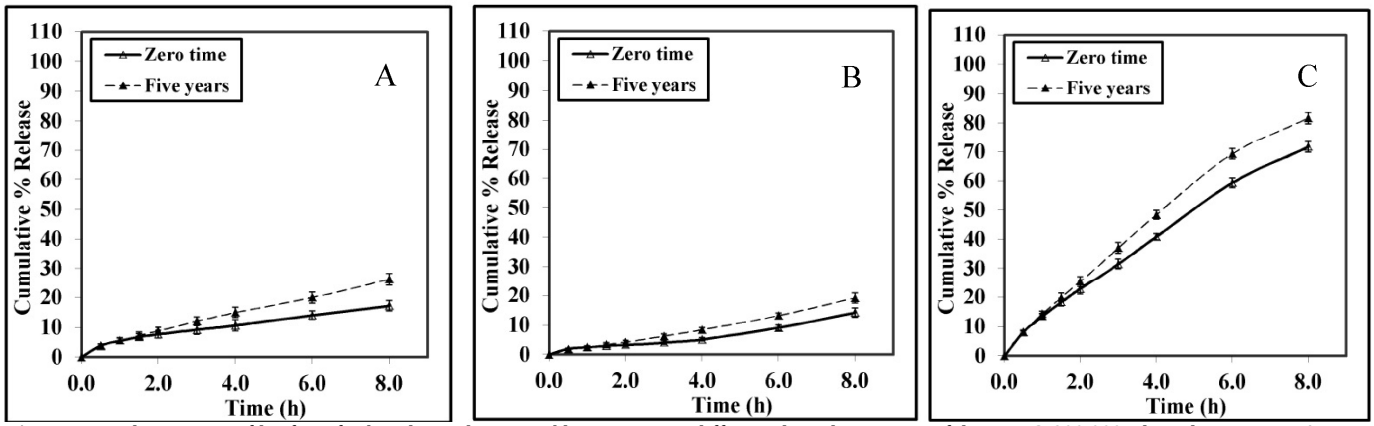

Fig. 4: DTZ release rate profiles from fresh and stored matrix tablets containing different electrolytes. Ratio of drug: PEO 900,000: electrolyte is 1:2:1, A = F4 (PSTPP); B = F5 (Na_2CO_3) and C = F6 (KCl); (Mean ± S.D., n = 3).

