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Research Article

Comparison of Plasticizer Effect on Thermo-responsive Properties of Eudragit RS Films

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Abstract. Preparation of an intelligent drug delivery system which releases the drug in response to the environmental stimuli in a controlled manner is one of the interesting subjects and it is the purpose of this study. Films composed of Eudragit RS and different percentages of plasticizers (0%, 5%, 10%, or 20% *w/w* based on polymer weight), poly ethylene glycol 400 or triethyl citrate (TEC), were prepared by solvent casting method. Glass transition temperatures of the films were determined by differential scanning colorimetery. Water uptake and drug permeation through membranes with the glass transition temperature (Tg) close to the body temperature were investigated. Propranolol hydrochloride and acetaminophen were used as model drugs in permeation studies. The results showed that Eudragit RS films with 20% of either plasticizer showed thermo-responsivity around body temperature. The water uptake of the films and the permeation rates of both drugs increased at temperatures above the Tg of the films. The films containing TEC was found to be more appropriate thermo-responsive membrane due to a higher sensitivity to temperature and more ability to control drug release.

KEY WORDS: drug permeation; glass transition temperature; plasticizer; polymeric film; thermosensitivity.

INTRODUCTION

Recently, stimuli-responsive drug delivery systems have been noticed since conventional drug delivery systems which are based on multiple dosing are usually accompanied by many failures specially when discontinuous release of drug is desirable (1). The volume of stimuli-responsive materials changes abruptly due to modest changes in environmental conditions, for instance, altering temperature, pH, ionic strength, *etc.* The unique characteristics of these materials make them appropriate for drug delivery (2–5).

Among the stimuli-responsive polymers, interpolymer complexes are insoluble macromolecular structures formed by the non-covalent interaction of different polymers. The polycomplexes are formed by association of monomers on different regions of the same chain (intrapolymer) or on different chains (interpolymer). The polycomplexes of poly (methyl methacrylate) (PMAA) and poly ethylene glycol (PEG), which is formed by hydrogen bonds between carboxyl and ether groups of PMAA and PEG respectively, are among the most widely studied polycomplexes (6).

Blending of hydrophilic–hydrophobic polymers by melt blending or solution casting (solvent casting) produces phase-separated composites and controlled-release drug delivery systems (6–8).

Eudragit RS (ethylacrylate–methylmethacrylate–trimethylammonioethyl methacrylate chloride copolymers with ratios of 1:2:0.1) is a safe polymer widely used as a film former in production of sustained and colonic drug delivery systems (9,10). Recently, the application of this polymer in design of thermo-responsive delivery system has also been noticed (8, 11). Eudragit RS and PEG blend polymers were prepared by Fujimori *et al.* as a novel thermo-responsive membrane in order to achieve a controlled-release of drug at body temperature. Their study indicated that the amount of drug permeation through the membrane increased by elevating the temperature above the Tg of polymer which was dependent on Eudragit/PEG ratios (8).

In the previous study, we demonstrated the plasticizing effect of both polyethylene glycol 400 (PEG 400) and triethylcitrate (TEC) on Eudragit RL films by their ability to change the mechanical properties of films (12). Due to the similarity in the structure of Eudragit RL and RS, here we investigated the effect of PEG 400 or TEC concentration on Tg and thermo-responsivity of Eudragit RS films. The thermo-responsive permeation of propranolol hydrochloride (highly water soluble) and acetaminophen (sparingly water soluble) model drugs from films which showed Tg close to body temperature was investigated at different temperatures above and below the Tg and compared for both plasticizers.

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MATERIALS AND METHOD

Materials

Eudragit RS was supplied by Rohm Pharma (Germany). PEG 400 and TEC were purchased from Merck (Germany). Propranolol hydrochloride and acetaminophen were obtained from Daru Pakhsh (Iran) and Sobhan (Iran), respectively.

Methods

Preparation of Eudragit RS Films

Eudragit RS was dissolved in ethanol 96% to make solutions containing 12% *w/v* of polymer. Plasticizer (PEG 400 or TEC) was added at concentrations of 0, 5%, 10% or 20% based on total weight of polymer in solution and stirred for at least for 15 min using a magnetic stirrer. The polymer solution was then casted on Teflon plate with dimension of 15 cm×15 cm. The plates were incubated at 40°C for 48 h in an oven (Memmert, Germany) to allow solvent evaporation. All dried films were kept in silica gel desiccators at room temperature (8,13).

