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Investigation of physicochemical factors affecting the stability of a pH-modulated solid dispersion and a tablet during storage

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ABSTRACT

The stability of solid dispersions (SD) during storage is of concern. We prepared the pH-modulated SD (pSD) and compressed tablets consisting of polyethylene glycol (PEG) 6000 as a carrier, drug and MgO (alkalizer). Telmisartan (TEL), an ionizable poorly water-soluble drug, was chosen as a model drug. The changes in physicochemical factors such as the dissolution rate, drug crystallinity, microenvironmental pH (pH_M) and intermolecular interactions of the pSD and the tablets were investigated over 3 months under different temperature and relative humidity (RH) conditions: refrigerator (5–8 °C), 25 °C/32% RH, 25 °C/55% RH, 25 °C/75% RH, 40 °C/32% RH, 40 °C/55% RH, and 40 °C/75% RH. Differential scanning calorimetry (DSC) analysis of all samples revealed no distinct changes in the drug melting point. In contrast, powder X-ray diffraction (PXRD) diffractograms revealed that samples stored at 40 °C/75% RH for 1 month, 25 °C/75% RH for 3 months and 40 °C at all humidity conditions for 3 months showed gradual recrystallization of the drug. Fourier transform infrared (FTIR) spectra indicated a reduced intensity of intermolecular interactions between TEL and MgO in the pSD and tablet. The pH_M also gradually decreased. These altered physicochemical factors under the stressed conditions resulted in decreased dissolution profiles in intestinal fluid (pH 6.8). In contrast, the dissolution rate in gastric fluid (pH 1.2) was almost unchanged because of the high intrinsic solubility of TEL at this pH.

1. Introduction

Solid dispersion (SD) has been widely applied to enhance the dissolution and absorption of poorly water-soluble drugs in the pharmaceutical industry (Serajuddin, 1999; Vasconcelos et al., 2007). Recently, SDs containing pH modifiers, pSD have been shown to greatly enhance drug dissolution via modulation of physicochemical factors such as the microenvironmental pH (pH_M), drug crystallinity and intermolecular hydrogen bonding in the cases of ionizable poorly water-soluble drugs (Tran et al., 2008, 2009, 2010). It is known that pH modifiers play an important role in enhancing a drug's solubility (Doherty and York, 1989; Streubel et al., 2000) and in maintaining the stability of a solid dosage form via the modulation of the pH_M (Badawy and Hussain, 2007).

However, the stability of SD is problematic for the further development of pharmaceutical dosage forms. Many reports have been published about stability issues of SDs (Ghebremeskel et al., 2006; Yoshioka et al., 1995; Marsac et al., 2006). The usefulness of SDs is limited by low stability because of the rearrangements of molecules to reach a local minimum in free energy, leading to crystallization during storage (Tang et al., 2002; Vadas, 2005). Thus, scientific knowledge of the physical and chemical stability of an SD formulation is very important in the pharmaceutical industry to ensure the quality of drug products on the shelf. As an index of SD stability, drug dissolution and drug contents are commonly determined. However, there have been few full reports about the effects of various storage conditions on the physicochemical factors of a SD containing a pH modifier.

The incorporation of an alkalizer such as MgO into PEG 6000-based SD, pH-modulated SD (pSD) has been proposed as a method to enhance the dissolution rate of telmisartan (TEL) (Tran et al., 2008). This enhancement in the dissolution rate was attributed not only to the modulation of the pH_M but also to the change in drug crystallinity, resulting in an amorphous form because of intermolecular hydrogen bonding interactions. Thus, the scientific understanding of the physical and chemical stability of a pSD formulation during storage can provide a pharmaceutical strategy to overcome the stability issues.

The aim of this work was to investigate the changes in the physicochemical factors of PEG 6000-based pSD and tablets

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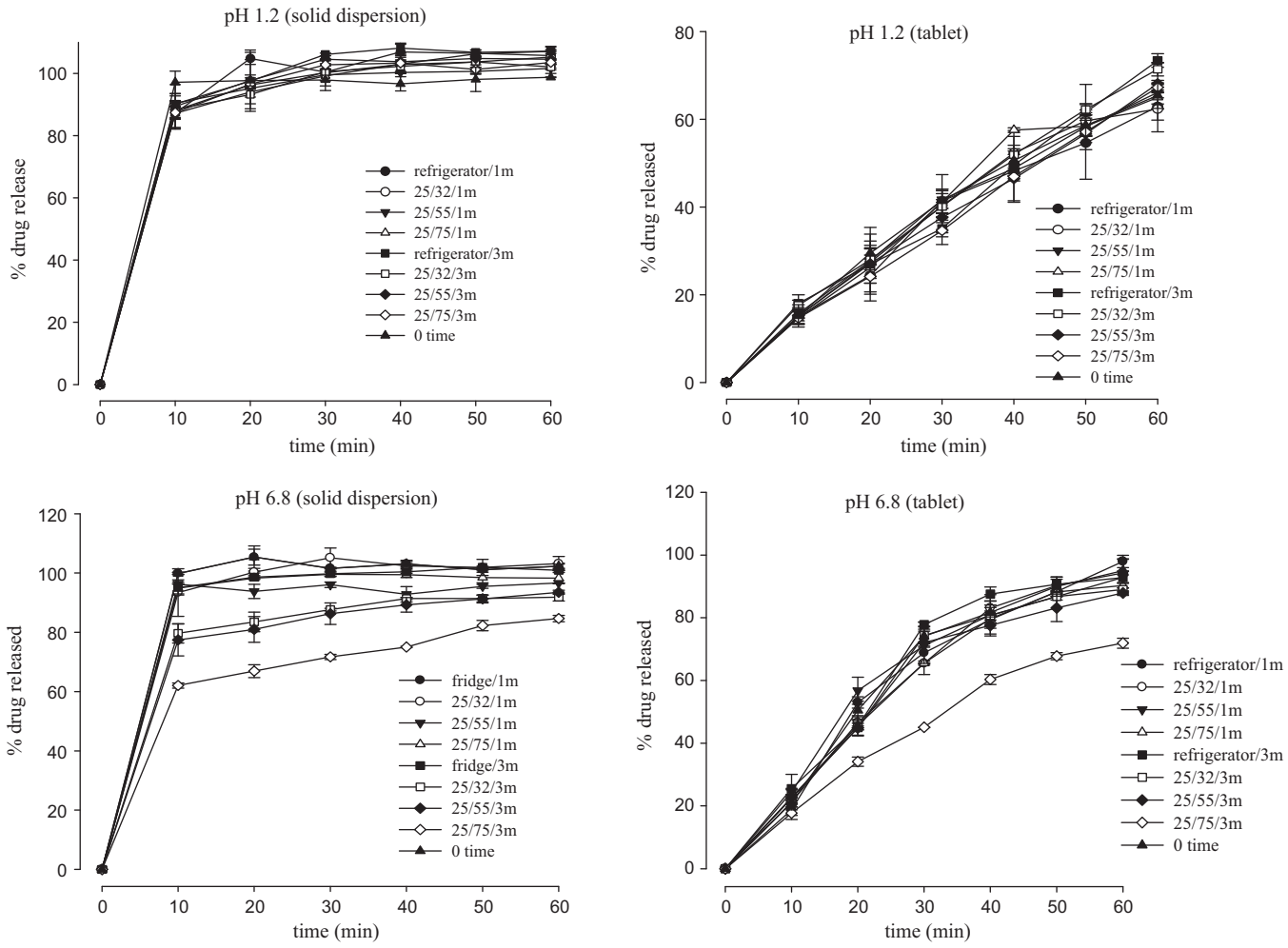

