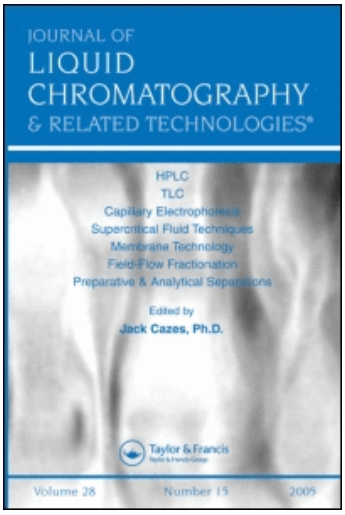

Journal of Liquid Chromatography & Related Technologies

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

Determination of Plasticizers Commonly Used In Pharmaceutical Dosage Forms by High Performance Liquid Chromatography

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To cite this Article Bodmeier, Roland and Paeratakul, Ornlaksana(1991) 'Determination of Plasticizers Commonly Used In Pharmaceutical Dosage Forms by High Performance Liquid Chromatography', Journal of Liquid Chromatography & Related Technologies, 14: 2, 365 — 375
To link to this Article: DOI: 10.1080/01483919108049621
URL: http://dx.doi.org/10.1080/01483919108049621

JOURNAL OF LIQUID CHROMATOGRAPHY, 14(2), 365-375 (1991)

DETERMINATION OF PLASTICIZERS COMMONLY USED IN PHARMACEUTICAL DOSAGE FORMS BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

A simple reversed-phase HPLC method was developed to identify and quantify plasticizers commonly used with polymers present in sustained or controlled release dosage forms. The plasticizers investigated included triethyl citrate, tributyl citrate, acetyl triethyl citrate, dibutyl sebacate, diethyl phthalate, dibutyl phthalate, and triacetin. The plasticizers were detected at 220 nm, the mobile phase being methanol:water (70:30 v/v%). The peak area response was linear over the studied concentration range of 0.5-5.0 mM/L for triethyl citrate, acetyl triethyl citrate, dibutyl sebacate, and triacetin, and 0.005 - 0.05 mM/L for diethyl phthalate. The recovery from solvent-cast ethyl cellulose and Eudragit RS 100 films was complete. Two pharmaceutical applications of this assay included the quantitation of plasticizers in polymer-coated sugar beads and a leaching study of a water-soluble plasticizer, triethyl citrate, from polymeric films into simulated intestinal fluids.

INTRODUCTION

Polymers are the most widely used materials to retard the drug release from sustained or controlled release drug delivery systems such as film-coated dosage forms, films, microparticles, or various matrix systems. Most FDA approved water-insoluble polymers are either of cellulosic (ethyl cellulose, cellulose acetate, cellulose acetate phthalate, etc.) or acrylic [poly (methacrylate), poly (methyl

methacrylate), and their copolymers] nature (1). Because of the high glass transition temperatures of most of these polymers, plasticizers have to be added to impart flexibility to the polymeric materials. Plasticizers decrease the intermolecular forces along the polymer chains, generally resulting in a decrease in tensile strength, a lowering of the softening and glass transition temperature, and an increase in the elongation and flexibility of the films (2).

Pharmaceutically acceptable plasticizers are based primarily on esters of either citric or phthalic acid (3). Traditionally, these plasticizers have been identified by gas chromatography (4-11). Surprisingly, despite the enhanced versatility, very few HPLC methods have been described in the literature. HPLC methods have been used to measure the release of D-2-ethylhexyl phthalate from intravenous administration sets into fat emulsions (12), to analyze various phthalate esters in post consumer scrap poly (vinyl chloride) (13), in aqueous solutions (14) and in river water (15-17).

The objective of this study was to develop a rapid HPLC assay, which allows the identification and quantitation of plasticizers commonly found in polymeric drug delivery systems.