Thermal Analysis of Films

Thermal analysis of the films was performed using differential scanning calorimeter (Mettler Toledo, Switzerland). Film samples (4.5–6 mg) were accurately weighed into aluminum pans and hermetically sealed. Empty pan was used as a reference. Each DSC run was conducted over a temperature range of −15°C to 90°C at the constant rate of 10°C/min. The glass transition temperature (Tg) was determined as the midpoint of the endothermic peak of phase transition that appeared in the thermograms (13,14).

Measurement of Water Uptake and Film Swelling

Water uptake of the polymeric films with 20% plasticizer content was investigated by soaking the films into the beakers containing phosphate buffer solution (PBS, pH 7.4) for 24 h at 27°C, 29°C, 37°C, and 42°C to determine the effect of temperature on degree of swelling. Every 30 min, the films were removed from the PBS. Excess water was blunted by lint free tissue paper and the weights of the swelled films were recorded. Then, the films were returned into the beakers containing PBS (pH 7.4). An increase in the weight of the films was measured at every 30 min intervals until the constant weight was achieved. This weight was considered as the weight of the swelled membrane at a specific temperature (w_1). The soaked films were dried by incubating at 60°C in an oven for 24 h, and the weight of each dried film was recorded (w_2). Each measurement was repeated three times. The swelling ratios of the membranes were calculated using the following equation:

$$\text{Swelling ratio} = (w_1 - w_2)/w_2$$

where w_1 is the weight of soaked film, and w_2 is the weight of dried film as mentioned before (8,15,16).

The results were reported as mean±SD. To investigate the significance of differences between the samples, the one way ANOVA analysis was performed and significance level of $P<0.05$ was considered significant in all cases.

Drug Permeation Studies

The aqueous solutions of acetaminophen (800 μg/mL) and propranolol hydrochloride (1,000 μg/mL) were prepared in PBS (pH 7.4) and distilled water respectively. Drug permeation experiments were performed using a side by side diffusion cell (Permegear, USA) with two half-cells and a water jacket. Eudragit RS films containing 20% plasticizer with a surface area of 2 cm^2 and a mean thickness in the range of 0.20–0.25 mm was inserted between the two half-cells of the diffusion cell. The donor and the receptor were filled by 3.4 mL of corresponding drug solution and the solvent, respectively and were stirred by a magnetic stirrer (500 rpm) to avoid the boundary layer formation. Temperature of the diffusion cell was maintained constant by circulating water through the jackets surrounding each half-cell. The experiments were performed at different constant temperatures over the range of 27 to 42°C. At each sampling time, aliquots (200 μL) were withdrawn from the receptor and substituted by the same amount of solvent to keep the volume of the receptor solution constant. The sampling procedure was continued for 5 h. Each sample was diluted by solvent to 1 mL and finally, the amount of propranolol hydrochloride and acetaminophen was determined using a UV-spectrophotometer (Shimadzu 160A, Japan) at wavelengths of 290 and 243 nm respectively. This experiment was repeated three times for each film and the mean value was considered as the total amount of the drug permeated at each sampling time (8,16).

Drug permeation coefficients at different temperatures were calculated from the data obtained in the permeation studies based on the following equation (17):

$$\log C_d = \log C_{d(0)} - \frac{PS}{2.303V_d}t$$

In which C_d is the concentration of the drug in the donor phase at time t, $C_{d(0)}$ is the initial concentration of the drug in the donor phase, P is the permeability coefficient, S is the surface area of the membrane, V_d is the volume of the medium in donor phase and t is time.

RESULTS

Thermal Analysis of the Membranes

Tg of the membranes composed of Eudragit RS and different percentages of plasticizers (PEG 400 or TEC) were determined using the DSC technique. The DCS thermograms for different films are shown in Fig. 1. Plasticizer was used to reduce the Tg of the membranes to around the body temperature. Table I presents the Tg resulted from the thermal study of the membranes with different percentages of PEG 400 and TEC. As it was expected, Tg decreased by an increase in the amount of plasticizer. Tg of the films at all plasticizer concentrations except 20% were similar for both plasticizers. The endothermic peak of Tg for Eudragit RS film containing 20% of TEC could not be detected in thermograms (Fig. 1d) and therefore no data has been given for this type of film.

