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Stability, compatibility and plasticizer extraction of miconazole injection added to infusion solutions and stored in PVC containers

Moulay El Abbes Faouzi [a], Thierry Dine [a,*], Michel Luyckx [a], Claude Brunet [a], Marie-Laurence Mallevais [b], Francis Goudaliez [b], Bernard Gressier [a], Micheline Cazin [a], Jerome Kablan [a], Jean Claude Cazin [a]

[a] *Laboratoire de Pharmacologie, Pharmacocinétique et Pharmacie Clinique, Faculté des Sciences Pharmaceutiques et Biologiques, rue du Professeur Laguesse, B.P. 83, 59006 Lille Cedex, France*

[b] *Laboratories MACOPHARMA, rue du Pont-Rompu, B.P. 464, 59338 Tourcoing Cedex, France*

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Abstract

The stability of miconazole in various diluents and polyvinyl chloride (PVC) containers was determined and the release of diethylhexyl phthalate (DEHP) from PVC bags into intravenous infusions of miconazole was measured. An injection formulation (80 ml) containing a 1% solution of miconazole with 11.5% of Cremophor EL was added to 250-ml PVC infusion bags containing 5% glucose injection or 0.9% sodium chloride injection, to give an initial nominal miconazole concentration of 2.42 mg ml^{-1}, the mean concentration commonly used in clinical practice. Samples were assayed by stability-indicating high-performance liquid chromatography (HPLC) and the clarity was determined visually. Experiments were conducted to determine whether the stability and compatibility of miconazole would be compromised, and whether DEHP would be leached from PVC bags and PVC administration sets during storage and simulated infusion.

There was no substantial loss of miconazole over 2 h simulated infusion irrespective of the diluent, and over 24 h storage irrespective of temperature (2–6°C and 22–26°C). All the solutions initially appeared slightly hazy. Leaching of DEHP was also detected during simulated delivery using PVC bags and PVC administration sets. There was a substantial difference between the amounts of DEHP released from PVC bags and from administration sets, and also between the amounts released in solutions stored in PVC bags at 2–6°C and 22–26°C over 24 h.

At the dilution studied, miconazole was visually and chemically stable for up to 24 h. The storage of miconazole solutions in PVC bags seems to be limited by the leaching of DEHP rather than by degradation. To minimize patient exposure to DEHP, miconazole solutions should be infused immediately after their preparation in PVC bags.

Keywords: Miconazole; DEHP; Stability; Compatibility; PVC infusion bags; Administration sets; Infusion solutions

1. Introduction

Miconazole is a synthetic imidazole derivative with broad-spectrum antifungal activity [1–3]. It is relatively non-toxic and has been used in the treatment of various systemic mycoses, including candidiasis, coccidiodomycosis, cryptococcocis and hystoplasmosis. To obtain a maximum antifungal activity, miconazole must be given by infusion and not by

* Corresponding author.

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bolus injection; however, manufacturers recommend that the injection be diluted to at least 200 ml before administration, and that it must be infused over at least 30 min [4]. For infusion, this formulation is diluted with either 0.9% sodium chloride injection or 5% dextrose injection.

For intravenous infusion of drugs, the containers may be of glass and plastic. Polyvinyl chloride (PVC) bags of infusion solutions offer several advantages over conventional glass containers, such as easier storage and shipping because of their relative resistance to breakage. However, several problems are reported with their use such as the loss of substantial amounts of drug from the solution by adsorption onto the plastic bags [5–7] and the leaching of potentially harmful substances into the solution [8–10], particularly a plasticizer, diethylhexyl phthalate (DEPH), that is incorporated into PVC to make the bags soft and pliable.

Because of the poor solubility of the drug in water, the current clinical formulation consists of a 1% solution of miconazole. The commercially available intravenous dosage form of miconazole contains 11.5% w/v of a non-ionic surfactant, polyoxyethylated castor oil (Cremophor EL). Because DEHP is fat soluble, intravenous fat emulsions containing Cremophor EL can extract a substantial amount of the plasticizer from PVC bags and tubing [11,12].

Pearson and Trissel [1] have recently evaluated the extent of leaching of DEHP into miconazole infusion solutions stored in PVC bags. However, those workers described only the release of DEHP into intravenous miconazole solutions, after 24 h storage and at ambient temperature.

To the present authors' knowledge, no adsorption study of miconazole on to PVC bags and intravenous administration sets during simulated infusion and no study in 0.9% sodium chloride injection and at 4°C have been reported. In addition, under these conditions, no data are available on the extent of leaching of DEHP into miconazole solutions infused or stored in PVC bags.

Like Venkataramanan et al. [9] who examined cyclosporin injection, Pearson and Trissel [12] reported that the agent responsible for the leaching of DEHP into solutions was probably the non-ionic surfactant Cremophor EL. DEHP appears to have a low order of acute toxicity when given either by injection or orally [13]. However, toxicity studies in animals have demonstrated an association between prolonged exposure to DEHP and changes in hepatocellular structure and liver function [14,15]. In addition, DEHP can induce in animals the development of hepatocellular carcinoma [16,17], and has been found to be teratogenic in rats [18,19].

