AAPS PharmSciTech, Vol. 14, No. 3, September 2013 (© 2013)
DOI: 10.1208/s12249-013-0013-7

Research Article

An Investigation into the Stabilization of Diltiazem HCl Release from Matrices Made from Aged Polyox Powders

Saeed Shojaee,[1] Kofi Asare-Addo,[2] Waseem Kaialy,[1,3] Ali Nokhodchi,[1,4] and Iain Cumming[1]

Received 18 April 2013; accepted 15 July 2013; published online 31 July 2013

Abstract. Matrices containing PEO fail to provide stable drug release profiles when stored at elevated temperatures for a period of time. The present study aims to stabilize diltiazem HCl release from matrices made from various molecular weights of polyox powders. To this end, various molecular weights of polyox with and without vitamin E (0.25, 0.5 and 1% *w*/*w*) were stored at 40°C for 0, 2, 4 and 8 weeks. The aged polyox powders were then mixed with the model drug at a ratio of 1:1 and compressed into tablets. At different time intervals, the aged polyox with vitamin E were taken out of oven and mixed with the drug (1:1 ratio) and compressed into tablets. Dissolution studies showed a significant increase in diltiazem HCl release rate to occur with increased storage time at 40°C±1 from tablets made from the aged polyox (no vitamin E). This was as a result of depolymerization of the aged polyox powders as compared to the fresh polyox samples. This was confirmed by differential scanning calorimetry (DSC) which showed a reduction in the melting point of the aged samples. Concentrations of vitamin E as low as 0.25% *w*/*w* was able to overcome the quick release of drug from the matrices made from aged polyox powders. DSC traces showed that the melting point of aged polyox samples containing vitamin E remained the same as that of the fresh samples. The presence of vitamin E is essential to stabilize the drug release from polyox matrices containing diltiazem HCl.

KEY WORDS: depolymerization; drug release kinetics; molecular weight; polyox matrices; thermal behaviour.

INTRODUCTION

Hydrophilic polymer matrices release entrapped drug into aqueous media by regulating the release of the drug through the management of swelling and cross-linking of polymers. This makes the appropriate polymer of choice with regards to controlled release applications. The high water affinity for these polymers mean that the molecular forces between water and the polymers are likely to be preferred over polymer–polymer interactions. A gel layer thus results upon contact of the hydrophilic polymer on or near the surface due to hydration. This hydration and gel layer controls water ingress into the matrix and as such controls or has an influence on the mechanism by which a drug is released. Erosion tends to be the dominant release mechanism as far as poorly soluble drugs are concerned. The other mechanistic approach is diffusion and this is the dominant release mechanism with regards to soluble drugs (1–4).

There are several types of polymers used to control the release of drugs from the dosage forms for absorption by the body. These include polymers such as hydroxypropylmethylcellulose (HPMC or hypromellose), sodium carboxymethylcellulose (Na CMC) and psyllium and sodium alginate (5,6).

Recently, polyethylene oxides (PEOs) have been suggested as alternatives to HPMC for the controlled polymeric matrix systems (7–9). Polyethylene oxide is a water-soluble non-ionic homo polymer of ethylene oxide, represented by the formula: $(OCH_2CH_2)^n$ wherein *n* represents the average number (ranges from 2 to 180) of oxy-ethylene oxide groups. The use of PEO is mostly attributed to the desirable hydration and modified release properties of the different grades and molecular weights ranging from 100,000 to 7,000,000 (9–12). PEOs have also been broadly employed for the preparation of sustained released tablets because of ease of production, insensitivity to the pH of the biological medium, high water solubility, high swelling and non-toxicity (8).

The main disadvantage with PEO matrices is the difficulty of obtaining a stable drug release when the tablets are stored for a period of time. This is due to the poor stability of polyox under storage conditions (13). Sako and coworkers (14) showed that a matrix tablet consisting of drug and PEO failed to release the drug adequately *in vivo*, despite it successfully achieving extended release *in vitro*. They attributed this to the difference in water conditions which affected the formation of hydrogel around the tablet (14).

[1] Chemistry and Drug Delivery Group, Medway School of Pharmacy, University of Kent, Kent, UK.
[2] School of Applied Science, University of Huddersfield, Huddersfield, UK.
[3] Pharmaceutics and Pharmaceutical Technology Department, School of Pharmacy, University of Damascus, Damascus, Syria.
[4] To whom correspondence should be addressed. (e-mail: a.nokhodchi@kent.ac.uk)

Diltiazem hydrochloride is a calcium channel blocker widely used in the treatment of angina pectoris and has recently become very popular for the treatment of old-age hypertension. The drug is well absorbed from gastrointestinal tract. The half-life of diltiazem HCl is 4.5 h and needs to be administrated three to four times a day. Because of its short biological half-life and frequent administration, it is considered as a suitable candidate to formulate it into a controlled release drug delivery system (15).

The main aim of the present work was to stabilize the drug release from the different molecular weighted polyox tablet matrices containing antioxidant stored at an elevated temperature.

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride was obtained from Elan Drug Technologies. PEO grades 750 (MW=3×10^5), 1105 (MW=9×10^5), 301 (MW=3×10^6), and 303 (MW=7×10^6) produced by Dow Chemical (Philadelphia, USA) and distributed by Colorcon (Kent, UK) were used. Vitamin E succinate as an antioxidant was purchased from Sigma-Aldrich (UK).

Preparation of Powders for Tabletting

In order to investigate the effect of storage time on the physicochemical properties of polyox polymers, 10 g of each polymer was stored at 40°C in a screw cap glass vial and subjected to ageing for a period of 0, 2, 4 or 8 weeks. Two different ratios of Diltiazem HCl/polyox at ratios of 1:1 and 2:1 were prepared and mixed in a turbula blender (Willy A. Bachofen AG, Maschinenfabrik, Basel, Switzerland) for 10 min after the respective storage periods. Matrix tablets of 8 mm in diameter with target weights of 240 and 180 mg for the ratios of 1:1 and 2:1, respectively, were prepared by the compression of the above mixtures at 1,500 psi (Model MTCM-1, Globe Pharma, US) . The tablets made from aged polyox powders were then subjected to dissolution testing.

To investigate the effect of vitamin E succinate on drug release rate, polyox powders were mixed with different concentration of vitamin E (0.25%, 0.5%, or 1% *w*/*w*) before being subjected to the ageing process as above at 40°C. At the different time intervals (0, 2, 4 or 8 weeks) these powders containing vitamin E were mixed with diltiazem HCl and compressed into tablets as described above.

