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Stability and compatibility studies of pefloxacin, ofloxacin and ciprofloxacin with PVC infusion bags

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Summary

A rapid isocratic technique was developed for the analysis of fluoroquinolones (pefloxacin, ofloxacin and ciprofloxacin) in parenteral solutions using high-performance liquid chromatography (HPLC) with fluorimetric detection and a 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 drug 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 without protection from light. The results show the stability of pefloxacin and ciprofloxacin during 6 h of storage to be satisfactory, irrespective of the infusion solution (5% glucose or 0.9% NaCl). However, we have observed more significant variations with ofloxacin in the solution of 5% glucose, but remaining below 10%.

Introduction

The fluoroquinolones (Fig. 1), pefloxacin (**A**), ofloxacin (**B**) and ciprofloxacin (**C**), form a homogeneous group not only in their chemical structure, but also in their mechanism of action. They are rapidly bactericidal on sensitive strains (Wolfson and Hooper, 1985; Rolin and Bouanchaud, 1988). Many studies have shown that this effect is due to an inhibitory activity of the fluoroquinolones on DNA synthesis. In contrast to what is observed in the majority of antibiotics where resistance is mostly transmitted by plasmids, bacteria resist fluoroquinolones exclusively by chromosomal mutation (Courvalin et al., 1985; Desplace et al., 1986; Nix and Devito, 1987; Neu, 1988). In case of emergency, the injectable form of fluoroquinolones is used and these drugs may be administered by perfusion which also presents advantages (Barre et al., 1984; Frydman et al.,

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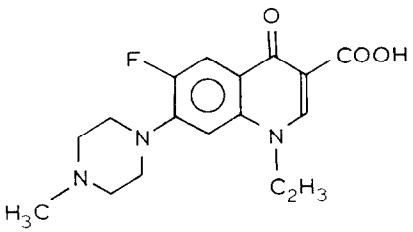
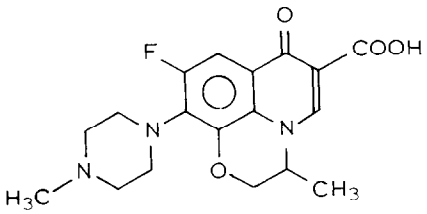
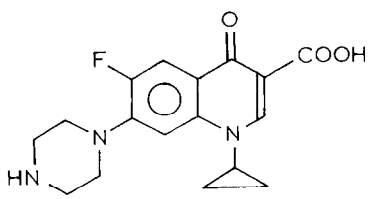


Pefloxacin (A)



Ofloxacin (B)



Ciprofloxacin (C)

Fig. 1. Structures of pefloxacin (**A**), ofloxacin (**B**) and ciprofloxacin (**C**).

1986; Lode et al., 1986). Therefore, with 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 fluoroquinolones in administration vehicles 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 (D'Arcy, 1983).

Previous studies (Moorhatch and Chiou, 1974; Kowaluk et al., 1981; Illum and Bundgaard, 1982) 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. Documentation of the compatibility of fluoroquinolones (Geelen and Waas, 1985; Bails et al., 1991; Goodwin et al., 1991) administered by plastic infusion bags and intravenous administration sets is limited.

The present study was undertaken with the following objectives: (i) to survey a range of drugs (fluoroquinolones), including those presently being administered by i.v. infusion for possible interaction with plastic infusion bags; (ii) to study the behaviour of these drugs in simulated infusion using PVC containers and administration sets; (iii) to conform with the condition of infusion routinely used in hospitals (infusion flow rate, dose, volume, temperature and light); and (iv) 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.

A high-performance liquid chromatography (HPLC) method has previously been reported by Montay and Tassel (1985) for the determination of **A** and by Warlich et al. (1990) for that of **B** in biological fluids. With some modifications, our method allowed the rapid determination not only of **A** and **B**, but also of **C** 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 in PVC bags.

