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Stability and compatibility studies of cephamandole nafate with PVC infusion bags

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Abstract: A rapid isocratic technique was developed for the analysis of cephamandole nafate and cephamandole in parenteral solutions using high-performance liquid chromatography (HPLC) with UV detection and C_{18} column. The availability and compatibility of drugs from solutions infused via plastic infusion bags through plastic administration sets have been examined. No significant drugs loss was observed during simulated infusions ($n = 4$) for 1 h using PVC infusion bags and administration sets. No significant difference was found between infusion solutions (5% glucose or 0.9% NaCl). The stability of drugs was also studied in solution in PVC bags after storage at room temperature and at 4°C without protection from light. The results show the stability of cephamandole nafate during 24 h at room temperature and 7 days storage at 4°C to be satisfactory, irrespective of the infusion solution (5% glucose or 0.9% NaCl). However, an almost immediate and total transformation of cephamandole nafate to cephamandole in 5% glucose has been observed, whereas in 0.9% NaCl both forms were found in similar proportions.

Keywords: *Stability; compatibility; cephamandole nafate; cephamandole; intravenous infusion; PVC bag; administration set; HPLC.*

Introduction

Cephamandole nafate (**A**; Fig. 1) for injection is a semisynthetic cephalosporin antibiotic for intramuscular and intravenous (i.v.) administration [1, 2]. Cephamandole nafate is the sodium salt of 7-D-mandelamido-3-[([methyl-1H-tetrazol-5-yl]-thio) methyl]-3-cephem-4-carboxylic acid formyl ester, and it is the preferred form of the product for reasons of crystallinity and stability. Upon reconstitution in solution, cephamandole nafate is hydrolysed to cephamandole (**B**; Fig. 1) and formate ion. Cephamandole is an antibiotic with broad spectrum and antimicrobial activity [3], it is bactericidal by inhibition of the synthesis of the bacterial wall in the growth phase. In comparison with former cephalosporins, cephamandole is relatively resistant to inactivation by betalactamases, not only those produced by gram-positive organisms, but also those produced by gram-negative organisms [3–5].

Therefore, with the increasing use of continuous i.v. infusion and intermittent small-volume i.v. infusion modes of administration, it is imperative that the stability and the compatibility of cephamandole nafate and cephamandole in administration sets and PVC containers be investigated. Consequently, when drugs are administered by continuous i.v. infusion with PVC material, knowledge of the rate of drug delivery to the patient is essential [6].

Previous studies [7–9] have reported the loss of certain drugs from aqueous solutions stored in plastic infusion bags for various periods of time. Generally, these losses have been attributed to interaction (adsorption or absorption) between the drug and the plastic infusion bag, and in some cases, may diminish the therapeutic response due to reduced drug delivery to the patient. The stability of cephalosporins in frozen solutions has been reported by several studies [10–15], but only one [13] included the compatibility of drugs administered with plastic infusion bags and i.v. administration sets.

The present study was undertaken with the following objectives: (i) to survey a possible interaction of **A** and **B** with plastic infusion bags; (ii) to study the behaviour of these drugs in simulated infusion using PVC containers and

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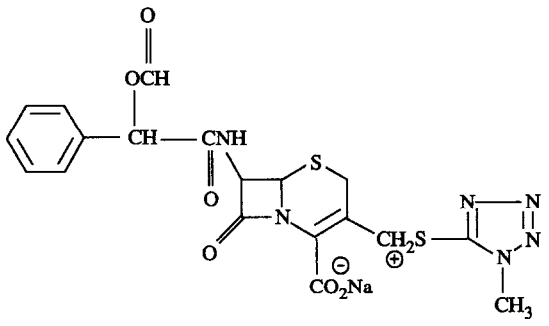
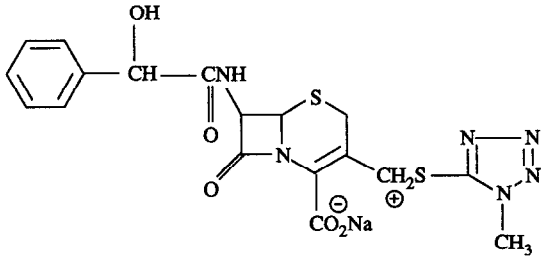


Cephamandole nafate



Cephamandole sodium

Figure 1
Structures of cephamandole nafate (**A**) and cephamandole sodium (**B**).

administration sets in conformity with the conditions of infusion routinely used in hospital (infusion flow rate, dose, volume, temperature and light); and (iii) to determine the differences in possible interactions between PVC containers and administration sets, as well as the differences in stability of the drugs in 0.9% NaCl and 5% glucose.

