The Effect of Plasticizers on Compatibility, Mechanical Properties, and Adhesion Strength of Drug-Free Eudragit E Films

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The use of plasticizers to affect the properties of drug-free, self-adhesive Eudragit E-100 films with higher transparency was tested for possible transdermal drug delivery. Triacetin was found to be an effective first plasticizer for Eudragit E-100 polymer. In order to improve the flexibility and adhesiveness of Eudragit E-100 film plasticized with triacetin, a more flexible and adhesive, secondary plasticizer was added. Plasticizer–polymer compatibility was evaluated by measuring transparency, surface topography, and solubility. Secondary plasticizers with a low molecular weight and a solubility parameter similar to that of Eudragit E-100 polymer and triacetin were compatible. Further, a lower molecular weight or higher concentration of the secondary plasticizers might lead to greater plasticizing action, reduce tensile strength, and increase film elongation, independent of the hydrophilicity of the plasticizer. The adhesive strength of Eudragit E-100 film under a 180° peel test was also affected by the molecular weight and solubility parameter of the secondary plasticizers used. The results indicate that PEG 200, propylene glycol, diethyl phthalate, and oleic acid can serve as a secondary plasticizer to improve the transparency, flexibility, and adhesion of Eudragit E-100 film.

KEY WORDS: Eudragit E film; plasticizer; compatibility; mechanical property; peel adhesion test.

INTRODUCTION

Transdermal drug delivery (TDD) is designed for long-term, local or systemic therapy (1,2). Use of TDD with a diffusion-controlled rate prevents pulse entry of drugs into the systemic circulation, which may be associated with side effects. Many techniques and patents have been used to prepare medicated TDD systems (3,4). Because of their physiological inertness and biocompatibility, medical biopolymers such as silicon elastomers and ethylene vinyl acetate have been utilized (5–7).

Eudragit acrylic resins have been widely used as a coating material in the pharmaceutical industry (8,9). Since these polymers are well tolerated by the skin and have a high capacity for incorporating drugs, Eudragit acrylic resins may be useful for a TDD system; however, only a few studies have reported acrylic resin as a transdermal drug delivery polymer (10,11).

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For the design of a self-adhesive transdermal drug-loading film, we examined seven types of drug-free film casts with different Eudragit acrylic resin containing different types and amounts of plasticizers to select a suitable polymer, plasticizer, or formulation. Results from a peel test, transparency, flexibility, and tack property were evaluated. Eudragit E-100, E 30D, RS-100, and RL-100 with triacetin as a plasticizer were most promising; based on their overall better performance in the screening study, we further selected Eudragit E-100 as a model film. The aim of this study was to examine the effects of different types and amounts of secondary plasticizers on the compatibility and mechanical properties of the drug-free Eudragit E-100 films plasticized with triacetin and to investigate the adhesive ability of these films.

EXPERIMENTAL

Materials

Seven types of acrylic copolymers were used as film-forming materials for the screening test: Eudragit E-100, S-100, RS-100, RL-100, E 30D, L 30D, and RL 30D (Rohm Pharma GmbH, Darmstadt, FRG). Polyethylene glycol 200 (PEG 200), PEG 1000, PEG 4000, PEG 6000, propylene glycol, PVP K-90, glycerin, diethyl phthalate, oleic acid, isopropyl myristate, liquid paraffin, triacetin, and glycerol monostearate were chosen as plasticizers and were reagent grade, purchased from the commercial market.

Preparation of Drug-Free Eudragit Films for the Screening Test

Eudragit E-100, S-100, RS-100, and RL-100 (6 g) were separately dissolved in acetone (20 ml) and homogeneously mixed with different amounts of the plasticizers (Table I). Eudagit E 30D, L 30D, or RL 30D aqueous dispersions were similarly mixed with different amounts of the plasticizers (Table I). Each mixture was cast on a Teflon plate using a TLC applicator (Braive Instruments, Belgium) and dried for 24 hr at 40°C and 50% RH (CH-type oven, Chen-Cheng Indus. Co. Ltd., Taipei, R.O.C.). After 24-hr drying, a polymeric film with 0.2 ± 0.02-mm thickness was obtained.

Screening Test for Drug-Free Eudragit Films

For choosing the most promising film, their transparency and flexibility were determined, and the peel test and thumb tack test were performed. Films were judged subjectively on whether they peel completely and for their transparency, degree of flexibility, and tackiness (Table I).