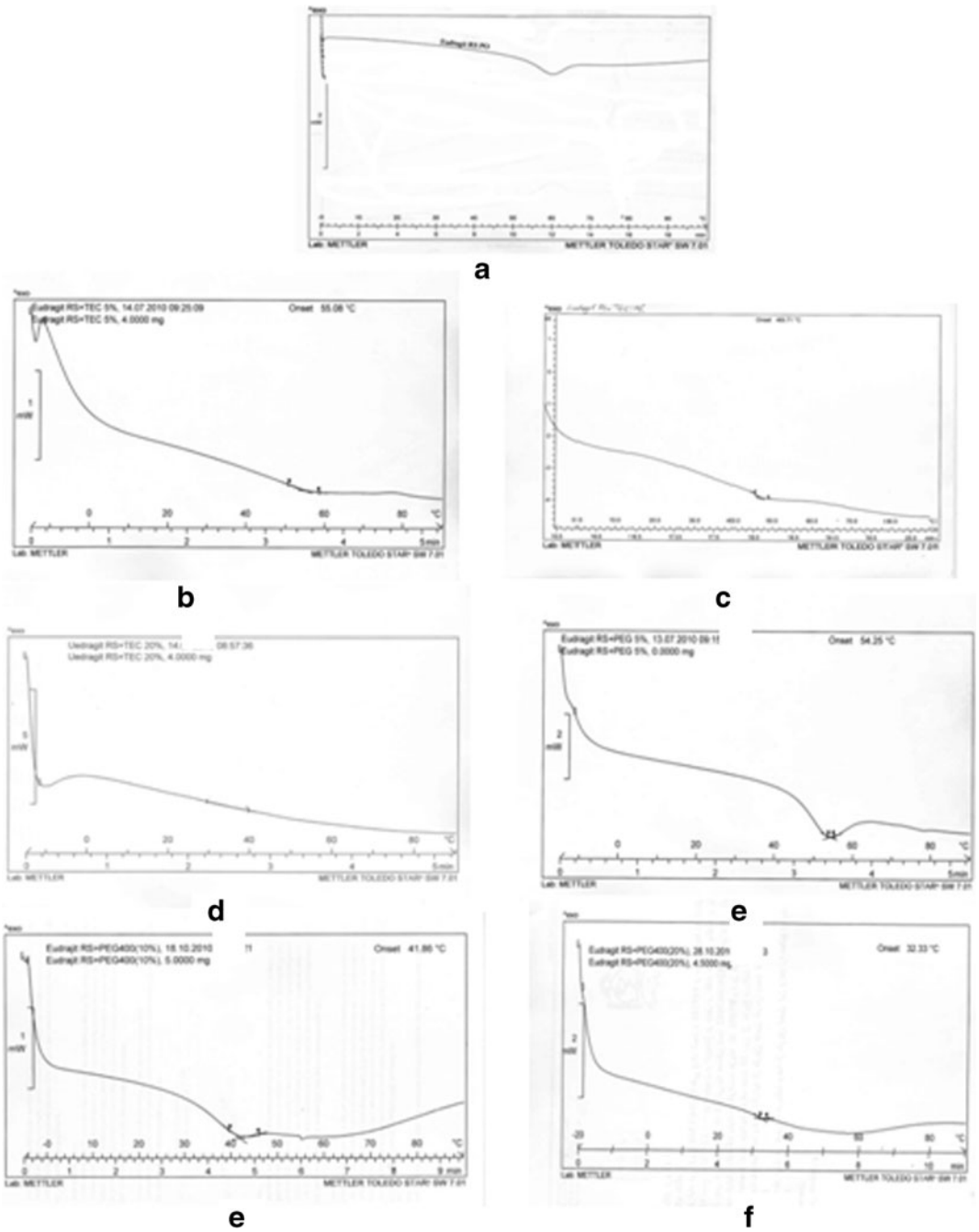

Fig. 1. DSC thermograms for (**a**) Eudragit RS, and Eudragit RS containing (**b**) 5% TEC, (**c**) 10% TEC, (**d**) 20% TEC, (**e**) 5% PEG 400, (**f**) 10% PEG 400 and (**g**) 20% PEG 400