This study forms part of a large screening of drugs being administered by i.v. infusion.

A high-performance liquid chromatography (HPLC) method has been developed for the determination of **A** and **B** in infusion solutions (5% glucose and 0.9% NaCl) using a suitable chromatographic column and mobile phase.

We have used this analytical technique to investigate the compatibility of the drugs with PVC containers and PVC infusion sets both during simulated infusions, and during storage at room temperature and 4°C in PVC bags.

Experimental

Chemicals

Cephamandole nafate and cephamandole free alcohol (hydrolysis product) were obtained from Lilly Laboratories (Saint-Cloud, France). Vials of cephamandole nafate for injection contained 750 mg of drug and in addition sodium carbonate. Phosphoric acid and triethylamine (Rectapur) were obtained from Prolabo (Paris, France). Acetonitrile (HPLC grade) was obtained from Touzart et Matignon (Vitry sur Seine, France). Injectable preparation water (sterile and apyrogen) obtained from Macopharma Laboratories (Tourcoing, France) was used for buffers, dilutions and standard solutions.

Chromatographic conditions and instrumentation

Chromatographic analysis was performed with an HP 1090 high performance liquid chromatograph (Hewlett Packard, Orsay, France), equipped with a variable volume injector, an automatic sampling system and an HP 79994A UV diode array detector operating at 254 nm. The output from the detector was connected to a Hewlett Packard 9000 model integrator and the data recorded on an HP Thinkjet terminal printer.

Analysis was performed on a 5-μm C_{18} Interchim column (100 × 4.6 mm i.d.; Interchim, Montluçon) operating at room temperature. Drugs **A** and **B** were eluted isocratically with a mobile phase consisting of acetonitrile and buffer (0.2% triethylamine adjusted to pH 2.5 with 85% phosphoric acid) mixture (24:76, v/v) at a flow rate of 1.5 ml min^{-1}.

For simulated infusions, we used a volumetric infusion pump (ref. P3000) and PVC infusions sets (S05, Ref. 72201) obtained from Becton Dickinson Laboratories, Division Vial Medical (Saint-Etienne de Saint-Geoirs, France). Macoflex® PVC infusions bags containing either 5% glucose or 0.9% NaCl in water (250 ml) were provided by Macopharma Laboratories (Tourcoing, France).

Preparation of standard solutions

To obtain standard stock solutions, **A** was reconstituted with distilled water. Working solutions were prepared from the standard solution of **A** by suitable dilutions with mobile phase in polypropylene tubes. The calibration curve was constructed between 20 and 60 μg ml^{-1}.

Simulated infusions

An infusion of **A** to patients was carried out under laboratory conditions simulating those

routinely used in hospitals. For this purpose, an infusion pump and plastic administration sets were used. The respective drug concentration in solution was 750 mg/250 ml (3 mg ml^{-1}) for **A**. The simulated infusions were carried out over a period of 1 h at a flow rate of 4.16 ml min^{-1}.

Infusion solutions of the drug were prepared in PVC infusion bags containing 250 ml of 5% glucose or 0.9% NaCl immediately before infusion. The bag containing the drug was then attached to an administration set connected to the infusion pump that allowed the solution to flow through at a constant rate. At specified times of infusion, samples (1 ml) were withdrawn at regular intervals into the PVC bags, and at the same time, an aliquot of effluent (1 ml) was collected from the administration set. Samples were kept frozen in polypropylene tubes at −20°C until analysis by HPLC.

All simulated infusions were carried out at least in duplicate (two infusions in 0.9% NaCl and two infusions in 5% glucose) at room temperature (20–24°C) and without protection from light.

Storage in infusion bags

Insofar as it was possible, conditions were employed in conformity with the drug concentrations normally used in hospital pharmacy departments for the storage of drugs in infusion bags. To infusion bags containing 250 ml of 0.9% NaCl or 5% glucose solution, a known amount of drug was added to achieve the following concentrations which are most often used in hospitals: cephamandole nafate 3 mg ml^{-1} in the bags.