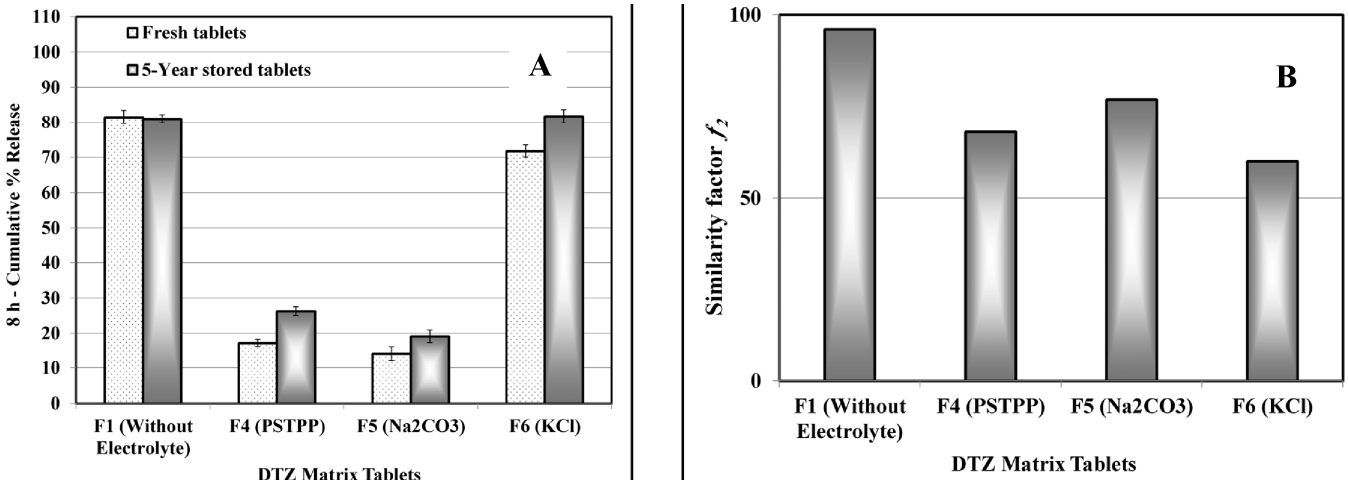

Fig. 5: Cumulative percentage DTZ released after 8 hours (A) and the similarity factor f_2 (B) of fresh and stored matrix tablets containing different electrolytes. Ratio of drug: PEO 900,000: electrolyte is 1:2:1.

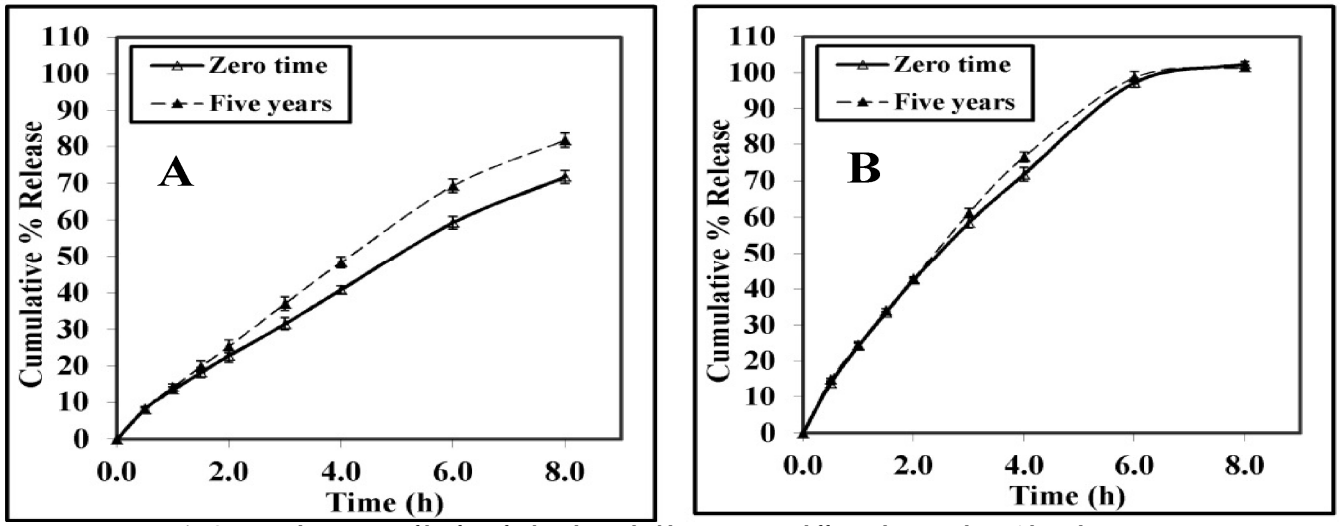

Fig. 6: DTZ release rate profiles from fresh and stored tablets containing different drug to polymer/electrolyte ratio. Ratio of drug: PEO 900,000: KCl (A, F6) 1:2:1; and (B, F7) 1:1:0.5. (Mean ± S.D., n = 3).

Table 4: Regression analysis, sum of squared residuals "SSR" and coefficient of determination "r^2" values for the different kinetic models for the release data of DTZ from F4 – F7 matrix tablets.