Preparation of Drug-Free Eudragit E-100 Films

Eudragit E-100 (6 g) and triacetin (0.9 g) were completely codissolved in acetone (20 ml) with different amounts of the secondary plasticizers (1.43–5.48%, w/w) (Table II). The clear solution was poured into a TLC applicator, cast on a Teflon plate, and dried as above to yield a uniform film of

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Table I. Screening Test for the Compatibility of Eudragit Films by Adding Different Types and Amounts of Plasticizers[a]

	PEG 200		PEG 6000		EVA,	Triacetin				GM,	PG				Glycerin	
	1%	9.1%	1%	16.7%	0.3%	1%	4.8%	9.1%	16.7%	1%	1%	4.8%	9.1%	16.7%	1%	9.1%
E-100																
(1)	++	++	x	x	++	++	++	++	++	++	++	++	++	++	++	++
(2)	++	+	x	x	x	++	++	++	++	++	++	++	++	++	++	++
(3)	x	x	x	x	x	++	++	++	++	x	x	x	++	++	x	x
(4)	x	x	x	x	x	x	x	++	++	x	x	x	x	x	x	x
S-100																
(1)	++	++	++	++	x	++	++	++	++	++	++	++	++	++	++	++
(2)	++	+	x	++	x	++	++	++	++	++	++	++	++	++	++	x
(3)	x	x	x	x	x	++	++	++	++	x	x	++	++	++	x	x
(4)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
RS-100																
(1)	++	++	x	++	++	++	++	++	++	++	++	++	++	++	++	++
(2)	++	+	x	x	x	++	++	++	++	++	x	++	++	++	++	++
(3)	x	++	x	x	x	++	++	++	++	x	x	x	x	x	x	x
(4)	x	x	x	x	x	x	x	++	++	x	x	x	x	x	x	x
RL-100																
(1)	++	++	x	++	++	++	++	++	++	++	++	++	++	++	++	++
(2)	++	+	x	x	+	++	++	++	++	++	++	++	++	++	++	++
(3)	++	++	x	x	x	x	++	++	++	++	++	x	x	x	x	x
(4)	x	x	x	x	x	x	x	++	++	x	x	x	x	x	x	x
E30D																
(1)	++	++	x	++	−	++	++	++	++	−	−	−	−	−	−	−
(2)	++	++	x	+	−	++	+	+	+	−	−	−	−	−	−	−
(3)	++	++	x	++	−	++	++	++	++	−	−	−	−	−	−	−
(4)	++	++	++	++	−	++	++	++	++	−	−	−	−	−	−	−
L30D																
(1)	++	++	++	++	++	++	++	++	++	−	++	++	++	++	++	++
(2)	++	++	x	+	x	++	+	+	+	−	+	+	x	x	x	x
(3)	x	x	++	x	x	x	x	x	++	−	x	x	++	++	x	x
(4)	x	x	x	x	x	x	x	x	++	−	x	x	x	x	x	x
RL30D																
(1)	x	x	x	x	x	x	x	++	++	x	x	x	++	++	++	++
(2)	++	++	x	+	++	++	++	++	+	x	++	++	++	++	x	x
(3)	x	x	x	x	x	x	x	x	++	x	x	x	x	++	x	x
(4)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

[a] PEG, polyethylene glycol; PG, propylene glycol; GM, glycerol monostearate; EVA, ethylene vinyl acetate. (1) Complete peel; (2) transparency; (3) flexibility; (4) tack. (++) Good; (+) may be used; (x) poor; (−) ppt.

0.2 ± 0.02-mm thickness. The films were then removed, wrapped in aluminum foil, and stored at 25°C and 50% RH.

Evaluation of Drug-Free Eudragit E-100 Films

Scanning Electron Microscopy. The surface topography of each Eudragit E-100 film prepared from each formulation was determined using a scanning electron microscope (520S, Hitachi Co., Japan).

Transparency. A strip of Eudragit E-100 film (12 × 30 mm) was mounted on the cell holder of the spectrophotometer (Model 320, Jasco, Japan), and the film transmittance was measured at 600 nm against air as the blank. Three strips were determined to obtain the mean with standard deviation (SD).

