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Compatibility of plastics with cytotoxic drug solutions—comparison of polyethylene with other container materials

C. Beitz [a,*], T. Bertsch [b], D. Hannak [b], W. Schrammel [c], C. Einberger [a], M. Wehling [d]

[a] *Hospital Pharmacy, Klinikum Mannheim gGmbH, Fakultät für Klinische Medizin Mannheim der Universität Heidelberg, Theodor-Kutzer-Ufer 1–3, 68135 Mannheim, Germany*

[b] *Institute of Clinical Chemistry, Klinikum Mannheim gGmbH, Fakultät für Klinische Medizin Mannheim der Universität Heidelberg, Theodor-Kutzer-Ufer 1–3, 68135 Mannheim, Germany*

[c] *B. Braun Melsungen AG, Germany*

[d] *Institute of Clinical Pharmacology, Klinikum Mannheim gGmbH, Fakultät für Klinische Medizin Mannheim der Universität Heidelberg, Theodor-Kutzer-Ufer 1–3, 68135 Mannheim, Germany*

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Abstract

In this study low density polyethylene (LDPE)-containers were compared to glass bottles and polyvinyl chloride (PVC) bags in view of adsorption effects with antineoplastic drugs. The infusion containers were supplemented with therapeutic doses of the nine common cytotoxic drugs carboplatin, carmustine, cytarabine, dacarbazine, fluorouracil, gemcitabine, melphalan, methotrexate and vinorelbine. 0.9% isotonic sodium chloride solution and 5% dextrose served as infusion solutions. The containers were stored at room temperature or at 4°C, protected from light, for periods of up to 168 h. Turbidity, change of colour and visible crystallization were not observed. Samples were collected at different time intervals and drug contents were determined with high-performance liquid chromatography (HPLC). Preparations of carmustine showed no adsorption phenomena when stored in LDPE or in glass at 4°C. At room temperature in LDPE, a slight decrease in concentration due to adsorption was monitored. However the drug loss in PVC bags was greater. Dacarbazine and melphalan showed decreases in concentration, which were independent on the type of container material. The remaining analyzed agents showed no drug loss at all. In conclusion, investigated drugs were stable in all three container types, with the best stability in glass bottles, followed by LDPE and PVC.

Keywords: Stability; Adsorption; Polyethylene; Polyvinylchloride; Container; Cytotoxic drugs; HPLC

1. Introduction

Antineoplastic agents are used for treatment of patients with cancer. To optimize cancer chemotherapy, a considerable amount of research

* Corresponding author.

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has been spent on studying pharmaceutic properties of antineoplastic agents in various infusion solution containers. Some authors have already reported e.g. on degradation reactions which depend on pH, temperature or light (Chatterji and Gallelli, 1978; Flora et al., 1979; Allsopp et al., 1991; Shetty et al., 1992; Anliker et al., 1994). Others found adsorption phenomena of certain drugs in containers consisting of polyvinyl chloride (PVC) (Kowaluk et al., 1981; Illum and Bundgaard, 1982; Fredriksson and Lundgren, 1986). The resulting drug loss may have a harmful effect on the therapy and is therefore clinically important. In contrast to PVC and glass (Benvenuto et al., 1981; Vincke et al. 1989; Dine et al., 1991a,b; Benaji et al., 1994; Pinguet et al., 1994), there is limited data concerning the compatibility of cytotoxic drug solutions with polyethylene containers. Previous studies have demonstrated, that drugs considered here, are not adsorbed to glass surfaces. Hence a comparative stability study was made of cytotoxic drug solutions in low density polyethylene (LDPE) containers and in glass bottles. Additionally PVC bags were included in the investigations, to compare the adsorption properties of PVC with LDPE.

2. Material and methods

2.1. Apparatus

All assays were performed by high-performance liquid chromatography (HPLC) at ambient temperature. The HPLC-equipment (Milton Roy®) consisted of a solvent pump (constametric®III), a variable-wavelength UV-vis detector (spectroMonitor® 3100 UV Detector). Peak retention times and areas were monitored using a computing integrator (CI 4000 integrator). Injections were made with an autosampler (Waters 712 WISP), equipped with amber HPLC vials (first class, 1 ml, 11.6 × 32 mm).