The objectives of the present study were to observe the stability and the physical appearance of the miconazole formulation diluted to a concentration that may be used clinically in 0.9% sodium chloride injection and 5% dextrose injection for 2 h simulated infusion in the laboratory, and during storage in PVC bags, in order to determine if the stability of miconazole is compromised during infusion and storage. Intravenous PVC administration sets are also used to deliver drug solutions and so may potentially contribute to the loss of miconazole and to the leaching of substantial quantities of DEHP into infusion solution. Thus, it is also important to investigate the compatibility of the drug with PVC bags and with giving sets. Finally, the extent of DEHP leaching was also determined during simulated infusion and storage because of the known leaching of the plasticizer from PVC bags by surfactants such as Cremophor EL. The objective was to evaluate the real and potential risks of the exposure of patients to DEHP during an infusion using PVC bags and administration sets.

For these studies, a stability-indicating high-performance liquid chromatographic (HPLC) method of determining miconazole was developed; a HPLC method was also developed to determine DEHP.

2. Experimental

2.1. Chemicals and materials

The drug substance studied was a commercial product suitable for clinical use. The miconazole ampoules (20 ml) (Daktarin* injectable containing a 1% solution of miconazole in 11.5% Cremophor EL) were kindly supplied by Janssen Laboratories (Boulogne, France). The internal standard, metronidazole, DEHP and di-*n*-nonyl phthalate (DNNP), used as standards, were obtained from Aldrich (Saint-Quentin-Fallavier, France). Phosphoric acid, triethylamine and NaH_2PO_4 were analyti-

cal grade and obtained from Prolabo (Paris, France). All organic solvents were HPLC grade and were obtained from Alchym (Marchiennes, France). The water used for buffers and dilutions was de-ionized and purified by distillation.

For simulated infusion, a volumetric infusion pump (ref. P3000) and PVC infusion sets (ref. S05, 72201) were obtained from Becton Dickinson Laboratories, Division Vial Medical (Saint-Etienne de Saint-Geoirs, France). Infusion bags of polyvinyl chloride (PVC, Macoflex®) containing either 0.9% sodium chloride or 5% dextrose were kindly provided by Macopharma Laboratories (Tourcoing, France). To measure the pH of injection solutions during storage in PVC bags, a model HI 8417 pH meter Hanna Instruments (Lingolsheim, France) was used.

2.2. Chromatography

HPLC analyses were performed using a Hewlett-Packard 1090M HPLC system equipped with a variable-volume injector, an automatic sampling system and a Hewlett-Packard 79994 linear photodiode array UV detector operating at suitable wavelengths. The output from the detector was connected to a Hewlett-Packard 9000 model 300 integrator to control data acquisition and integration. Retention times and peak areas were determined by computer recorded to a Hewlett-Packard Thinkjet terminal printer.

Miconazole concentrations were determined by a stability-indicating HPLC assay. Chromatography was performed on a 5-μm C18 Sperisorb ODS column (150 × 4.6 mm i.d.) (Interchim, Montluçon, France) operating at room temperature. Miconazole was eluted isocratically with a mobile phase of acetonitrile–0.01 M NaH_2PO_4 (adjusted to pH 8 with trimethylamine) (15:85, v/v). The flow-rate was 1.5 ml min^{-1}, and detection was set at 250 nm. 10 μl of each sample was injected on to the analytical column. Metronidazole was used as the internal standard.

DEHP concentrations were measured with the same liquid chromatograph. The mobile phase was acetonitrile–triethylamine (0.2% adjusted to pH 2.5 with phosphoric acid) (90:10, v/v), eluted isocratically at a flow-rate of 1.5 ml min^{-1} on a 5-μm C18 Hypersil ODS column (250 × 4.6 mm i.d.) (Touzart et Matignon, Paris, France) operating at room temperature. Detection was set at 222 nm. 20 μl of each sample was injected on to the analytical column and DNNP was used as the internal standard.

2.3. Calibration curves

Miconazole and DEHP calibration curves were constructed at concentration ranges of 100–200 μg ml^{-1} and 3.12–50 μg ml^{-1}, respectively. Standard stock solutions (1 mg ml^{-1}) of miconazole, metronidazole, DEHP and DNNP were prepared daily in methanol. A series of dilutions was made to prepare the standard solutions of the desired concentrations. Samples were diluted with the mobile phase before injection on to the column. Calibration curves were constructed from a linear plot of peak-area ratio (miconazole/metronidazole, DEHP/DNNP) versus concentration.

The assay was validated by establishing the within-day and between-day variations. Five sets of samples were prepared on the same day to establish the within-day variation. The assay was repeated weekly for five weeks to establish the between-day variation.