Fig. 1. Effect of humidity on the dissolution profiles of pSD and the corresponding tablets during storage in the refrigerator or at 25 °C in gastric (pH 1.2) or intestinal fluid (pH 6.8).

containing an alkalizer (MgO) and TEL under various storage conditions. This drug was chosen as a model in the study because it is an ionizable drug with a very specific pH solubility profile; TEL is very soluble at pH 1.2 and pH 10 but is poorly soluble at pH 6.8 (Tran et al., 2008). The solid dosage forms of the pSD and tablets containing TEL were stored for 3 months at three different temperatures and three levels of relative humidity (RH): refrigerator (5–8 °C), 25 °C/32% RH, 25 °C/55% RH, 25 °C/75% RH, 40 °C/32% RH, 40 °C/55% RH, and 40 °C/75% RH. Then the changes in physicochemical factors, such as the dissolution rate in enzyme-free gastric fluid (pH 1.2) and intestinal fluid (pH 6.8), drug crystallinity, pH_M and intermolecular interactions, of the pSD and tablets were investigated. The structural behaviors and molecular interactions of the pSD containing alkalizers were examined by instrumental characterization using differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and Fourier transform infrared spectroscopy (FTIR). The gradient changes of the pH_M when TEL was in tablet form were also investigated as a function of time at different fractional distances of the tablet length to elucidate the pH-modifying mechanism.

2. Materials and methods

2.1. Materials

TEL was purchased from NJMMM Co. (Nanjing, China). PEG 6000 was purchased from Yakuri Pure Chemicals Co. Ltd. (Osaka, Japan). Magnesium oxide (MgO) and glucose were purchased from Junsei Chemical Co. Ltd. (Japan). Magnesium chloride ($MgCl_2$) was purchased from Duksan Chemical Co. Ltd. (Korea), and sodium chloride (NaCl) was purchased from Sigma–Aldrich (USA). The solvents used were high-performance liquid chromatography (HPLC) grade. All other chemicals were of analytical grade and were used without further purification.

2.2. Methods

2.2.1. Preparation of pSD and tablets

MgO, drug and PEG 6000 were homogenously mixed at a weight ratio of 1:8:24. PEG 6000 was placed in a beaker with a magnetic stirrer and melted using a hot plate (60 °C). Ethanol was then added to the beaker containing the melted PEG 6000, and the solution was mixed at room temperature. When a clear solution was obtained, the alkalizer (MgO) was added. Finally, TEL was added, and the solution was stirred until a uniform mixture was obtained. The system was evaporated and then dried in a vacuum dryer.

Tablets (400 mg, diameter 12 mm, hardness 60 ± 5 N) based on the ternary pSD were prepared by the direct compressing method using a single punch press. The pSD was milled, passed through a mesh 40 (425 μm) sieve, and then mixed with other excipients to make the tablets.

