ELSEVIER

International Journal of Pharmaceutics 140 (1996) 169–174

international journal of pharmaceutics

Migration of impurities from a multilayer plastics container into a parenteral infusion fluid

Ch. Sarbach[a,b,*], N. Yagoubi[b], J. Sauzieres[c], Ch. Renaux[d], D. Ferrier[b], E. Postaire[e]

[a]*AR2i, 361 av. du Général de Gaulle, 92140 Clamart, France*
[b]*School of Pharmacy, Department of Analytical chemistry III, 5 rue JB Clément, 92290 Châtenay-Malabry, France*
[c]*International Biopharmaceutical Services, 89 Av. Paul Vaillant-Couturier, 94250 Gentilly, France*
[d]*Bieffe Medital France, 20 quater rue Schnapper, 78100 Saint-Germain-en Layel, France*
[e]*Central Hospitals Pharmacy, Scientific Direction, 7 rue du Fer à Moulin, 75005 Paris, France*

Received 1 August 1995; revised 24 April 1996; accepted 30 April 1996

Abstract

Plastics materials are commonly used in the packaging of pharmaceutical products, especially for the parenteral solutions. Thereby, the study of the compatibility of these containers with different contents is required for drug registration. This paper describes the migration phenomena which occurred between a tri-laminated film and a parenteral solution of metronidazole at 0.5%. The main migration products found in the solution were ϵ-caprolactam and a phthalic derivative. Several non-identified compounds were separated, coming from the polyurethane adhesive. However the aromatic amines were not detected. Thereby, it is important to study the compatibility of these containers with different contents. In addition, we have disclosed traces of butylhydroxytoluene, which constitute a degradation product of Irganox 1010 (phenolic antioxidant).

Keywords: ϵ-Caprolactam; Content-container interactions; Aromatic amines; Planar chromatography; Phthalates; Plastics materials; Polymers; Additives

1. Introduction

Plastics materials are commonly used in the packaging of pharmaceutical products. One application is protecting manufactured products from degradation, but these pharmaceutical packagings should not induce chemical interaction with the contents. However, the inertia of the plastics material is never complete. In fact, the sorption of drugs on the surface of perfusion bags has been described (De Muynck et al., 1990; Legras et al., 1991; Airaudo et al., 1993). However, the transfer occurs not only from the packaged product to the

* Corresponding author.

PII S0378-5173(96)04581-4

Table 1
Calibration range for planar chromatography

Substance	Solution 1	Solution 2	Solution 3	Solution 4
ϵ-Caprolactam	0	0.5 mg	1.0 mg	2.5 mg
4,4′-MDA	0	10 μg	20 μg	50 μg
Irganox 1010	0	5 μg	10 μg	25 μg

plastics container, but also in the opposite direction.

The aim of this work was to study the compatibility between metronidazole aqueous solution at 0.5% and multilayer plastics material constituted by polypropylene on the outside, polyamide 6 in the middle and polyethylene in direct contact with the solution. Thus, several potential migration products were researched in parenteral solutions and among them: ϵ-caprolactam, the monomer of polyamide 6; 4.4′-methylene dianiline (MDA), a potential degradation compound of 4.4′-diphenylmethane diisocyanate (MDI) commonly used in the formulation of polyurethane adhesives and described as mutagenic, cancerogenic and hepatotoxic (INRS, 1987, Fiche toxicologique No. 218) and Irganox 1010 (pentaerythrityle tetrakis [(di-tert-butyl-3,5 hydroxy-4 phenyl)-3 propionate], one phenolic antioxidant used in the manufacture of polypropylene and polyethylene for the multi-laminate material.

The method proceeded by comparison between infusion solutions of metronidazole 0.5% (Bieffe Medital, Italy) packaged in glass bottles (control) and solutions packaged in Clear-Flex™ bags (Bieffe Medital, Italy). In two cases the solution was steam-sterilized (121°C/30 min). The dosages were simultaneously performed by a thin-layer chromatography technique (planar chromatography).

