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LEACHING OF WATER-SOLUBLE PLASTICIZERS FROM POLYMERIC FILMS PREPARED FROM AQUEOUS COLLOIDAL POLYMER DISPERSIONS

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ABSTRACT

The leaching of water-soluble plasticizers from polymeric films prepared by casting and drying of plasticized colloidal polymer dispersions was investigated with respect to the type and concentration of plasticizer (triethyl citrate or triacetin), film thickness, type of colloidal polymer dispersions (acrylic: Eudragit RS30D, RL30D, or L30D; cellulosic: Aquacoat), Eudragit RS30D/RL30D ratio, and method of film preparation (solvent- or pseudolatex-casting). The leaching increased with increasing level of plasticizer as indicated by an increase in the release rate constant while the release rate constant was independent of the film thickness. The leaching was more rapid from Aquacoat films than from Eudragit RS30D films at all plasticizer concentrations. Increasing the amount of the more hydrophilic polymer dispersion, Eudragit RL30D, in mixed Eudragit RS/RL films increased the rate of

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leaching. The incorporation of propranolol HCl into the polymeric films significantly increased the leaching rate constant when compared to drug-free films. The leaching from pseudolatex-cast films was faster when compared to the leaching from solvent-cast films due to the denser structure of the solvent-cast films.

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INTRODUCTION

Films of water-insoluble polymers have been prepared by casting or spraying either organic solutions or aqueous colloidal dispersions (latexes or pseudolatexes) of the polymers (1,2). Various properties of the polymeric films including permeability and mechanical characteristics are usually evaluated in order to predict the performance of these films as coatings around solid dosage forms or possibly as free films for oral or topical applications (3-5). Plasticizers are often added to improve the mechanical properties of the polymeric films. With colloidal polymer dispersions, the addition of plasticizers serves a second purpose. The minimum film formation temperature of most pharmaceutically used polymer dispersions is above the coating or drying temperature; plasticizers soften the colloidal polymer particles and enhance coalescence and film formation (6,7).

The plasticizers are generally solvents with high boiling points and low volatility (8). During dissolution studies or in biological fluids, water will come in contact with, and diffuse into and across the polymeric films or coatings. The permanence of the plasticizer in the coating under these "wet" conditions will primarily depend on its solubility in water and affinity for the polymer. Water-soluble plasticizers could leach from the polymeric coating, possibly changing its mechanical and permeability characteristics. Recently, the mechanical properties of dry and wet films plasticized with different plasticizers were investigated by a puncture test (9). Significant reductions in puncture strength and elongation were

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observed with wet films plasticized with water-soluble plasticizers because of the leaching of the plasticizer into the aqueous medium.

The objective of this study was to investigate the leaching of the water-soluble plasticizer, triethyl citrate, from films cast from various acrylic (Eudragit RS30D, RL30D, L30D) and one cellulosic (Aquacoat) colloidal polymer dispersions commonly used in the coating of pharmaceutical dosage forms.

MATERIALS AND METHODS

Materials

The following chemicals were obtained from commercial suppliers and used as received: triethyl citrate (Citroflex-2; Morflex Chemical Co., Greensboro, NC); glyceryl triacetate (triacetin; Eastman Kodak Co., Rochester, NY); 25% w/w aqueous ethyl cellulose dispersion (Aquacoat®, FMC Corporation, Newark, DE); 30% w/w aqueous dispersion of 50:50 poly (ethyl acrylate - methacrylic acid) copolymer (Eudragit L30D®), 30% w/w aqueous dispersion of poly (ethyl acrylate - methyl methacrylate - trimethyl ammonioethylmethacrylate chloride) copolymers with ratios of 1:2:0.1 and 1:2:0.2 (Eudragit RS30D® and Eudragit RL30D®) (Röhm Pharma, Darmstadt, Germany); methanol (Mallinckrodt Specialty Chemicals Co., Paris, KY), water was double-distilled.

Methods

The colloidal polymer dispersions (Aquacoat or Eudragit) were mixed with the plasticizer, triethyl citrate, (10 - 40 %w/w based on polymer; total film weight = 700 mg; volume of casting = 6 ml; plasticization time = 5 h). The plasticized dispersions were then cast into aluminum petri-dishes (5 cm in diameter) and dried for 48 hours at 40 °C and 30 % relative humidity. Films of different thicknesses

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were prepared by diluting the polymer dispersion with water to obtain films with varying solids content. With drug-containing films, propranolol HCl (5 %w/w of total film weight) was first dissolved in water and added into the plasticized dispersions (total weight of polymer and plasticizer = 700 mg). Solvent-cast films were prepared by dissolving the polymer powder (obtained from freeze-drying of the polymer dispersions) and plasticizer in a solvent blend [volume of casting = 6 ml; methylene chloride:methanol (2:1 v/v%)]. Film composition and total film weight were identical to those cast from the aqueous polymer dispersions. The polymer solution was cast and dried in aluminum dishes at room temperature for 24 h. The dried films were further dried in an oven at 40°C and 30% relative humidity for an additional 24 h. The thickness of the films was determined in 5 places using a micrometer (Paul N. Gardner Company, Inc., Pompano Beach, FL). The standard formulation (total film weight = 700 mg) resulted in films with a thickness of approximately 300 μm. It did not vary by more than 5 % over the film surface.