2.2. Material

LDPE containers (Ecoflac®) and glass bottles were obtained from B. Braun Melsungen AG, (Melsungen, Germany). The PVC bags (Viaflex®) were purchased from Baxter (Unterschleißheim, Germany). In all cases the contents were 250 ml infusion fluid, except containers used for carmustine preparations with a nominal vol. of 500 ml. Table 1 gives details about the cytotoxic admixtures and the storage conditions.

Methanol (Merck®) and acetonitrile (Fisher Scientific UK) were of HPLC-grade. All other chemicals and buffer substances were of reagent grade. The buffer solutions were prepared with twice distilled water.

2.3. Preparation

All preparations were produced under aseptic conditions in a vertical laminar-airflow safety cabinet class II. Each mixture was prepared in duplicate. The drug contents were adjusted to the concentrations which are used in therapeutic regimes. Because of possible conversion to cisplatin (Cheung et al., 1987), 5% dextrose solution was favoured for preparations of carboplatin. According to valid guidelines (Krämer 1996) we also preferred 5% dextrose for carmustine admixtures. The remaining agents were prepared in 0.9% saline or in 5% dextrose (Table 1).

2.4. Storage

All preparations were stored light protected at ambient temperature or refrigerated. The PVC bags were kept in a prone position, the glass and LDPE containers in an upright position in order to avoid possible interaction with the rubber stoppers. Concerning the length of storage, we oriented towards the manufacturers specifications, but extended the storage times in relation to the expected decrease in concentrations (Table 1).

2.5. Sampling

Immediately after preparation and then for at least a further five times, aliquotes of 1 ml were removed and transferred into HPLC vials. The solutions were mixed by rapid shaking beforehand. At the same time a visual examination was made for discolouration, turbidity or precipita-

Table 1
Periods and conditions of storage

Drug	Commercial preparation	Manufacturer	Cytotoxic admixture	
			Storage period (h)	Final concentration[e] (mg/ml)
Carmustine	Carmubris®	Bristol	72 [b,c,d]	0.200
Carboplatin	Ribocarbo®-L	Ribosepharm	72 [a,b,c,d]	0.720
Cytarabine	Alexan®	Mack	72 [a,b,c,d]	0.144
Dacarbazine	Detimedac®	Medac	48 [a,c,d]	0.640
Fluorouracil	5-FU®	Medac	72 [a,b,c,d]	1.440
Gemcitabine	Gemzar®	Lilly	48 [a,c]	5.120
Melphalan	Alkeran®	Glaxo Wellcome	24 [a,d]/8 [a,c]	0.060
Methotrexate	Methotrexat	Medac	72 [a,b,c,d]	0.360
Vinorelbine	Navelbine®	Pierre-Fabre	168[a,c]	0.385

[a] Used influsion solution: 0.9% isotonic sodium chloride;
[b] dextrose 5%; used storage conditions:
[c] room temperature,
[d] 4°C,
[e] based on calculation of the theoretical final drug contents in the containers.

tion. Gemcitabine samples had to be diluted 10-fold with 0.9% isotonic sodium chloride solution and were stored at −20°C before HPLC assaying. All the other samples were kept until analysis without any further preparations (carmustine, melphalan and vinorelbine at −20°C, the remaining samples at 4°C). Preliminary experiments confirmed that there were no cases of apparent drug loss during the storage time under these conditions.

2.6. Analysis of drugs

2.6.1. Validation

All analyses were carried out with external standard methods and an isocratic technique (Table 2). Assuming, that the contents were within the declared range, the pharmaceutical preparations (Table 1) were used as standard stock solutions. The diluents were primarily isotonic 0.9% sodium chloride, or 5% dextrose solution, depending on the analytes maximal stability (Krämer, 1996). The linearity and the intra-assay precision of the HPLC methods were checked in a range between the calculated initial concentrations and 10% there of. Each calibration standard was determined 8-fold. To ensure the intermediate precision of the HPLC procedures, control solutions of each drug, with contents in the range of the initial concentrations, were assayed in duplicate after every four samples.

