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Report

Determination of Potential Migrants from Commercial Amber Polyethylene Terephthalate Bottle Wall

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Potential migrants were isolated from commercial polyethylene terephthalate (PET) bottles using Soxhlet extraction. The concentrated extract was then subjected to GC/MS analysis. A total of 19 migrants has been identified. The majority of compounds appeared to be intermediate reaction products or residual monomers of their dehydration and transesterification products. Several processing aids such as fatty acids and commonly used plasticizers were also identified. The amount of seven compounds present in the major portion of exhaustive extract of the PET bottle wall ranged from 800 μg/g polymer to as low as 0.6 μg/g.

KEY WORDS: Amber polyethylene terephthalate (PET) bottle; potential migrants; source for phthalates; monomers and intermediate reaction products.

INTRODUCTION

As part of the product development process for new pharmaceutical forms as well as new package forms, the compatibility of the product with packaging material is an important parameter which must be evaluated.

A significant part of this evaluation requires studies on the identification and determination of the degree of migration of components of the packaging material into the drug product and, conversely, the loss of drug or other essential component of the pharmaceutical product into the package.

The use of plastics as a packaging material has grown exponentially in the last few decades. Polyethylene terephthalate (PET) is widely used for blow-molded products because of its ability to be oriented by a drawing process and crystallized to yield high-strength products. Its uses range from a variety of containers for food, beverages, and pharmaceuticals to food trays for microwave and conventional ovens. (1). The increasing application of plastics has focused attention on the migration of molecules from the plastic material.

Migration from packaging materials to drug contents generally does not involve major macromolecular components such as the polymer itself, which is intrinsically odorless, tasteless, and nontoxic, but is concerned with minor constituents which can and do affect the quality of the contained product by sensory or toxicological hazards. The more complex the contents, the more difficult is the quantification of actual migration during the period of time from packaging to consumer use. This period is defined as the shelf life and is finite for practically all products and rarely exceeds 3 years for drugs.

Our recent studies showed that product stability in view of migration can be efficiently assessed by using a prolonged Soxhlet extraction (2). The rationale is that partition or solvency can be defined by an exhaustive extraction with an array of solvents of differing polarity used with relatively large amounts of the contacting package structure. If a migrant is found at this stage at a significant level, the identification and quantitative analysis method can be applied to the actual conditions of use by analysis of a product itself.

This study was performed to determine the migration characteristics from amber colored PET bottles to the simulated contacting phase. Amber-colored containers are widely used, especially for light-sensitive products in the pharmaceutical industry.

MATERIALS AND METHODS

Samples and Materials

Three different types of amber-colored PET bottles of 16-oz size, coded as Nos. 710, 122, and 214, were obtained. Two of them, Nos. 710 and 122, were made by the same bottle manufacturer using clear PET resin and amber color concentrate resin as major starting materials. However, No. 214 was made by a different manufacturer using precolored PET resin. Clear PET resin and color concentrate resin to produce No. 710 were obtained from the bottle manufacturer.

Standards employed were diethyl phthalate (I), dibutyl phthalate (II), bis-(2-ethylhexyl) phthalate (III), diethyl terephthalate (IV), bis-(2-ethylhexyl) phthalate (V), ethylene glycol (VI), terephthalic acid (VII), and pyrogallol (VIII). All were purchased from Fisher Scientific Co., Inc. (Springfield, NJ).

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Determination of Moisture Permeabilities

The official procedure of USP XXI:671 was followed, with the use of 2 ± 0.1 g of polystyrene as an inert filler in the bottom of each container (3).

The average moisture permeability of each type of bottle was obtained and the least significant difference (LSD) between the different types of bottles was used to ascertain whether or not there was a significant difference among them.

Sample Preparation

A total of 22 g of PET bottle wall No. 710 was cut into small pieces and extracted with absolute ethanol for 48 hr using Soxhlet apparatus. The same procedure was followed with an empty thimble and PET bottle wall of No. 214. Fifty grams of color concentrate and clear PET resin was extracted, respectively, in the same way. Although the most popular vehicles for pharmaceutical systems are aqueous or hydroalcoholic, migrants could be completely depleted from polymeric containers to the contacting phase. Absolute ethanol was used to isolate potential migrants for the identification.

The Soxhlet extracts were concentrated by distillation followed by nitrogen flushing, to a final volume of 2 ml. A total of five concentrates was obtained and labeled A for PET bottle wall No. 710, B for No. 214, and C for clear PET resin, D for color concentrate resin, and E for blank.