Release-Model		Matrix Tablets							
		F4		F5		F6		F7	
		0 time	Five-year storage	0 time	Five-year storage	0 time	Five-year storage	0 time	Five-year storage
Zero-Order	**SSR**	**1.283**	**0.941**	**5.889**	**2.420**	**15.684**	**46.718**	**360.873**	**506.649**
	r^2	0.9907	0.9977	0.9523	0.9907	0.9956	0.9906	0.9525	0.9339
	k ($mol.l^{-1}.h^{-1}$)	1.6910	2.9442	1.5656	2.2901	8.6150	10.1010	12.2740	12.2160
	$t_{1/2}$ (h)	29.57	16.98	31.94	21.83	5.80	4.95	4.07	4.09
First-Order	**SSR**	**1.030**	**0.546**	**6.877**	**3.857**	**53.382**	**133.097**	**2663.129**	**2572.673**
	r^2	0.9934	0.9986	0.9453	0.9849	0.9900	0.9861	0.9463	0.9242
	k (h^{-1})	0.0189	0.0348	0.0170	0.0256	0.1573	0.2163	0.6271	0.6709
	$t_{1/2}$ (h)	36.70	19.93	40.66	27.11	4.41	3.20	1.11	1.03
Second-Order	**SSR**	**1.409**	**1.384**	**11.242**	**7.562**	**756.567**	**6109.167**	**17143.090**	**17056.712**
	r^2	0.9950	0.9963	0.9379	0.9776	0.9408	0.9059	0.0641	0.0198
	k ($mol^{-1}.l.h^{-1}$)	0.0002	0.0004	0.0002	0.0003	0.0032	0.0055	0.0199	0.0205
	$t_{1/2}$ (h)	50.00	25.00	50.00	33.33	3.13	1.82	0.50	0.49
	SSR	**1.649**	**7.786**	**17.004**	**17.257**	**60.411**	**65.894**	**83.815**	**146.622**
Higuchi Square	r^2	0.9881	0.9813	0.8624	0.9321	0.9831	0.9867	0.9890	0.9809
Root of Time	**k ($mol.l^{-1}.h^{-1/2}$)**	6.0808	10.5140	5.3647	7.9985	30.8250	36.3000	45.0360	45.0780
	$t_{1/2}$ (h)	69.65	27.59	99.61	48.94	4.89	3.99	2.39	2.31
	SSR	**1.099**	**0.567**	**6.525**	**3.307**	**13.745**	**25.846**	**1615.688**	**1215.951**
Hixson and Crowell	r^2	0.9926	0.9986	0.9477	0.9870	0.9970	0.9966	0.9316	0.9585
Cube-Root	**k($mol^{1/3}.l^{-1/3}.h^{-1}$)**	0.0282	0.0508	0.0256	0.0381	0.1970	0.2547	0.7249	0.7230
	$t_{1/2}$ (h)	31.84	18.11	37.28	25.25	4.85	3.95	2.15	2.08
Suggested Release Model (Smallest SSR)		First-Order	First-Order	Zero-Order	Zero-Order	Hixson and Crowell Cube-Root	Hixson and Crowell Cube-Root	Higuchi Square Root of Time	Higuchi Square Root of Time

SSR is the sum of squared residuals; r^2 is the coefficient of determination; **k** is the release rate constant for the respective models;
$t_{1/2}$ is the period of time required for the concentration or amount of drug in the tablet to be reduced to exactly one-half of the initial concentration or amount.