Tensile Strength. Tensile strength was measured on an Instron tensile tester (Autograph DCS-500, Shimadzu Co., Japan) modified from the ASTM D-412 test (12,13). The tester was equipped with a 100-g-tension load cell. The cross-head speed was controlled at 20 mm/min. Six strips (2 × 10 mm) for each Eudragit E-100 film were examined for their tensile strength and elongation at break of the films, and the mean ± SD was calculated.

$$\text{Tensile strength} = \frac{\text{break force}}{a\,b}\left(1 + \frac{\Delta L}{L}\right) \quad (1)$$

$$\text{Elongation (\%)} = \left(\frac{\Delta L}{L}\right) \times 100\% \quad (2)$$

where L, a, and b are length, thickness, and width of the test strip, respectively, and ΔL is the elongation at break.

Peel Adhesion Test. The peel adhesion test of drug-free Eudragit E-100 films followed method 1 of the PSTC test (14). The film was applied to a Teflon plate pretreated with 10% Na_2CO_3 and washed with distilled water to remove the surface oil, backed with tape, and then pulled from the substrate at a 180° angle using an Instron tester (Autograph DCS-500, Shimadzu Co., Japan) to measure the force. A 5-kg-tension load cell was chosen, and the cross-head speed

Table II. Formulations for Preparing Eudragit E-100 Film with Different Plasticizers

Component	Formulation											
	A	B	C	D	E	F	G	H	I	J	K	L
Eudragit E-100	+	+	+	+	+	+	+	+	+	+	+	+
Triacetin	–	+	+	+	+	+	+	+	+	+	+	+
PEG 200	–	–	+	–	–	–	–	–	–	–	–	–
PEG 1000	–	–	–	+	–	–	–	–	–	–	–	–
PEG 4000	–	–	–	–	+	–	–	–	–	–	–	–
Propylene glycol	–	–	–	–	–	+	–	–	–	–	–	–
PVP K-90	–	–	–	–	–	–	+	–	–	–	–	–
Glycerin	–	–	–	–	–	–	–	+	–	–	–	–
Diethyl phthalate	–	–	–	–	–	–	–	–	+	–	–	–
Oleic acid	–	–	–	–	–	–	–	–	–	+	–	–
Isopropyl myristate	–	–	–	–	–	–	–	–	–	–	+	–
Liquid paraffin	–	–	–	–	–	–	–	–	–	–	–	+

was set at 20 mm/min. Six strips were tested and the mean ± SD was obtained.

RESULTS AND DISCUSSION

TDD systems often employ a unpalatable patch-type device with metallic plastic laminate. It is therefore desirable to prepare a medicated self-adhesive TDD system having a higher transparency and flexibility.

Plasticizers used in pharmaceutical tablet film coating include polyols, organic esters, vegetable oils, and glycerides (15). In the present study, glycerin, propylene glycol, and PEG 200–6000 as polyols, triacetin and diethyl phthalate as organic esters, and oleic acid, isopropyl myristate, glycerol monostearate, and liquid paraffin as vegetable oils and glycerides were chosen. PVP K-90 and ethylene vinylacetate were used as high molecular weight hydrophilic and hydrophobic plasticizers, respectively. Table I shows the results of four screening tests. Eudragit E-100, E 30D, RS-100, and RL-100 with triacetin performed better as a plasticizer than other polymers. Eudragit E polymers were considered preferable because of their good skin tolerance in clinical trials (16). Since Eudragit E 30D and water-insoluble drugs were not rapidly miscible, we selected the Eudragit E-100 polymer as a model film by plasticizing with triacetin.