The stability-indicating assay for miconazole was established by adding concentrated hydrochloric acid (for acidic conditions), 0.1 M sodium hydroxide (for alkaline conditions) and 1% hydrogen peroxide to samples of miconazole injection in 0.9% sodium chloride injection and 5% dextrose injection. In addition, the purity and homogeneity of the miconazole peak in samples was confirmed by determining the drug at three wavelengths (230, 250 and 280 nm) using the corresponding calibration curves.

Since DEHP is a persistent environmental pollutant [20], rigorous precautions were taken to avoid contamination during both sample handling and sample analysis. All the samples were prepared and diluted in glass or polypropylene tubes washed previously with a methanol/acetonitrile mixture, and analyzed in duplicate.

2.4. Simulated IV infusions of miconazole formulation diluted with injection solutions

Infusions of miconazole were carried out under laboratory conditions simulating those routinely used in clinical practice in the hospital; for this purpose, an infusion pump and PVC administration sets were used. The mi-

conazole formulation was added to 250-ml PVC infusion bags containing 5% dextrose injection or 0.9% sodium chloride injection to yield an initial nominal concentration of 2.42 mg ml^{-1}, the mean concentration commonly used in clinical practice. To prepare the infusion, one ampoule (20 ml) of the formulation was opened and the entire contents were drawn twice into a 10-ml glass syringe through a 22-gauge needle; the needle was then inserted into the IV fluid container and the formulation was slowly expelled into the IV fluid. To obtain a nominal concentration of 2.42 mg ml^{-1}, the entire contents of four ampoules were added to 250-ml containers of the IV fluid.

Thus, 800 mg of miconazole in 80 ml of solution was introduced into each injection container yielding a final concentration of 800 mg in 330 ml. 80 ml represented the maximum volume of injection solution that could be added to a PVC bag. To avoid too much handling and to minimize risk of dilution error, an equal volume of IV fluid was not removed from the container.

Infusion solutions of drug were prepared in PVC bags immediately before infusion. The bags containing the drug were agitated by bending, flexing, massaging and shaking for about 1 min after preparation to simulate the agitation a bag may undergo during preparation, transportation and administration. The bags were then attached to an administration set connected to the infusion pump that allowed the solution to flow through at a constant rate. The flow was adjusted and the infusion was started.

During infusion, 1 ml of solution was withdrawn at zero time and at regular intervals from the PVC bags; at the same time, an aliquot of effluent (1 ml) was collected from the administration set in order to evaluate the bags and giving sets separately for stability, compatibility of miconazole and leaching of DEHP.

Samples were kept frozen in polypropylene tubes at −20°C until analysis by HPLC for miconazole and DEHP. Preliminary stability trials after freezing were conducted for one month during reproducibility assays. After thawing, one portion of the sample was immediately diluted with the mobile phase and analyzed for miconazole. A second portion was diluted with acetonitrile and water and analyzed for DEHP.

Simulated infusions were prepared in quadruplicate (two infusions in 0.9% sodium chloride injection and two infusions in 5% dextrose injection) at ambient temperature (22–26°C) without protection from light.

2.5. Stability of miconazole injection in IV fluids in PVC bags

Four ampoules of the miconazole formulation were diluted in 250 ml of 0.9% sodium chloride injection or 5% dextrose injection in PVC bags to produce a nominal miconazole concentration of 2.42 mg ml^{-1} by the same procedure.

All bags were prepared in duplicate. After preparation, the bags were agitated by flexing and shaking for about 1 min; two of each type of container were then stored at 22–26°C and two at 2–6°C sheltered from light. 3 ml was removed from each bag at zero time, 1, 2, 4, 6, 8 and 24 h, and the pH was immediately measured. After agitation at each time point, the samples were placed in clear glass test tubes and were visually inspected for colour and clarity by following European Pharmacopeia protocols V.6.1. (1983) and V.6.2. (1980). The samples were then kept frozen in polypropylene tubes at −20°C until analysis by HPLC for miconazole and DEHP.

3. Results and discussion

3.1. Chromatography

A typical chromatogram of miconazole (150 μg ml^{-1}) with the internal standard metronidazole (25 μg ml^{-1}) in solution obtained immediately after mixing is illustrated in Fig. 1(a). Figure 1(b) shows a chromatogram of DEHP (50 μg ml^{-1}) and DNNP (IS) (50 μg ml^{-1}). Miconazole and DEHP were rapidly identified and quantified. Miconazole eluted at 3.93 min and DEHP eluted at 10.11 min. The k' values (capacity factors) were 3.57 and 1.75 for miconazole and its IS, respectively, showing satisfactory separation and a relatively short analysis time. For DEHP and DNNP, the k' values were of 14.45 and 16, respectively. During the specific stability-indicating assay miconazole was chemically stable under acidic or alkaline conditions. The homogeneity of the miconazole peak was confirmed by determining the drug at the three wave-