EXPERIMENTAL

Materials - The following chemicals were used as received: triethyl citrate (Citroflex-2), acetyl triethyl citrate (Citroflex A-2), tributyl citrate (Citroflex-4) (Morflex Chemical Co., Greensboro, NC), dibutyl sebacate, diethyl phthalate, dibutyl phthalate, triacetin (Eastman Kodak Co., Rochester, NY), Aquacoat (25 % w/w ethyl cellulose pseudolatex, FMC Corporation, Princeton, NJ), ethylcellulose (Ethocel STD 10 Premium, Dow Chemical Co., Midland, MI), poly (ethylacrylate-methylmethacrylate-trimethylammonioethylmethacrylate chloride (Eudragit RS 100, Röhm Pharma, Darmstadt, West Germany). The solvents used were HPLC grade and the water was double-distilled.

Chromatographic conditions - The chromatographic system consisted of an HPLC pump (Beckman 110B Solvent delivery module), a variable wavelength UV absorbance detector (Beckman 163 Variable wavelength detector), a low dead volume sample injector with 20 microliter-loop (Rheodyne Model 7125, Cotati, CA), a column inlet filter (0.5 μm filter element, Rainin Instrument, Woburn, MA),

an analytical column (Beckman-Ultrasphere, C-18, 5 μm particle size, 25 cm X 4.6 mm ID), and an integrator (C-R3A Chromatopac, Shimadzu, Kyoto, Japan). The mobile phase consisted of methanol:water (70:30 v/v%). The solvents were mixed, vacuum-filtered through a 0.45 μm nylon 66 filter (Applied Science Lab., Deerfield, IL), and degassed by sonication under vacuum prior to use. The flow rate was 0.9 ml/min, resulting in a pressure of 2000-2500 psi. The sensitivity was set at 0.1 AUFS at 220 nm. Quantitation was by peak area measurements and temperature was ambient.

Stock and standard solutions, precision - Stock solutions were prepared by dissolving 0.01M of the plasticizers in the mobile phase [triethyl citrate (2.76 g) or triacetin (2.18 g)], or in methanol [acetyl triethyl citrate (3.18 g), dibutyl sebacate (3.14 g), or diethyl phthalate (2.22 g)], to make 100 ml. The standard solutions were prepared by diluting the stock solutions with the mobile phase to obtain a concentration range of 0.5 - 5.0 mM/L for triethyl citrate, acetyl triethyl citrate, dibutyl sebacate, and triacetin, and a concentration range of 0.005 - 0.05 mM/L for diethyl phthalate (n = 2). Linear regression analysis of peak area versus concentration gave slope, intercept, and coefficient of correlation.

Within-run precision was determined by calculating the coefficient of variation on 5 replicate analyses of standard solutions containing 0.5 and 5.0 mM/L for triethyl citrate, acetyl triethyl citrate, dibutyl sebacate, and triacetin, and 0.005 and 0.05 mM/L for diethyl phthalate.

Recovery study - Polymeric films of ethylcellulose or Eudragit RS 100 [poly(ethylacrylate-methylmethacrylate-trimethylammonioethylmethacrylate chloride)] containing known amounts of plasticizers were prepared by dissolving the polymer (750 mg) and the plasticizer (250 mg) in acetone (7 ml), followed by casting the solution into aluminum petri dishes (6 cm in diameter, n = 2). The films were dried at room temperature for 48 hours and stored in a desiccator for 24 hours prior to analysis. Accurately weighed amounts of films (50 - 200 mg) were dissolved in methanol (10 ml), followed by the addition of water (10 ml) to precipitate the polymer, and centrifugation. The supernatant (2 ml) was diluted with the mobile phase (18 ml) prior to injection. The percent recovery was calculated as 100% * plasticizer found in polymer / plasticizer added to polymer.