2.6.2. Measurement and evaluation

The refrigerated or frozen solutions were brought to room temperature and were immediately determined in duplicate by HPLC. (In the end each drug concentration was determined from the average of four chromatographic measurements). Sample analyses were performed after all the aliquots had been removed to minimize the inter-day assay variations. The initial concentrations were stated as 100%. All subsequent concentrations were expressed as percentages, whereas 95–105% of the initial concentration was defined as physico–chemically stable.

3. Results

Drug peaks were well separated from the solvent front or decomposition product peaks in all cases. A good linearity between peak area ratios and concentrations was observed. The ten point calibration curves fitted by the least-squares method gave correlation coefficients all above 0.999. In all cases the total coefficients of varia-

Table 2
HPLC conditions for the analysis of antitumor agents

Drug	Stationary[a,b] and mobile phases[c]		Flow rate (ml/min)	Retentiontime (min)	Injection vol. (μl)	Wave-length (nm)	AUFS
Carboplatin	[a]	Water	2.0	1.45	10	210	0.1
Carmustine	[a]	0.1 M NaH_2PO_4 (pH 3)/CH_3CN 60:40 (v/v)	2.0	1.16	20	237	0.2
Cytarabine	[a]	0.05 M $NH_4H_2PO_4$/CH_3CN 96:4 (v/v)	1.5	1.18	10	280	0.5
Dacarbazine	[b]	0.1 M KH_2PO_4[d] pH 7/CH_3CN (90:10 v/v)	2.0	1.84	10	250	1.0
Fluorouracil	[a]	Water/methanol (95:5 v/v)	1.5	1.41	5	260	0.1
Gemcitabine	[b]	13.8 g/l $NaH_2PO_4H_2O$ pH 2.5/CH_3OH (97:3 v/v)	2.0	1.56	5	278	0.05
Melphalan	[b]	714.3 ml 0.01 M NaH_2PO_4 pH 3/285.7 ml CH_3CN	2.0	2.08	20	254	0.1
Methotrexate	[a]	6.66 g/l KH_2PO_4 pH 2.3/ CH_3CN (80:20 v/v)	1.5	1.24	10	301	0.1
Vinorelbine	[a]	13.8 g/l $NaH_2PO_4H_2O$ pH 3/CH_3CN (60:40 v/v)	1.5	1.11	10	220	0.2

[a] Merck Lichrospher RP 18; 5 μm; 125 × 4 mm and pre-column;
[b] Merck Lichrospher RP 8; 5 μm; 125 × 4 mm and pre-column;
[c] solvents were purified on 0.45 μm filters and degassed prior to use;
[d] mixed with 0.04 M triethylamine.

Table 3
Results of validation

Drug	Range (μg/ml)	Coefficients of variation			Correlation
		Total (%)	Inter-day (*n*)	Intra-day[a] (%)	Coefficient[b]
Carboplatin	80–800	0.30	1.31% (4)	1.12	0.9999
Carmustine	30–300	0.34	1.36% (4)	1.10	0.9998
Cytarabine	15–150	0.67	0.45% (6)	1.42	0.9997
Dacarbazine	80–800	1.03	0.71% (4)	1.32	0.9998
Fluorouracil	150–1500	1.43	2.00% (6)	2.67	0.9992
Gemcitabine	60–600	1.12	1.98% (4)	1.88	1.0000
Melphalan	7.5–67.5	0.71	1.58% (5)	0.90	1.0000
Methotrexate	40–400	0.46	0.32% (3)	1.19	0.9996
Vinorelbine	50–500	0.28	1.22% (3)	1.29	0.9993

[a] Calculated from at least eight controls.
[b] Calculated from a linear plot of peak area ratios versus concentrations in the signed ranges.

tion CV_t (Logan et al., 1984) were below 1.5%. The intra-day and inter-day variations for fluorouracil were 2.67% ($n = 16$) and 2.00% ($n = 6$), respectively. All the other drugs gave values below 2.00%. Table 3 summarises the data validating the calibration procedure for each drug.