True Density Measurement of Powders

True densities of powders before and after storage times (0, 2, 4, and 8 weeks) were measured using the Ultra pycnometer 1000 (Quantochrom, USA). To carry out this test 3 to 5 g of sample was used and the results reported are the mean and standard deviation of three determinations.

Hardness Measurement of Tablets

The Dr. Schleuniger tablet hardness tester (8M, Switzerland) was used to investigate any changes in the tablet hardness of matrices before and after the storage times. The hardness of at least 3 tablets was determined.

Dissolution Studies

The USP paddle method (16) (Erweka, Germany) was used to monitor the dissolution profiles of the diltiazem HCl tablet matrices. The dissolution medium used was 900 ml of distilled water equilibrated to 37°C±0.1°C. The paddles were rotated at 100 rpm. Samples were withdrawn every 15 min up to 2 h, then every 30 min up to 12 h from the dissolution flask using a peristaltic pump. The concentration of diltiazem HCl in the samples was determined by UV spectrophotometer at 240 nm using a Shimadzu UV-visible spectrophotometer.

Dissolution Parameters

Dissolution efficiency and mean dissolution rate were used to represent the dissolution rate from various preparations. Dissolution efficiency was used as the criterion for comparing the effect of polymer and antioxidant on the release rate of diltiazem HCl. The dissolution efficiency (DE) of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time, *t*, expressed as percentage of the area of the rectangle described by 100% dissolution in the same time (17) as detailed elsewhere (18).

An alternative parameter that describes the dissolution rate is the mean dissolution time (MDT); the most likely time for a molecule to be dissolved from a solid dosage form. Therefore, MDT is the mean time for the drug to dissolve under *in vitro* dissolution conditions as detailed elsewhere (18).

Kinetics Models

The kinetic models were used to elucidate the mechanism of drug transport by simply comparing the release data to mathematical models such as Peppas model, Higuchi model, zero- and first-order kinetics. To study the mechanism of drug release from matrix tablets, the release data were fitted to well known empirical equation proposed by Korsmeyer and Peppas (19).

$$M_t/M_\infty = K_p t^n \tag{1}$$

$$\log M_t/M_\infty = \log K_p + n \log t \tag{2}$$

Where M_t/M is the fractional drug release, t is the release time, k denotes as the kinetic constant and n is the diffusion exponent characteristics of the release mechanism. For a cylinder matrix that can swell, $0.89<n<1$ indicates a supper case II, and $n=0.89$ shows for the case II release kinetics, while $0.45<n<0.89$ shows anomalous release kinetics and when $n<0.45$ shows Fickian diffusion release kinetics (20,21).

Similarity Factor (f_2) Measurement

The equation of similarity factor proposed by Moore and Flanner (22) is represented in Eq. 1:

$$f_2 = 50 \log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n} w_t(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \tag{3}$$

Where f_2 is similarity factor, n is the number of observations, R_t is percentage of drug dissolved from reference

formulation and T_t is average percentage of drug dissolved from test formulation.

If the value of f_2 is greater than 50 then we can conclude that products show similar dissolution. In contrast, if the f_2 values are less than 50, there is no similarity between reference and test formulation (22).

Differential Scanning Calorimetry (DSC) Study

Differential scanning calorimetry (DSC; DSC7, Mettler Toledo, Switzerland) was used to study the thermal properties of fresh and aged polyox polymers. The effect of vitamin E on the thermal behaviour of polyox samples was also investigated. The DSC equipment was calibrated using indium. Approximately 4–5 mg of sample was weighed and heated in the range of 25 to 250°C at a scanning rate of 10°C/min in aluminum pans under nitrogen gas.

Viscosity Measurement

Ground tablet samples were prepared at a 0.5% *w/v* concentration in distilled water using gentle agitation on a radial shaker for 12 h at 25°C. They were tested using a Brookfield Model DV-II+ Pro viscometer Harlow, UK using spindles 61 and 62 together with rotation speeds of 60 rpm. Results presented are an average of three runs.

RESULTS AND DISCUSSION

The Influence of Storage Conditions on True Density and Hardness

All formulations were relatively robust in terms of hardness. The results demonstrated that there was no significant difference between true density of powders before and after storing the powders for up to 8 weeks at 40°C (data not included). The range of true density values for fresh samples was between 1.22 and 1.25 g/cm^3 and after 8 weeks was almost the same (1.21–1.25 g/cm^3). Similar results were obtained for polyox powders containing different concentrations of antioxidant (0.25%, 0.5% and 1% *w/w*). The effect of storage conditions on the hardness of tablets made from aged polyox powders with different ratios of drug/polymer (1:1 and 2:1) is shown in Table I. Table I shows that an increase in the molecular weight of polyox brings about an increase in the hardness. This phenomenon could be due to a better compactibility of PEO with high molecular weight as compared to lower molecular weighted PEO (Table I). These results also indicated a slight decrease in hardness values of the tablets made from aged polyox powders during storage time. However, the slight decrease in the hardness was not significantly different in all cases. The slight reduction in the hardness might be due to degradation, depolymerisation and crystallinity changes of the aged PEO samples.

In other words, generally, the longer the storage time the lower the hardness. Similar results were reported by Nokhodchi *et al.* (23) who reported that elevated temperatures can alter the mechanical properties of tablets. Engineer *et al.* (24) investigated the effect of temperature on the hardness of sustained release diphenhydramine HCl tablets. They showed that the maximum hardness was achieved much quicker for the tablets stored at 40°C than for the tablets stored at 25°C, which could be attributed to a faster acquisition of equilibrium moisture content at high temperatures.

Table I. Effect of Storage Time on the Hardness of Matrices Made from Powder Stored at Different Storage Times

PEO	Storage time (weeks)	Hardness 1:1 (N)	Hardness 2:1 (N)
750	0	93.0±3.0	54.0±1.0
1105	0	95.1±1.0	58.1±2.0
301	0	97.0±1.4	63.5 ±3.2
303	0	100.0±2.0	60.5±3.1
750	2	92.1±3.0	55.8±3.1
1105	2	93.9±1.0	56.5±1.3
301	2	96.5±3.0	58 .0±1.5
303	2	97.5±1.0	59.6±3.0
750	4	90.4±3.0	53.0±2.1
1105	4	91.1±2.7	54.0±1.0
301	4	93.4±1.0	55.8±2.0
303	4	95.5±2.0	56.5±3.3
750	8	88.0±3.0	52.0±2.0
1105	8	90.3±1.0	53.6±1.1
301	8	95.1±3.0	55.0±2.0
303	8	97.0±1.5	56.0±2.5

The results also illustrated that there was a remarkable difference (ANOVA $p>0.05$) between hardness of tablets prepared from 1:1 and 2:1 drug/polymer ratios which would be owing to the different amounts of drug in the tablets. The results showed that an increase in the concentration of drug in the formulations (drug/polymer 1:1 and 2:1 ratios) resulted in a reduction in the hardness of tablet matrices. Similar pattern was observed for other polyox polymers as shown in Table I. This could be due to poor compactibility of drug compared to polyox polymer as the contribution of drug in 2:1 ratio is higher than 1:1 ratio. On the other hand, polyox polymers show better compactibility compared to pure drug, thus more polymer in the formulation higher the hardness (13).