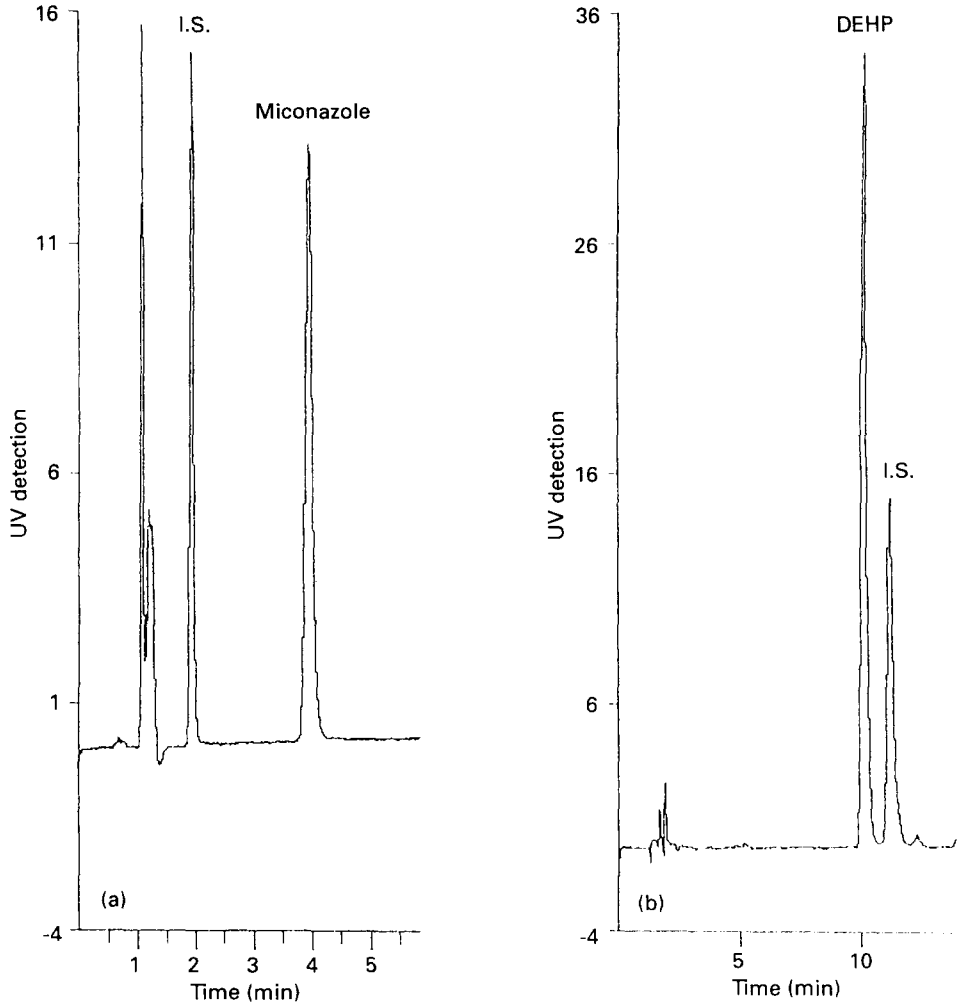

Fig. 1. Chromatograms of (a) miconazole with metronidazole (IS), and (b) DEHP with DNNP (IS).

lengths (230, 250 and 280 nm) using the respective calibration curves.

The resulting chromatograms were compared with chromatograms of intact miconazole, DEHP, 0.9% sodium chloride and 5% dextrose. No degradation products interfered and the drug was eluted with the same retention time as that of the parent miconazole peak. Preliminary studies showed that miconazole was stable for 1 month at −20°C.

Table 1 summarizes the validation data of the assay procedure for miconazile and DEHP. The precision of the miconazole assay was determined by using five series of five measurements at three theoretical concentrations. As shown in Table 1, the within-day and between-day RSD values were lower than 1.02% and 1.25%, respectively, indicating good reproducibility for miconazole. Calibration curves were constructed from a linear plot of peak-area ratio (miconazole/IS) versus concentration (100–200 μg ml^{-1}). The correlation coefficient of the standard curve was greater than 0.998, indicating good linearity.

Fig. 2 shows an uneven baseline for a chromatogram of an admixture (5% dextrose or 0.9% NaCl) in PVC bags and there was evidence of numerous interfering compounds; for this reason, miconazole injection calibration curves were constructed. The miconazole standard curve did not differ significantly from the miconazole injection curve (Student's t test, $p > 0.05$). No significant differences were observed between equation parameters. Standard curves did not pass through the origin.

For the assay of DEHP, the within-day and between-day RSD values were lower than 0.75% and 4.36%, respectively. The lower limit of detection was 1 μg ml^{-1}. The calibration curves covered the range of 3.12–50 μg ml^{-1} with a correlation coefficient better than 0.999.