Table I. The Values for Tg of the Eudragit RS Films Containing Different Percentages of PEG 400 or TEC

Plasticizer content in the film (%)	Tg of films with PEG 400 (°C)	Tg of films with TEC (°C)
0	63.02	63.02
5	54.25	55.08
10	41.86	46.71
20	32.33	–

However, Eudragit RS films containing 20% PEG 400 showed a Tg around the body temperature and therefore this type of the film was chosen for further studies. As the values for Tg of the films containing 5 or 10% of PEG 400 or TEC were almost similar, it was postulated that Tg of films containing 20% TEC could also be around the body temperature, similar to those containing 20% PEG 400. Thermomechanical analysis showed that Tg for Eudragit RS film with 20% TEC was around 34°C and confirmed the above postulation. Therefore, the film containing 20% of TEC was also used for the comparison.

Water Uptake and Swelling Ratios of the Membranes with 20% Plasticizer

Water uptake studies carried out on the films containing 20% plasticizer with a Tg around the body temperature. As it is shown in Fig. 2, an abrupt change in the swelling ratios was observed when the temperature raised to the amounts higher than the Tg of the membranes ($P<0.0001$).

Drug Permeability

Acetaminophen and propranolol hydrochloride were used as model drugs to study the drug permeation through the Eudragit RS films containing 20% PEG 400 or TEC, at different temperatures. The results are presented in Figs. 3, 4, 5, and 6. Drug permeation through the membranes showed the temperature-dependent behavior and changed negligibly below the Tg of the membranes. The permeability of acetaminophen and propranolol hydrochloride increased markedly at temperatures above the Tg of the films. The patterns of enhancement in the permeation of each drug through both types of the films were similar, but the amount of drug permeated was higher in the films containing PEG 400 compared to TEC.

The permeability coefficients (P) of different membranes for both drugs were calculated and the results were shown in Figs. 7 and 8. In the case of propranolol hydrochloride, the values of the permeation coefficients were higher for the films containing PEG 400 compared to those with TEC ($P<0.05$). Overall increase in temperature increased the value of permeation coefficients in all cases; however, a drastic enhancement for the permeability coefficients was observed when the temperature increased to the values above the Tg of the membranes.

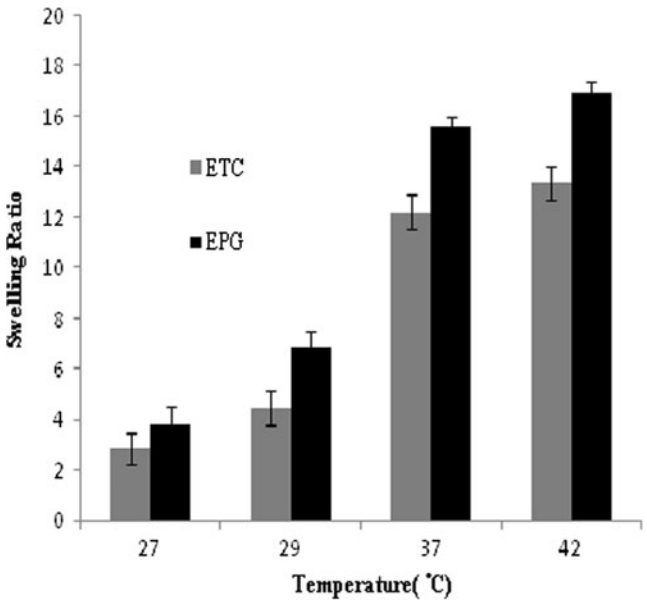

Fig. 2. The swelling ratios for Eudragit RS films containing 20% TEC (ETC) or 20% PEG 400 (EPG) at different temperatures