As expected, the carmustine concentration decreased in dependence on the storage temperature and the type of container material. At room temperature a decrease of 5% occured in PVC containers after 45 min. In LDPE containers the same decrease was demonstrated after 2.5 h and in glass after 5.5 h (Fig. 1). At 4°C the threshold value 95% was reached in PVC after 3 h, in LDPE and glass after 48 h (Fig. 2).

Dacarbazine and melphalan showed decreases in concentration which were independent on the type of container material. Unseparated peak-group area ratios increased simultaneously with drug losses of dacarbazine and melphalan. After 48 h at room temperature, the concentration of dacarbazine decreased by about 5% (Table 4). At 4°C no apparent drug loss was noticed, but a very small increase of degradation products in the range of the detection limit was registrated. The loss of melphalan was about 5% after 1.5 h ambient storage and 24 h at 4°C (Table 5).

The concentrations of carboplatin, cytarabine, fluorouracil, gemcitabine, methotrexate and vinorelbine remained stable over the storage period with a variation of 3% in the range of the initial concentration. In these cases as well as carmustine no degradation peaks appeared. No turbidity, visible changes in colour or precipitation were noted in any of the preparations.

4. Discussion

The HPLC procedures described in this paper are rapid and reproducible. The performance characteristics of the assays (all coefficients of variation below 2.7%) indicate precise measurements and stable HPLC conditions (Table 3). The results of our investigation represent a comprehensive overview of the compatibility of LDPE and PVC containers with different anticancer drugs. Due to the fact that the sorption capacity of the containers inside surfaces is limited (Krämer, 1996), we adjusted in each case a lower, but still therapeutical drug concentration in order to increase the sensitivity for possible adsorption phenomena. In principle none of these cytotoxic drugs are susceptible to adsorption on glass as described in the literature (Benvenuto et al., 1981; Bosanquet, 1985; Cheung et al., 1987; Vincke et al., 1989) and by a personal communication with Pierre Fabre, Germany, regarding the vinca alcaloid vinorelbine. In general, a decreased concentration in plastic containers compared to glass bottles, is attributed to adsorption effects. Therefore glass bottles were used as a reference to