Compatibility of the Drug-Free Eudragit E-100 Film with Different Plasticizers

Methods to demonstrate compatibility include scanning electron microscopic observation, thermal analysis, and solubility parameter analysis (17,18). We used spectrophotometry to determine the transparency of the plasticized Eudragit E-100 films. The results indicate that Eudragit E-100 films can be completely plasticized with PEG 200 and propylene glycol; however, nonuniformity or haziness was observed in films with some hydrophilic plasticizers (Formulation D, E, G, and H) by increasing plasticizer concentration, which adversely affects film transparency, indicative of phase separation or precipitation because of poor compatibility. In contrast, films plasticized with hydrophobic plasticizers (Formulations I, J, K, and L) formed a more highly transparent film. Figure 1 shows the surface topographs of Eudragit E-100 film plasticized with different secondary plasticizers. The surface topography of the Eudragit E-100 film plasticized with the higher concentration of PEG 1000, PEG 4000, PVP K-90, or glycerin appeared porous, whereas the surface topography of the films plasticized with hydrophobic plasticizers was uniform and smooth. The porous structure of the former films might be due to the phase separation that occurred between polymer and plasticizer. Scott has suggested that a solution of two polymers in a common solvent will separate into two phases if the total concentration is increased a few percent (19). Allen *et al.* have also reported that the extent of phase separation increases with the molecular weight of the polymer (20). Therefore, the phase separation by the higher molecular weight PEG 1000, PEG 4000, or PVP K-90 could account for the haziness of the film. However, the film plasticized with glycerin was independent of its molecular weight, but was dependent on their solubility parameters.

The solubility parameter also permits evaluation of plasticizer compatibility. Hildebrand and Scott have defined the solubility parameter (δ) of a substance as the square root of its cohesive energy density (21). Thus heat of mixing (ΔH) is represented by Eq. (3):

$$\Delta H = V(\delta_1 - \delta_2)\phi_1\phi_2 \quad (3)$$

where V is the total volume of the mixture, ϕ_1 and ϕ_2 are the volume fractions of components 1 and 2 in the mixture, and δ_1 and δ_2 are the solubility parameters of components 1 and 2, respectively. If the values of these two components are nearly equal, the heat of mixing approaches zero and the substances will be miscible. Methods for calculating δ from physical constants have been described by Burrell and Immergut (22). The calculation from the structured formula should be a rapid and realistic method for estimating solubility parameters (23,24), as shown in Eq. (4):

$$\delta = d\Sigma G/M \quad (4)$$

where ΣG is the sum of all the atoms and groups in the molecular, i.e., the molar attraction constant, d is the density, and M is the molecular weight. This equation was applied to calculate the δ value of Eudragit E-100 and plasticizers. The obtained δ value together with the data from the literature are given in Table III (22,24). PEG 200, propylene