2. Planar chromatography (pc)

2.1. Calibration range

Calibration was carried out in 100 ml glass bottles containing metronidazole 0.5% with ϵ-caprolactam, 4,4′-MDA or Irganox 1010 added (Table 1).

2.2. Samples

The samples were 100 ml of 0.5% metronidazole solution packaged in plastics bags.

2.3. Extraction method

One hundred milliliters of each solution were treated by solid-phase extraction (SEP PAK™ C18 cartridges, WATERS, USA) with 3 ml of chloroform. Then, the samples were evaporated to dryness and dissolved in 50 μl of absolute ethanol.

2.4. Chromatographic conditions

Ten microliters of each extract were applied onto a HPTLC plate (silica gel 10 × 20 cm ref. 5641, Merck-Darmstadt-Germany) using the automatic device AS30 (Desaga-Heidelberg-Germany). The mobile phase was a mixture of acetone/chloroform/concentrated sodium hydroxide (20:80:0.2) (v/v/v) (Prolabo-Paris-France). The development was carried out in a classical tank. The plate was cleaned up by a preliminary development in the mobile phase before application of the samples. The detection was performed with a photodensitometer scanner CD60 (Desaga-Heidelberg-Germany) at the following detection wavelengths: (a) 200 and 234 nm (before derivatization); (b) 388 nm (after derivatization with ninhydrin reagent) and 580 nm (after derivatization with Bratton/Marshall reagent constituted of sodium nitrite and naphthylethylenediamine).

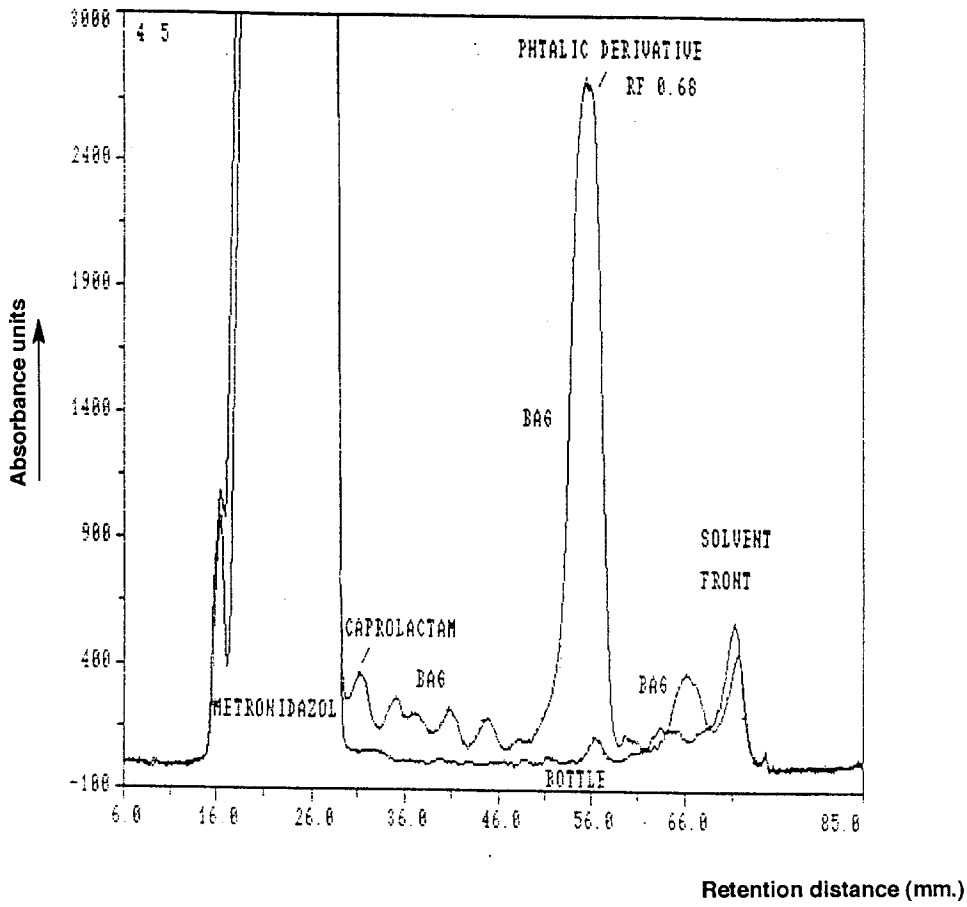

Fig. 1. Superposed chromatograms at 200 nm of extracts from bag and bottle (for chromatographic conditions, see text).