A previously developed HPLC assay was used for the analysis of the plasticizers (10). The chromatographic system consisted of a solvent delivery module (LC-9A), a UV spectrophotometric detector (SPD-6A), an automatic sample injector (SIL-6A), an integrator (Chromatopac CR601) (Shimadzu, Kyoto, Japan), and an analytical column (Beckman-Ultrasphere, C-18, 5 μm-particle size, 25 cm x 4.6 cm ID). The mobile phase consisted of methanol:water (70:30 v/v%).

The leaching of the plasticizer from the films was determined using the USP XXI rotating paddle apparatus (37 °C, 25 rpm, 500 ml 0.1 M NaCl, n = 2 or 3, coefficient of variation < 5%). The edges of the films were sealed with a high vacuum grease (Dow Corning Corp., Midland, MI) to avoid penetration of the leaching medium along and plasticizer diffusion from the edges. The films stayed within the aluminum dishes at the bottom of the dissolution vessel during the

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dissolution study. Samples were withdrawn at predetermined intervals and assayed by HPLC after dilution with methanol (sample, 1 ml; methanol, 2 ml). The residual plasticizer content in the films after the dissolution study was determined for selected samples after vacuum-drying of the film and extraction in methanol. The amount of plasticizer leached and the residual plasticizer content in the films matched the original content within 2-5 %. Hydrolysis or degradation of triethyl citrate or triacetin in the dissolution medium was minimal (98.5 % and 96.7 % recovery at a concentration of 0.05 %w/v in 0.1 M NaCl at 37 °C after 100 h). The leaching rate constant, k, was obtained by plotting the cumulative amount of plasticizer leached per unit area versus the square-root of time. The linear portion of the curve was determined statistically by linear regression analysis. The slope represented the leaching rate constant.

The following variables were investigated: plasticizer (triethyl citrate) concentration, 10-40 %w/w based on polymer solids (Eudragit RS30D and Aquacoat), 5-10 % increments; film thickness of Aquacoat films, 150 - 450 μm; Eudragit RS/RL ratio, 10:0, 9:1, 8:2, 7:3, 5:5, 3:7, 2:8, 1:9, and 0:10; type of aqueous colloidal dispersion (Eudragit RS30D, RL30D, L30D, and Aquacoat), solvent- vs pseudolatex-cast (with Eudragit RS30D); type of plasticizer, triethyl citrate or triacetin (with Eudragit L30D).

The water uptake of the films was determined as follows: water uptake = (weight of wet film after leaching - weight of dried film after leaching) / weight of polymer in film; the water uptake was expressed as g, water / g, polymer. The water uptake was based on the polymer and not on the weight of the dry film before or after leaching in order to eliminate the effect of the plasticizer, which was present in the films at different levels after the leaching study.

The surface morphology of selected films after leaching was examined by scanning electron microscopy (SEM). The dried films were coated for 70 seconds

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under an argon atmosphere with gold-palladium (Pelco Model 3 Sputter Coater) and then observed with a scanning electron microscope (Jeol JSM 35C).

RESULTS AND DISCUSSION

Triethyl citrate is a popular, pharmaceutically acceptable, and water-soluble plasticizer. It has been recommended for a variety of acrylic and cellulosic dispersions. In this study, various variables affecting the leaching of triethyl citrate from films cast from colloidal polymer dispersions were investigated.

Plasticizers are often added in varying concentrations to pharmaceutical colloidal dispersions to reduce the minimum film formation temperature below the coating or casting temperature. The effect of triethyl citrate concentration on plasticizer leaching from Eudragit RS30D and Aquacoat is shown in Figure 1. The amount of plasticizer leached increased with increasing plasticizer concentration, with the duration of leaching being inversely correlated to the plasticizer concentration. Scanning electron micrographs of Eudragit RS30D films after exposure to 0.1 M NaCl and drying revealed a porous structure above a TEC concentration of 30 % (Figure 2 A and B, 20 and 40 %w/w TEC). The films had a smooth surface prior to exposure to the aqueous medium. Unlike water-soluble plasticizers, leaching of water-insoluble plasticizers is limited due to their low solubilities in the aqueous medium. Negligible portions of acetyl tributyl citrate, a water-insoluble plasticizer, leached from Eudragit RS30D films during the exposure to the dissolution fluids (9).