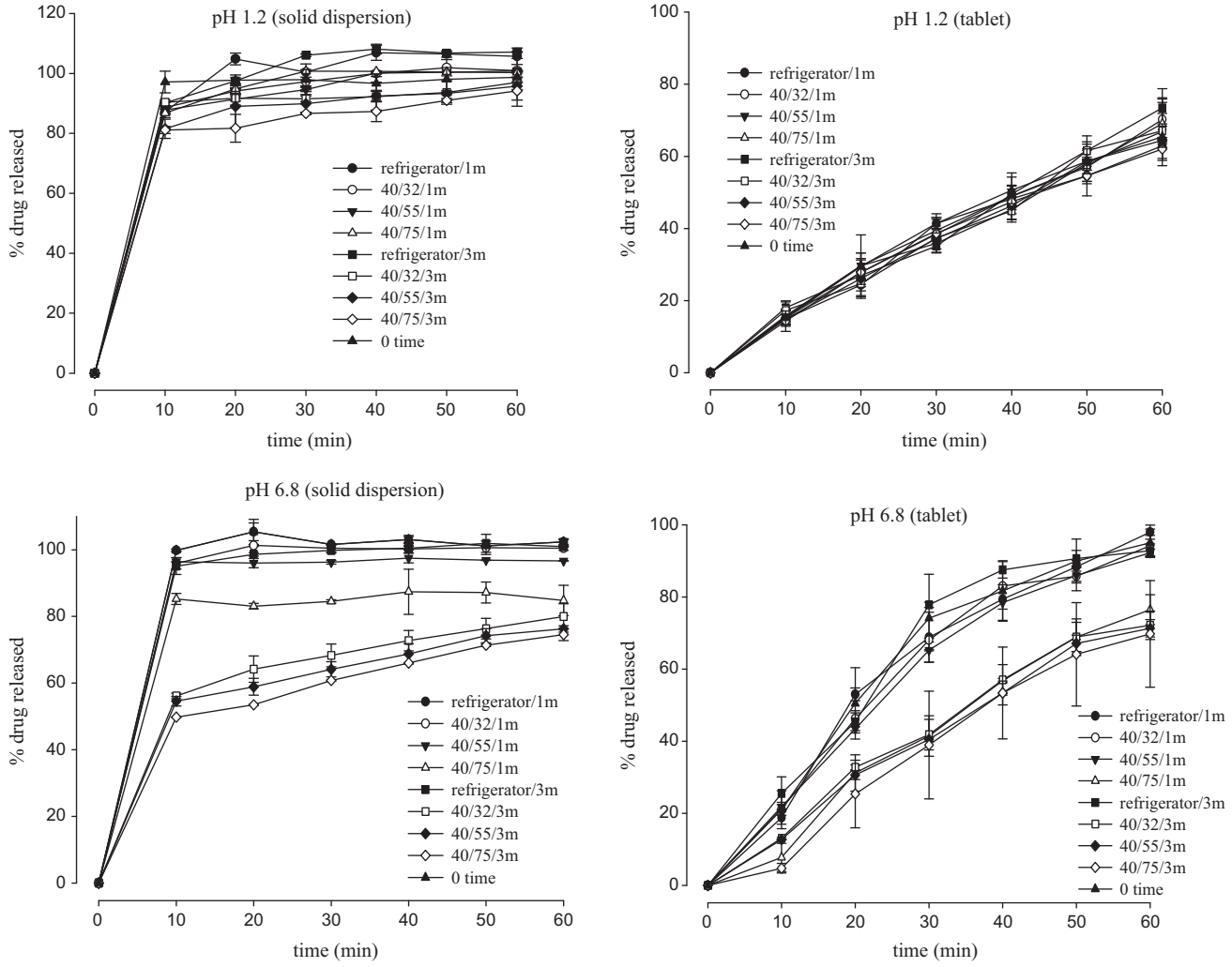

Fig. 2. Effect of humidity on the dissolution profiles of pSD and the corresponding tablets during storage in the refrigerator or at 40 °C in gastric (pH 1.2) or intestinal fluid (pH 6.8).

2.2.2. Storage of pSD and tablets

The pSD and tablets were stored in the refrigerator (5–8 °C) and at 25 °C/32% RH, 25 °C/55% RH, 25 °C/75% RH, 40 °C/32% RH, 40 °C/55% RH, and 40 °C/75% RH for 3 months. The humidity levels of 32% RH, 55% RH and 75% RH were created by making saturated solutions of $MgCl_2$, glucose and NaCl, respectively, with deionized water (Winston and Bates, 1960). The dissolution profiles of the pSD and tablets were determined after 1 month and 3 months of storage and were compared to those of the initial samples (0 time point). Instrumental characterization using DSC, PXRD and FTIR and pH_M determination were also completed simultaneously after those storage periods.

Samples were named in this manuscript as follows: refrigerator/1 m, 25/32/1 m, 25/55/1 m, 25/75/1 m, 40/32/1 m, 40/55/1 m, 40/75/1 m, refrigerator/3 m, 25/32/3 m, 25/55/3 m, 25/75/3 m, 40/32/3 m, 40/55/3 m, 40/75/3 m, with the three terms corresponding to temperature/relative humidity/months.

2.2.3. In vitro dissolution

Dissolution studies were conducted using a USP II apparatus (50 rpm, 37 °C and 900 ml dissolution medium) with a DST-810 dissolution tester (Labfine, Seoul, Korea). The pSD and tablets equivalent to 80 mg TEL were exposed to enzyme-free gastric fluid (pH 1.2) and intestinal fluid (pH 6.8) for 1 hr. Samples were withdrawn from the dissolution medium at predetermined intervals (10, 20, 30, 40, 50 and 60 min), and then the drug concentration was determined by HPLC. An equivalent amount of fresh medium was added to maintain a constant dissolution volume.

Enzyme-free gastric fluid was prepared by dissolving sodium chloride (NaCl) in deionized water and adjusting the pH with dilute HCl solution (7.4%). Enzyme-free intestinal fluid was prepared by dissolving monobasic potassium phosphate (KH_2PO_4) in deionized water and then adding 1 N NaOH solution to adjust the pH.

2.2.4. HPLC conditions

TEL was analyzed using an HPLC system (Water, USA) consisting of a pump (Waters™ 600 Controller), a UV-VIS spectrophotometer detector (Waters™ Tunable Absorbance Detector), an autosampler (Waters™ 717 plus Autosampler), a degasser (Waters™ In-line Degasser), a reverse phase column (150 mm × 4.6 mm, Luna 5u C18 100 A) and Borwin 1.20 software. The mobile phase consisted of a 75:25 (%v/v) mixture of methanol and 51.8 mM ammonium acetate; the flow rate was 1.0 ml/min; the detection wavelength was 296 nm; the injection volume was 20 μl; and the running time was 6 min. The entire solution was filtered using a 0.45 μM membrane filter (Millipore™, Millipore Corporation, Bedford) before running the HPLC analysis.

