Application of Eudragit RS to Thermo-Sensitive Drug Delivery Systems. I. Thermo-Sensitive Drug Release from Acetaminophen Matrix Tablets Consisting of Eudragit RS/PEG 400 Blend Polymers

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Received August 30, 2001; accepted December 18, 2001

In order to develop the polymer materials having temperature-sensitive and high biological safety, Eudragit RS-PO and polyethylene glycol 400 (PEG 400) blend polymers (EPG) were prepared. The EPGs that have the glass transition temperature (T_g) at around the body temperature were prepared by the addition of 5—13% PEG 400 to Eudragit RS. As glassy polymers are not in thermodynamic equilibrium below their T_g, the effects of isothermal aging on the T_gs of Eudragit RS and EPG containing 10% PEG 400 (10% EPG) were also studied at various aging temperatures. The T_g values of Eudragit RS increased with the aging time and after 30 d of aging, they apparently reached constant values which markedly differed depending on the aging temperatures. On the other hand, the T_g values of 10% EPG were almost independent of the aging temperature and reached around 33 °C at 30 d after aging. The ability as thermo-sensitive polymer of EPG was evaluated by the dissolution test of the acetaminophen (AAP) matrix tablets prepared with EPG. The AAP release rate from the EPG matrix tablets slightly changed below the T_g of tablets, and then, it markedly increased above the T_g. Considering high biological safety of Eudragit RS and PEG 400, EPG might be available to develop the novel thermo-sensitive drug delivery systems.

Key words thermo-sensitive polymer; eudragit; polyethylene glycol; glass transition temperature; controlled release

For so-called chemotherapy to carry out clinical treatment with drugs, ideally, a drug at the minimum essential dose should be delivered only to a topical lesion to be treated, where the action of the drug should be exerted for only a required duration. Therefore, active research and development works have been conducted in recent years as regards drug delivery systems.

As one group of the essential materials for the progress in drug delivery systems, intelligent polymers are illustrated. Depending on the change in temperature, light, pH, glucose concentration in blood and the like, the drug release ability of intelligent polymers developed up to now changes.[1—5] Among others, thermo-sensitive polymers make it possible to develop the thermo-sensitive controlled release systems, which are responsive to body temperature changes due to diseases. As typical thermo-sensitive polymers, poly-*N*-isopropylacrylamide and interpenetrating polymer network (IPN) have been studied.[6] The drug release of the systems from these polymers depends on hydration and dehydration of poly-*N*-isopropylacrylamide at the lower critical solution temperature (LCST). In addition, polymer films incorporated various liquid-crystalline molecules have been also prepared as thermo-sensitive membranes.[7] However, application of these thermo-sensitive materials to pharmaceutical excipients is difficult from the standpoint of biological safety.

In this paper, to develop the polymer materials having temperature-sensitive and high biological safety, Eudragit RS-PO and polyethylene glycol 400 blend polymers (EPG) having glass transition temperature (T_g) at around the body temperature were prepared. Then the effects of polyethylene glycol 400 contents and isothermal aging on the T_g of EPG were studied. It has been well known that the specific heat, volume, viscosity of a glassy polymer and the diffusion coefficient of a gas through the polymer matrix discontinuity vary at the T_g of the polymer. The effect of the temperature on acetaminophen release from the matrix tablets consisting of the EPG was also examined.

Experimental

Materials Eudragit RS-PO (Eudragit RS, Rohm Pharma GmbH) was kindly supplied by Higuchi Co., Ltd. Polyethylene glycol 400 (PEG 400) was of Japanese Pharmacopeia (JP) XIII grade. Acetaminophen (AAP) was purchased from Sigma Chemical Co. All other reagents were of special reagent grade.