Experimental

Chemicals

A was obtained from Roger Bellon Laboratories (Neuilly sur Seine, France) in vials of 400 mg/5 ml water. **B** was purchased from Diamant

Laboratories (Puteaux, France) in vials of 200 mg/40 ml saline solution ready for use. **C** was obtained from Bayer Laboratories (Sens, France) in vials of 200 mg/100 ml water solution ready for use. Sodium acetate, sodium citrate acid and triethylamine (Rectapur) were supplied by 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 1046A fluorescence detector operating at excitation and emission wavelengths of 277 and 435 nm for **A**, 290 and 490 nm for **B** and 276 and 451 nm for **C**. The output from the detector was connected to a Hewlett Packard 9000 model integrator and the data recorded on an HP Thinkjet terminal printer.

Analyses were performed on a 5 μm C_{18} Interchim column (100 × 4.6 mm i.d.) (Interchim, Montluçon) operating at room temperature. **A** was eluted isocratically with a mobile phase consisting of acetonitrile and buffer (triethylamine 0.1% adjusted to pH 3.3 with 85% phosphoric acid) mixture (50:50, v/v) at a flow rate of 2 ml/min. **B** and **C** were also eluted isocratically with a mobile phase consisting of acetonitrile and buffer (2 g of sodium acetate, 2 g of sodium citrate, 1 ml of triethylamine in 850 ml of water, pH 4.5) mixture (40:60, v/v) at a flow rate of 1 ml/min for **B** and 1.5 ml/min for **C**.

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–C** were reconstituted with distilled water. Working solutions were prepared from the standard solutions of **A–C** by suitable dilutions with distilled water in polypropylene tubes. Calibration curves were constructed between 6 and 12 μg/ml for **A**, between 5 and 12.5 μg/ml for **B** and between 5 and 15 μg/ml for **C**.

Simulated infusions

Infusion of **A–C** to patients was carried out under laboratory conditions simulating those routinely used in hospitals. For this purpose, we used an infusion pump and plastic administration sets. The respective drug concentrations in solution were 400 mg/250 ml (1600 μg/ml) for **A**, 200 mg/250 ml (800 μg/ml) for **B** and 200 mg/250 ml (800 μg/ml) for **C**. The simulated infusions were carried out over a period of 1 h at a flow rate of 4.16 ml/min.

Infusion solutions of drug were prepared in PVC infusion bags containing 250 ml of 5% glucose or 0.9% NaCl immediately before infusion. The bag containing 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, we employed conditions 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 concentra-

TABLE 1

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

Sample substance	Concentrations (μg/ml)	Average concentrations found ($\pm$SD) (μg/ml)	C.V. Intra-assay (%)	C.V. Inter-assay (%)	Accuracy (%)	Linear regression equation ($y = ax + b$)	Correlation coefficient (r)
Pefloxacin	6	6.08 + 0.08	1.10	1.31	101.33		
	7.5	7.39 + 0.09	0.34	1.22	98.53		
	9	8.97 + 0.04	0.23	0.44	99.66	$y = 23.349x - 7.758$	0.999
	12	12.03 + 0.08	0.36	0.66	100.25		
Ofloxacin	5	5.00 + 0.07	0.96	1.40	100.00		
	7.5	7.44 + 0.08	0.86	1.07	99.20		
	10	10.08 + 0.08	0.45	0.79	100.80	$y = 13.173x + 0.924$	0.999
	12.5	12.45 + 0.12	0.70	0.96	99.60		
Ciprofloxacin	5	5.04 + 0.04	0.68	0.79	100.80		
	10	9.94 + 0.13	1.12	1.30	99.40		
	12.5	12.42 + 0.12	0.54	0.96	99.36	$y = 15.616x - 1.583$	0.998
	15	15.08 + 0.34	1.85	2.25	100.53		

SD, standard deviation; C.V., coefficient of variation.

tions which are most often used in hospitals: **A**, 1600 μg/ml; **B** and **C**, 800 μg/ml in the bags.

After mixing the drug in the bag by rapid shaking, samples (1 ml) were withdrawn at regular intervals and stored in polypropylene tubes at −20°C until HPLC analysis. Infusion bags containing the drug were stored at room temperature for a period of 6 h without protection from light. Drug storage in these bags was carried out in 0.9% NaCl and 5% glucose.

Results and Discussion

HPLC

The chromatographs of the three drugs in solution obtained immediately after mixing are illustrated in Fig. 2. (a, pefloxacin; b, ofloxacin; c, ciprofloxacin). Drugs were rapidly identified and quantified. The components were satisfactorily resolved by this HPLC method and had retention times of 1.59, 1.45 and 1.06 min (**A–C**, respectively).