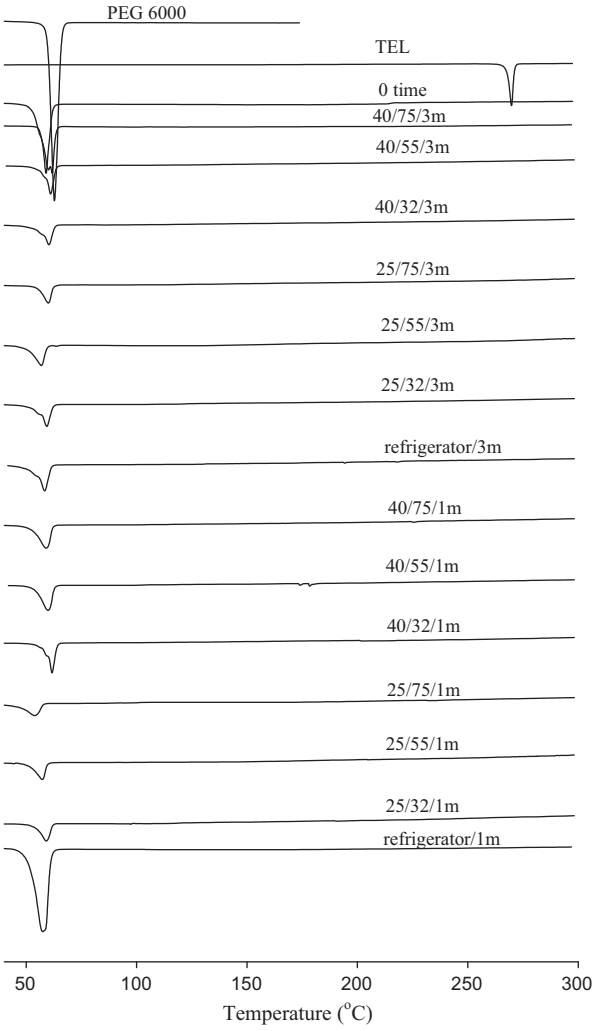

Fig. 3. DSC thermograms of pSD stored under various conditions.

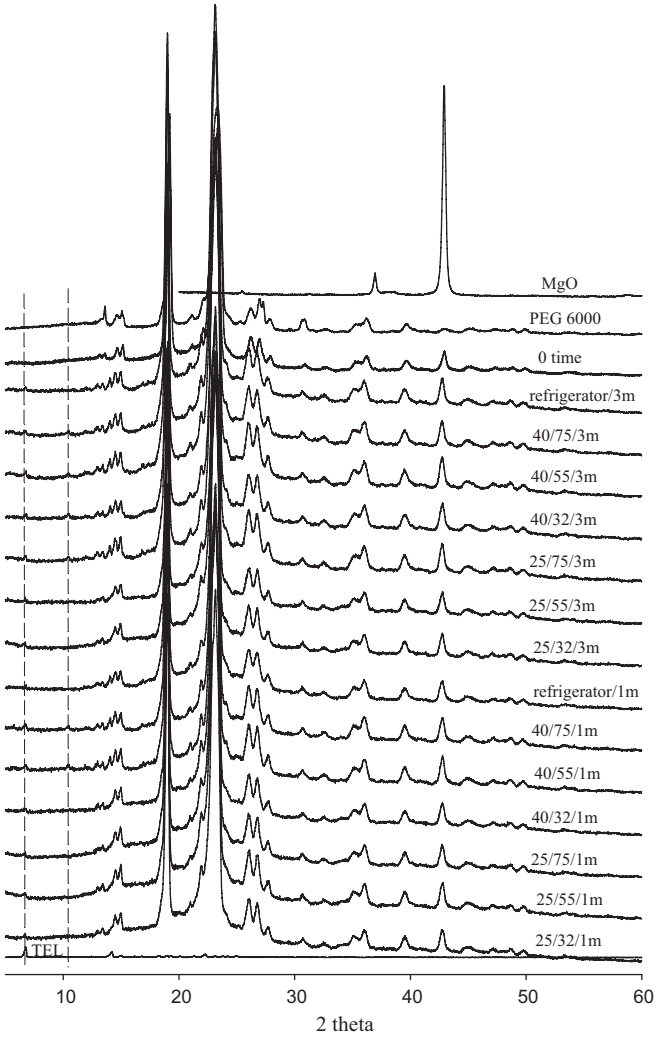

Fig. 4. PXRD patterns of pSD stored under various conditions.

2.2.5. Determination of pH_M

After specific time intervals, tablets were removed from the dissolution medium and dried at ambient temperature. The pH_M was determined potentiometrically using a surface pH electrode (Metoxy pH Meter HM-17MX, DKK-TOA Corp., Japan). The pH_M gradient from the surface to the tablet center was determined as a function of time. Tablets were cut into three slices. Depending on the fractional dimension of tablet length, the tablet surface and inner regions were determined and designated as $d/d_0 = 0$, 1/3, 2/3 or 1, respectively; d_0 was the distance from the edge to the center. We assumed that the pH gradients from the center of the tablet to both margins were similar; $d/d_0 = 1$ represents the center, whereas $d/d_0 = 0$ indicates the edge (surface) of the tablet. The pH_M was plotted as a function of time at different fractional distances (d/d_0).

2.2.6. Thermal analysis (DSC)

A TA Instruments differential scanning calorimeter (Model 2910, USA) was used to investigate the thermal behaviors of TEL, PEG 6000 and different pSD. The amount of sample used ranged from 1 to 2 mg for the pSD and PEG 6000 and was 0.4 mg for pure TEL. The samples were weighed in a standard open aluminum pan, while an empty pan of the same type was used as a reference. The heat running for each sample was increased from 19 to 300 °C at 10 °C/min, using nitrogen as the purge gas. Calibration of the temperature and heat flow was performed with indium.