Preparation of Eudragit RS and PEG 400 Blend Polymers Eudragit RS and PEG 400 blend polymers (EPG) were prepared according to the procedure as shown in Chart 1. The various proportions of Eudragit RS and PEG 400 were mixed and put on the teflon dish. The dish was placed at 25 °C for 2 h in a desiccator moistened with ethanol. The amount of ethanol sorbed to the mixture was about 16% of the sample weight and Eudragit RS resulted in gelation. After the removal of ethanol in the gel, the remaining solid was pulverized at the temperature below its T_g and the 80—150 mesh fraction was collected. The obtained blend polymer (EPG) was stored in a desiccator over silica gel until required.

Differential Scanning Calorimeter (DSC) Analysis The glass transition temperatures (T_g) of the samples were determined with a Perkin Elmer DSC-7 differential scanning calorimeter. The instrument was calibrated with an indium standard. The EPG granules (80—150 mesh) or two slices of the tablet (2×2×0.5 mm) were weighed in aluminium pans, hermetically sealed and heated at 20 °C/min from −15 °C to 90 °C under a dry nitrogen flow (20—30 ml/min). In the present study, the T_g values were calculated with the onset temperature of the change in the heat capacity during the thermal event. The enthalpy relaxation of the glassy polymer, which occurs with time

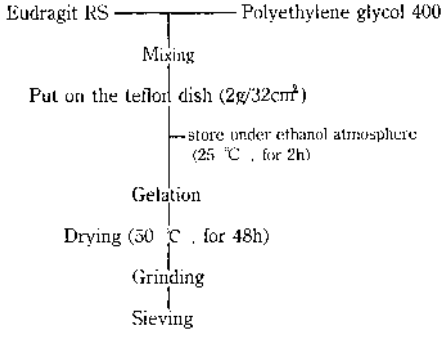

Chart 1. Preparation of Eudragit RS-PEG 400 Binary Polymer (EPG)

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due to the normal molecular motions below T_g, was estimated from the area under the anomalous endothermic peak (the maximum of heat capacity).

Preparation of Acetaminophen EPG Matrix Tablets Eudragit RS or EPG matrix tablets containing AAP (20 mg) with a diameter of 8 mm were prepared by directly compressing 120 mg of a mixture of polymer and drug. A tableting pressure was 4 t/cm^2 at 60 °C.

Dissolution Test The dissolution tests of AAP from the EPG matrix tablets were performed using the JP XIII paddle method with a Toyama NTR-VS type dissolution tester (50 rpm). Nine hundreds milliliters of the distilled water was used as the dissolution test medium and the temperature was varied between 24 °C and 42 °C in 3 °C steps. Five milliliters samples of the test medium were withdrawn at appropriate intervals through a Fine Filter F (Ishikawa Seisakusho Co., Ltd.) and immediately replaced with an equal volume of the medium. The concentrations of AAP in the collected sample solution were spectrophotometrically determined at 244 nm using a Shimadzu UV-160 spectrophotometer.

Results and Discussion

Effect of PEG 400 Contents on the Glass Transition Temperature of Eudragit RS In order to lower the T_g of Eudragit RS to around the body temperature (32—42 °C), PEG 400 was used as a plasticizer in this study. The DSC curves of Eudragit RS, EPG containing 5% PEG 400 and 10% PEG 400 by weight (5% EPG and 10% EPG, respectively) are shown in Fig. 1; a jump of heat capacity and an anomalous endothermic peak (the maximum of heat capacity) can be seen. These results indicated that the Eudragit RS and EPG existed in a glassy state. The T_g value of Eudragit RS was around 55 °C and no significant modification of the T_g value was observed in the physical mixture of Eudragit RS and PEG 400 containing 10% PEG 400 by weight. On the other hand, the T_g of the EPG shifted to the lower temperature. This phenomenon shows that the EPG prepared by gelation of Eudragit RS with ethanol are the thermodynamically miscible blends. The effect of the PEG 400 content on the T_g of Eudragit RS is shown in Fig. 2. The T_g of Eudragit RS decreased nonlinearly with increasing the PEG 400 contents. It was proved that the EPG having the T_g at around the body temperature could be prepared by the addition of 5—13% PEG 400 to Eudragit RS.