Table 1
Validation data of the HPLC assay procedure[a]

Substance	Concentration ($\mu g\ ml^{-1}$)	Mean concentration found ($\pm$SD) ($mg\ ml^{-1}$)	RSD		Accuracy (%)	Linear regression equation ($y = ax + b$)[b]	Correlation coefficient (r)
			Within-day (%)	Between-day (%)			
Miconazole	100	103.68 ± 1.30	0.88	1.25	103.68	$y = 0.0090x + 0.0401$	0.998
	150	149.77 ± 1.44	0.87	0.96	99.84		
	200	205.81 ± 1.26	1.02	0.62	102.90		
DEHP	3.12	3.01 ± 0.10	0.71	3.51	96.47	$y = 0.0328x + 0.0096$	0.999
	6.25	6.14 ± 0.19	0.75	3.14	98.24		
	12.5	12.89 ± 0.56	0.75	4.36	103.13		
	25	24.89 ± 0.56	0.20	0.89	99.56		
	50	49.54 ± 0.52	0.40	1.06	99.08		

[a] $n = 5$.
[b] $a \pm SD = 0.0090 \pm 0.0001$, $b \pm SD = 0.0401 \pm 0.0070$ for miconazole; $a \pm SD = 0.0328 \pm 0.0003$, $b \pm SD = 0.0096 \pm 0.0013$ for DEHP.

3.2. Stability of miconazole in IV fluids during simulated infusion using PVC infusion bags and giving sets

The analysis of each sample was performed by HPLC after suitable dilution in the mobile phase in order to fit the calibration curve. For all the miconazole infusion solutions, the initial concentration of miconazole was designated as 800 mg/330 ml. All subsequently measured concentrations were expressed with respect to the initial concentration at a particular time. Stability was defined as a concentration within 90–105% of the initial concentration, in accordance with the Health Registration of France, the French regulatory agency for drug and drug-related products.

As shown in Table 2, when miconazole solutions were infused through PVC infusion sets from PVC infusion bags for 2 h, the variation in drug concentration in both the PVC bags and effluent in no case exceeded 10%. There was no substantial difference between miconazole concentrations at zero time and at any subsequent time intervals. This demonstrates that the drug was not sorbed by the plastic infusion bags and sets during infusion at ambient temperature. No additional peak corresponding to degradation products was observed on chromatograms. No significant difference was observed between the miconazole concentrations of solutions collected in PVC bags and from giving sets. No significant difference was observed between 5% dextrose injection and 0.9% sodium chloride injection with respect to drug stability during simulated infusions.

Since no degradation and no loss of drug was observed during simulated infusion using PVC bags containing 5% dextrose injection or 0.9% sodium chloride injection and administration sets, it is concluded that the miconazole infusion solution is chemically stable for up to 2 h.

3.3. Compatibility of miconazole and extent of DEHP leaching from PVC bags and giving sets during simulated infusion

The amount of DEHP leached into the miconazole solutions during 2 h simulated infusion was calculated from the graph of concentration against time of DEHP (Fig. 3).

No significant difference in the leaching of DEHP was observed between 5% dextrose injection and 0.9% sodium chloride injection. However, a significant difference was observed in amounts of DEHP leached into solution from PVC bags and from giving sets. A total of 0.64 mg of DEHP was leached into solutions from PVC bags and a total of 1.35 mg of DEHP was leached into solutions delivered from administration sets.

A drug is considered incompatible with the PVC containers if DEHP was detected in the drug solution. In accordance with the results, this is the case for the miconazole formulation. Other drugs such as taxol [11] and cyclosporin [9] were considered incompatible with PVC containers.

Higher amounts of DEHP were extracted from PVC infusion bags and administration sets by solutions containing the taxol formula-