2.2.7. Powder X-ray diffraction (PXRD)

Powder X-ray diffraction was performed with a D5005 diffractometer (Bruker, Germany) using Cu Kα radiation at a voltage of 40 kV and a current of 50 mA. The samples, which included TEL, PEG 6000 and different pSD, were scanned in increments of 0.02° from 5° to 60° (diffraction angle 2θ) with a rate of 1 s per step, using a zero background sample holder.

2.2.8. FTIR spectroscopy

The spectra of the samples including TEL, PEG 6000 and different pSD were recorded using an FTIR spectrophotometer (Bio-Rad, USA Model Excalibur Series UMA-500). KBr pellets were prepared by gently mixing 1 mg of the sample with 200 mg KBr. FTIR (400–4000 cm^{-1}) spectra were obtained with a resolution of 2 cm^{-1}.

3. Results and discussion

3.1. Dissolution test of pSD and tablets after storage

The dissolution rate of pSD at the initial time (0 time point) is consistent with those of our previous research (Tran et al., 2008). The incorporation of an alkalizer, in this case MgO, enhanced the TEL dissolution rate. Specifically, the effect of MgO on TEL dissolution at pH 6.8 was more obvious than its effect at pH 1.2 because the

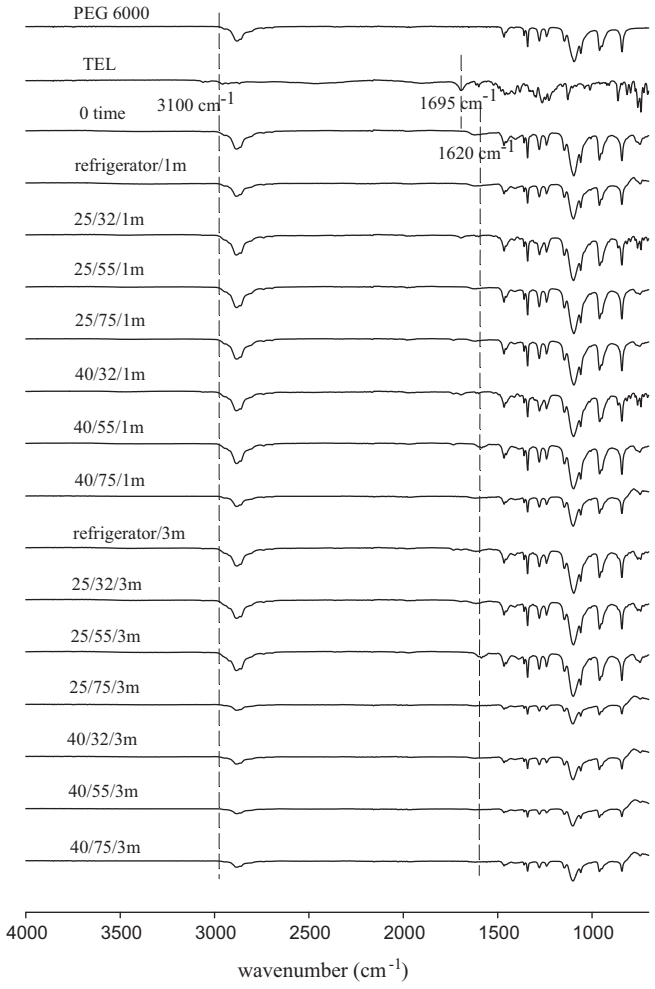

Fig. 5. FTIR spectra of pSD stored under various conditions.

drug release rate at pH 1.2 was the same as that of the pure drug. All of the samples stored under various conditions were compared with the initial sample. The samples stored in the refrigerator had dissolution profiles almost identical to those of the samples at the 0 time point. For easy comparison and analysis of the interrelation between the effects of temperature and humidity on the dissolution of pSD and tablets, we classified the dissolution profiles into two main groups based on temperature (25 or 40 °C). Fig. 1 shows the dissolution profiles of pSD and tablets after storage for 1 and 3 months at 25 °C at various levels of humidity at pH 1.2 and pH 6.8. Similarly, Fig. 2 shows the dissolution profiles at 40 °C. In general, the dissolution profiles of pSD and tablets at pH 1.2 were stable under all of the test conditions for 3 months. The intrinsic dissolution rates of pure TEL and pSD were about 100%, while the drug dissolution rate from tablets decreased to about 70%. This reduction could be attributed to the ability of tablet compaction to cause a change in the pH_M inside the tablet, which is described as the pH of the saturated solution in the immediate vicinity surrounding the drug particles (Siepe et al., 2006).

In the case of samples at pH 6.8, there was no consistent pattern of profiles. For all of the tests at 25 and 40 °C, there was a decrease in the drug dissolution release under humid conditions relative to the drug dissolution rate of the samples kept in the refrigerator and samples at the 0 time point. However, the variations of the dissolution profiles of tablets correlated with those of the corresponding pSD. If the dissolution rate of pSD was decreased, the corresponding tablet's dissolution also decreased. For 1 month, the dissolution profiles for all of the humid conditions at 25 °C changed negligibly, while there was a more obvious decrease for the 55% RH condition and a bigger decrease at 75% RH at 40 °C. After 3 months, dissolution was lower for the humid conditions. At 25 °C, the dissolution of the 25/32/3 m, 25/55/3 m samples was not much different from those of the samples stored in the refrigerator and the samples at the 0 time point (about 5%), but there was a significant decrease for the 25/75/3 m sample (about 20% compared to the samples at the 0 time point). At 40 °C, after 3 months, there was a noticeable decrease for all three humidity levels (about 20% compared to the samples at the 0 time point).