Effect of Isothermal Aging on the T_g of EPG As glassy polymers are not in thermodynamic equilibrium below the T_g, so glassy state approaches its more stable state changing the T_g with aging. Therefore, the T_g changes with aging time for Eudragit RS and 10% EPG, which were reheated to above T_g (55 °C and 33 °C, respectively), were studied at various aging temperatures (Fig. 3). The T_g values of Eudragit RS except the T_g-time course at 20 °C increased with the aging time. After 30 d, they apparently reached constant values widely differing in the aging temperature. On the other hand, the T_g values of 10% EPG were almost independent of the aging temperature and reached around 33 °C after 30 d. This result may suggest that the thermo-sensitive drug delivery systems prepared with EPG have a constant T_g value regardless of the storage temperature.

In order to consider the difference of the effect of aging temperature on T_g between Eudragit RS and 10% EPG, the enthalpy relaxation (ΔH) represented as the area under the anomalous endothermic peak of the DSC curves was measured.[9] Figure 4 shows the effect of temperature on the rates of enthalpy relaxation for Eudragit RS and 10% EPG during isothermal aging below T_g. The rates of relaxation for the two polymers increased with an increase in the aging temperature. The difference between Eudragit RS and 10% EPG could be detected in the temperature dependence of the relaxation rates, that is, the aging temperature didn't affect the rates of 10% EPG as much as ones of Eudragit RS and the former rates were higher than the latter ones. The enthalpy relaxation is generally observed in the glassy polymers during storage, being related to a transition from a disordered

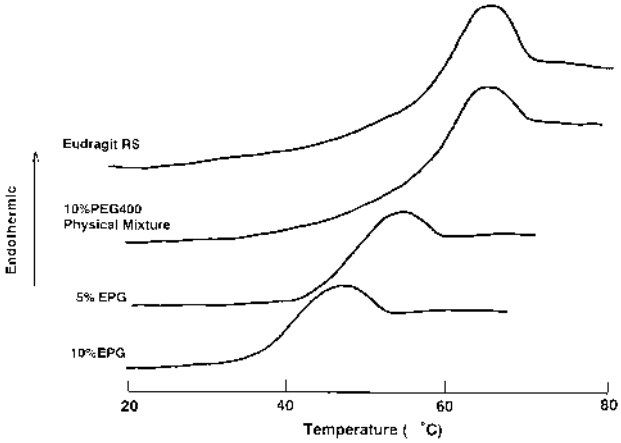

Fig. 1. DSC Curves of Eudragit RS and Various Eudragit RS-PEG 400 Blend Polymer (EPG)

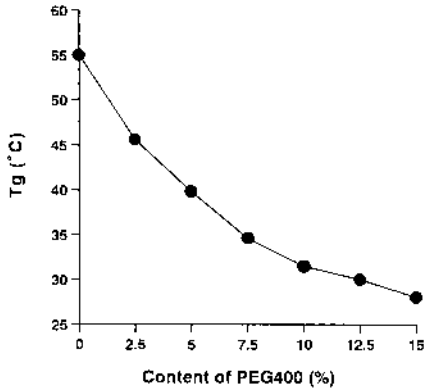

Fig. 2. Effect of PEG 400 Content on Glass Transition Temperature (T_g) of Eudragit RS

* Heating rate, 20 °C/min.

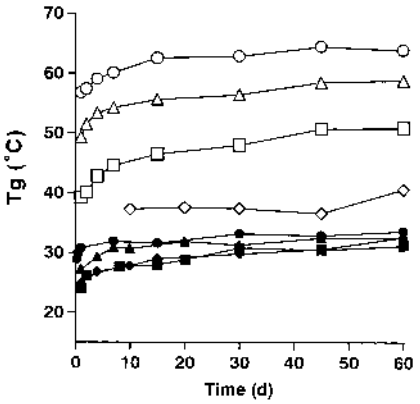

Fig. 3. Glass Transition Temperature (T_g) Changes with Aging Time for Eudragit RS and 10% EPG at Various Temperatures

Eudragit RS: (○) 50 °C; (△) 40 °C; (□) 30 °C; (◇) 20 °C, 10% EPG: (●) 30 °C; (▲) 20 °C; (■) 10 °C; (◆) 4 °C.