Instrumental Analyses

One milliliter of A was placed in a 5-ml screw-cap vial and the solvent was evaporated to dryness in a water bath kept at 40°C using nitrogen flushing and redissolved with 1.0 ml of pyridine. One milliliter of bis-(trimethylsilyl) trifluoroacetamide (BSTFA) was added into pyridine extract, then sealed with a Teflon-faced screw cap, and the sample was heated in a water bath at 80°C for 1 hr. Upon completion of heating it was cooled to room temperature and labeled S-A for injection to the GC/MS. Extract S-A was subjected to GC/MS (VG 7070 EQ, VG Instrument, Co.) with 30-m × 0.25-mm fused silica capillary column with bonded phase DB-1, 0.25-μm thickness (J & W Scientific, Inc., Rancho Cordova, CA).

Extract A and extract D were also directly subjected to GC/MS and the instrument used was a GC/MS (Finnigan Mat, Model 8230, Germany) with the same column as above. Helium was used as the carrier gas at a flow rate of 1 ml/min. Injection port temperature was kept at 280°C. Column temperature was programmed from 50°C for 10 min to 280°C at the rate of 10°C/min for extract S-A and from 100°C for 4 min to 280°C at the rate of 10°C/min for extracts A and D. Scan speed was 0.8 sec/decade. Mass spectra of each peak were obtained and compared to published spectra for identification. Extract S-A and extract A were quantitatively analyzed using the SIM (Selected Ion Monitor) mode of GC/MS. The instrument used was a GC/MS (HP 5990A) and the column used was a fused silica megabore column, 15-m × 0.53-mm, with bonded phase DB-1, 1-μm thickness (J & W Scientific, Inc., Rancho Cordova, CA). Helium was used as carrier gas at a flow rate of 5 ml/min. The column temperature program and the injection port temperature were the same as above.

Extracts A, B, C, D, and E were also injected into a gas chromatograph equipped with a flame ionization detector to obtain a chromatographic profile of each sample. The instrument used was HP-5710A (Hewlett Packard, CA) and the column used was a 1.8-m × 3.2-mm stainless-steel column packed with 5% OV-101 on 80/100-mesh Supelcoport (Supelco Inc., Bellefonte, PA). The flow rates of helium, hydrogen, and air were 30, 30, and 240 ml/min, respectively. The temperatures of the injection port and detector were kept at 250 and 350°C. The integrator used was HP3390AC and the sensitivity of 10^{-11} × AFS was used.

Standard solutions were prepared covering the desired range for each of seven potential migrants identified by GC/MS. The calibration curve of each compound was obtained by subjecting each standard solution to SIM mode GC/MS

Table I. Moisture Permeability of Different PET Containers

PET Bottle	Average (mg/liter/day)
No. 710	28 ± 2
No. 214	30 ± 1
No. 122	34 ± 2

Table II. Compounds Identified in the Extract of the PET Bottle Wall

Peak No.[a]	Compound
	Ethylene glycol
	Terephthalic acid
II-6	Diethyl terephthalate
II-13	Bis-(4-ethyl carboxybenzoyl), ethanediyl ester
II-4	Methyl ethyl terephthalate
II-5	Diethyl phthalate
II-8	Dibutyl phthalate
II-7	Butyloctyl phthalate
II-10	Bis-(2-ethylhexyl) adipate
II-11	Bis-(2-ethylhexyl) phthalate
II-12	Diisooctyl phthalate
II-9	Ethyl palmitate
	Palmitic acid
	Stearic acid
	Oleic acid
II-1	*N*-Cyclohexyl acetamide
II-2	Butylatedhydroxy toluene (BHT)
II-3	2,6-Bis-(1,1-methylethyl)-4-ethyl phenol
	Pyrogallol

[a] II-1–II-13 indicate each peak number in Fig. 2.

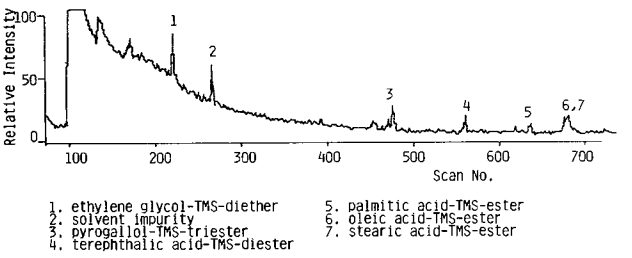

Fig. 1. Reconstructed ion chromatogram of silylated ethanol extract of PET bottle wall of No. 710.