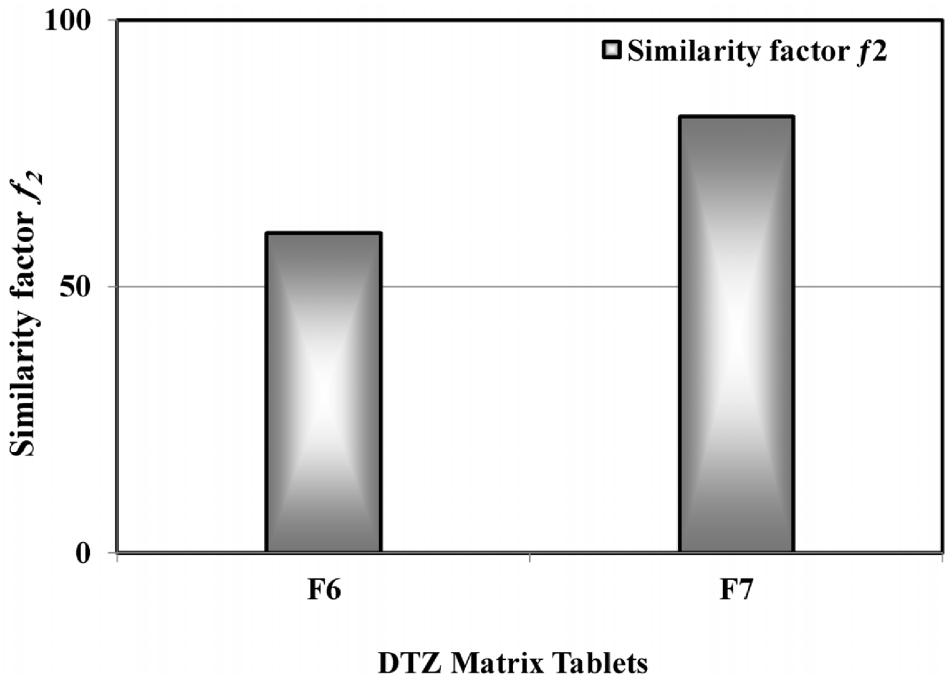

Fig. 7: Similarity factor (f_2) values comparing the release rate profiles of DTZ before and after five year storage of matrix tablets. Ratio of drug: PEO 900,000: KCl, F6=1:2:1; and F7= 1:1:0.5.