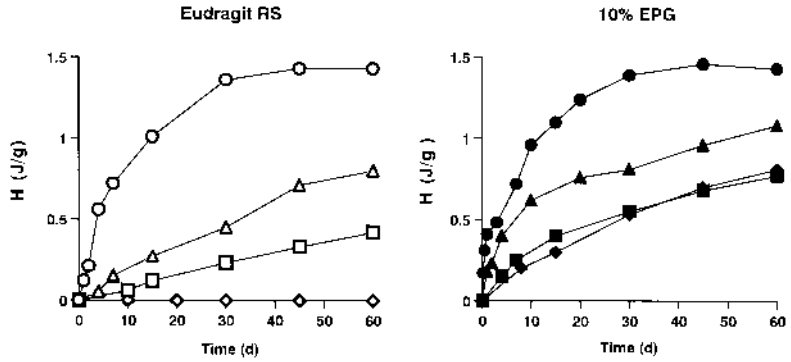

Fig. 4. Effect of Temperature on the Rates of Enthalpy Relaxation for Eudragit RS (Open Symbols) and 10% EPG (Closed Symbols) during Isothermal Aging Below T_g

(○) 50 °C; (△) 40 °C; (□) 30 °C; (◇) 20 °C; (●) 30 °C; (▲) 20 °C; (■) 10 °C; (◆) 4 °C.

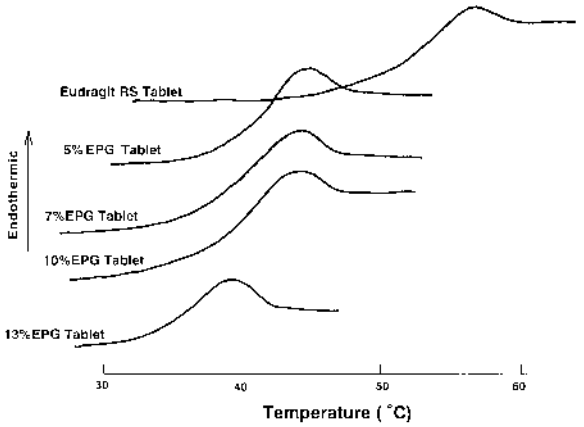

Fig. 5. DSC Curves of Eudragit RS and Various Eudragit RS-PEG 400 (EPG) Matrix Tablets Containing 20 mg Acetaminophen.

glassy state to a more ordered one.[10] Therefore, these relaxation behaviors may suggest that the stabilization rate and stable glassy state for 10% EPG was hardly influenced by aging temperature, and so its T_g may rapidly reach a constant value independent of the temperature.

Confirmation of Glass Transition Temperature for Acetaminophen EPG Matrix Tablets Figure 5 shows the DSC curves of Eudragit RS and various EPG matrix tablets containing AAP. In spite of the compression of the powder at 60 °C and the presence of AAP, a jump of heat capacity and an anomalous endothermic peak can be seen for all matrix tablets. The T_g values of Eudragit RS, 5% EPG, 7% EPG, 10% EPG and 13% EPG matrix tablets were 48, 39, 36, 35, and 33 °C, respectively.