Influence of Storage Conditions and Various Molecular Weights on Drug Release

In the preliminary experiments, two different ratios of drug/polyox (1:1 and 2:1) were chosen to investigate the effect of drug or polymer concentration on the release rate of diltiazem HCl from polyox matrices (fresh samples). Figure 1 compares the drug release from different ratios of drug/polymer for all grades of polyox used. It was observed that when the tablets made from the polyox powder was introduced into the dissolution medium that the extent of swelling decreased with the increasing the amount of drug. An increase in the concentration of drug in the formulation also resulted in an increase in the release of diltiazem HCl from the polyox matrices (Fig. 1). In matrices with low concentration of polyox there is a less degree of swelling that probably results in the formation of more areas of low microviscosity in the gel structure for the drug to channel through, and this could have resulted in a faster drug release (25).

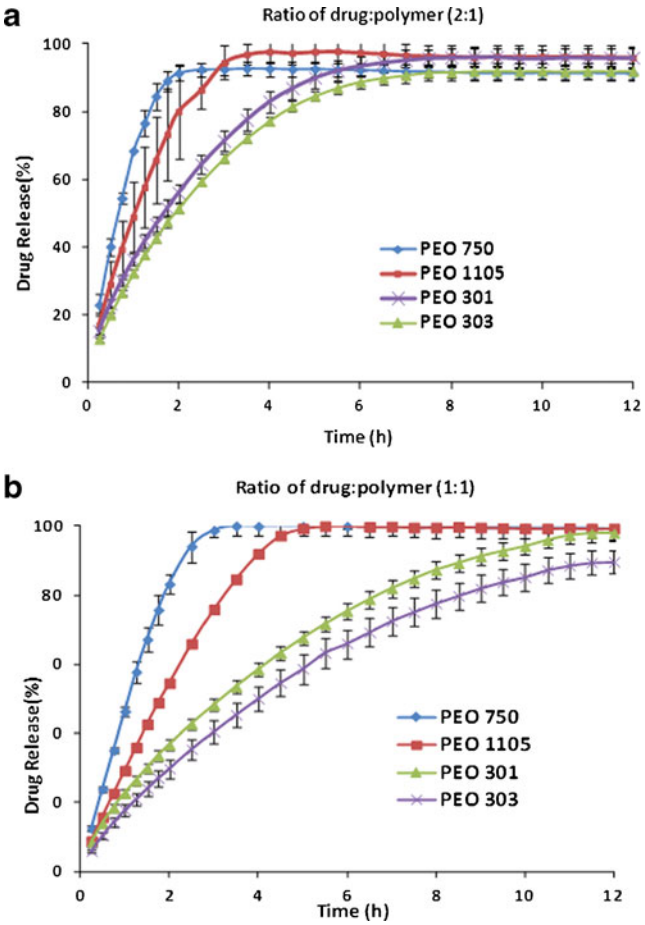

Fig. 1. Drug release profiles of various molecular weight PEO from drug/polymer **a** 2:1 and **b** 1:1

The figure also shows drug release from matrices containing low molecular weight PEO to be faster than high molecular weight in both ratios. This could be due to the low viscosity of the gel formed around tablets. Similarity f_2 test showed that there is a significant difference between drug release from different molecular weights and also different ratios of drug/polymer (f_2<50). On the basis of the release profiles (Fig. 1), we came to this conclusion that the ratio of drug/polymer 1:1 gives reasonable release profile for period of 12 h to investigate the effect of storage conditions on the drug release. Therefore, this ratio was chosen for further investigation as explained below.

In order to investigate the effects of storage conditions and different molecular weight PEO on drug release rate of diltiazem hydrochloride, various molecular weight of PEO were chosen as the inert matrix. Figure 2 shows the drug release profiles of diltiazem hydrochloride from the tablets made from varying molecular weight PEO powder stored at 40°C for different period of times (0, 2, 4 and 8 weeks). The results demonstrated that the release rate of diltiazem hydrochloride was dependent on the molecular weight of the polymer and the storage time. Diltiazem hydrochloride's release was significantly increased from the tablets made from aged polyox powders as compared to the fresh tablets (fresh or 0 weeks) (Fig. 2). Drug release was therefore ranked as follows (8>4>2>0 weeks). This increase in drug release could be due to oxidative degradation primarily in the amorphous region of the polymers