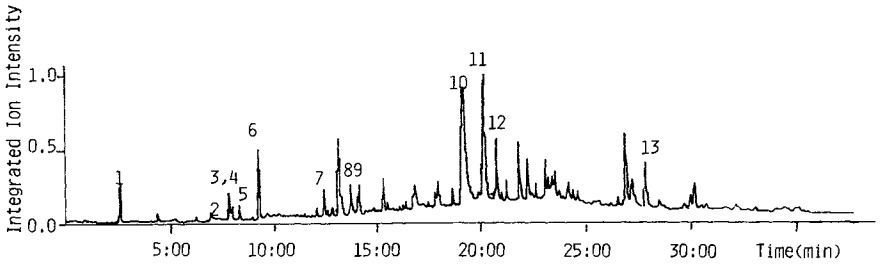

Fig. 2. Reconstructed ion chromatogram of ethanol extract of PET bottle wall of No. 710.

under the same conditions used for the analysis of the sample.

RESULTS AND DISCUSSION

The average moisture permeability of each PET bottle is presented in Table I. According to the USP specification, all PET containers of each code are considered very "tight containers." The average moisture permeabilities of each container type, using the LSD value, were calculated as 2 mg/liter/day at a 99% confidence level, and there was no significant difference between No. 710 and No. 214.

A total of 19 compounds was identified in the amber PET bottle wall of No. 710 (Table II). The reconstructed ion chromatogram of extract S-A obtained by GC/MS is shown in Fig. 1, and that of extract A is shown in Fig. 2. Among the compounds identified, pyrogallol is considered a contaminant of unknown origin. The presence of 2,6-bis-(1,1-methylethyl)-4-ethyl phenol, a breakdown product of the commonly used antioxidant BHT, shows that the antioxidant was degraded, possibly during processing, and may migrate into the food or drugs stored in the packaging material. Since the identified fatty acids and their esters are considered GRAS (Generally Recognized as Safe) by the FDA, quantitative analyses were not performed. Compounds I, II, III, V, VI, VII, and VIII were quantitatively analyzed by using SIM mode GC/MS. The ratio of ions at m/z 147, 73, 103, and 148 of 100:70:20:18 with the retention time of 17.3 min was used for the verification of ethylene glycol-TMS-diester. The results in Table III were calculated assuming 100% extractability by prolonged extraction with absolute alcohol.

The amount obtained by Soxhlet extraction represents the maximum level of migration of direct and/or indirect additives. In the actual contact situation such an amount may never be attained, or it may need excessively long-term storage to reach that level.

Most of the other compounds found were the expected monomers and dehydration and/or transesterification products of the monomers (see also Refs. 4–8).

The source of the phthalate esters was questionable, although the amounts are far below the level of concern for toxicity based on published data (9). Even though phthalates have been widely used as plasticizers, especially in PVC up to 20–30%, their use in PET bottle manufacturing has not previously been reported. The toxicological risks produced by the leaching of plasticizers in PVC containers used for biological fluids is widely recognized and the biological actions of phthalic acid esters have been reviewed in detail

Table III. The Quantitative Data of Eight Potential Migrants

Compound	Amount (μg/g polymer)
Ethylene glycol	14.4
Terephthalic acid	19.7
Bis-(2-ethylhexyl) phthalate	820
Bis-(2-ethylhexyl) adipate	560
Dibutyl phthalate	220
Diethyl phthalate	120
Pyrogallol	0.6

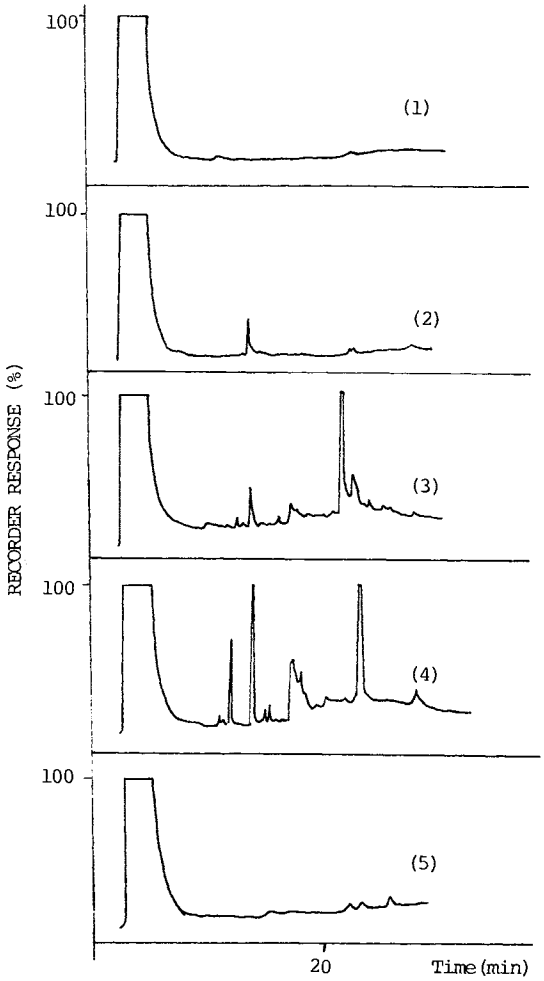

Fig. 3. Gas chromatographic profiles of alcohol extracts: (1) blank, (2) clear PET resin, (3) PET bottle wall of No. 710, (4) color concentrate resin, and (5) PET bottle wall of No. 214.