After mixing the drug in the bag by rapid shaking, samples (1 ml) were withdrawn at regular intervals and stored in polyproylene tubes at −20°C until HPLC analysis. Infusion bags containing the drug were stored at room temperature for a period of 24 h and at 4°C for a period of 7 days without protection from light. The drug storage in these bags was carried out in 0.9% NaCl and 5% glucose.

Results and Discussion

HPLC

The chromatographs of the drugs in solution obtained immediately after mixing are illustrated in Fig. 2 [(a) cephamandole nafate in 5% glucose and (b) cephamandole nafate in 0.9% NaCl]. Drugs (**A** and **B**) were rapidly identified and quantified by comparison with standard products. The components were satisfactorily resolved by this HPLC method and had retention times of 1.79 and 4.17 min (**B**–**A**, respectively).

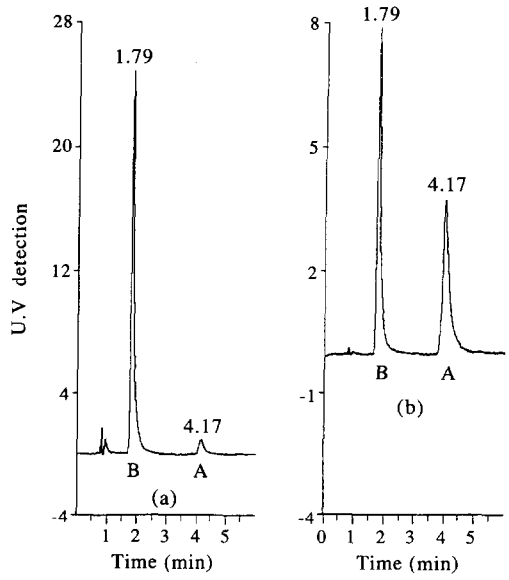


Figure 2
Chromatographs: (a) cephamandole, **B**, and cephamandole nafate, **A**, in 5% glucose; (b) **B** and **A** in 0.9% NaCl. Peaks were identified and quantified by comparison with standard products.

Table 1 summarizes the validation data of the assay procedure for the drug. For quantification of cephamandole nafate and cephamandole (hydrolysis product), the total area obtained at each point of the calibration curve was the sum of the individual peak areas corresponding to the amount of cephamandole nafate added. Good linearity was obtained between peak area and concentrations. The calibration curve was fitted by the least-square method for the peak area of the sample substance (y) versus the concentration of the analysed product (x). The correlation coefficients were all above 0.999.

To assess reproducibility, the same concentration was analysed five times for each point of the calibration curve. The results demonstrate that this analytical method had acceptable accuracy and precision.

Stability of cephamandole nafate during simulated infusions using PVC infusion bags and sets

The analysis of each sample was performed by HPLC after suitable dilution in mobile phase in order to fit the calibration curve.

Table 1
Validation data of the HPLC assay procedure (n = 5)

Sample substance	Concentrations ($\mu g\ ml^{-1}$)	Average concentration found ($\pm$SD) ($\mu g\ ml^{-1}$)	RSD Intra-assay (%)	RSD Inter-assay (%)	Accuracy (%)	Linear regression equation ($y = ax + b$)*	Correlation coefficient (r)
Cefamandole	20	19.95 ± 0.23	0.97	1.15	99.75	$y = 3.521x + 7.216$	0.999
	40	40.09 ± 0.57	0.78	1.42	100.22		
	60	59.97 ± 0.46	0.71	0.77	99.95		

*$a \pm SD = 3.521 \pm 0.036$; $b \pm SD = 7.216 \pm 0.040$.
SD, standard deviation; RSD, relative standard deviation.

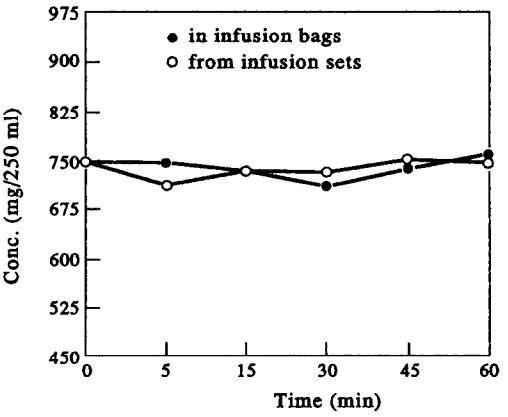


Figure 3
Total concentration kinetics of cephamandole nafate and cephamandole during simulated infusion (n = 4) using plastic infusion bags and sets.