Effect of Temperature on AAP Release from EPG Matrix Tablets The ability as thermo-sensitive polymer of EPG was evaluated by the dissolution test of the AAP matrix tablets prepared with EPG. Figure 6 shows the AAP release from the Eudragit RS and the 10% EPG matrix tablets in the range between 24 and 42 °C in a step of 3 °C. The dissolution curves for both matrix tablets showed sustained release profiles over 6 h at all temperatures. In the case of the Eudragit RS matrix tablet, the release rate of AAP monotonously increased with a rise in temperature. This increase of AAP release rate approximately corresponded to the increases of AAP solubility with temperature (AAP solubility: about 13.7 mg/ml, 21.5 mg/ml and 26.1 mg/ml at 24, 36, and 42 °C, respectively). On the other hand, the AAP release rate from the 10% EPG matrix tablet slightly changed below 33 °C, and then, it increased markedly at temperatures above 36 °C. The significant change of the AAP release rate at 36 °C may be due to the glass transition of the 10% EPG matrix tablet. Figure 7 shows the effects of temperature on the AAP release from the 5—13% EPG matrix tablets. The temperature, at which the AAP release rate increased markedly, gradually lowered with an increase of the PEG 400 contents formulated in the EPG and nearly corresponded to the T_g of the EPG matrix tablets.

Effect of Temperature on AAP Release Mechanism To investigate the effect of temperature on the mechanism of AAP release from the EPG matrix tablets, the AAP dissolution-time curves were analyzed according to the following equation.[11]

$$Mt/M_\infty = kt^n$$

where Mt/M_∞ is the amount of AAP (%) released at time t (h), k is the apparent release rate and n is a diffusional exponent. In Table 1, k and n values obtained from the AAP dissolution curves of Eudragit RS and the 10% EPG matrix tablets are listed. Concerning both matrix tablets, k values showed the same tendency against the temperature, namely the values simply increased with a rise in temperature. In the case of a diffusional exponent, n, the values of the Eudragit RS matrix tablet were approximately constant (=0.6) independent of the temperature. The exponent n is the characteristic of the mechanism of diffusional release. When n=0.5, Fickian diffusion is observed and release rate is dependent on the square-root of time. Therefore, the result obtained in the Eudragit RS matrix tablet may suggest a non-Fickian release behavior and its release mechanism shouldn't alter with the change of temperature. On the other hand, the n values of the 10% EPG matrix tablet were close to 0.5 below 33 °C, but it tended to increase above 36 °C. This increase may indicate that the change of AAP release mechanism occurred by the glass transition of the 10% EPG matrix tablet. The change of release mechanism may be explained on the basis of an increase of free volume caused by the transition from glassy state of EPG to supercooling one. Figure 8 shows the effects of temperature on the n values for AAP release from the Eudragit RS and the 5—13% EPG matrix tablets. In all EPG

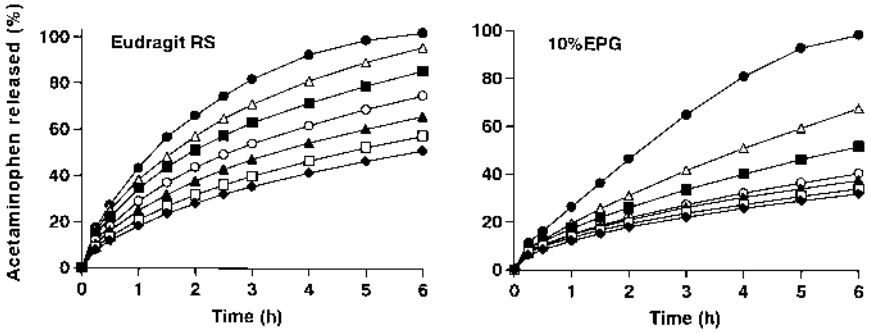

Fig. 6. Effect of Temperature on Acetaminophen Release from Eudragit RS and Eudragit RS-10% PEG 400 (10% EPG) Matrix Tablets in Distilled Water
(◆) 24 °C; (□) 27 °C; (▲) 30 °C; (○) 33 °C; (■) 36 °C; (△) 39 °C; (●) 42 °C.