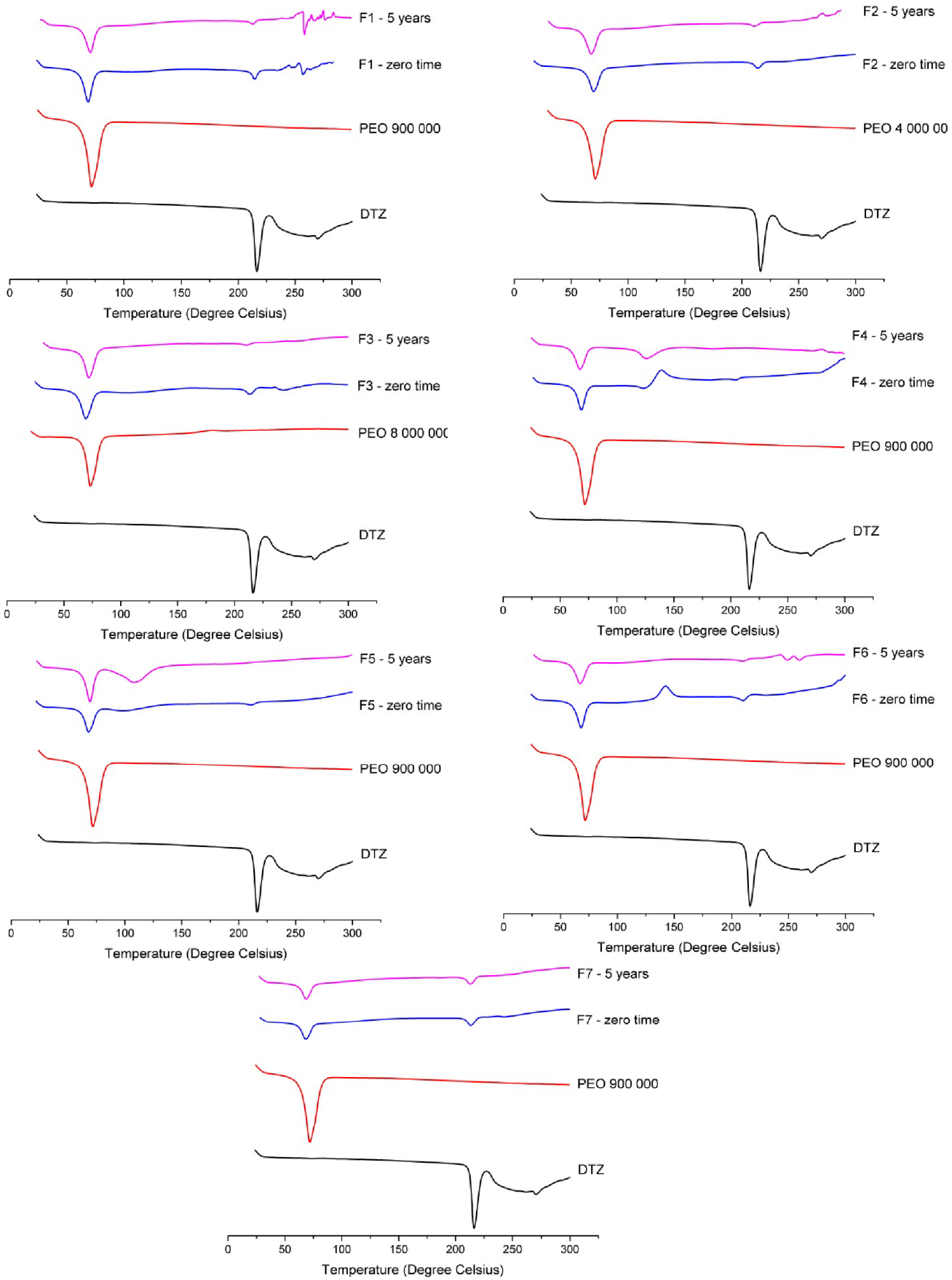

Fig. 8: DSC thermograms of DTZ ground matrix samples at zero time and after five years of storage at room temperature.

Effect of polymer / electrolyte ratio

This part of the study showed the effect of drug to polymer/KCl ratios (drug: polymer: electrolyte 1: 2: 1 and 1: 1: 0.5) in the matrix tablets on the DTZ release rate profiles before and after five-year storage (F6 and F7, cf. Table 1). Figure 6 demonstrated that this 50% reduction of polymer/electrolyte ratio led to an increase of the release rate of DTZ from the matrix tablets. Where, after 4 h of the release study, the amounts of DTZ released were 40.92 % and 71.81 % from fresh tablets and were 48.47 % and 76.51 % from stored tablets at different polymer/KCl ratios (F6 and F7, respectively). Also, after 8 h, the amounts of DTZ released were 71.76 % and 102.51 % from fresh tablets and 81.76 % and 101.56 % from stored tablets (F6 and F7, respectively). Figure 7 also showed that decreasing the polymer/electrolyte content led to an increase in system stability as indicted by the higher (f_2) values of 60 to 82 for F6 and F7 tablets, respectively.

In this regards, we should compare our results with the study of Shojaee et. al. (Shojaee *et al.*, 2013) which indicated that after eight weeks, under stress conditions of storage, all the release profiles clearly exhibited an immediate release profile (Shojaee *et al.*, 2013). They recognized that possible differences observed under the accelerated conditions might not arise under routine storage. This expectation was found to be true as proved by our study which showed excellent system stability for up to five years at room temperature. However, their study reported that these effects were much more dramatic than they expected.

Kinetics of drug release data

The drug release rate kinetics from PEO matrices is controlled by the polymer molecular weight (Apicella *et al.*, 1993; Lee and Peppas, 1987; Narasimhan and Peppas, 1997; Yang and Fassihi, 1997). For the polymers having identical chemical structure and under identical hydrodynamic conditions, polymer erosion rate and gel thickness usually vary as a function of the molecular weight of the polymer. Increase in polymer molecular weight results in the deceleration of polymer erosion rate and augmentation of gel thickness. In addition, it should be noted that the swelling velocity of high-M_W PEO is far greater than its erosion rate. Continuous swelling leads to increase in gel thickness and retardation of drug release, with possible deviation from linearity. Therefore, diffusion of the drug through the swollen gel region and the drug solubility play a decisive role in drug release modulation from high-M_W PEO matrices (Apicella *et al.*, 1993; Lee and Peppas, 1987; Narasimhan and Peppas, 1997; Yang and Fassihi, 1997).