Nonpareil seeds (sugar beads) were coated in a fluid-bed coater (Uni-Glatt Laboratory Unit, Wurster insert, Glatt Air Technique, Ramsey, NJ; 400 g charge, inlet temperature = 45-50 °C, outlet temperature = 40 - 45 °C, spray rate = 1 ml/min

for 10 min, then 3-5 ml/min, pre-heating time = 15 min, post-drying time = 5 min) with an ethyl cellulose pseudolatexes (Aquacoat) containing known amounts of plasticizer (30% w/w of total solids) until a 10 % weight gain was achieved. The plasticizers were either dissolved or emulsified into the pseudolatex 2 hours prior to coating. To recover the plasticizer, the beads (500-800 mg) were added to methanol (10 ml) to dissolve the polymer and plasticizer, followed by centrifugation to separate the undissolved sugar beads. The subsequent treatment of the methanolic solution was the same as the method described above for polymeric films.

Leaching of triethyl citrate - The USP XXII rotating paddle method (18) was used to study the leaching of triethyl citrate from the Eudragit RS 100 films into simulated intestinal fluid (37 °C, 25 rpm, 500 ml 0.1 M pH 7.4 phosphate buffer, n=2). Samples were taken from the dissolution medium at specified time points and analyzed for plasticizer content by HPLC.

RESULTS AND DISCUSSION

The chromatograms and retention times of the plasticizers, triethyl citrate, acetyl triethyl citrate, tributyl citrate, triacetin, dibutyl sebacate, diethyl phthalate and dibutyl phthalate (only retention time) are shown in Figure 1 and Table 1.

As expected, the retention times increased with increasing hydrophobicity of molecules with similar functional groups. Two peaks were obtained with triethyl citrate and acetyl triethyl citrate. Except for dibutyl phthalate, the retention times were short and less than 10 minutes. The retention times could be further shortened

TABLE 1

Retention Times of the Plasticizers.

Plasticizer	Retention time, minutes
Triethyl citrate	4.26, 7.90
Acetyl triethyl citrate	5.78, 7.90
Triacetin	3.21
Dibutyl sebacate	4.07
Diethyl phthalate	6.25
Dibutyl phthalate	31.95
Tributyl citrate	8.99