In conclusion, it appears that various levels of humidity had no effect on the dissolution profiles over 3 months at different temperatures at pH 1.2. At pH 6.8, when samples were kept at 75% RH, the formulations at both 25 and 40 °C had decreased release rates after 3 months. Moreover, there was a tendency for the higher humidity and higher temperature to cause more decreased release rates. Specifically, the formulation stored at 40 °C/75% RH had a decreased dissolution rate after 1 month of storage (sample 40/75/1 m). After 3 months, there was a reduction of dissolution for all humidity conditions at 40 °C. Thus, tablets should not be stored at both high humidity and high temperature. In other words, tablets can retain their initial properties if they are stored under conditions similar to those of the refrigerator, as shown in the figures. Further instrumental characterization and the pH_M modulation results presented below could explain the variation of the samples.

3.2. Instrumental characterization

Changes in drug crystallinity during storage could be one of the main reasons that a formulation is unstable, especially for an pSD (Serajuddin, 1999). Therefore, DSC and PXRD analyses were carried out to investigate the structural behaviors of pSD. Moreover, the molecular interactions of pSD were also examined using FTIR spectra to determine if there were any new interactions or changes that would cause a decrease in TEL dissolution. As the results of dissolution showed, the changes in the drug dissolution from the tablets were consistent with those of the corresponding pSD. Hence, instrumental characterization of pSD was used to analyze the whole samples after storage under the investigated conditions.

3.2.1. Thermal analysis

Fig. 3 shows the DSC thermograms of initial pSD and of the samples after storage under various conditions for 1 and 3 months. The thermograms of pure TEL and PEG 6000 are also given for the purpose of comparison. The DSC curves of pure TEL and PEG 6000 exhibited single endothermic peaks at 269.79 and 62.76 °C, respectively, which corresponded to their melting points. No characteristic melting peak for TEL could be identified in the DSC curves obtained for the pSD; only the peak for PEG 6000 was observed. The absence of any endothermic peak in the thermograms of the pSD, corresponding to the melting point of TEL, indicates that this system is amorphous (Leuner and Dressman, 2000). Therefore, the DSC analysis of the pSD prior to exposing the samples to the various conditions did not provide enough information to determine the stability of the samples over time. In other words, the DSC results only showed that all of the samples still existed in an amorphous state over time and seemed to be as intact as the initial sample. However, the reduction of drug dissolution of the samples stored at 75% RH or 40 °C for 3 months indicates that there must have been changes.

3.2.2. Powder X-ray diffraction (PXRD)

The effect of humidity during storage on the dissolution profiles of TEL pSD and tablets was investigated as described in the previous section. The results did not differ greatly from the