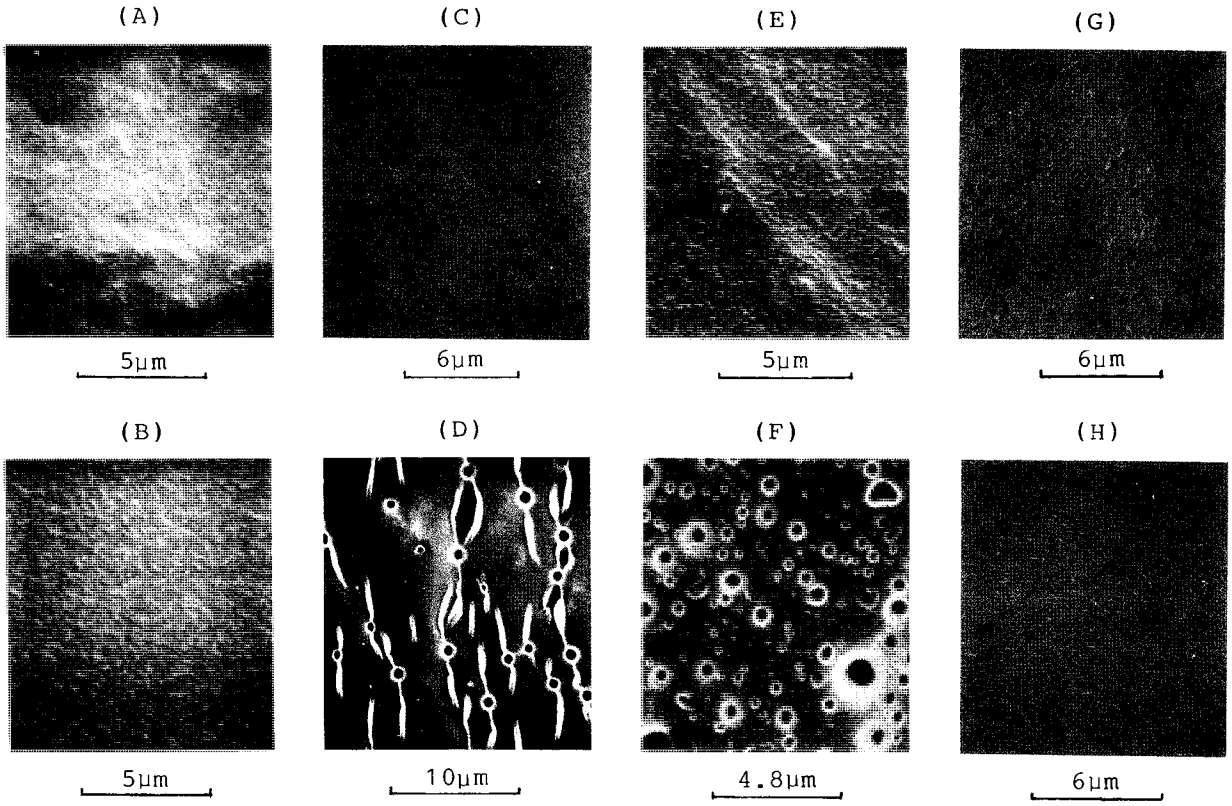

Fig. 1. Surface topographs of Eudragit E-100 films plasticized with different types and amounts of plasticizers. (A) Formulation A; (B) Formulation B; (C) Formulation E, PEG 4000, 1.5%; (D) Formulation E, PEG 4000, 2.0%; (E) Formulation C; (F) Formulation H; (G) Formulation I; (H) Formulation J.

glycol, or diethyl phthalate exhibited δ values near that of Eudragit E-100 (9.7) or triacetin, and this correlated with a higher film transparency. Hence, these plasticizers appear to be compatible with Eudragit E-100 polymer and triacetin.

Table III. Physical Properties and Solubility Parameters of Some Plasticizers[a]

Plasticizer	MW	Sp grav	Solubility parameter (cal/ml) Calculated	Solubility parameter (cal/ml) Literature value (22,24)
Triacetin	218.2	1.155	9.7	
PEG 200	200	1.127	9.7	11.7
PEG 1000	1,000	1.151	9.0	9.8
PEG 4000	4,000	1.183	8.8	9.4
PEG 6000	6,000	1.185	9.1	11.7
Propylene glycol	76.1	1.038	9.7	12.6
PVP K-90	90,000	1.175	13.1	
Glycerin	92.1	1.260	15.3	16.5
Diethyl phthalate	222.2	1.232	9.9	10.0
Isopropyl myristate	270.5	0.855	8.3	
Oleic acid	282.5	0.895	8.6	
Liquid paraffin	348	0.870	8.5	

[a] Acetone, 9.9; Eudragit E-100 polymer, 9.7.

When the δ value deviated from 9.7, incompatibility was found, and the greater the difference of δ values, the greater the incompatibility. On the other hand, although the δ value of PEG 1000 or PEG 4000 was near the δ value of Eudragit E-100, incompatibility still occurred between Eudragit E-100 and PEG 1000 or PEG 4000, possibly because of the higher molecular weight of PEG.

Mechanical Properties of the Drug-Free Eudragit E-100 Film

Stress–strain curves of tensile tests serve to characterize polymer properties (25). A soft and weak polymer is characterized by a low ultimate tensile strength (UTS) and low elongation, a hard and brittle polymer is defined by a moderate UTS and low elongation, and a soft and tough polymer is characterized by a moderate UTS and high elongation, whereas a hard and tough polymer is characterized by a high UTS and high elongation (26). An ideal film for TDD system should be both soft and tough. In this study, three typical stress–strain curves are shown in Fig. 2. When the molecular weight of PEG decreased or the concentration of PEG 200 increased, the elongation at break became high. All the stress–strain curves for the drug-free Eudragit E-100 films with different plasticizers, except PVP K-90, exhibited a pattern similar to that of PEG 200. These Eudragit E-100 films were hard and strong; however, the elongation at break was low and independent of the concentration of PVP K-90 used, possibly because the molecular weight of PVP K-90 was too high to reduce the mean molecular weight of the