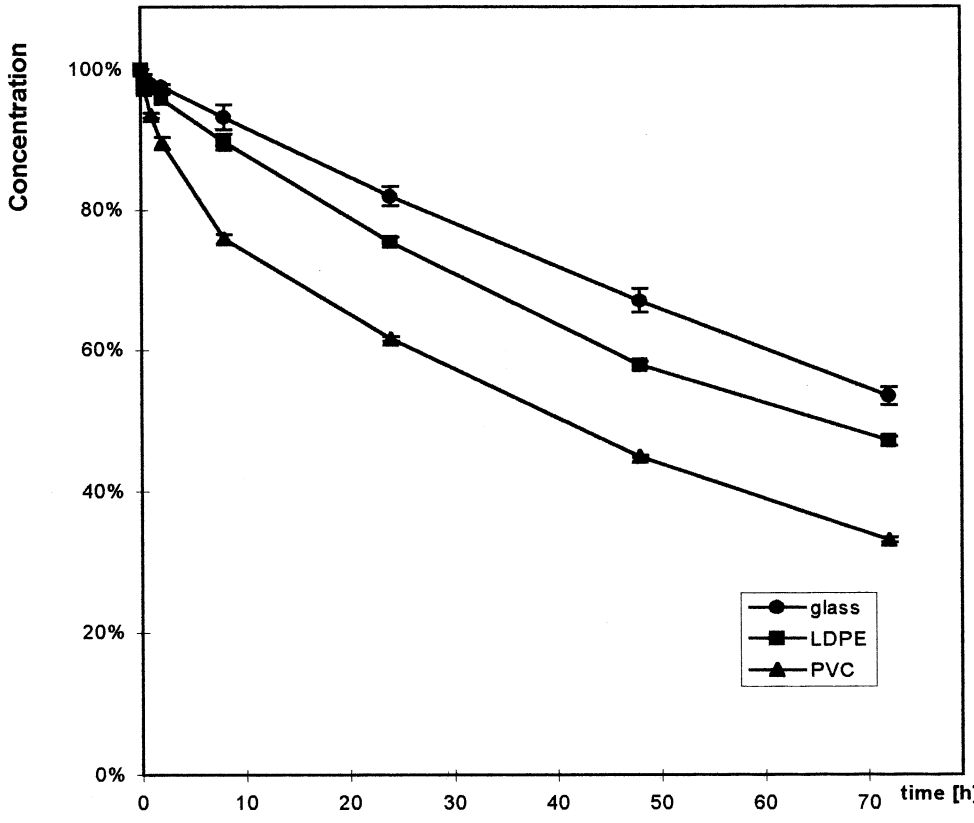

Fig. 1. Loss of carmustine in plastic and glass containers at room temperature. Mean value ± SD, $n = 4$.

distinguish adsorption from degradation. This procedure is especially applicable for the cytotoxic agents dacarbazine (main degradation product 2-azahypoxanthine) (Shetty et al., 1992), melphalan (degradation products monohydroxymelphalan and dihydroxymelphalan) (Flora et al., 1979) and carmustine (degradation products N_2, CO_2, acetaldehyde, and 2-chorethylamin) (Fredriksson and Lundgren, 1986). On the basis of the nitrosourea derivative carmustine it was shown, that very lipophile drugs were adsorbed in LDPE to a relatively small extent at room temperature and to a relatively higher extent in PVC. (Fig. 1). In refrigerated conditions the relatively low drug losses due to degradation in LDPE and glass are similar, whereas the drug decrease in PVC due to an additional adsorption effect is comparatively higher (Fig. 2). From a physico-chemical point of view, the results of our study lead to the following conclusions: Carmustine preparations should be stored in glass or LDPE containers at 4°C not longer than 48 h; at room temperature in glass bottles not longer than 5.5 h and in LDPE containers not longer than 2.5 h. The use of PVC bags should be avoided. The other drugs investigated can be prepared and stored in LDPE, glass or in PVC containers without any compatibility problems. Gemcitabine can be kept at least 2 days, carboplatin, cytarabine, fluorouracil, methotrexate at least 3 days and vinorelbine at least 7 days. The physico-chemical stability of melphalan is ensured for at most 24 h at 4°C and 1.5 h at room temperature. Particularly for preparations of melphalan and carmustine it is essential not to fall below stated threshold values of concentration. For dacarbazine on the other hand avoidance of toxicant degradation products is up-