Table 1 summarises the validation data of the assay procedure for each drug. We observed good linearity between peak area and concentrations. The calibration curves were fitted by the least-square method for the peak area of the sample substance (y) vs the concentration of the analysed product (x). The correlation coefficients were all above 0.998 and no significant differences were found between the equation parameters.

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

Stability of fluoroquinolones during simulated infusions using PVC infusion bags and sets

The analysis of each sample was performed by HPLC after suitable dilution in water in order to fit the calibration curves. Fig. 3. depicts the concentration kinetics of all three drugs during simulated infusion ($n = 4$), using PVC infusion bags and sets. When solutions of **A–C** were 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–C**, were not sorbed by the PVC infusion bags and sets during infusion at room temperature. No significant difference was observed with

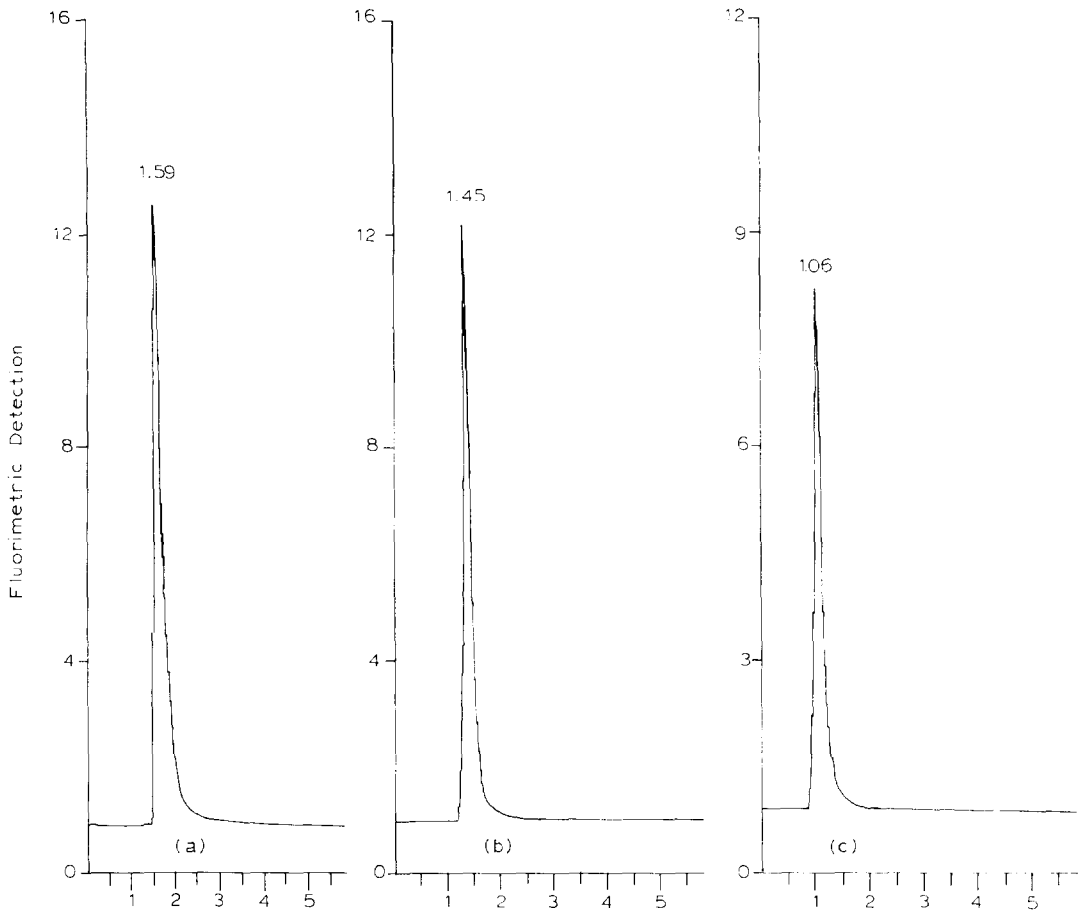


Fig. 2. Chromatographs of (a) pefloxacin, (b) ofloxacin, (c) ciprofloxacin.