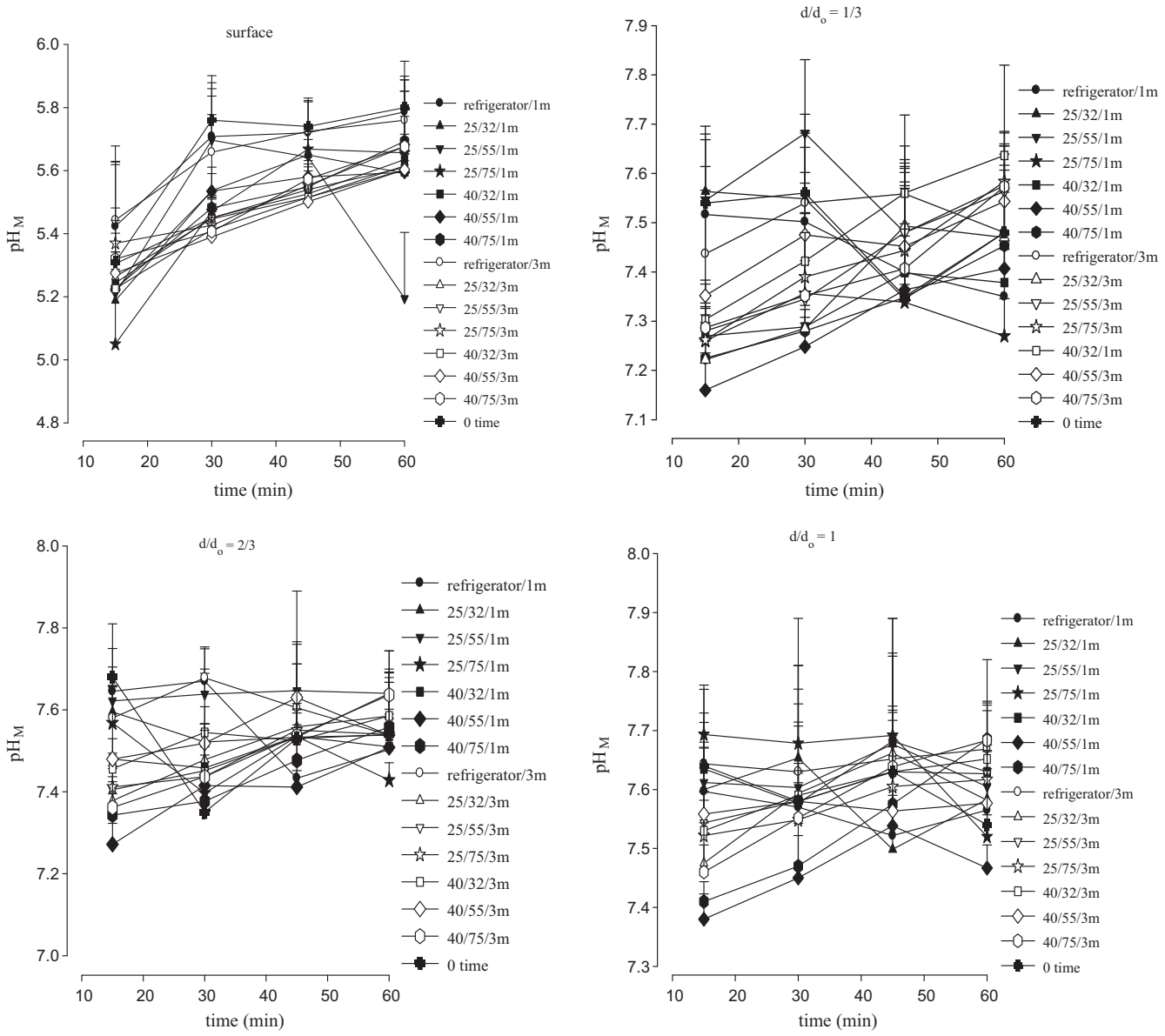

Fig. 6. The changes in the pH_M at different fractional distances of the tablet as a function of the time in gastric fluid (pH 1.2) under various storage conditions.

theoretical results presented in the literature. The potential change of a drug from an amorphous phase to a crystalline phase is always present with an pSD system because amorphous molecules are not thermodynamically stable relative to crystalline molecules (Suzuki and Sunada, 1998). One of the most common and important factors triggering this change of amorphous systems is considered to be the relative humidity. The reduced dissolution for many pSD is caused by high humidity. Our DSC results could not provide a satisfactory explanation, while crystalline peaks of TEL were apparent in the PXRD diffractograms. The PXRD patterns of pure TEL, PEG 6000, initial pSD and samples after storage under various conditions for 1 and 3 months are shown in Fig. 4. Two characteristic peaks should be noted at the positions of 6.8° and 10.5°. The disappearance of a characteristic peak or a large reduction in the number of characteristic peaks indicates that a high concentration of drug is dissolved in the solid state or that the drug is in an amorphous state (Sheen et al., 1995; Hu et al., 2003). While the diffractogram of the initial sample showed that the distinctive peak at 6.8° of TEL was absent, the other diffractograms showed that this peak was present for samples under storage stored for 1 month, though this peak was small. The intensity of the peak increased after 3 months of storage for all of the samples except for the initial one. For the position of 2θ at 10.5°, the patterns of samples 40/55/1 m and 40/75/1 m contained this peak, while the patterns of all of the samples stored at 40 °C for 3 months (40/32/3 m, 40/55/3 m, 40/75/3 m) had peaks at this position. For this reason, the drug dissolution rate of the samples decreased after storage at 40 °C under humid conditions. This peak was also present for sample 25/75/3 m, indicating that humidity played an important role in reducing the TEL dissolution rate by facilitating the conversion of the drug from an amorphous state to a crystalline state. These results are matched with the dissolution profiles above, indicating that there was a change in the structural behaviors of the drug in the pSD system (i.e., the drug crystallized) under the test conditions, resulting in a decrease in the drug release rate.

3.2.3. *Fourier transform infrared spectroscopy (FTIR)*

The FTIR spectra of pure TEL, PEG 6000, the initial pSD and the samples stored under conditions for 1 month and 3 months are shown in Fig. 5. The results indicate that there was an interaction