It is well known that the drug release from monolithic solutions can be linearly described by a square root of time relationship during the early time approximations and by a first order equation during the late time approximation (11). Triethyl citrate was dissolved in the polymeric films as indicated by the clear and homogeneous appearance of the plasticized films. Plasticizer leaching rates

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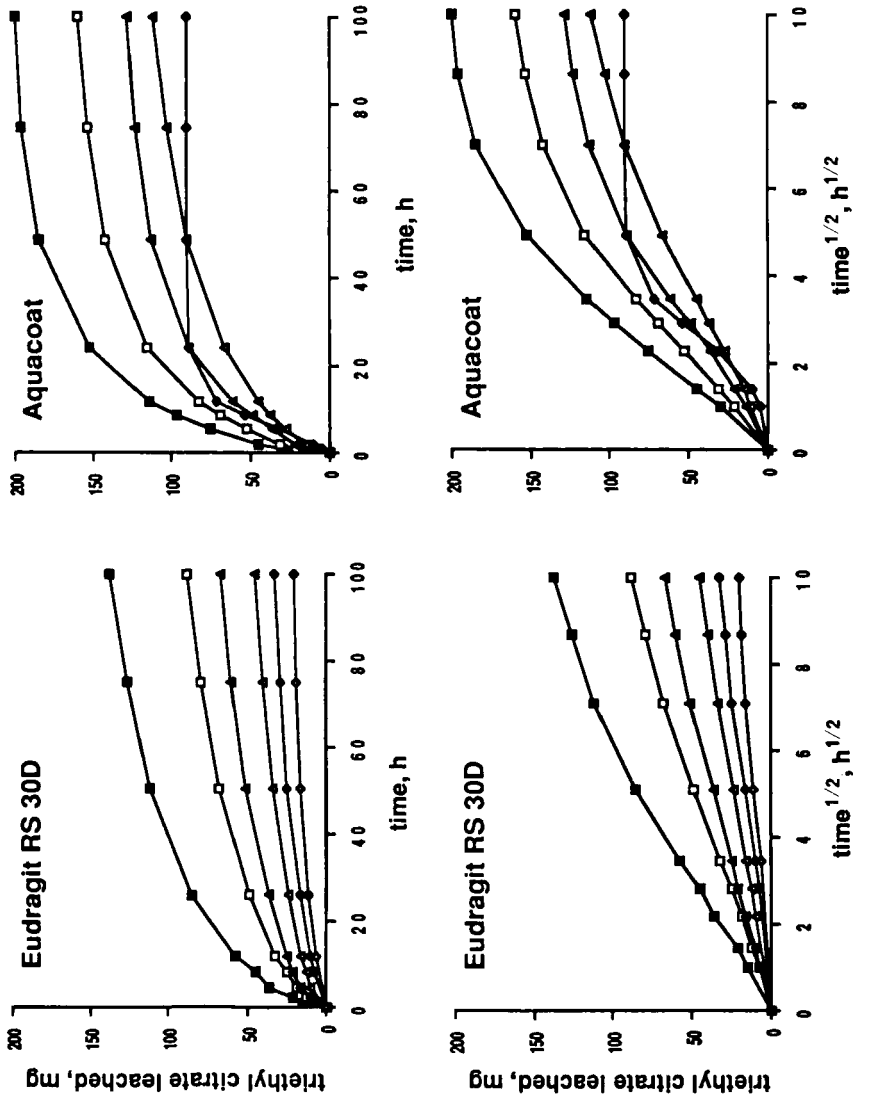

FIGURE 1
Effect of triethyl citrate concentration on the plasticizer leaching from Eudragit RS30D and Aquacoat films containing: (■) 40%, 200 mg; (□) 30%, 162 mg; (▲) 25%, 140 mg; (△) 20%, 117 mg; (◆) 15%, 91 mg; and (◇) 10%w/w, 64 mg triethyl citrate (film thickness = 279 - 339 μm).