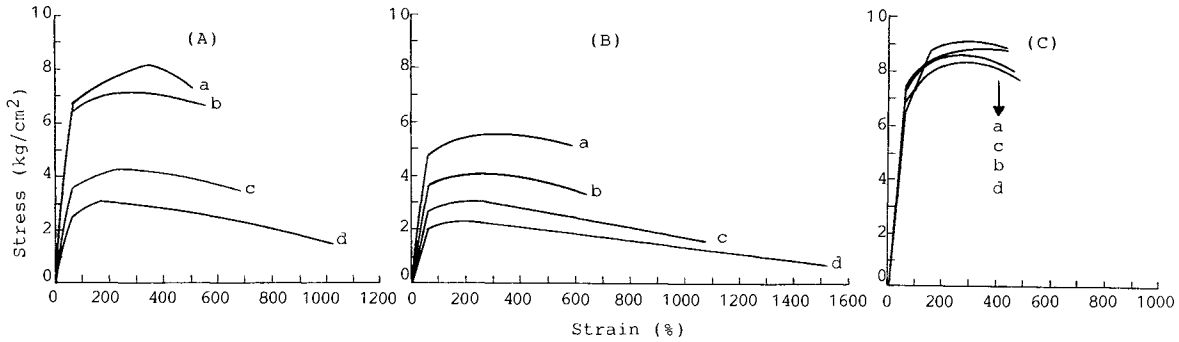

Fig. 2. Stress–strain curves for Eudragit E-100 films plasticized with PEG series (A), PEG 200 (B), and PVP K-90 (C). (A) (a) Formulation B; (b) Formulation C; (c) Formulation D; (d) Formulation E. (B) PEG 200 amounts: (a) 1.43%; (b) 2.82%; (c) 4.17%; (d) 5.48%. (C) PVP K-90 amounts: (a) 1.43%; (b) 2.82%; (c) 4.17%; (d) 5.48%.

mixed polymer and, thus, exerted little influence on the mechanical properties of the Eudragit E-100 film. The results of UTS and elongation at break are given in Fig. 3. The mean of these six tests and the coefficient of variation were approximately 15% for UTS and 23% for elongation at break. The tensile strength can be reduced by the addition of plasticizers. A lower molecular weight or a higher concentration of plasticizers results in greater plasticizing action to reduce tensile strength and to increase film elongation, independent of whether the plasticizer is hydrophilic or hydrophobic. Possibly, the presence of plasticizer reduced the number of active centers available for binding sites and polymer–polymer contacts, decreasing the rigidity of the polymer structure (27). Moreover, plasticizer of low molecular weight (e.g., PEG 200) should be more efficient owing to its larger surface area as compared with the same plasticizer of higher molecular weight (e.g., PEG 4000). Thus, the plasticizing efficiency of plasticizers may be related to the size and amount of plasticizer molecules and the number of interchain bonding sites in the polymer.

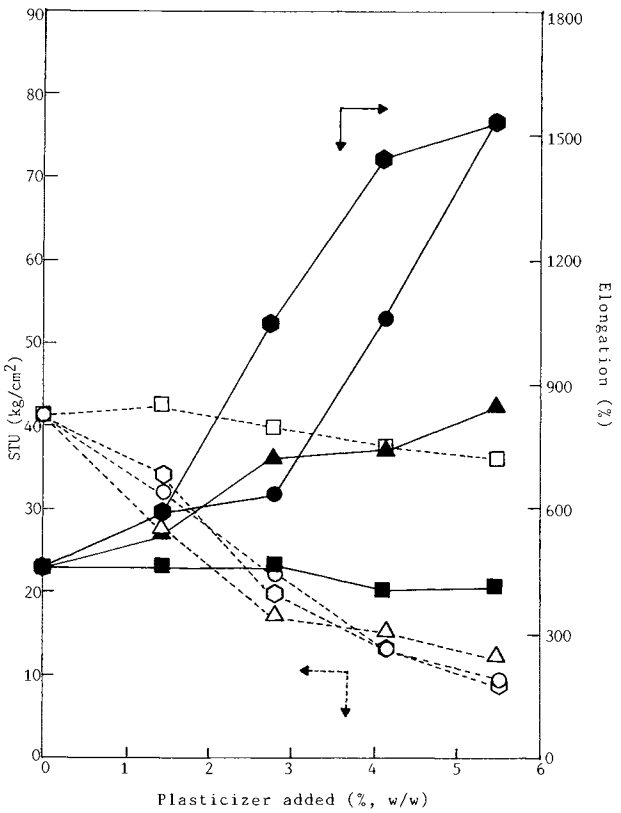

Fig. 3. Tensile strength and elongation of Eudragit E-100 films. (○, ●) Formulation C; (□, ■) Formulation F; (△, ▲) Formulation I; (⬡, ⬢) Formulation J.