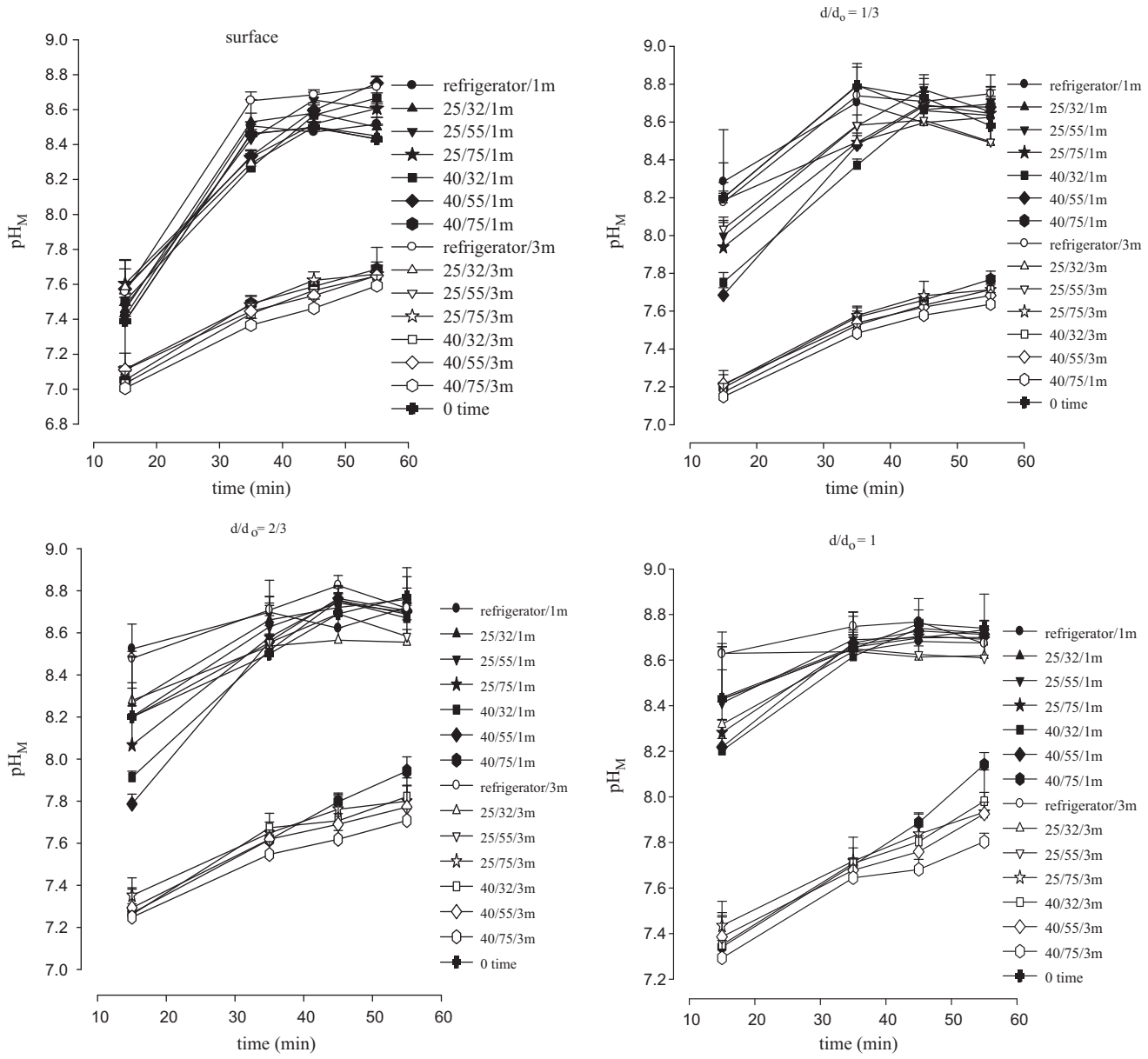

Fig. 7. The changes in the pH_M at different fractional distances of the tablet as a function of the time in intestinal fluid (pH 6.8) under various storage conditions.

between TEL and MgO that was contributed to the enhancement of TEL release. This interaction, illustrated by the disappearance of the OH peak at 3100 cm^{-1} and the shift of the C=O bond peak from 1695 to 1580 cm^{-1}, showed that there was almost no difference among formulations over time and under different test conditions. However, the intensity of the 1580 cm^{-1} band decreased for some samples. The first sample showing this change was the sample 40/75/1 m. One difference between the FTIR results and the PXRD results was that a change in the IR spectrum was not seen with the sample 40/55/1 m. This difference seemed to be corresponding with the above dissolution profiles, in which sample at 40 °C/55% RH had a slighter lower dissolution than sample 40 °C/75% RH. The decreased intensity was also observed for the sample stored for 3 months at 25 °C/75% RH (25/75/3 m) and all of the samples stored at 40 °C. Thus, the FTIR spectra again confirmed that humidity had a significant effect on the pSD system, resulting in increased crystallinity and molecular interaction changes in the samples stored at 25 °C and 75% RH or at high temperature (40 °C). Generally, this result was not unexpected and is reasonable because the reduced intensity indicates an increase in crystallinity (Dhanikula and Panchagnula, 2004).

3.3. Determination of pH_M

To elucidate the influence of pH modifier (MgO) on the maintenance of the basic environment of the tablets and the duration of pH control over 3 months, the pH_M of the tablets stored at various conditions were also determined and compared with the initial pH_M. Figs. 6 and 7 show the pH_M at different fractional distances of the tablet as a function of time in gastric fluid (pH 1.2) or intestinal fluid (pH 6.8) for 1 and 3 months.

As our previous research showed (Tran et al., 2008), incorporating an alkalizer enhanced the TEL dissolution rate by modulating the pH_M of the tablet. Specifically, tablets were more basic in the core and had a slightly acidic surface at pH 1.2, whereas the pH_M gradually increased at the surface at pH 6.8. The high dissolution rate of tablets containing MgO was due to the high pH_M in the tablet interior. The modulation was more obvious at pH 6.8 because TEL

has a high solubility in gastric fluid (pH 1.2). For samples stored under the stability test condition, the tablets generally still showed a higher pH_M in the core. Moreover, the pH_M values of all samples at pH 1.2 were almost identical to the initial value for the duration of the stability test. This result is consistent with those of the dissolution profiles. This result also indicates that the TEL formulation is stable at pH 1.2 for at least 3 months. However, results at pH 6.8 were different. As time passed, there were some differences among samples that could explain the changes in the rate of dissolution. The pH_M values of sample 40/75/1 m and samples stored for 3 months, including 25/75/3 m, 40/32/3 m, 40/55/3 m and 40/75/3 m, were lower at both the surface and the core. Similar to the FTIR results, this phenomenon was not seen with the sample stored at 40 °C/55% RH for 1 month. This result complements the FTIR results and helps to determine the reason that the sample 40/55/1 m had a crystalline peak at 10.5° but showed a higher rate of dissolution. This result was consistent with the PXRD and FTIR results. The changes in the structural behaviors could be the reason for these assembly consequences, including the lower intensity of FTIR spectra and the reduction of the pH_M during the time of test. The FTIR spectra help to explain the pH_M results because of the decreased intensity, which implies a weaker interaction between TEL and MgO.

Therefore, the decrease in the drug release rate was attributed to the following factors: (1) increased crystallinity due to humidity and high temperature and (2) the decrease in the pH_M. These results are reasonable because TEL is very hygroscopic (Quinzler et al., 2006). Formulations with better TEL dissolution rates should be coated with a film to protect the drug from the environment.

4. Conclusions

This research contributes to the knowledge of the stability of pSD and tablet. We attempted to analyze all of the relevant behaviors and mechanisms of an pSD containing an alkalizer over a storage period of 3 months. Under high temperature and high humidity conditions, the structure of the TEL in the pSD changed, with an increase in the level of crystallinity and a weaker interaction between TEL and MgO, leading to a reduced pH_M. The intrinsic solubility of TEL is also important because the stability of pSD is less sensitive at pH 1.2 solutions. The pSD formulation containing MgO is believed to be as safe after storage in a refrigerator as it is before storage. Preferably, tablets should be coated to prevent the negative effects of environmental moisture. In addition, the avoidance of stressed storage conditions, the use of water-proof packaging and the addition of stabilizers can guarantee the long-term stability of pSD containing pH modifiers and poorly water-soluble drugs.

Acknowledgments

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