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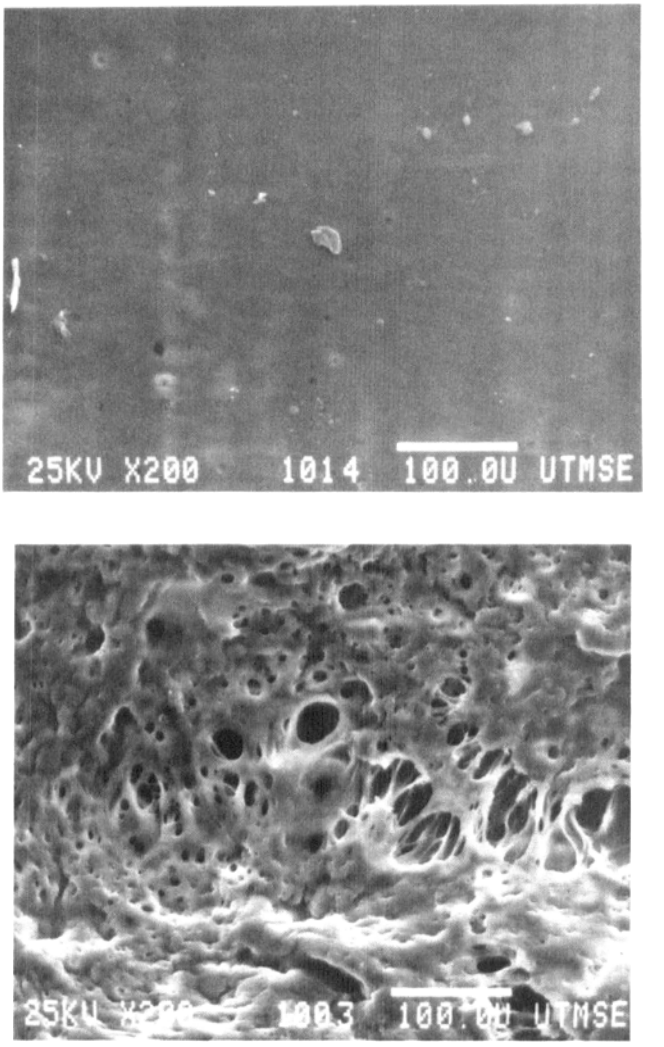

FIGURE 2
Scanning electron micrographs of the surfaces of Eudragit RS30D films plasticized with (A) 20 % and (B) 40 % w/w triethyl citrate after exposure to 0.1 M NaCl and drying.

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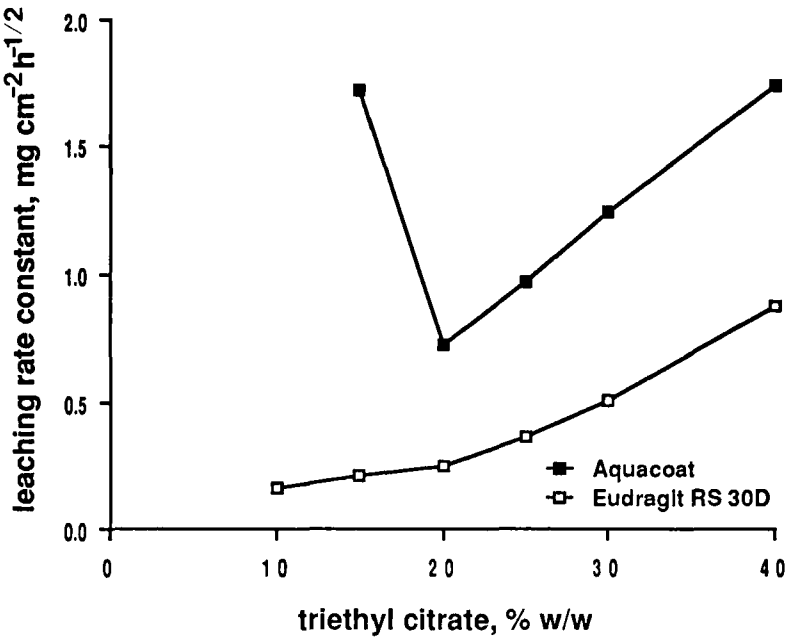

FIGURE 3
Leaching rate constant as a function of triethyl citrate concentration in Eudragit RS30D and Aquacoat films

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were obtained from the slopes of the linear portions of graphs of the amount of plasticizer leached vs. square root of time (shown in Figure 1). The leaching rate constants for the two polymeric dispersions as a function of triethyl citrate concentration are shown in Figure 3. The rate constant increased with increasing plasticizer concentration, the rate constants being higher with the Aquacoat films than with the Eudragit RS30D films at the corresponding plasticizer levels. The leaching of the plasticizer from polymeric films will be influenced by the hydration of the polymer, the polymer-plasticizer interaction, and by other ingredients present in the polymeric film. Aquacoat contains sodium lauryl sulfate as an emulsifying agent (4% w/w of total solids) to stabilize the ethyl cellulose dispersion during preparation and storage. This anionic surfactant dramatically influenced the drug

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release from coated beads (12), and may have contributed to the more rapid leaching of triethyl citrate from the Aquacoat films when compared to the surfactant-free Eudragit RS30D films. The rapid leaching of triethyl citrate from Aquacoat films at a plasticizer level of 15 %w/w, as indicated by a high release rate constant, could probably be explained with the incomplete film formation of the ethyl cellulose pseudolatex. The films were very brittle indicating incomplete fusion of the colloidal polymer particles in a homogeneous film. In addition, Aquacoat films plasticized with 10% triethyl citrate did not form continuous films but cracked into mosaic-like chips upon drying.