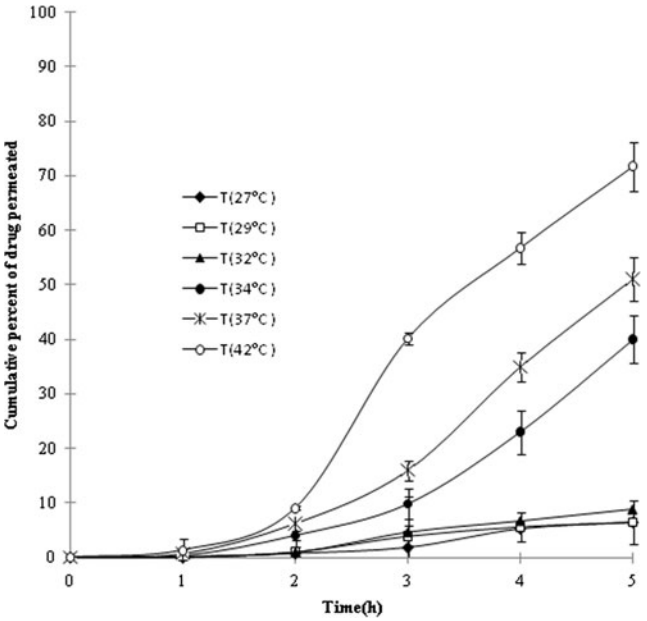

Fig. 3. The permeation of propranolol hydrochloride through Eudragit RS films containing 20% PEG 400 at different temperatures

DISCUSSION

Polymers are extensively used to prepare various drug delivery systems (18,19). Pure polymeric films are often brittle and poorly permeable to the drugs. Addition of a suitable plasticizer to the polymer network could overcome these restrictions by reducing the attractive forces between polymeric chains and increasing their mobility. Tg which is the temperature at which the polymers transition from glassy to rubbery state occurs, is an

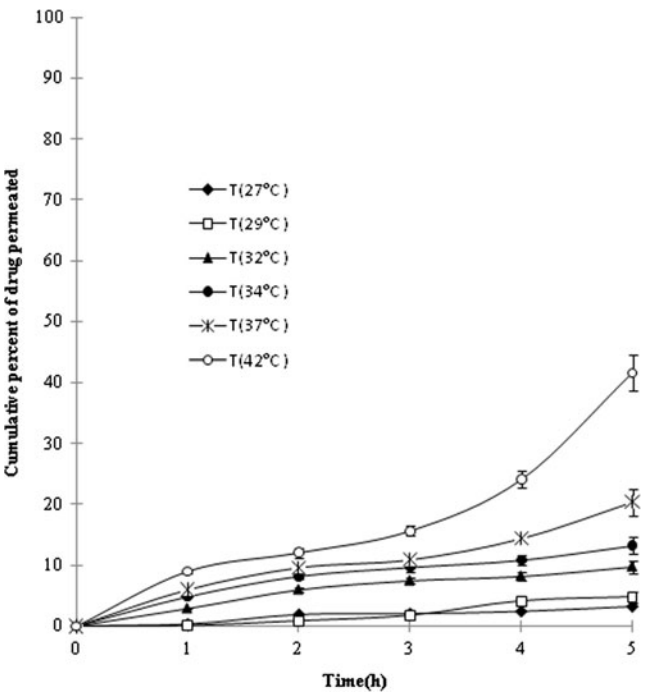

Fig. 4. The permeation of propranolol hydrochloride through Eudragit RS films containing 20% TEC at different temperatures