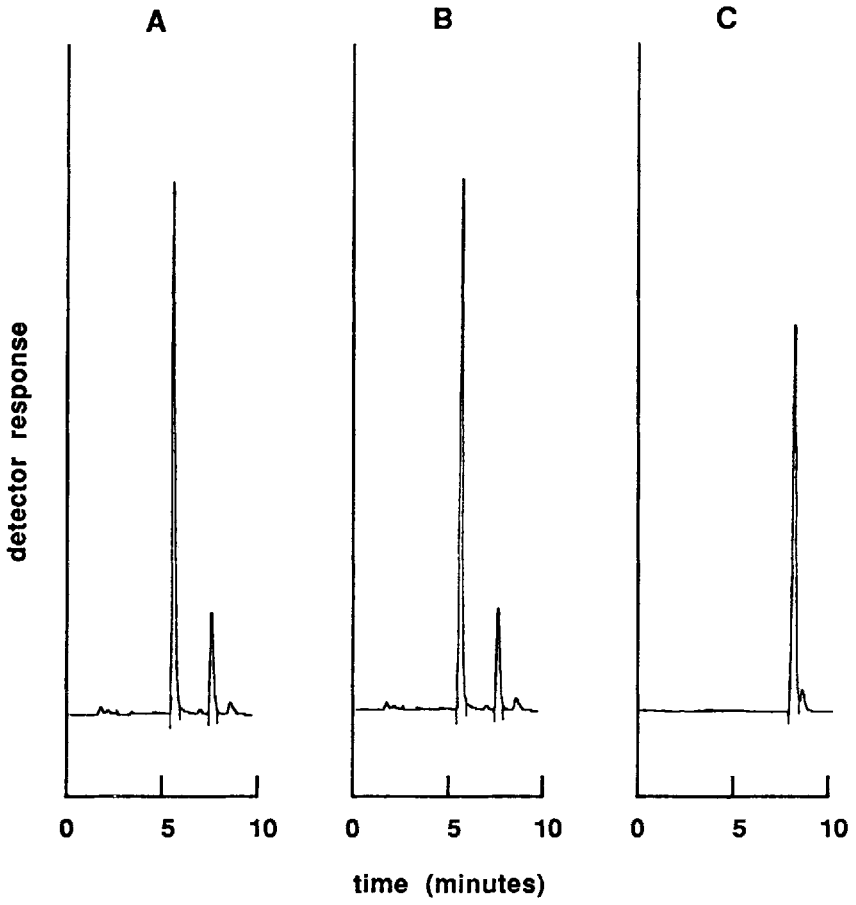

FIGURE 1
Chromatogram of standard solutions of (A) triethyl citrate (2 mM/L), (B) acetyl triethyl citrate (2 mM/L), (C) tributyl citrate (10 mM/L), (D) triacetin (4 mM/L), (E) dibutyl sebacate (5 mM/L), and (F) diethyl phthalate (0.05 mM/L).

(continued)

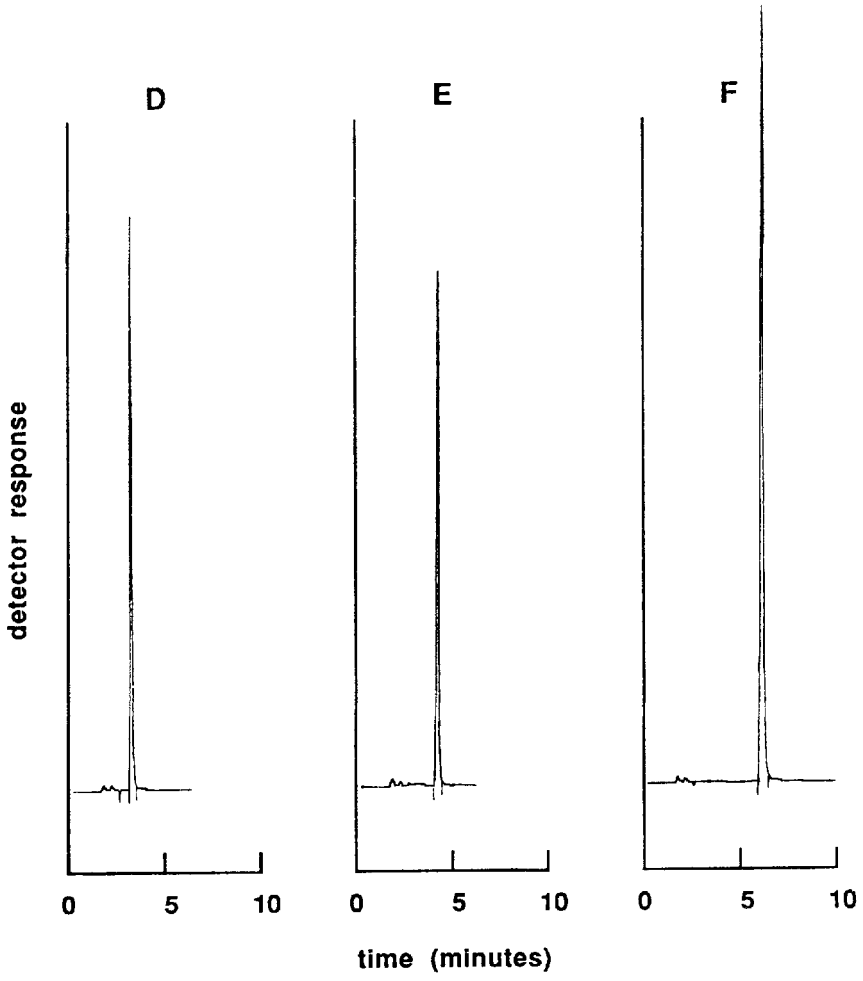

FIGURE 1 (continued)

by increasing the methanol content of the mobile phase. The identification of unknown plasticizers will be straightforward since only individual and not mixtures of plasticizers are generally used in polymeric drug delivery systems.