Drug-containing films have been prepared from colloidal polymer dispersions by dissolving the drug in the dispersion prior to film casting (13,14). In this study, propranolol HCl (5%w/w of total solids) was added to Eudragit RS30D dispersions prior to casting the films. The presence of the highly water-soluble drug in the polymeric film significantly increased the leaching rate constant when compared to drug-free films at corresponding triethyl citrate concentrations (Figure 4). The presence of drug in polymeric coatings around solid drug cores could therefore significantly affect the drug release. It is therefore advisable to minimize the contact of highly water-soluble drug cores and water during coating with aqueous colloidal polymer dispersions. Otherwise, the drug could dissolve and be present in the polymeric film after drying, resulting in faster and irreproducible drug release patterns.

The effect of film thickness on the leaching of triethyl citrate (30 %w/w) from Aquacoat films is shown in Figure 5. Film thickness had no effect on the release rate constant as shown by the overlap of the initial portions of the leaching curves. As expected, the duration of leaching increased with increasing thickness. In general, film thickness only affects the duration of release but not the release rate

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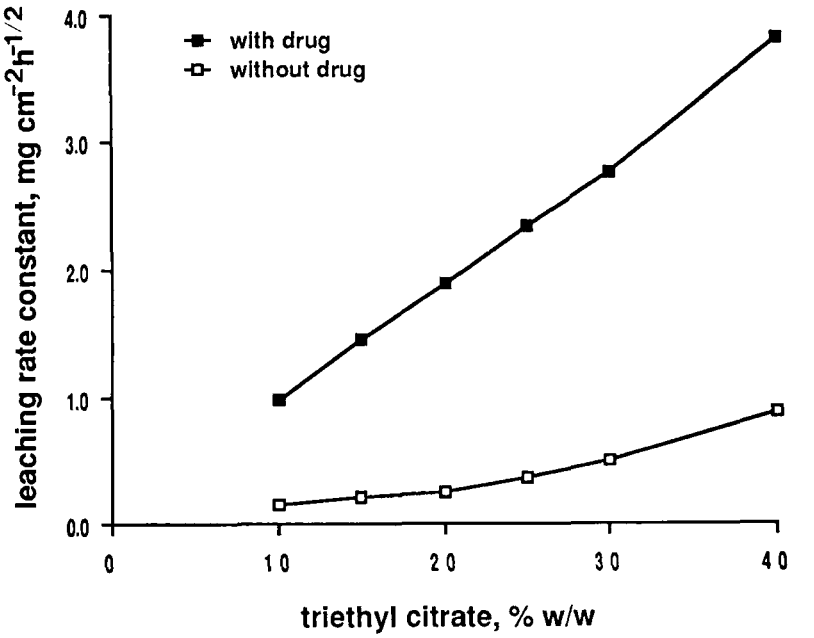

FIGURE 4
Leaching rate constants of Eudragit RS30D films containing propranolol HCl (5% w/w) and of drug-free Eudragit RS30D films

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constant unless changes in the microstructure of the polymeric films occurred during release studies (13).

Eudragit RS30D or RL30D are pseudolatexes based on poly (ethylacrylate-methylmethacrylate-trimethylammonioethyl methacrylate chloride) copolymers with ratios of 1:2:0.1 and 1:2:0.2. The colloidal dispersions are stabilized by the quaternary ammonium groups, which are also responsible for the hydration and swelling of these polymers. The two dispersions were mixed in various proportions in order to study the leaching of triethyl citrate as a function of the Eudragit RS/RL ratio (Figure 6). The mixed films had intermediate leaching patterns when compared to those of pure films. The higher proportion of quaternary ammonium groups in Eudragit RL films resulted in faster hydration and leaching of the plasticizer. The