3. HPLC method

3.1. A bag extract was analysed by this method

The liquid chromatograph consisted of a Jasco Pu 880 pump (Prolabo, Paris, France), a Rheodyne injection valve equipped with a 20 μl loop (Touzart et Matignon, Vitry, France). The separations were achieved on a Lichrosorb C18; ODS2; 250 × 4.6 mm ID column packed with 5 μm silica (Prolabo, Paris, France) in isocratic elution mode using acetonitrile/water (70:30). Spectra were collected with a diode array detector (Waters 990) connected to a computer NEC APC4. The detection was performed at 280 nm.

The researched products were identified by PC with their R_f and UV spectra compared to references.

The chromatograms (Fig. 1) of the metronidazole solution stored in multilayer bags, submitted to extraction and analyzed by planar chromatography reveal several peaks. The metronidazole was eluted at $R_f \approx 0.15$ and 4,4′-MDA at $R_f \approx 0.37$. Its identification was confirmed by derivatization with the reagents described above (Jork et al., 1990). The presence of ϵ-caprolactam was also identified as a migration product ($R_f \approx 0.23$). This compound is a starting material for the synthesis of Nylon polymer. The residual amount can be partially eliminated by washing of plastics material. Leaching of ϵ-caprolactam from the plastics bags was not commonly mentioned in the literature because the use of polyamide 6 is not frequent in the manufacture of containers. Nevertheless, the migration of ϵ-caprolactam into