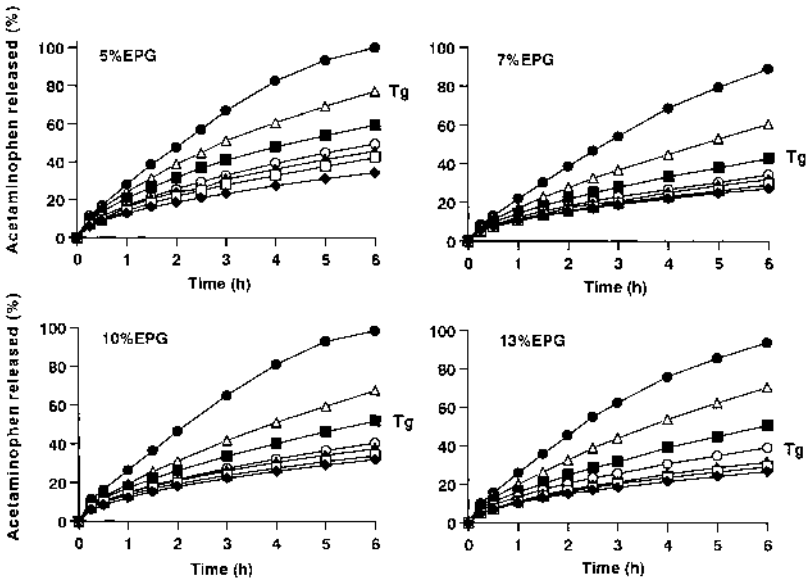

Fig. 7. Effect of Temperature on Acetaminophen Release from Various Eudragit RS-PEG 400 (EPG) Matrix Tablets in Distilled Water
(◆) 24 °C; (□) 27 °C; (▲) 30 °C; (○) 33 °C; (■) 36 °C; (△) 39 °C; (●) 42 °C.

Table 1. Apparent Release Rate Constant (k), Diffusional Exponents (n) and Correlation Coefficients (r) for Acetaminophen Release from Eudragit RS and 100% EPG Matrix Tablets

Temperature (°C)	Eudragit RS			10% EPG		
	k	n	r	k	n	r
24	18.33	0.589	0.999	12.48	0.527	0.999
27	20.73	0.587	0.999	14.49	0.514	0.999
30	24.43	0.582	0.998	15.20	0.518	0.999
33	28.20	0.575	0.998	15.47	0.528	0.999
36	33.26	0.561	0.997	18.22	0.566	0.998
39	37.20	0.565	0.998	20.47	0.650	0.998
42	42.02	0.590	0.996	28.43	0.726	0.997

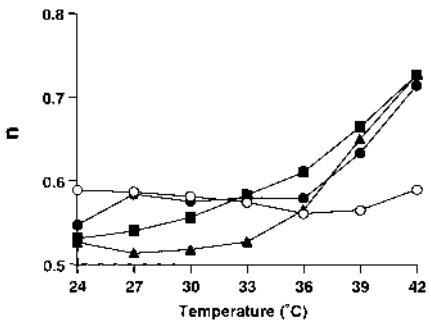

Fig. 8. Effect of Temperature on Diffusional Exponent (n) for Acetaminophen Release from Eudragit RS and Various Eudragit RS-PEG 400 (EPG) Matrix Tablets
(○) Eudragit RS; (●) 5% EPG; (▲) 10% EPG; (■) 13% EPG.

matrix tablets, similar behavior was observed; the n values significantly increased above the T_g of each EPG matrix tablet, hence it was clarified that the AAP release mechanism from the EPG matrix tablets was affected by the glass transition of EPG.

Conclusion

The function as a thermo-sensitive polymer of EPG has been demonstrated by a significant changes in AAP release rate and AAP release mechanism at the T_g of EPG matrix tablets. Considering high biological safety of Eudragit RS and PEG 400, EPG might be available to develop the novel thermo-sensitive drug delivery systems.

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