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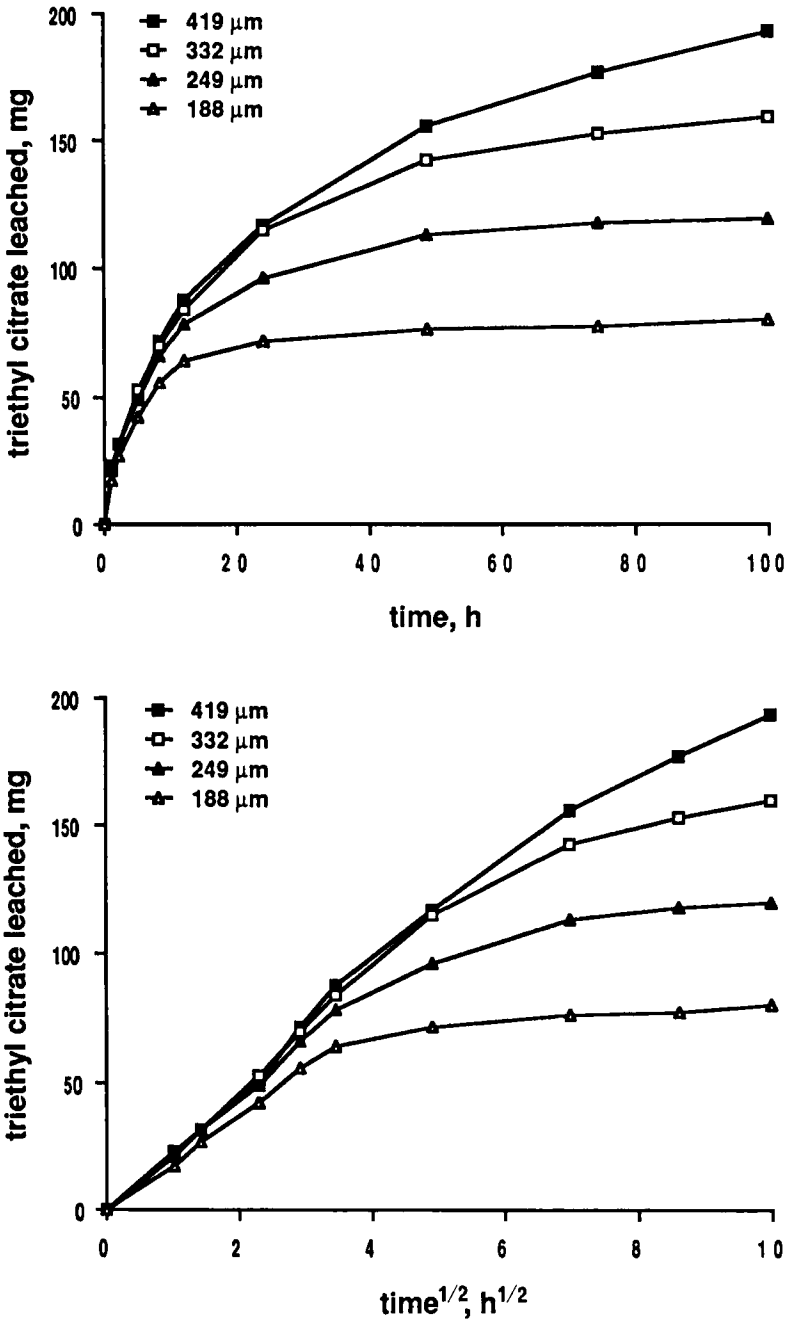

FIGURE 5
Effect of film thickness on plasticizer leaching from Aquacoat films (triethyl citrate concentration, 30% w/w)

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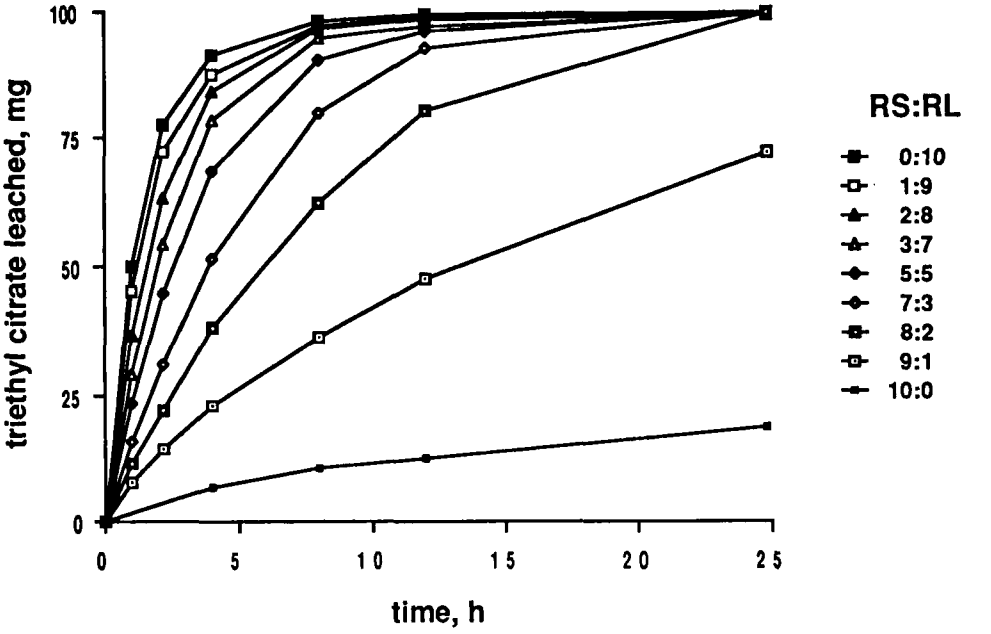

FIGURE 6
Effect of Eudragit RS/RL30D ratio on plasticizer leaching from mixed Eudragit RS/RL30D films (triethyl citrate concentration, 20% w/w; film thickness = 315 - 350 μm)

release rate constants (obtained from square root of time vs amount triethyl citrate leached) initially increased rapidly with increasing proportion of Eudragit RL30D, but levelled off at concentrations above 60 % Eudragit RL30D (Figure 7). The presence of only 10 or 20 % Eudragit RL30D in mixed films resulted in a significant increase in triethyl citrate leaching.