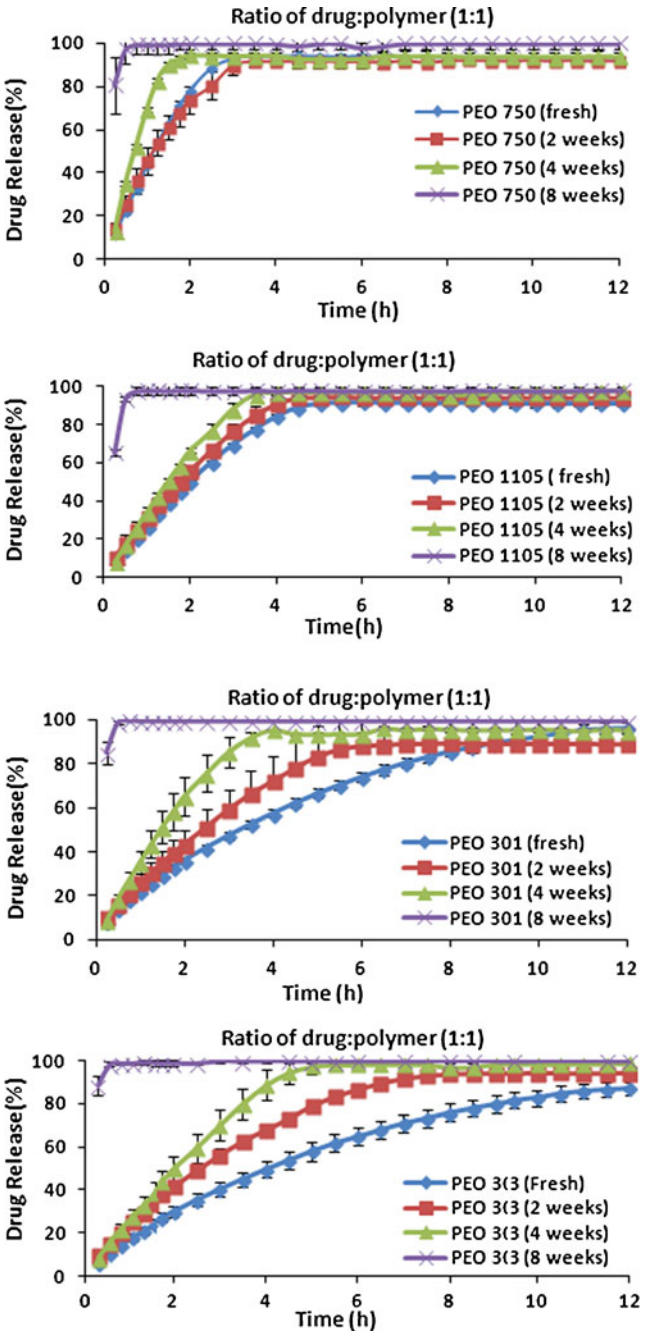

Fig. 2. The effect of storage time and various molecular weights on drug release from tablets made from fresh aged polyox powders

(26). Comparing Fig. 2a (lowest polyox molecular weight) and d (highest polyox molecular weight) indicates that the higher molecular weighted polyox is more sensitive to storage conditions than lower molecular weighted polyox in terms of drug release. This phenomenon could be due to more structural changes in higher molecular weight compared to lower molecular weight, *i.e.* an increase in the degree of crystallinity and volume relaxation (27). The structural changes of PEO leads to stronger polymer–polymer interactions and results in the decrease of the strength of the binary bonds formed between the PEO chains and other molecules (28).

DE and MDT were used to compare the dissolution data (Table II). Dissolution efficiency values are consistent

Table II. Effect of Storage Time on Dissolution Parameters of PEO Powder Matrices

PEO	Storage Time (weeks)	DE (%)	MDT (h)
750	0	80.6±4.8	1.60±0.34
	2	82.4±3.2	1.05±0.13
	4	88.0±2.7	0.72±0.07
	8	98.1±3.0	0.16±0.06
1105	0	76.5±1.0	1.92±0.04
	2	76.8±3.3	1.81±0.04
	4	85.7±2.2	1.57±0.09
	8	96.1±2.0	0.22±0.01
301	0	66.5±2.1	3.71±0.05
	2	72.3±5.1	2.29±0.13
	4	83.0±1.1	1.66±0.09
	8	88.5±0.2	0.18±0.02
303	0	58.4±3.3	3.95±0.22
	2	72.7±0.8	2.72±0.18
	4	81.0±3.7	2.14±0.18
	8	85.5±0.9	0.17±0.01

DE dissolution efficiency, *MDT* mean dissolution test, *MDR* mean dissolution rate

with dissolution profiles and these data confirmed that the drug release rate from various PEO is faster when they are stored at 40°C for different times. For instance, the dissolution efficiency value of PEO 303 at time 0 weeks (fresh samples) was 58.4% whereas this value increased to 85.5% for matrices made from polyox powder stored for 8 weeks at 40°C. Similar patterns were observed for the other molecular weighted PEO (Table II). The results obtained for MDT also confirmed the same conclusion drawn from DE data. For instance, MDT for fresh PEO 750 tablets was 1.60 h while this value decreased to 0.16 h at 8 weeks storage time which is an indication of very fast drug release for the tablets stored at 40°C for 8 weeks. All these results indicated that obtaining a stable drug release from polyox tablets made from aged polyox powder stored at 40°C seems to be very difficult.

All f_2 values were less than 50 when the fresh tablets were compared to the aged polyox powder which is an indication of no similarity between their release profiles.

To elucidate the dissolution results further, the thermal behaviour of the fresh polyox and aged powder were studied by DSC thermograms (Fig. 3). The endothermic peak at 70°C for fresh sample (0 week) corresponds to its melting point. As the storage time was increased, there was a shift of the melting peak towards lower temperatures for the aged samples (Table III). This behaviour can be attributed to the degradation and depolymerisation of the PEO polymer during the storage times. The reduction in melting points of polyox samples stored for different period of times also showed a reduction in their enthalpies with increased storage times. For example, the enthalpy of the fresh polyox 303 was 169 J g^{-1}whereas this value reduced to 128 J g^{-1} for the same sample when stored at 40°C for 8 weeks. This could mean that there is a change in the amorphous content and/or crystallinity of the polymer (28). The explanation for this decreasing melting enthalpy with storage time suggests that a depolymerization occurred in the amorphous part of PEO during storage time. Similar patterns were obtained for other polyox samples with different molecular

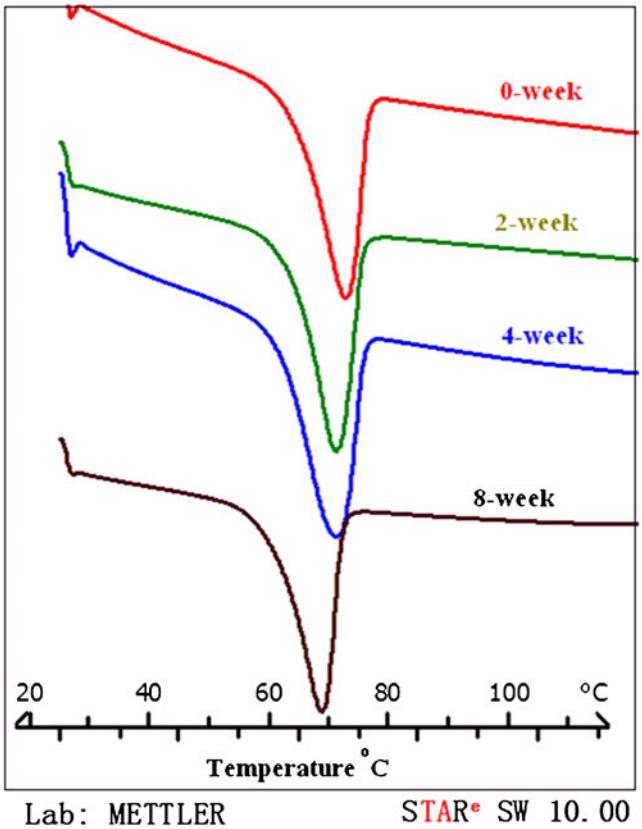

Fig. 3. DSC thermograms of PEO 303 at the different storage times of 0, 2, 4 and 8

weights. Viscosity data also confirmed a reduction in the molecular weight of the polyox samples as the viscosities of 0.5% fresh polyox 750 (the lowest molecular weight) and 303 (the highest molecular weight) in water were 46 and 720 cP respectively, whereas after 8 weeks storage at 40°C the viscosity reduced to 39 and 91 cP respectively. This also indicates that the sensitivity of the highest molecular weight