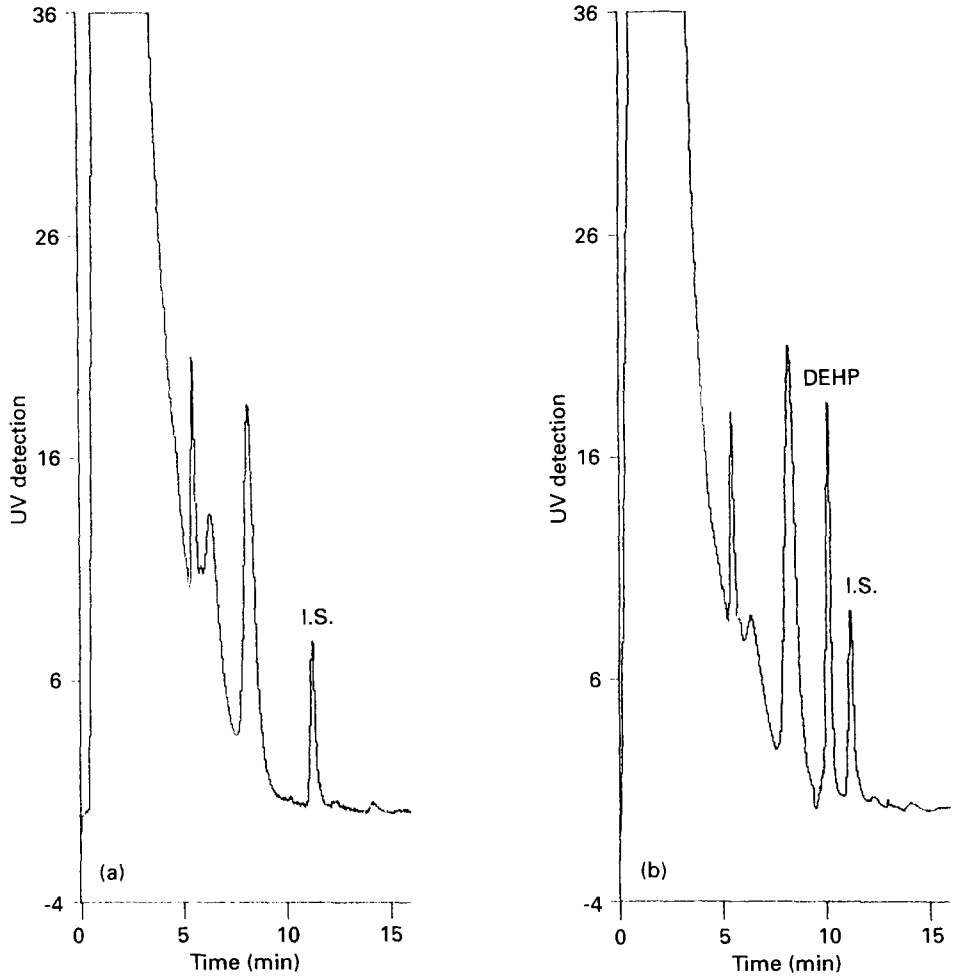

Fig. 2. Chromatograms of DEHP and DNNP (IS) in the bags containing 800 mg of miconazole in 330 ml (a) immediately after mixing and (b) after storage for 24 h at room temperature.

tion. Waugh et al. [11] proposed that the leaching of DEHP was due to the vehicle containing a large percentage of Cremophor EL (50%) and to the duration of infusion. For example, in one experiment, an infusion solution containing a taxol formulation was delivered in 4.5 h and a total of 9.9 mg of DEHP was leached from the PVC tubing. The agent responsible for the leaching of DEHP was probably the non-ionic surfactant Cremophor EL. The lower amounts of DEHP leached in the present study were due to the lower concentration of Cremophor EL (11.5%) present in the miconazole formulation and the shorter duration (2 h) of simulated infusion. The clinical consequences of using plastic bags and infusing DEHP into patients are not really known at present. If the patients receive their dose of miconazole during infusion for 2 h, they are likely to receive a total of 4 mg of DEHP every day, corresponding to 800 mg of miconazole three times a day.

However, higher amounts of DEHP have been extracted from blood, plasma or concentrated platelets stored in PVC bags at 4°C and transfused to patients [21]. Studies [22,23] esti-

Table 2
Leaching of miconazole during simulated infusion[a] for 120 min using plastic infusion bags and sets

Time (min)	Concentrations in the infusion bags (±SD) (mg(330 ml)$^{-1}$)	Concentrations from infusion sets (±SD) (mg(330 ml)$^{-1}$)
0	800 ± 0	800 ± 0
5	791 ± 10	770 ± 25
15	801 ± 12	778 ± 22
30	787 ± 18	782 ± 14
60	781 ± 29	775 ± 13
90	775 ± 13	781 ± 7
120	779 ± 10	790 ± 26

[a] $n = 4$.

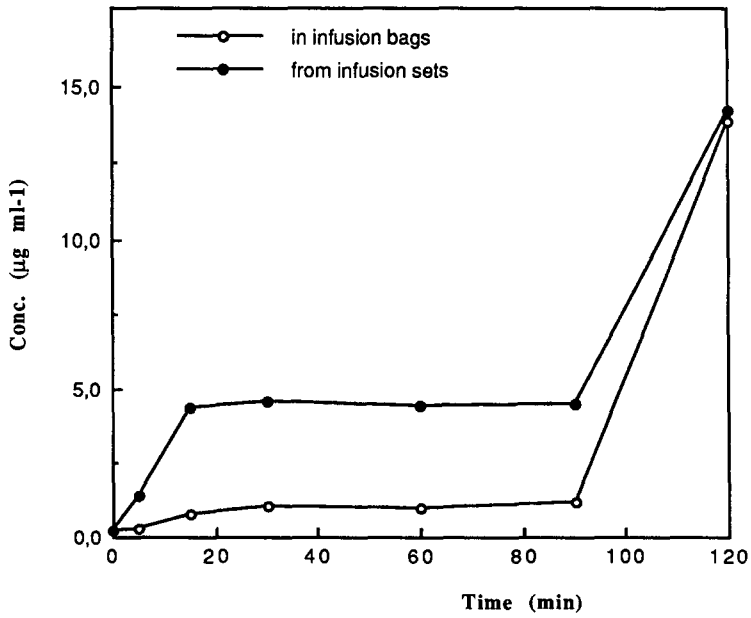

Fig. 3. Graph of concentration against time of DEHP leached from 250-ml polyvinyl chloride (PVC) bags during simulated infusion ($n = 4$) using plastic infusion bags and sets.

mated that patients on haemodialysis therapy using PVC tubes containing plasticizer can receive 9–150 mg of DEHP during haemodialysis for 5 h.