Adhesion Strength of the Drug-Free Eudragit E-100 Film

A pressure-sensitive adhesive TDD system must adhere spontaneously to the skin surface with only light finger pressure, leave no adhesive residue when removed from the skin surface, and lack skin irritation. Variables such as molecular weight of the adhesive polymer, type and amount of adhesives, and polymer composition can influence the peel adhesion properties (28). Table I shows that only triacetin can exhibit both complete peel effects and tack. The adhesive property of the Eudragit E-100 film plasticized with triacetin might be attributed to one or several proposed mechanisms (adsorption, diffusion, and electrostatic force) (29). The effects of the secondary plasticizers on the adhesion strength of Eudragit E-100 films premixed with triacetin are shown in Fig. 4. Three different patterns were obtained. In the first pattern (Fig. 4A), the adhesion strength increased with plasticizer amount; PEG 200 and glycerin belonged to this group. In the second pattern (Fig. 4B), the adhesion strength decreased with increasing concentrations of plasticizer; isopropyl myristate and liquid paraffin belonged to this group. In the third pattern (Fig. 4C), the adhesion strength was independent of the concentration of plasticizer, such as PEG 1000, diethyl phthalate, propylene glycol, oleic acid, PVP K-90, or PEG 4000, used. Whether a plasticizer increases or decreases the autoadhesive strength was found to depend on the nature of the polymer and plasticizer, on the amount of plasticizer used, and on the conditions of its introduction (28). The molecular weight and solubility parameter of the plasticizer seemed to play an important role in changing the adhesive strength of the drug-free Eudragit E-100 film. A high molecular weight or low solubility parameter of the plasticizer decreased the film adhesion strength, whereas a low molecular weight or high solubility parameter of the plasticizer increased the adhesion strength. Although the molecular weight of PEG 1000 was higher than that of PEG 200, its solubility parameter was near that of Eudragit E-100

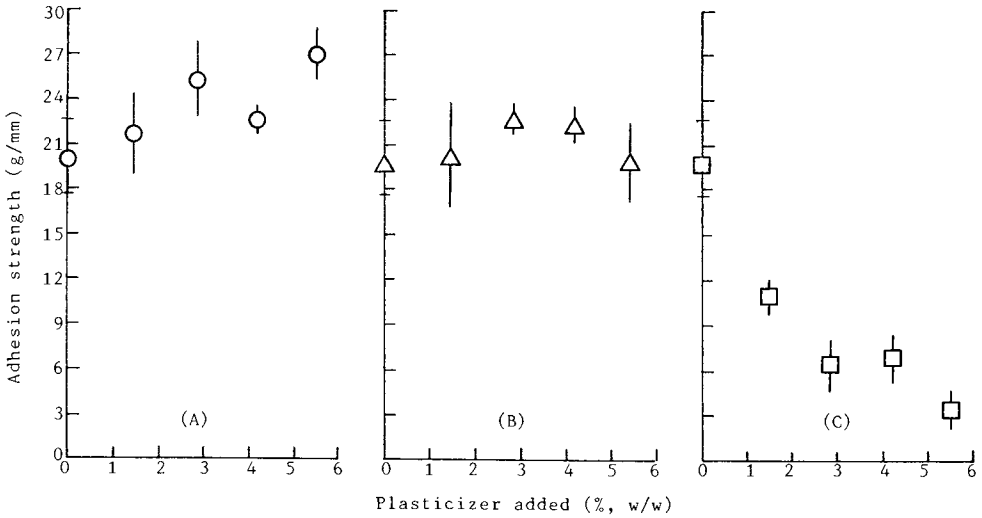

Fig. 4. Three patterns of adhesive strength of Eudragit E-100 films. (A) Formulation C; (B) Formulation D; (C) Formulation K.

polymer and triacetin, and adhesion strength was unaffected. Possibly, certain plasticizers might prevent crystallization of Eudragit polymer and thus decrease the aggregate force caused by the intermolecular attraction of the polymer, thereby increasing adhesive strength. Other plasticizers might reduce adhesive strength by favoring sliding of molecules, thus weakening the bond between two polymers, but could migrate on the surface of the high polymer layers, causing reduced autohesion.

In summary, PEG 200, propylene glycol, diethyl phthalate, and oleic acid as the secondary plasticizer afford a higher transparency, flexibility, and adhesion of Eudragit E-100 film.

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