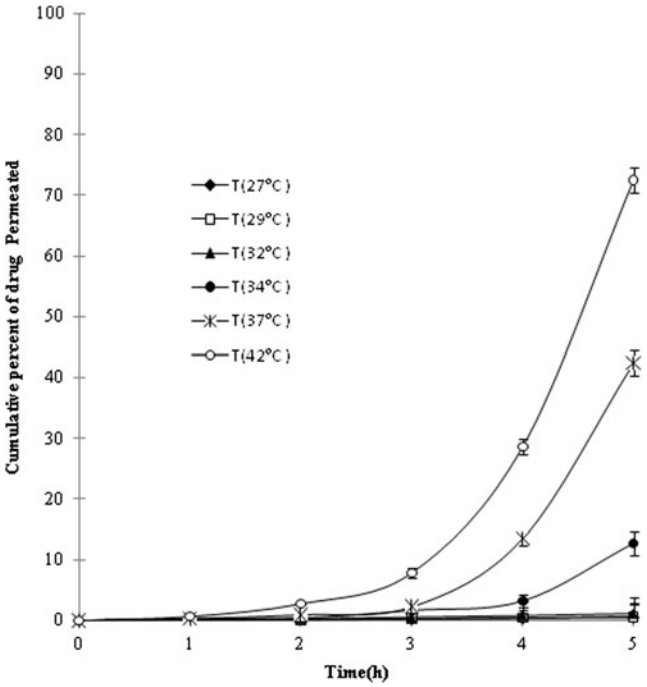

Fig. 5. The permeation of acetaminophen through Eudragit RS films containing 20% PEG 400 at different temperatures

important parameter that indicates the efficiency of plasticizers (20–22). As it was shown in Fig. 1 and Table I, by increasing the percentage of plasticizers, the Tg of the Eudragit RS films decreased due to a higher mobility of the chains in the polymer networks. The effect of both plasticizers in the reduction of the Tg of Eudragit RS films was almost similar at 5% or 10% plasticizer concentration. The endothermic peak related to the Tg of Eudragit RS films containing 20% TEC could not be detected;

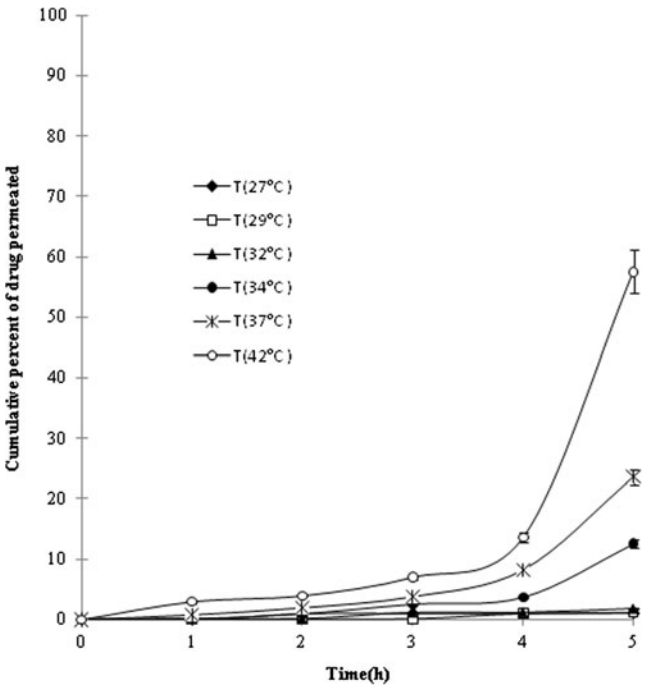

Fig. 6. The permeation of acetaminophen through Eudragit RS films containing 20% TEC at different temperatures

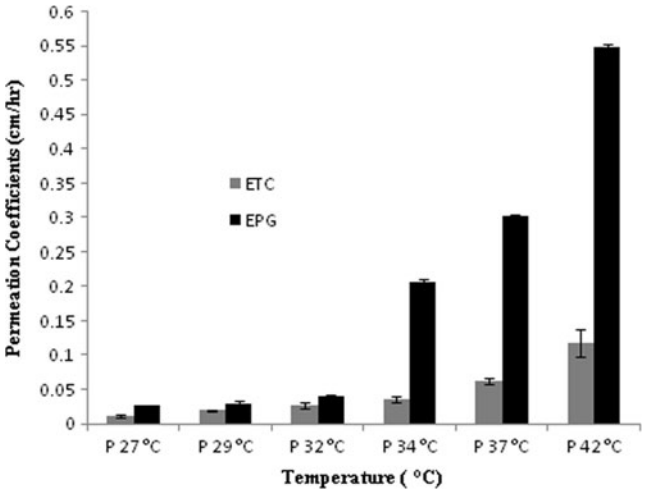

Fig. 7. The values of the permeability coefficients of propranolol hydrochloride through Eudragit RS films containing 20% TEC (ETC) or PEG 400 (EPG) at different temperatures

however, the Tg of Eudragit RS membrane containing 20% PEG 400 was found to be around the body temperature. As the Tg of Eudragit RS films containing 5% or 10% plasticizer were similar for both PEG 400 or TEC and the membrane with 20% PEG 400 showed Tg values around the body temperature, therefore 20% plasticizer concentration was considered as the optimum amount of each plasticizer for preparations of the films used in the swelling and permeation studies.