The rate of release of DEHP into the blood is 6.1 mg h^{-1} [24]. Although DEHP has a short elimination half-life (about 12 h) and is rapidly metabolized and excreted in healthy subjects [25], this plasticizer or its metabolites might accumulate in patients with chronic exposure. Whether this contributes to any long-term toxic effects is unknown.

For DEHP exposure caused by the miconazole formulation during infusion over 2 h and where the reconstituted solutions are infused immediately after their preparation, the undesirable side effects should be very limited in accordance with the low amounts of DEHP leached.

3.4. Stability of miconazole in IV fluids stored in PVC bags

After 24 h of storage at room temperature or at 4°C and protected from light, there was no substantial difference between miconazole concentrations at zero time and at any subsequent time intervals. Initially, all the diluted miconazole formulation solutions appeared slightly hazy but there was increase in haziness with time (over 24 h). No colour variation was observed during the 24-h study and there was no precipitation. The pH of solutions did not vary from the range of 3.9–4.7. No additional peaks corresponding to degradation products were observed on chromatograms. No significant difference was observed between 5% dextrose injection and 0.9% sodium chloride injection with respect to drug stability.

It can be concluded that the stability of miconazole solutions is satisfactory during 24 h at room temperature and at 4°C.

3.5. Compatibility of miconazole and extent of DEHP leaching from PVC bags during storage

The amount of DEHP that leached into the miconazole solutions stored in 250-ml PVC containers increased with time. This phenomenon was exaggerated at a higher temperature (Fig. 4). Indeed, a significant difference was observed between the amount of DEHP leached into solutions stored at 4°C (16.9 µg ml^{-1}) and the amount leached into solutions stored at room temperature (57.9 µg ml^{-1}).

This phenomenon has been previously described in studies on other drugs [9,10,12]. In the present study, DEHP concentrations are lower than those observed by Pearson and Trissel [12] when bags were stored at room temperature: they detected 63–67 µg ml^{-1} DEHP in 5% dextrose. One of the reasons for this difference was probably the higher percent-

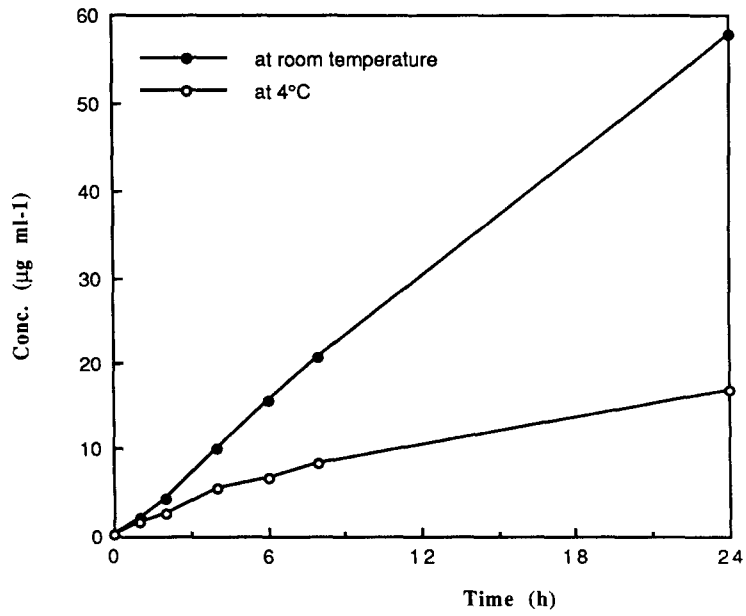

Fig. 4. Graph of concentration against time of DEHP leached from 250-ml polyvinyl chloride (PVC) infusion bags containing 800 mg of miconazole ($n = 4$), at room temperature and at 4°C.

age of Cremophor EL introduced into the injection solution. However, to minimize the extent of leaching of DEHP, it is necessary to store PVC bags at a refrigerated temperature (2–6°C) as shown in the results of the present work.

There did not appear to be any substantial difference in the amount of DEHP leached from the PVC bags containing 0.9% sodium chloride injection and that from the bags containing 5% dextrose injection.

As reported in previous studies with other drug formulations [10,11], when the extent of DEHP extraction by the vehicle was compared in the presence or absence of drug, there was no difference in the present study. The drug itself did not appear to contribute to the leaching of DEHP from the PVC bags.