The leaching of triethyl citrate from different colloidal polymer dispersions is shown in Figure 8. The order of leaching was Eudragit RL30D > Aquacoat > Eudragit L30D > Eudragit RS30D. The leaching from polymers is affected primarily by the hydration of the polymer and the affinity of the polymer for the plasticizer. The hydration of the films (Table 1), as measured by the water uptake, correlated well with the order of leaching.

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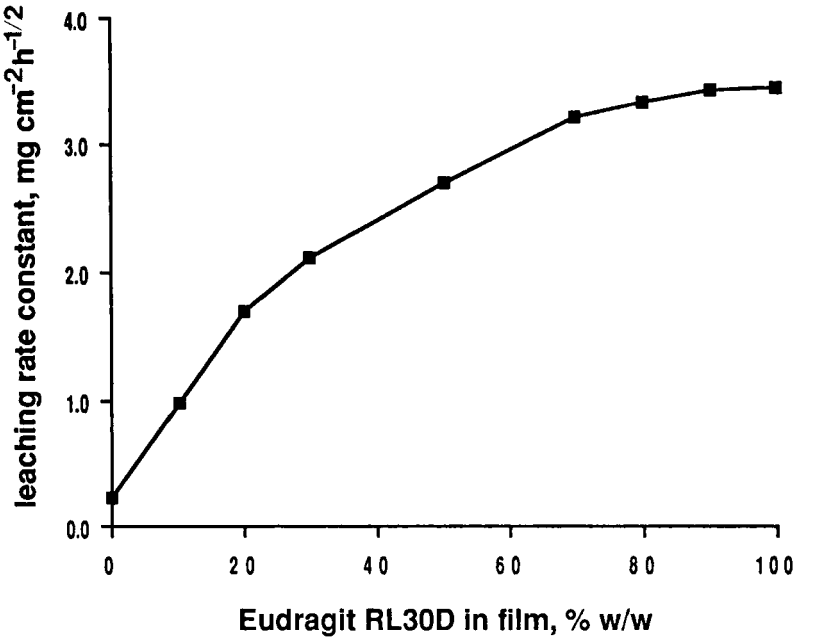

FIGURE 7
Leaching rate constant as a function of Eudragit RL30D content in the mixed Eudragit RS/RL30D films.

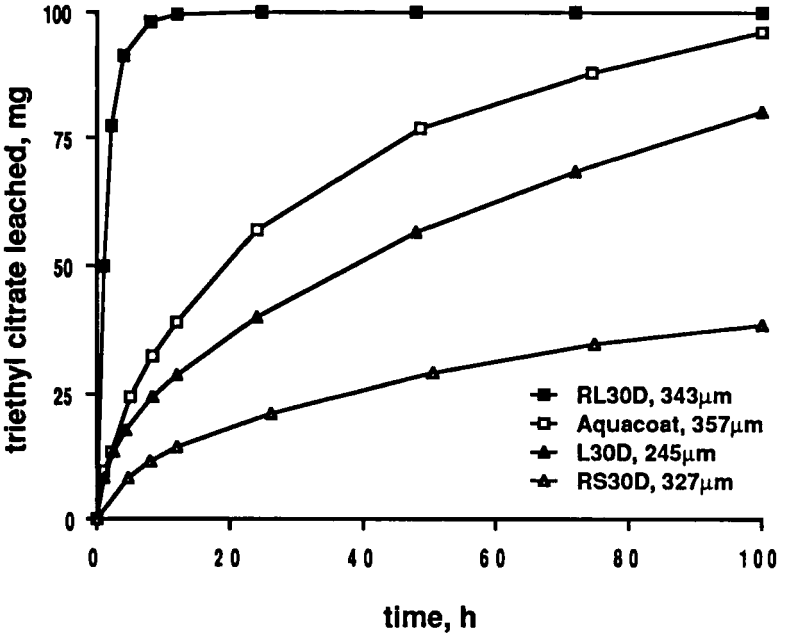

FIGURE 8
Leaching of triethyl citrate from films prepared from different colloidal polymer dispersions (triethyl citrate concentration, 20% w/w)

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TABLE 1

Water Uptake of Films Prepared From Different Colloidal Polymer Dispersions
(Triethyl Citrate, 20% w/w, n=3)

Colloidal Polymer Dispersion	Water Uptake, g, water / g, polymer
Eudragit RL 30D	1.470 ± 0.040
Aquacoat	0.667 ± 0.008
Eudragit L 30D	0.459 ± 0.032
Eudragit RS 30D	0.302 ± 0.007