The quaternary ammonium groups in the Eudragit RS chemical structure and their interactions with plasticizers have an important effect on the water uptake and the swelling ratios of the polymers (8). Temperature is another factor that has a crucial effect on the water uptake of the thermo-responsive polymers (23,24). The results of the water uptake experiments (Fig. 2) indicated that there were no significant changes in the swelling ratios of the films with variations in the temperature below the Tg of the polymer. This was due to the glassy state of polymer below the Tg and a low mobility of macromolecule chains.

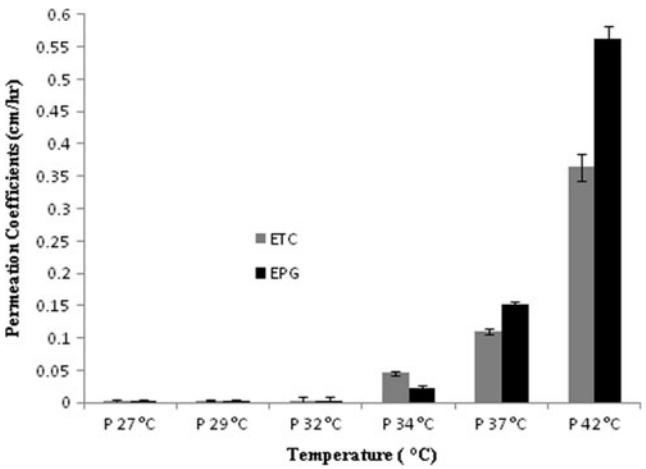

Fig. 8. The values of the permeability coefficients of acetaminophen through Eudragit RS films containing 20% TEC (ETC) or PEG 400 (EPG) at different temperatures

When the temperature rose to above the Tg, the polymer transition to a rubbery state with a higher molecular motion allowed the polymer to absorb much more water and as a result, an abrupt change in swelling ratio was observed at temperatures around the Tg. This was consistent with other studies (25,26).

The permeation rate of both drugs was slow at temperatures below the Tg of the membrane containing PEG 400 (32°C). However, the permeation rate increased markedly at temperatures above Tg of the membrane. The permeability coefficients of propranolol HCl and acetaminophen at 34°C were significantly higher than that obtained at 32°C ($P<0.0001$). Similar results were obtained for membranes containing 20% TEC. Permeability of both drugs through the films increased with an increase in temperature to above the 32°C ($P<0.0001$). Overall, by increasing the temperature above the Tg of the films, the drug permeation abruptly increased due to the higher movement of molecules and higher swelling ratios which increased the pore size of the swelled membrane (26). This could explain the benefits of membranes with responsiveness to temperatures around the body temperature as a thermo-sensitive drug delivery system. These systems release minimum amounts of drug at room temperature but higher amounts of it at body temperature.

Although drug permeation through Eudragit RS films containing 20% PEG 400 was higher and faster than the films containing TEC due to the higher solubility of PEG in water, a close look at permeation profiles especially during the initial hours of permeation studies showed that the Eudragit RS membrane containing 20% TEC were more sensitive to the changes in temperature. In other words, any small changes in temperature resulted in great changes in permeation rate of drugs at initial hours of permeation studies. Therefore, the film containing 20% TEC was considered as a better thermo-responsive membrane for preparing a temperature responsive drug delivery system.

CONCLUSIONS

The thermo-responsive behavior of the Eudragit RS films was achieved by adding suitable amount of plasticizer such as TEC or PEG 400 (20%) to the membranes. Eudragit RS films containing TEC as a plasticizer were more thermo-responsive than those containing PEG 400. However, the permeation rates of drugs were higher in the films containing PEG 400. This was due to the higher solubility of PEG 400 in water. Films containing 20% TEC provided better control on drug permeation and it was more appropriate for preparing thermo-responsive and controlled-release drug delivery systems.

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