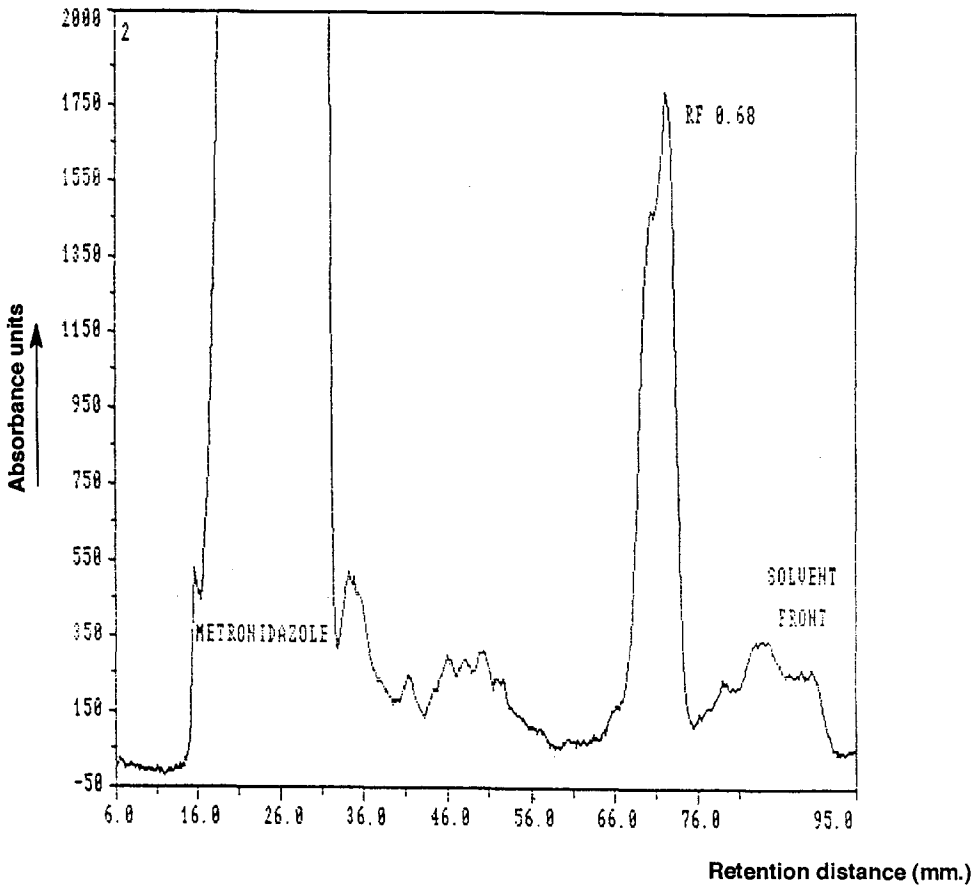

Fig. 2. Chromatogram at 200 nm of bottle + polyurethane glue (for chromatographic conditions, see text).

aqueous solutions has already been described (Ulsaker and Teien, 1992); this compound migrated from the overwrap, through the PVC of the bag. The amounts measured (HPLC technique) in 100 ml PVC bags were about 8–15 ppm. Moreover, ϵ-caprolactam levels of 40 ppm were measured after 2 years of storage in 100 ml PVC bags, overwrapped with a laminate of polyamid 6 and polyethylene (Arbin, 1986). The ϵ-caprolactam migrated through the polyethylene and PVC layers into the sodium chloride solution.

In addition to these compounds, several non-identified peaks have been detected at 200 nm including one main peak at $R_f \approx 0.68$ (Fig. 1). Their origin was determined by use of four different 100 ml glass bottles of metronidazole at 0.5%, each including a constituent of Clear-Flex™ film: polypropylene (1240 cm^2 of film, about 3.2 g), polyamide 6 (1240 cm^2 of film, about 2.0 g), polyethylene (1240 cm^2 of film, about 11.4 g) or polyurethane cement (about 1.9 g).

Each bottle was placed in an oven at 130°C for 1 h 30 min. Then, the same extraction and chromatographic process as for bags was carried out.

The results obtained prove that the ϵ-caprolactam came from Nylon 6. The analysis of the solution containing polyurethane showed principally the peak eluted at $R_f \approx 0.68$ (Fig. 2). This peak was studied by FTIR spectrometry and mass spectrometry. The IR spectrum showed an absorption band at 1716 cm^{-1}, which indicated the presence of an ester group. The mass spectrum showed the typical profile of a phthalate structure (compared to di-hexyl phthalate). The presence of

this derivative can be explained by the possible use of phthalic acid in the synthesis of the adhesive.

Consequently, a quantitative evaluation of the phthalic derivative was performed by PC compared to a calibration range of DEHP which is known as the most widely used plasticizer. The calibration range was realized in glass bottles of 0.5% metronidazole and extracted under the same conditions. The detection wavelength was 228 nm, which is the maximum for DEHP and corresponds to a high relative absorption zone for the phthalic derivative.

The results related to the levels of phthalate, expressed in DEHP, were for the three batches of bags of metronidazole 0.5%: 128, 149 and 142 μg/100 ml (respectively 1.3, 1.5 and 1.4 ppm).

By comparison, a dosage of DEHP in PVC bags containing aqueous solutions was performed by PC.

The product was 100 ml Viaflex™ bags filled with sodium chloride 0.9% and steam-sterilized (Baxter, USA). Two conditions of storage were chosen: normal conservation (three samples) and rotational agitation (15 min at 50 rev./min) in order to simulate the action of a nurse for example (three samples).

The samples were analysed by the same method with a calibration range of DEHP in a solution of sodium chloride 0.9% (in 20 ml glass flasks) and steam-sterilized: 0, 0.5, 2.5 and 5.0 ppm.

The results showed a detection limit (DL) at 0.30 ppm. In normal conditions, DEHP levels were 0.77, 0.70 and 0.53 ppm, respectively, and after agitation, 0.54, 0.50 and < 0.30 ppm.

These results were reliable with those previously obtained by HPLC technique from 0.9% sodium chloride solutions packaged in PVC bags (Dumortier et al., 1990; Aignasse et al., 1995).