Table III. DSC Parameters of Various PEO at Different Storage Times (0, 2, 4 and 8 Weeks), and DSC Parameters of PEO 301 without and with Three Concentrations Vitamin E (0.25, 0.5 and 1% *w/w*) at Week 8

PEO	Storage time (weeks)	Enthalpy (J g^{-1})	Onset (°C)	Peak (°C)
303	0	169.0	63.6	71.6
	2	155.2	62.4	70.4
	4	154.0	61.9	69.0
	8	128.0	60.1	68.2
301	0	162.0	62.6	69.8
	2	139.0	62.1	69.3
	4	124.0	61.9	69.0
	8	113.0	60.6	66.8
1105	0	159.0	63.0	70.9
	2	154.9	62.6	69.3
	4	142.4	62.5	69.1
	8	138.1	60.3	68.0
750	0	134.0	62.8	69.9
	2	128.8	61.0	68.5
	4	121.4	60.6	68.0
	8	116.0	60.0	66.7

(polyox 303) against storage time was more than that of the lowest molecular weight (polyox 750).

The Effect of Vitamin E Succinate and their Concentrations on Drug Release Stability and DSC Thermogram

The Effect of Vitamin E on Drug Release Stability

Figures 4, 5, 6 and 7 show the effect of the three concentrations of vitamin E succinate (0.25%, 0.5%, and 1% *w*/*w*) on the release rate of diltiazem HCl from the matrices made from various molecular weight polyox powders stored for different times (0, 2, 4 and 8 weeks) at 40°C. The results showed that the inclusion of vitamin E to polyox powders stored at the elevated temperature had a remarkable difference in the drug release as compared to the matrices without vitamin E (Fig. 2, 4, 5, 6 and 7). The vitamin E therefore stabilized the PEO and prevented rapid drug release at different storage times (0, 2, 4, 8 weeks). This indicates that the presence of vitamin E in polyox samples is crucial to obtain similar drug release profiles when they are stored at elevated temperature. When vitamin E is dispersed into the PEO powders, the antioxidant nature of vitamin E (29) may have delayed the penetration of oxygen into the PEO powders during the storage time thus making the polyox polymer stable in the presence of vitamin E (30).

Figures 4, 5, 6, and 7 also show the effect of vitamin E concentration on the drug release. The results of the effect of three different concentrations of vitamin E on drug release profiles from various PEO matrices demonstrated that when higher concentration of vitamin E (0.5 and 1%) was used in the formulation no difference was observed between the dissolution profiles of polyox matrices stored at 40°C for different period of times ($p>0.05$). Whereas the difference in the drug release for different storage times is more obvious when vitamin E with 0.25% was used particularly in case of polyox 303 (Fig. 7). Figure 7 showed vitamin E to perform best (as a stabilizer) in the matrices made from the highest molecular weight polyox powder stored at elevated temperature up to 8 weeks. f_2 test was employed to investigate the effect of vitamin E and all f_2 values obtained were above 50 which is an indication of similarity in dissolution profiles between fresh samples and aged samples containing vitamin E.

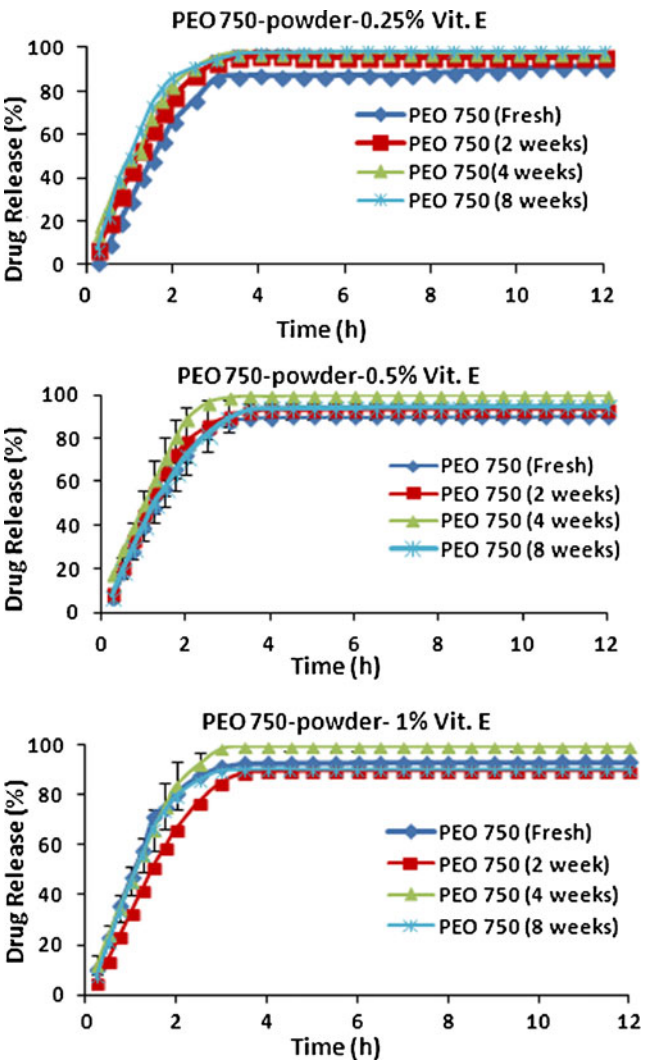

Fig. 4. Effect of concentration of vitamin E on drug release stability from matrices containing aged PEO 750 powders