The results of regression analysis of drug release rates from the prepared DTZ matrix tablets, before and after five-year storage, presenting the suggested release model with the smallest SSR, were shown in Tables 3 and 4. According to the tablet compositions (Table 1), the drug release rates from fresh DTZ matrix tablets were found to follow: (i) Hixson-Crowell cube root model (F1 and F6 tablets), explaining that the release of the drug from these systems depended on the change in surface area and diameter of the tablets with time which is a typical case of systems that dissolute or erode over time (Philip and Pathak, 2006), (ii) Higuchi square root of time model (F2 and F7 tablets), which described the release of the drug from an insoluble matrix to be linearly related to the square root of time and is based on Fickian diffusion (Philip and Pathak, 2006), (iii) the first order release kinetics (F3 and F4 tablets), meaning that the release rate is concentration-dependent (Philip and Pathak, 2006), and (iv) zero-order kinetics (F5 tablets), i.e. DTZ release rate was independent of its concentration (Philip and Pathak, 2006).

It was found that the suggested release rate kinetic model, after five-year storage, was changed from Hixson-Crowell cube root model to Higuchi square root of time model and from Higuchi square root of time model to the first order release for F1 (containing PEO M_w 900,000) and F3 (containing PEO M_w 8,000,000) tablets, respectively. On the other hand, the addition of electrolytes (F4-F7 tablets in comparison to F1 tablets) kept the model of release rate kinetics to be the same for fresh tablets and after five-year stored tablets for F4-F7 (cf. Tables 4). Therefore, addition of the proposed electrolyte to tablets based on PEO M_w 900,000 stabilized both release rate and kinetics of DTZ.

DSC

Figure 8 showed the thermal analysis of the various ground matrix tablet samples which had been prepared in this study. The DSC thermograms of pure DTZ showed a melting endotherm at 216.06 °C with normalized energy of 113.73 J/g. This endothermic peak was much less distinctive in all DTZ matrix tablets, which indicated that most of the drug was uniformly dispersed in the PEO matrix and thus might reveal some changes in the physical properties of DTZ. All tablets showed almost the same DSC thermograms before and after five-year storage, which indicated good system stability (Figure 8). Visual observations showed typical thermograms of F1 & F7 for fresh and stored samples which could be confirmed by the highest (f_2) values of 96 and 82 for F1 and F7 tablets, respectively (Figures 3 & 7). F4 and F6 samples showed exothermic peaks at 139.18 °C and 142.25 °C, respectively, in fresh samples which were changed into an endothermic peak at 125.82 °C, in case of F4 sample, after five-year storage and disappeared in case of F6 sample. However, these changes of DSC thermograms after five-year storage did not show any impact on all other parameters such as DTZ content and release rate similarity.

CONCLUSION

This stability study of DTZ matrix tablets based on PEO with different M_w proved that all the formulae were stable up-to five-year storage. It was fortunate that one of these stable formulations was subjected to in vivo study with 8 healthy human male volunteers and gave encouraging results. Therefore, these systems deserve further in vivo evaluation with increasing the sample size and also, it should be carried out under fed and fasting conditions according to reference guidelines. Moreover, this is the

first five-year long-term stability study reported concerning PEO matrix tablets. In addition, this study might throw light on the difference observed between long-term stability of the water soluble drug such as DTZ in PEO matrix at room temperature and the accelerated stability testing under stress conditions (Shojaee *et al.,* 2013; Kiss *et al.,* 2008; Dandagi *et al.,* 2014). From this body of literature, it is proposed that stability of PEO/DTZ systems is highly affected by temperature. In this regards, these systems deserve accelerated stability study to prove this assumption.

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