The levels were much lower than those released from PVC bags containing lipophilic solutions (Pearson and Trissel, 1993). A typical case is the influence of surfactants like Tween 80 (Moorhatch and Chiou, 1974) or polyoxyethylated castor oil (Cremophor EL) in formulations, which present an important DEHP extraction power. Indeed, several recent studies performed on Taxol™, teniposide or cyclosporine formulations used in perfusion PVC bags showed leaching of large amounts of DEHP: about 800 ppm in 100 ml Taxol™ solution (Waugh et al., 1991), about 200

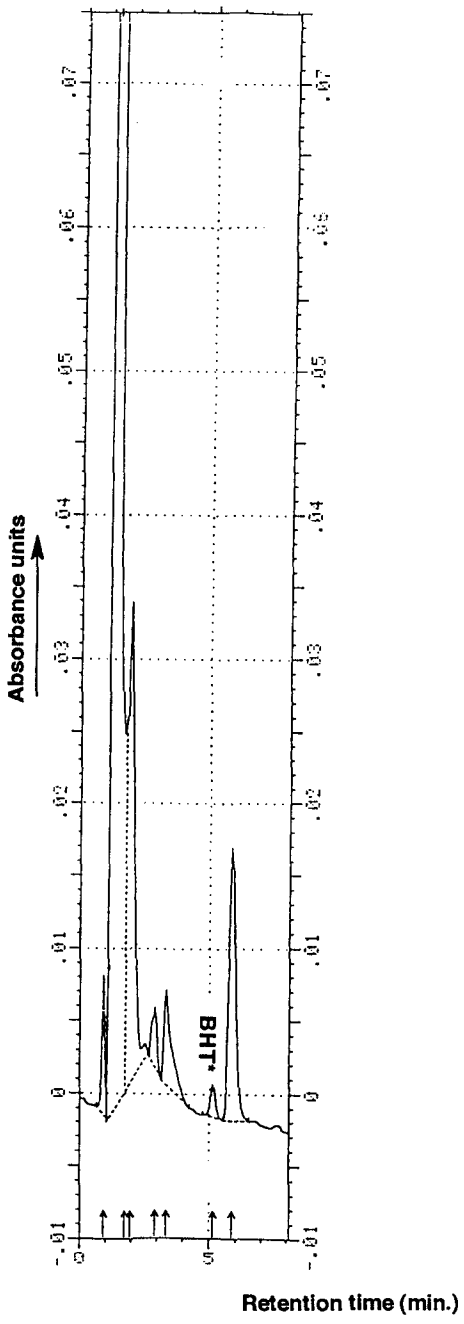

Fig. 3. HPLC chromatogram of an extract from bag (for chromatographic conditions, see text).

ppm into 250 ml teniposide solution after 48 h at room temperature (Faouzi et al., 1994) and about 450 ppm into 50 ml cyclosporine solution after 48 h at room temperature (Venkataramanan et al., 1986). Furthermore, the concentration of DEHP in human blood packaged in PVC bags can reach 50–100 ppm (De Gerlache and Solvay, 1991).

The absence of migration of Irganox 1010 from the polyethylene material into solution of metronidazole should be explained by its low volatility and solubility in aqueous solution and its high molecular weight. However, the HPLC analysis of the solution led to a chromatogram showing several peaks, among them butylhydroxytoluene (BHT) which was identified according to its retention time (Fig. 3). The polycyclic phenolic antioxidant (Irganox 1010) is constituted by at least one entity of BHT, which is released by scission after sterilisation. As BHT exhibits a relatively high polarity and low molecular weight, its migration is very easy. A recent study also showed the production of BHT after radio-sterilisation of polyethylene vinyl acetate containing Irganox 1010 (Yagoubi et al., 1996).

Planar chromatography (PC) allied to multimodal detection is of interest in the analysis of traces of impurities. Content/container interactions studies of pharmaceutical products were usually performed by HPLC methods and this work illustrates the performance of PC in this field.

Further quantitative evaluations will be performed on other products packaged in ClearFlex™ bags and qualitative studies will be carried out to determine the structure of non-identified peaks detected by PC.

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