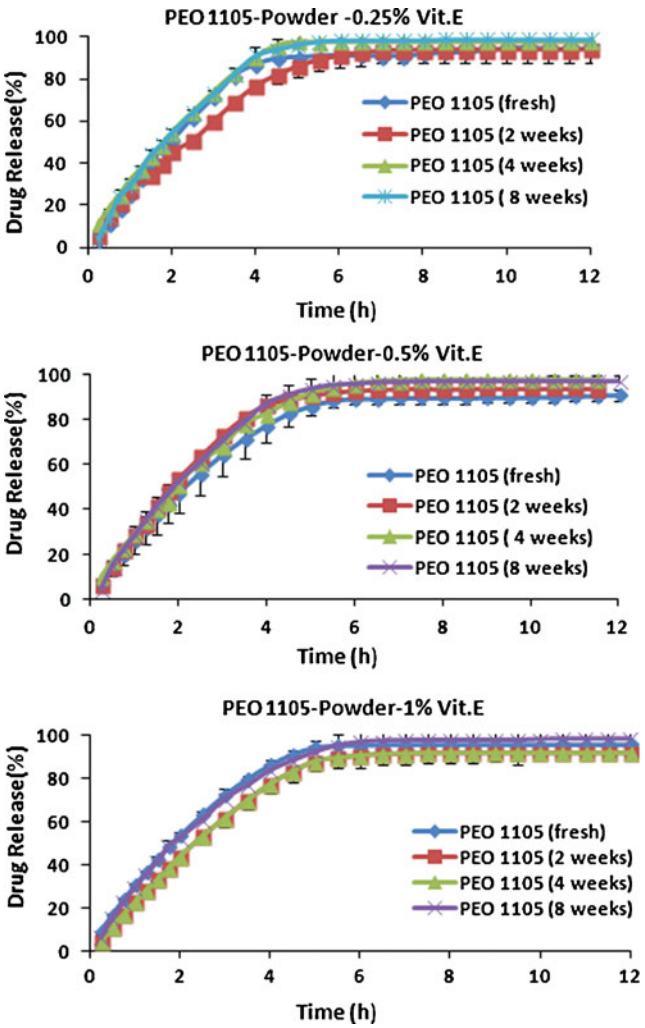

Fig. 5. Effect of concentration of vitamin E on drug release stability from matrices containing fresh or aged PEO 1105 powders

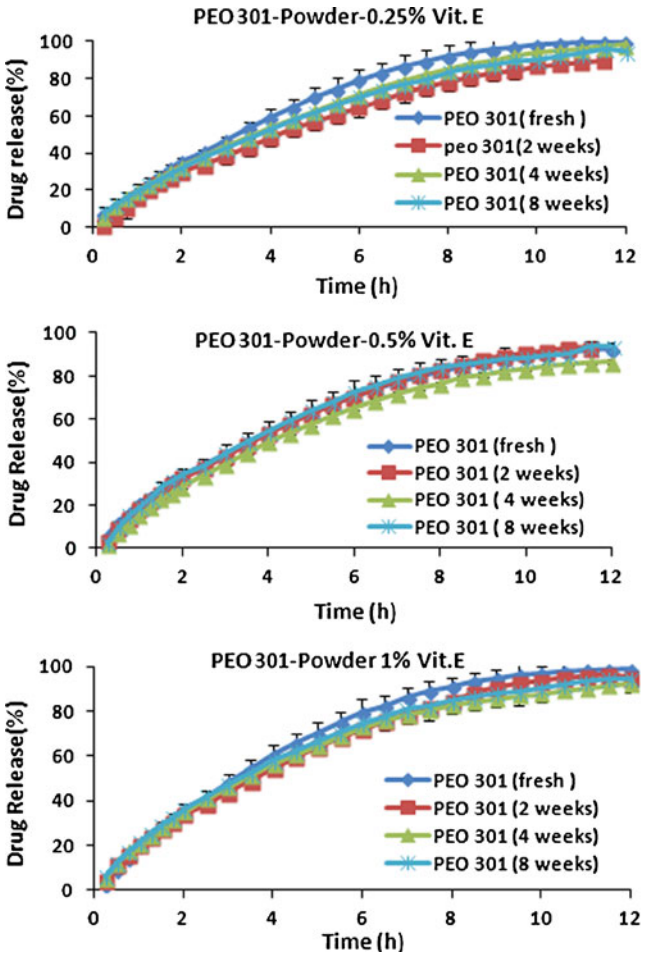

Fig. 6. Effect of concentration of vitamin E on drug release stability from matrices containing fresh or aged PEO 301 powder

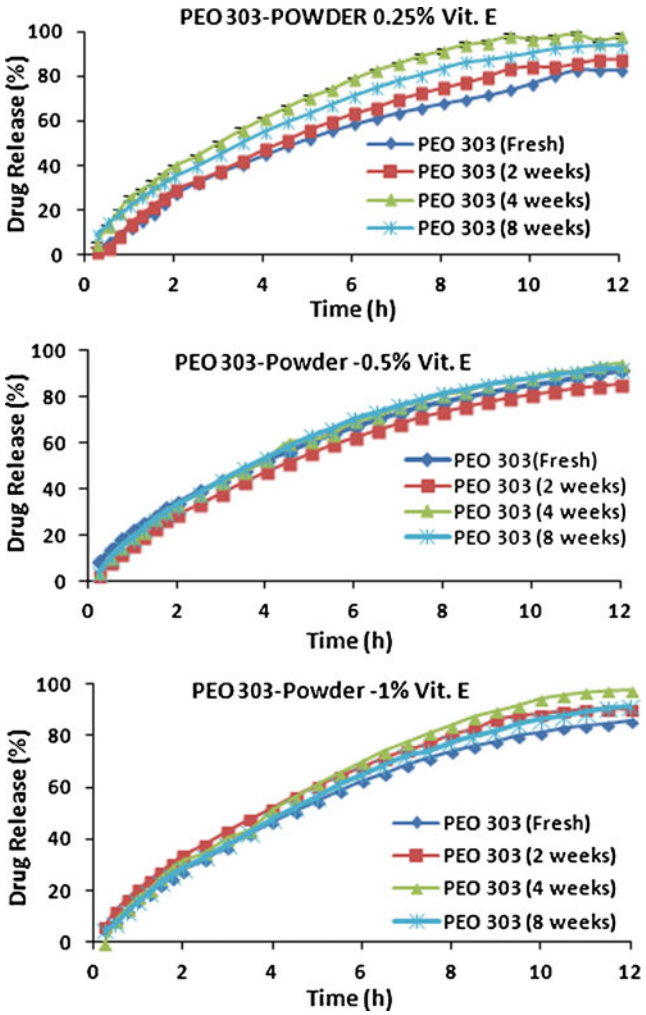

Fig. 7. Effect of concentration of vitamin E on drug release stability from matrices containing fresh or aged PEO 303 powder

Effect of Vitamin E Succinate on DSC Thermograms

DSC thermograms of polyox powder (PEO 303) with and without vitamin E stored for 8 weeks at 40°C are shown in Fig. 8. These show that samples containing 0.5% or 1% vitamin E showed similar melting points (71 and 72°C) to the fresh samples (72°C), whereas sample without vitamin E stored for 8 weeks showed melting point around 68°C. This behaviour can be attributed to the effect of vitamin E on degradation and depolymerization of the PEO polymer during its storage time. The DSC traces of fresh PEO 750 (the lowest molecular eight) also showed an endothermic peak at 70°C which was reduced to 66.7°C when it was stored for 8 weeks at 40°C. The presence of vitamin E stabilized the melting point of aged samples around the melting point of the fresh sample. These results also demonstrated when vitamin E succinate was incorporated into the PEO powders, depolymerisation and degradation of PEO delayed leading to more stability of polymer against temperature.