Figure 3 depicts the concentration kinetics of the drugs during simulated infusion (n = 4), using PVC infusion bags and sets. When the solution of cephamandole nafate was infused through infusion sets from PVC infusion bags over a period of 1 h, the variation in drug concentration in both the PVC bags and effluent in no case exceeded 10%. This demonstrates that the drugs (**A** and **B**) were not sorbed by the PVC infusion bags and sets during infusion at room temperature. No significant difference was observed with respect to drug stability during simulated infusions using 5% glucose or 0.9% NaCl.

Stability of the cephamandole nafate in infusion bags during storage at room temperature and at 4°C without protection from light

The analysis of each sample was performed by HPLC after suitable dilution in mobile phase in order to fit the calibration curve. The concentrations of cephamandole nafate and cephamandole present in solution after various periods of storage in PVC infusion bags at room temperature and at 4°C, and without protection from light are listed in Tables 2 and 3, respectively. No significant disappearance of drug was observed in PVC infusion bags for cephamandole nafate and cephamandole.

No precipitation of drugs, no alteration and no change of colour of the solution was observed during storage at room temperature and at 4°C for cephamandole nafate and cephamandole after reconstitution in PVC bags, and that, irrespective of the infusion solution (0.9% NaCl or 5% glucose).

Table 2
Total concentrations (mg/250 ml) of cephamandole nafate and cephamandole after storage in plastic bags at room temperature

Storage time (h)	Infusion solution	Drug	
		Glucose (5%)	NaCl (0.9%)
0		750	750
1		695	714
2		715	728
4		722	716
6		714	735
8		712	744
24		710	732

Table 3
Total concentrations (mg/250 ml) of cephamandole nafate and cephamandole after storage in plastic bags at 4°C

Storage time (day)	Infusion solution	Drug	
		Glucose (5%)	NaCl (0.9%)
0		750	750
1		770	733
2		724	747
3		763	735
4		735	734
6		739	755
7		761	742

The choice of infusion solution (5% glucose or 0.9% NaCl) can change the formation of cephamandole from cephamandole nafate. This transformation also seems to be pH dependent. The cephamandole form is the major component in 5% glucose, whereas in 0.9% NaCl both forms are found in almost similar proportions (Tables 4 and 5). According to Dr Indelicato [16] of Lilly Research Laboratories, this increase in the rate of hydrolysis is due to nucleophilic attack of glucose upon the carbonyl carbon of the formyl ester moiety. This alternate reaction pathway, transesterification, competes with the base-catalysed ester hydrolysis and produces small amounts of primarily D-glucose-6-formate plus other D-glucose diformates. This reaction is not clinically significant inasmuch as the antibiotic potency and stability of cephamandole were unaffected and no toxicological differences were observed. From a therapeutic point of view, cephamandole and cephamandole nafate have the same antibacterial activity, and, both hydrolysed and non-hydrolysed compounds are considered equally effective biologically.

Table 4
Percentage of cephamandole nafate hydrolysed after storage at room temperature

Storage time (h)	Drug	
	Glucose (5%)	NaCl (0.9%)
1	98.4	51.4
2	97.9	53.0
4	96.9	53.6
6	98.4	55.3
8	96.2	55.8
24	93.5	58.5

Table 5
Percentage of cephamandole nafate hydrolysed after storage 4°C

Storage time (day)	Drug	
	Glucose (5%)	NaCl (0.9%)
1	96.0	47.4
2	94.9	49.3
3	95.6	53.0
4	97.2	53.7
6	95.5	56.1
7	93.9	56.3

Conclusions

The HPLC procedure described in this paper is rapid and reproducible for the determination of cephamandole nafate and the hydrolysed compound, cephamandole, in parenteral solutions. The present study has examined the kinetics of cephamandole nafate and cephamandole concentration during simulated infusion using PVC infusion bags and administration sets. The results demonstrate satisfactory compatibility of cephamandole nafate with PVC infusion material over a 1 h infusion period. In aqueous solution the hydrolysis of cephamandole nafate to cephamandole was much faster in 5% glucose than in 0.9% NaCl. 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. This type of study is important concerning the packaging of pharmaceuticals in PVC containers in general, and might be carried out for all drugs administered in PVC infusion bags.

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