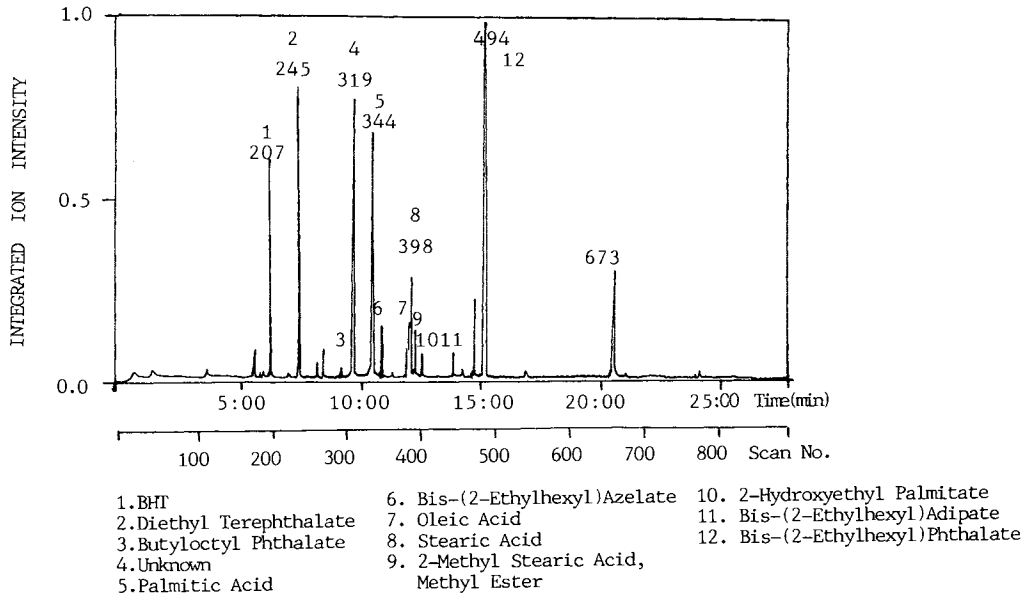

Fig. 4. Reconstructed ion chromatogram of ethanol extract of color concentrate resin.

with particular focus on bis-(2-ethylhexyl) phthalate and its principal metabolites (10). Therefore, the major starting materials for manufacturing amber colored PET bottles were analyzed to investigate the possible source of the phthalates.

The gas chromatographic profiles of extracts A, B, C, D, and E (Fig. 3) show that negligible contamination occurred during the sample preparation procedure. A comparison of the chromatograms supports the conclusion that the source of phthalates was the color concentrate. The extract profiles differed sharply between No. 710 and No. 214, which indicates that the manufacturing procedure may cause significant differences in the content of potential migrants.

Eleven compounds were identified in the extract of a color concentrate (Extract D) by using GC/MS (Fig. 4). Since DOP (V) was a major phthalate in the color concentrate, the other identified phthalates are considered to be formed through transesterification as well as thermal decomposition of V during the processing. DOP is known to be liable to heat-induced reactions (11), and it could have been used as a dispersing agent during the processing of the color concentrate.

Since many pharmaceutical industries as well as food industries, including the liquor industry, use colored bottles and are considering the introduction of plastic bottles, a more careful migration study is required before such bottles are commercialized.

In summary, a total of 19 compounds was identified in the alcohol extract of PET bottle walls. Although the concentrations of potential migrants were below limits under the pertinent FDA regulation, the presence of phthalates was unusual and previously unreported in commercial PET bottles. The source for these compounds was identified as a color concentrate resin. Although extractable profiles of different PET bottles were different from each other, the moisture permeability was similar. In addition, this study shows that BHT and its breakdown products when used in excess, can migrate into the contacting phase. The majority of the other compounds appeared to be intermediate reaction products of terephthalic acid and ethylene glycol or their transesterification products, indicating that many reactions can occur during processing at temperatures as high as 320°C (1).

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