Linear responses between peak area and plasticizer concentrations, as indicated by correlation coefficients > 0.99, were obtained over the studied concentration range of 0.5 - 5 mM/L for triethyl citrate, acetyl triethyl citrate, dibutyl sebacate, or triacetin, and 0.005 - 0.05 mM/L for diethyl phthalate. The calibration curves for the plasticizers (except diethyl phthalate) are shown in Figure 2. Within-run precision was determined on 5 replicate analyses on standard solutions containing 0.5 and 5.0 mM/L of triethyl citrate, acetyl triethyl citrate, dibutyl sebacate, or triacetin, or 0.05 and 0.5 mM/L of diethyl phthalate. The coefficients of variation were 1.09 and 0.50 % for triethyl citrate, 0.87 and 0.80 % for acetyl triethyl citrate, 1.43 and 1.50 % for dibutyl sebacate, 0.74 and 0.63 % for triacetin, and 0.68 and 0.29 % for diethyl phthalate, respectively.

To determine the accuracy of the method, polymeric films of ethyl cellulose and Eudragit RS 100 with known amounts of plasticizer were prepared by casting polymer-plasticizer solutions in acetone. The recovery from the films was complete as shown in Table 2. The retention times after extraction corresponded to the retention times of the standard solutions.

This method allows the determination of plasticizers in both organic and aqueous solvent systems. Potential applications include the quantitation of plasticizers within polymeric drug delivery systems after preparation and as a function of time during storage or stability studies. The preparation of polymer-coated solid dosage forms or of cast films is often done at elevated temperatures (19, 20). Some plasticizers are volatile or unstable, and could be lost or degrade during the manufacturing process and storage.

In order to determine the amount of plasticizers present in polymeric films after the coating of solid dosage forms, sugar beads were coated with aqueous ethyl cellulose pseudolatexes containing either triethyl citrate, dibutyl sebacate, or diethyl phthalate as the plasticizer. The recovery of the different plasticizers is shown in Table 3. Only 91 % of triethyl citrate were recovered indicating that some plasticizer was lost during the coating process.

Water-soluble plasticizers may leach into surrounding body fluids during the administration of the polymeric drug delivery system. This is exemplified with the leaching of the partially water-soluble plasticizer, triethyl citrate (solubility in water = 6.5 % w/v), from Eudragit RS 100 films (Figure 3). Films containing different

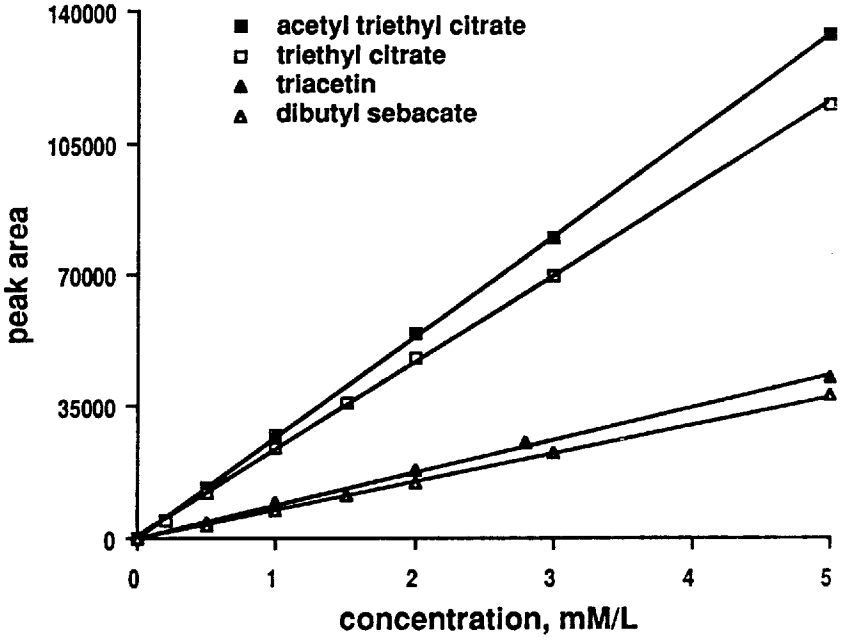

FIGURE 2
Calibration curves for standard solutions of acetyl triethyl citrate, triethyl citrate, triacetin, and dibutyl sebacate (0.5 - 5.0 mM/L).