Therefore, the storage of miconazole solutions in PVC bags seems to be limited by the leaching of DEHP rather than by degradation. Although DEHP appears to have a low order of acute toxicity when given either by injection or orally [26], and although prolonged exposure of humans to DEHP leached into bags and tubing (blood products, haemodialysis therapy) has not been associated with specific toxicity [21,27], it would be advisable to limit the potential exposure of patients to DEHP as much as possible.

If PVC bags and PVC giving sets are used for intravenous miconazole administration, the solutions should be used immediately after preparation, thereby minimizing leaching of DEHP from these containers.

With the increasing use of continuous IV infusion and lintermittent small-volume IV infusion modes of administration, it is imperative that the stability and compatibility of drugs in injection solutions and PVC containers be investigated. Consequently, when drugs are administered by continuous IV infusion with PVC material, knowledge of the rate of drug delivery to the patient is essential.

It is likely that other drugs interact with PVC infusion bags and administration sets, leading to a reduction in the clinical effectiveness of the drug or to exposure of patients to DEHP. This type of study is important for the packaging of pharmaceuticals in plastic containers in general, and might be carried out for all drugs administered in PVC infusion bags.

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References

[1] E.F. Godefroi, J. Heeres, J. VanCutsem and P.A.J. Janssen, J. Med. Chem., 12 (1969) 784.

[2] J.P. Brugmans, J. Vancutsem, J. Heykants, V. Schuermans and D. Thienpont, Eur. J. Clin. Pharmacol., 5 (1972) 93.

[3] J.M. Vancutsem and D. Thienpont, Chemotherapy, 17 (1972) 392.

[4] Janssen Laboratories, Daktarin Injectable.

[5] P.F. D'Arcy, Drugs Intell. Clin. Pharm., 17 (1983) 726–731.

[6] L. Illum and H. Bundgaard, Int. J. Pharm., 10 (1982) 339–351.

[7] E.A. Kowaluk, M.S. Roberts, H.D. Blackburn and A.E. Polack, Am. J. Hosp. Pharm., 38 (1981) 1308–1314.

[8] P. Moorhatch and W.L. Chiou, Am. J. Hosp. Pharm., 31 (1974) 149–152.

[9] R. Venkataramanan, G.J. Burchart and R.J. Ptachcinski, Am. J. Hosp. Pharm., 43 (1986) 2800–2802.

[10] D.M.C. Barther, E.B. Rockard, I.J. Pouliquen, S.M. Rabouan and P.Y. Courtois, Am. J. Hosp. Pharm., 51 (1994) 2706–2709.

[11] W.N. Waugh, L.A. Trissel and V.J. Stella, Am. J. Hosp. Pharm., 48 (1991) 1520–1524.

[12] S.D. Pearson and L.A. Trissel, Am. J. Hosp. Pharm., 50 (1993) 1405–1409.

[13] D. Calley, J. Autian and W.J. Guess, J. Pharm. Sci., 55 (1966) 158–162.

[14] S.V. Kevy and M. Jacobson, Contri. Nephrol., 9 (1983) 36–82.

[15] A.E. Ganning, U. Brunk and G. Dallner, Hepatology, 4 (1984) 541–547.

[16] C.O. Schultz, R.J. Rubin and G.M. Hutchins, J. Ind. Hyg. Toxicol., 27 (1945) 130–135.

[17] S.V. Kevy and M.S. Jacobson, Environ. Health Perspect., 45 (1982) 57–64.

[18] A.R. Singh, W.H. Laurence and J. Autian, J. Pharm. Sci., 55 (1972) 158–162.

[19] J.W. Peters and R.M. Cook, Environ. Health Perspect., 3 (1973) 91–94.

[20] C.S. Giam, H.S. Chan and G.S. Neff, Science, 199 (1978) 419–421.

[21] T. Dine, M. Luyckx, M. Cazin, Cl. Brunet, F. Goudaliez and J.C. Cazin, Biomed. Chromatogr., 5 (1991) 94–97.

[22] T.P. Gibson, W.A. Briggs and B.J. Boone, J. Lab. Clin. Med., 87 (1976) 519–524.

[23] L.M. Flaminio, R. Bergia, L. De Angelis, M. Ferazza, M. Marinovich, G. Galli and C.L. Galli, Intern. J. Artif. Organs, 11(6) (1988) 428–435.

[24] M.L. Lewis, T.W. Fleschtner, J. Kerkay, K.H. Pearson and S. Nakamoto, Clin. Chem., 24(5) (1978) 741–746.

[25] P. Schmidt and C.H. Schlatter, Xenobiotica, 15(3) (1985) 251–256.

[26] B.G. Lake, H.S.D. Gangolli, P. Grasso and A.A.G. Lloyd, Toxicol Appl. Pharmacol., 32 (1975) 355–360.

[27] G.M. Pollack, J.F. Buchanan, R.K.K. Slaughter and D.D. Shen, Toxicol. Appl. Pharm., 79 (1985) 257–267.