These results are confirmed by the DSC data in Table IV which shows enthalpy, onset and melting points for the highest and lowest PEO molecular weight stored for 8 weeks in the absence and the presence of vitamin E. As can be seen from Table IV there is an increase in enthalpies when vitamin E was incorporated into the formulation. The explanation for this increasing melting enthalpy suggests that repair crystallinity occurred in amorphous part of PEO after adding and incorporating vitamin E with PEO powder (30).

KINETICS STUDY

An increase in the molecular weight of polyox changed the mechanism of drug release from Fickian diffusion to the combination of erosion and diffusion (Fig. 9). Similar patterns were observed for all matrices made from aged polyox samples without vitamin E. Figure 9 also showed that for the given molecular weight an increase in the storage time resulted in a reduction in *n* values. This indicates that the storage time also has an influence on the mechanism of drug release. For example, at the lowest molecular weight (PEO 750) all *n* values for different storage times were below 0.45 (Fickian diffusion), whereas in case of PEO 1105 when the storage time was increased from 0 to 8 weeks the *n* value significantly decreased such that the mechanism of drug release was changed from the combination of erosion and diffusion to diffusion only (Fig. 9). The reduction in the *n* values from the matrices containing

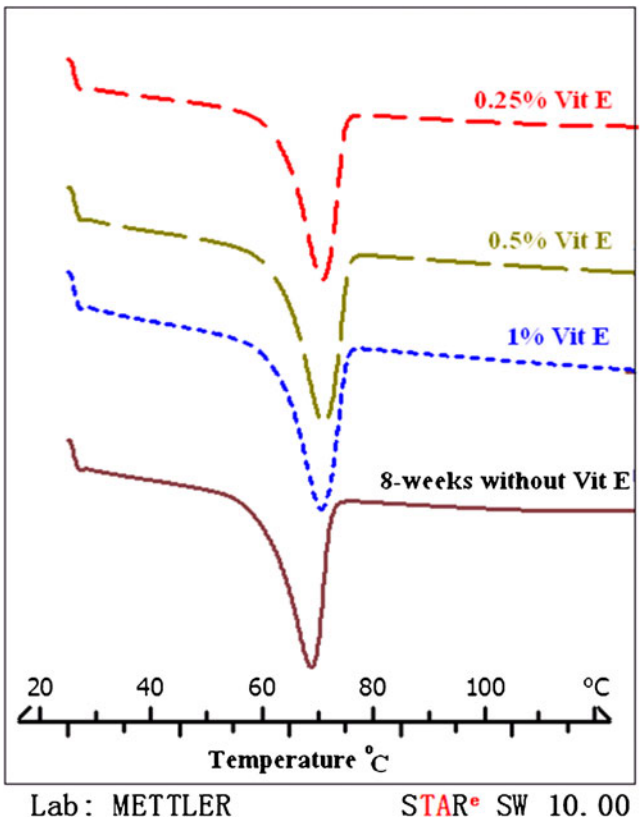

Fig. 8. DSC thermograms of PEO 303 at 8 weeks containing vitamin E

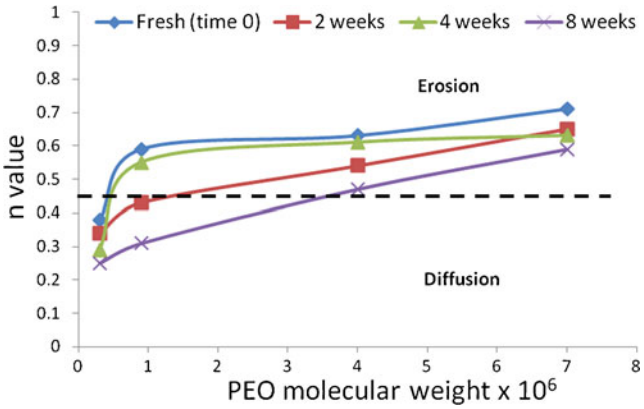

Fig. 9. The effect of molecular weight of polyox and storage time on the mechanisms of drug release from polyox matrices without vitamin E (*n* values)

vitamin E was smaller than their counterparts without vitamin E (Table V). *n* values did not decrease at 8 weeks storage time when vitamin E was present in the samples. In the case of PEO 303, the *n* value decreased from 0.71 (fresh sample) to 0.59 (aged sample without vitamin E), but when vitamin E with different concentrations was incorporated as antioxidant the *n* values varied between 0.62–0.75 (depending on the concentration of vitamin E) which was closer to the *n* value of the fresh sample. The *n* value of most of the samples in the presence of vitamin E was above 0.45 which is an indication of anomalous transport as the kinetics of drug release (19,31–33).

Table IV. Effect of Vitamin E on the Thermal Behaviour of Polyox Samples

Polyox	Storage time (weeks)	Enthalpy (J g^{-1})	Onset (°C)	Melting peak (°C)
750 fresh	0	134.0	62.8	69.9
750 no vitamin E	8	125.2	62.1	66.7
750 with 0.25% vitamin E	8	130.8	61.0	69.9
750 with 0.5% vitamin E	8	134.0	61.0	67.1
750 with 1% vitamin E	8	136.2	62.6	68.7
303 fresh	0	169.0	63.0	71.6
303 no vitamin E	8	134.7	59.9	69.1
303 with 0.25% vitamin E	8	145.1	61.1	69.9
303 with 0.5% vitamin E	8	151.3	61.4	71.0
303 with 1% vitamin E	8	155.0	61.1	72.4

CONCLUSION

Different molecular weights of polyethylene oxide (PEO 750, 1105, 301 and 303) can be used successfully in controlled release drug delivery due to their excellent matrix forming properties. However, when matrices made from aged polyox powders or tablets made from fresh polyox stored at elevated temperature, significant increases in drug release was observed. The incorporation of vitamin E at different concentrations can increase the stability of polyox polymers hence desirable release profiles. The molecular weight of polyox and storage time at elevated temperatures have a significant effect on the mechanism of drug release. The higher molecular weighted PEO was more sensitive and susceptible to temperature as compared to the lower polyox molecular weight. Although the presence of 0.25% *w*/*w* vitamin E can stabilize the drug release from polyox matrices, this concentration might not be enough in long term storage, therefore, the present study suggests that incorporation of vitamin E concentration ≥0.5% *w*/*w* would be ideal.