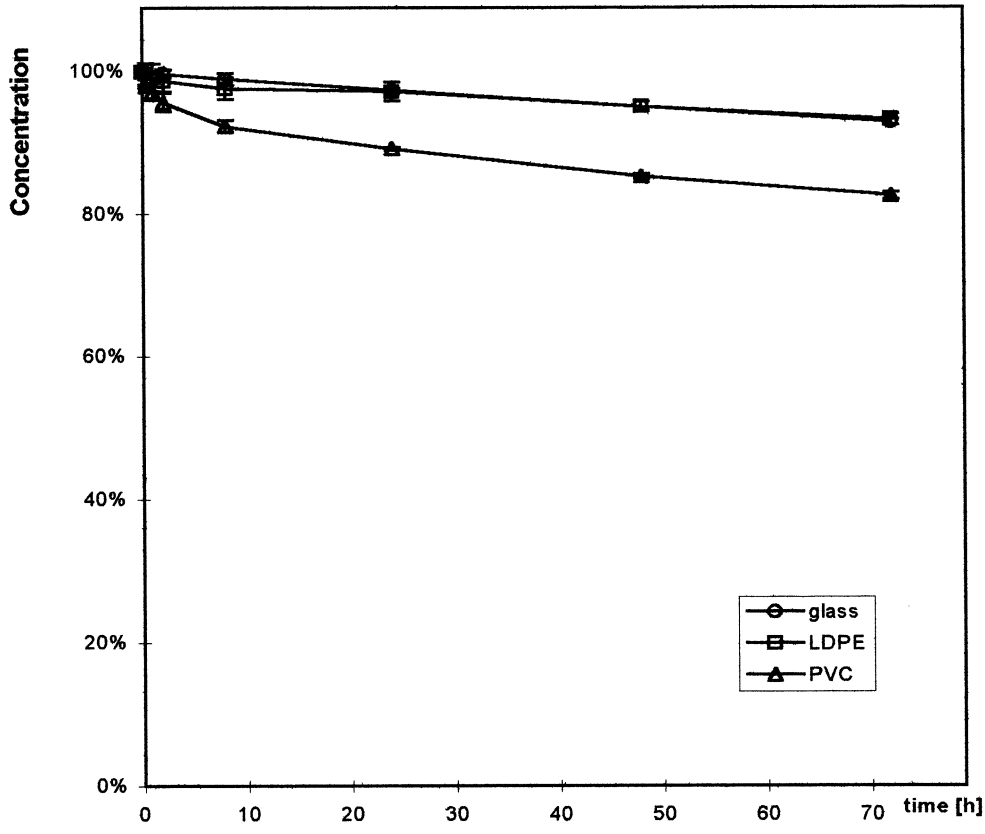

Fig. 2. Loss of carmustine in plastic and glass containers at 4°C. Mean value ± SD, $n = 4$.

Table 4
Stability of Dacarbazine

Time of storage (h)	% Initial concentration ± SD ($n = 4$)					
	Room temperature (23 ± 1°C)			Refrigerated (4°C)		
	Glass	LDPE	PVC	Glass	LDPE	PVC
0	100.0	100.0	100.0	100.0	100.0	100.0
2	100.2 ± 0.53	100.8 ± 0.13	99.5 ± 0.20	99.8 ± 0.64	99.5 ± 1.47	99.0 ± 0.56
4	99.8 ± 0.52	98.8 ± 1.72	99.6 ± 0.23	99.0 ± 0.28	100.3 ± 0.80	99.3 ± 0.57
8	99.3 ± 0.55	99.6 ± 0.32	99.1 ± 0.49	99.4 ± 1.11	99.6 ± 0.12	98.7 ± 1.37
24	98.1 ± 0.44	96.2 ± 1.77	97.3 ± 0.45	100.6 ± 0.55	99.6 ± 0.22	99.5 ± 0.19
48	95.3 ± 0.47	95.6 ± 0.11	95.0 ± 0.09	100.3 ± 0.16	99.5 ± 0.26	99.4 ± 0.25

permost. From this point of view dacarbazine admixtures should be kept no longer than 8 h at room temperature and 24 h refrigerated.

In summary LDPE is suitable for the storage of the here investigated cytotoxic drugs and shows properties comparable to glass and PVC. Container-specific limitations in terms of stability were found for preparations of carmustine at room temperature when stored in PE, and in a larger extent in PVC.

Table 5
Stability of Melphalan

Time of storage (h)	% Initial concentration ± SD ($n = 4$)					
	Room temperature (23 ± 1°C)			Refrigerated (4°C)		
	Glass	LDPE	PVC	Glass	LDPE	PVC
0	100.0	100.0	100.0	100.0	100.0	100.0
1	96.2 ± 0.23	96.7 ± 0.46	96.0 ± 0.3	-----	-----	-----
2	92.1 ± 0.84	92.6 ± 0.86	91.9 ± 0.7	99.3 ± 0.63	99.0 ± 1.21	99.3 ± 0.2
3	88.5 ± 0.81	88.7 ± 0.27	88.3 ± 0.7	-----	-----	-----
4	-----[a]	-----	-----	98.6 ± 0.42	98.4 ± 0.27	98.9 ± 0.3
5	80.7 ± 1.13	81.4 ± 0.74	80.9 ± 0.7	-----	-----	-----
8	70.3 ± 1.62	71.6 ± 0.18	71.3 ± 0.9	97.8 ± 0.26	97.3 ± 0.80	98.2 ± 0.4
12	-----	-----	-----	96.1 ± 0.45	97.3 ± 1.28	97.3 ± 1.0
24	-----	-----	-----	94.8 ± 0.37	95.2 ± 1.13	96.1 ± 0.4

[a] -----, not performed.

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