amounts of plasticizers (20, 30 or 40 %w/w) were prepared and placed into simulated intestinal fluids (0.1 M pH 7.4 phosphate buffer). The percent triethyl citrate leached during the dissolution study was significant (between 20 and 60 % over a 24 hour period) and increased with increasing amount of plasticizer. The loss of plasticizer into biological fluids, such as gastrointestinal fluids with oral polymeric drug delivery system, could negatively affect the performance of the system, e.g. the mechanical strength and integrity of film coatings. Mechanical failure or rupture of a film coating would result in a loss of the sustained release properties.

In conclusion, a simple HPLC method has been developed as an alternative to the widely used gas chromatographic methods to determine commonly used plasticizers in polymeric drug delivery systems. The method is precise and accurate, and could be used for the identification and quantitation of plasticizers in both aqueous and organic solvent systems.

TABLE 2

Recovery of the Plasticizers, Triethyl citrate, Acetyl triethyl citrate, Dibutyl sebacate, Diethyl phthalate, and Triacetin from Ethyl Cellulose and Eudragit RS 100 films (25% w/w theoretical plasticizer content).

Plasticizer	% Recovery	
	Ethyl cellulose	Eudragit RS 100
Triethyl citrate	100.65 ± 1.34	99.71 ± 0.30
Acetyl triethyl citrate	102.08 ± 1.60	102.91 ± 0.02
Dibutyl sebacate	102.24 ± 0.72	99.39 ± 1.35
Diethyl phthalate	100.28 ± 2.46	101.22 ± 1.40
Triacetin	97.19 ± 2.21	100.62 ± 0.61

TABLE 3

Recovery of the Plasticizers, Triethyl citrate, Dibutyl sebacate, and Diethyl phthalate from sugar beads coated with ethyl cellulose pseudolatexes.

Plasticizer	% Recovery
Triethyl citrate	91.72 ± 4.16
Dibutyl sebacate	99.85 ± 6.01
Diethyl phthalate	100.61 ± 0.53

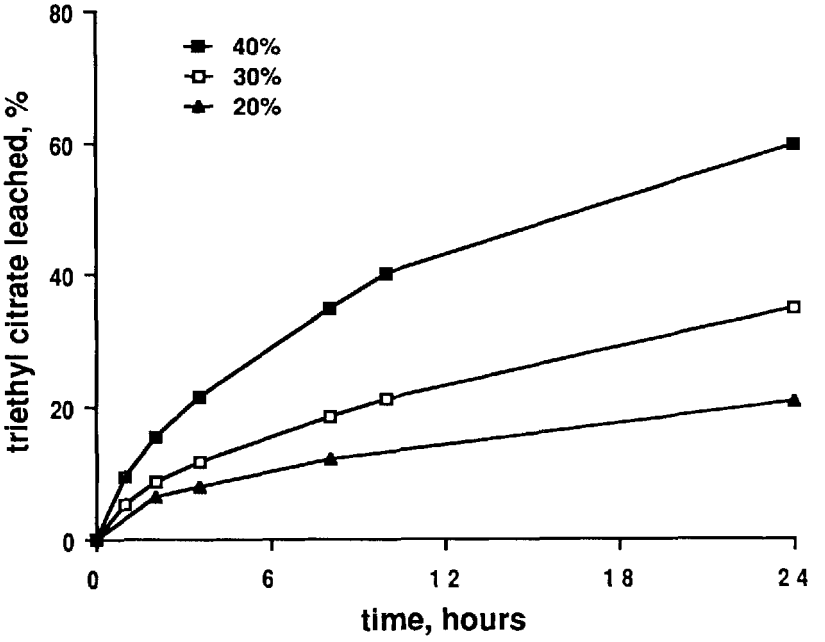

FIGURE 3
Leaching of triethyl citrate from Eudragit RS 100 films containing 20, 30, or 40% w/w plasticizer in simulated intestinal fluid (0.1 M pH 7.4 phosphate buffer).

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