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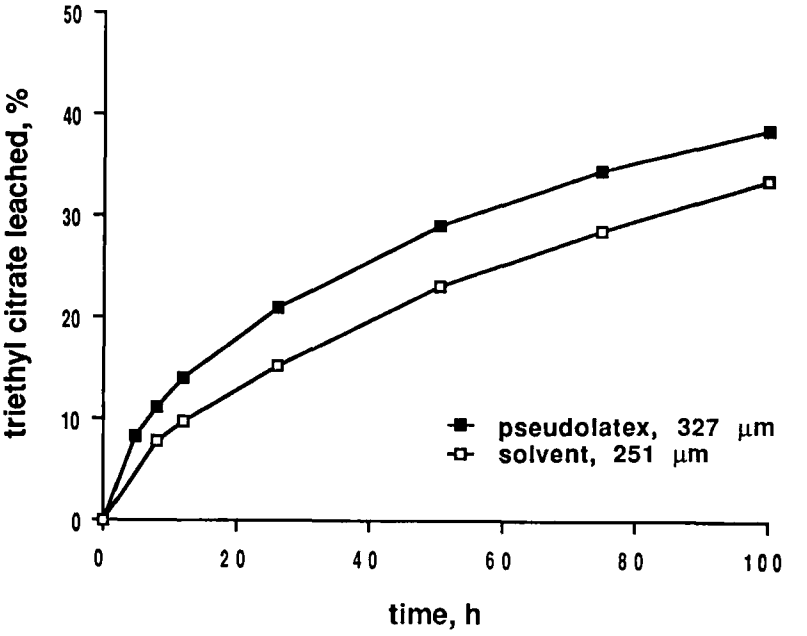

FIGURE 9
Effect of film preparation on triethyl citrate leaching from Eudragit RS30D films
(triethyl citrate concentration, 20% w/w)

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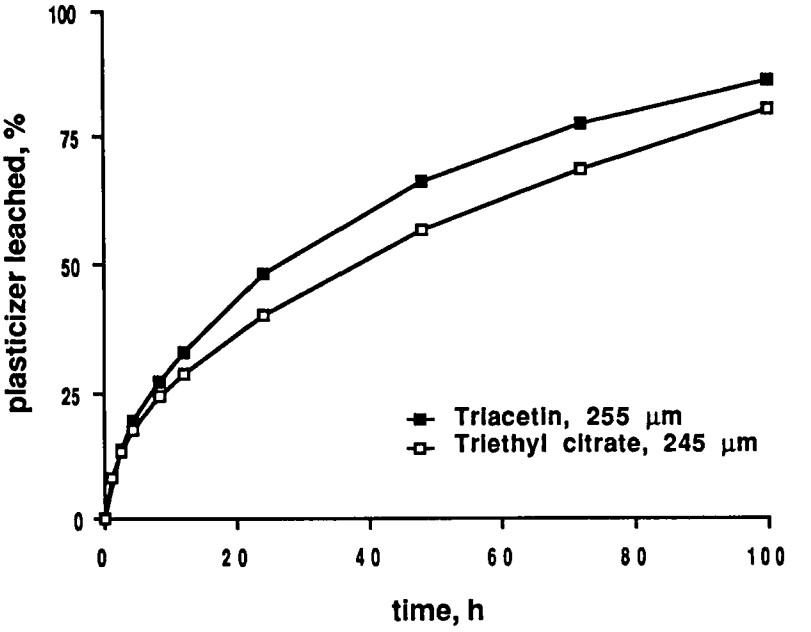

FIGURE 10
Effect of plasticizer type on plasticizer leaching from Eudragit L30D films (plasticizer concentration, 20% w/w)

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Figure 9 compares the leaching of triethyl citrate from pseudolatex- and solvent-cast Eudragit RS30D films. Both films had the same solids content and composition; the solvent-cast films were prepared by freeze-drying the pseudolatex and casting the film from a solution of the powder and plasticizer in a methylene chloride/methanol (2:1 v/v) solvent mixture. The leaching was faster from the pseudolatex-cast film. This could be explained with the different densities of the films; at the same solids content, the solvent-cast films were thinner and therefore denser. Similar results were observed in a previous study with the release of drugs from solvent- or pseudolatex-cast films (14).

Eudragit L is an anionic, enteric polymer synthesized from methacrylic acid and acrylic acid ethyl esters. Besides triethyl citrate, triacetin is recommended by the

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manufacturer as a suitable plasticizer. At the same solids content and film thickness, triacetin leached faster from the Eudragit L films than triethyl citrate (Figure 10). Triacetin had a higher solubility in the dissolution medium when compared to triethyl citrate (triacetin, 77.8 ± 0.5 mg/ml and triethyl citrate, 55.4 ± 0.0 mg/ml), thus explaining the more rapid leaching.

The leaching behaviour or non-permanence of the widely used water-soluble plasticizer, triethyl citrate, was investigated. Although the selection of a leachable plasticizer had no negative effect on the film formation from aqueous polymer dispersions, it could have a significant impact on the permeability and mechanical properties of polymeric coatings during dissolution studies or in a biological environment.

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