Table V. Effect of Vitamin E on the *n* Values Generated from Korsmeyer and Peppas Equation

PEO	Fresh samples	Aged samples for 8 weeks without vitamin E	Aged samples for 8 weeks containing vitamin E (0.25–1%)
303	0.71	0.59	0.62–0.75
301	0.63	0.47	0.68–0.77
1105	0.59	0.31	0.67–0.68
750	0.38	0.25	0.45–0.62

ACKNOWLEDGMENTS

Authors thank Colorcon for donating polyethylene oxides polymers and Elan for donating diltiazem hydrochloride.

REFERENCES

1. Abrahamsson B, Johansson D, Torstensson A, Wingstrand K. Evaluation of solubilizers in the drug release testing of hydrophilic matrix extended-release tablets of felodipine. Pharm Res. 1994;11:1093–7.
2. Johnson JL, Holinej J, Williams MD. Influence of ionic strength on matrix integrity and drug release from hydroxypropyl cellulose compacts. Int J Pharm. 1993;90:151–9.
3. Lindner WD, Lippold BC. Drug-release from hydrocolloid embeddings with high or low susceptibility to hydrodynamic stress. Pharm Res. 1995;12:1781–5.
4. Skoug JW, Mikelsons MV, Vigneron CN, Stemm NL. Qualitative evaluation of the mechanism of release of matrix sustained-release dosage forms by measurement of polymer release. J Control Release. 1993;27:227–45.
5. Kaialy W, Emami P, Asare-Addo K, Shojaee S, Nokhodchi A. Psyllium: a promising polymer for sustained release formulations in combination with HPMC polymers' Pharmaceutical Development and Technology. 2013; (in press).
6. Nokhodchi, A, Raja S, Patel P, Asare-Addo K. The role of oral controlled release matrix tablets in drug delivery systems. BioImpacts, 2012; 2:
7. Kim CJ. Effect of drug solubility, drug loading and polymer molecular weight on drug release from polyox tablets. Drug Dev Ind Pharm. 1998;24:645–51.
8. Kim CJ. Drug release from compressed hydrophilic Polyox-WSR tablets. J Pharm Sci. 1995;84:303–6.
9. Apicella A, Cappello B, Del Nobile MA, La Rotonda MI, Mensitieri G, Nicolais L. Polyethylene oxide (PEO) and different molecular weight PEO blends monolithic devices for drug release. Biomaterials. 1993;14:83–90.
10. Zhang F, McGinity JW. Properties of sustained-release tablets prepared by hot-melt extrusion. Pharm Dev Technol. 1999;4:241–50.
11. Razaghi AM, Schwartz JB. Investigation of cyclobenzaprine hydrochloride release from oral osmotic delivery systems containing a water-swellable polymer. Drug Dev Ind Pharm. 2002;28:631–9.
12. Chois U, Lee J, Choi YW. Development of a directly compressible poly ethylene oxide matrix for the sustained release of dihydrocodeine bitartrate. Drug Dev Ind Pharm. 2003;29:1045–52.
13. Asare-Addo K, Kaialy W, Levina M, Rajabi-Siahboomi A, Ghori MU, Supuk E, *et al*. The influence of agitation sequence and ionic strength on in-vitro drug release from hypromellose (E4M and K4M) ER matrices—the use of the USP III apparatus. Colloids Surf B: Biointerfaces. 2013;104:54–60.
14. Sako K, Nakashima H, Sawada T, Fukui M. Relationship between gelation rate of controlled-release acetaminophen tablet containing polyethylene oxide and colonic drug release in dogs. Pharm Res. 1996;13:594–8.
15. Dollery C. Eds. In: Therapeutic drugs, Vol. 1, Churchill Livingstone, London, 1991, 43.
16. Pinto JF, Wander KF, Okoloekwa A. Evaluation of the potential use of poly ethylene oxide as tablet- and extrudate-forming material. AAPS Pharm Sci. 2004;6: article 15.
17. USP Pharmacopoeia 26, National Formulary 21, USP Convention, Rockville, 2003, pp. 320.
18. Khan KA. Concept of dissolution efficiency. J Pharm Sci. 1975;271:48–9.
19. Ritger PL, Peppas NL. A simple equation for description of solute release, II, Fickian and anomalous release from swelling devices. J Control Release. 1987;5:37–42.
20. Peppas NA, Sahlin JJ. A simple equation for description of solute release, III, coupling of diffusion and relaxation. Int J Pharm. 1989;57:169–72.
21. Colombo P. Swelling controlled release in hydrogel matrices for oral rout. Adv Drug Del Rev. 1993;11:37–57.
22. Moore JW, Flanner HH. Mathematical comparison of dissolution profiles. Pharm Tech. 1996;20:64–74.
23. Nokhodchi A, Javadzade Y. The effect of storage times on the physical stability of tablets. Pharm Tech Eur. 2007;19:437–59.
24. Engineer S, Shao ZJ, Khagani NA. The effect of temperature on the hardness of sustained release diphenhydramine HCl. Drug Dev Ind Pharm. 2004;30:1089–94.
25. Rangarao KV, Devi KP. Swelling controlled release systems: recent development and application. Int J Pharm. 1998;47:1–16.
26. Crowley MM, Zhang F, Koleng JJ, McGinity JW. Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion. Biomaterials. 2002;23:4241–8.
27. Kiss D, Suvegh K, Marek T, Devenyi L, Novak C, Zelko R. Tracking the physical ageing of PEO: a technical note. AAPS Pharm. Sci. Tech., 2006; 7:article 95.
28. Kiss D, Suvegh K, Zelko R. The effect of storage and active ingredient properties on the drug release profiles of poly ethylene oxides matrix tablets. Carbohydr Polym. 2008;74:930–3.
29. Strickley RG. Solubilising excipients in oral and injectable formulations. Pharm Res. 2004;21:201–30.
30. Repka MA, McGinity JW. Influence of vitamin E TPGS on the properties of hydrophilic films produced by hot melt extrusion. Int J Pharm. 2000;202:63–70.
31. Colombo P, Bettini R, Massimo G, Catellania PL, Santi P, Peppas NA. Drug diffusion front movement is important in drug release control from swellable matrix tablets. J Pharm Sci. 1995;84:991–7.
32. Korsmeyer RW, Peppas NA. Swelling-controlled delivery system for pharmaceutical applications macro molecular and modelling considerations. J Control Release. 1983;15:25–35.
33. Lee PI, Peppas NA. Prediction of polymer dissolution in swellable controlled-release systems. J Control Release. 1987;6:207–15.