TABLE 2

*Concentrations (mg / 250 ml) of **A–C** in solution after storage in plastic bags at room temperature*

Storage time (h)	Drug					
	A		**B**		**C**	
Infusion solution:	NaCl (0.9%)	Glucose (5%)	NaCl (0.9%)	Glucose (5%)	NaCl (0.9%)	Glucose (5%)
0	400	400	200	200	200	200
1	398	407	201	200	200	198
2	412	406	215	182	201	192
3	407	420	209	188	195	194
5	412	408	211	184	200	198
6	407	403	212	181	203	206

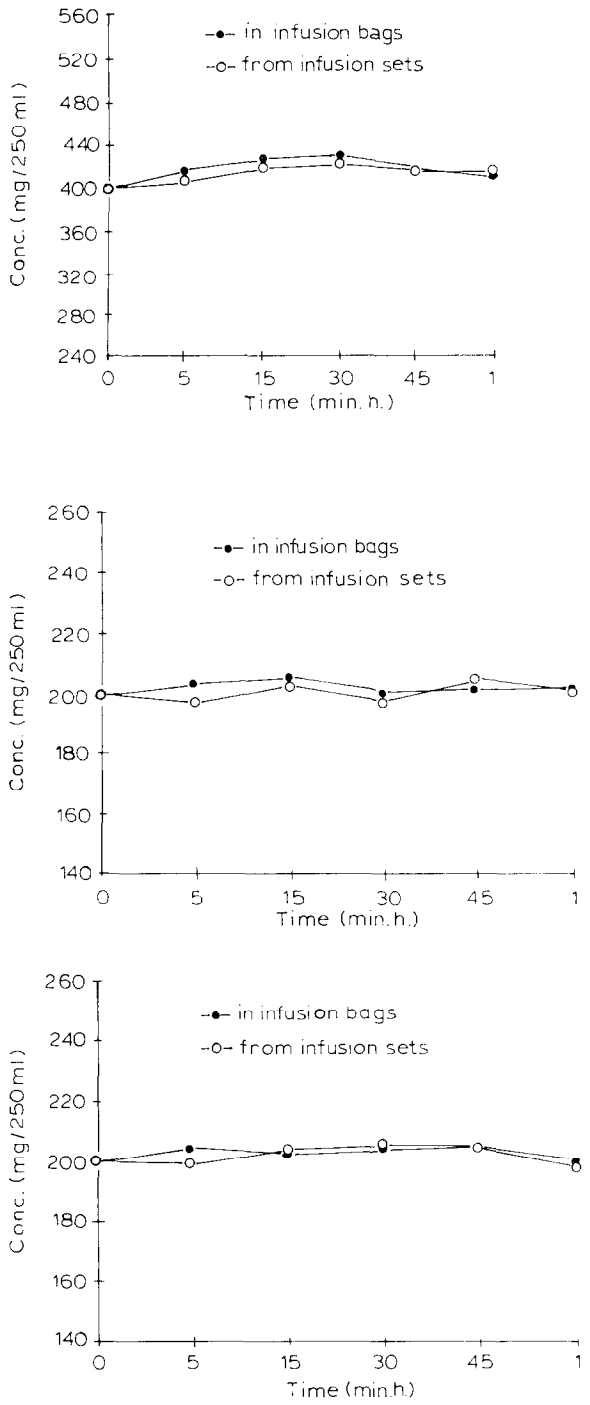


Fig. 3. Concentration kinetics of **A**–**C** during simulated infusions ($n = 4$) using plastic infusion bags and sets.

respect to drug stability during simulated infusions using 5% glucose or 0.9% NaCl.

Stability of the fluoroquinolones in infusion bags during storage at room temperature and without protection from light

The analysis of each sample was performed by HPLC after suitable dilution in water in order to fit the calibration curves. The concentrations of **A**–**C** present in solution after various periods of storage in PVC infusion bags at room temperature and without protection from light are listed in Table 2. No significant disappearance of drug was observed in PVC infusion bags for **A** and **C**. However, we have observed more significant variations with **B** in a solution of 5% glucose, but remaining below 10%. On the other hand, these variations were not statistically significant.

Neither precipitation of drugs, nor alteration or change in colour of the solution was observed during storage at room temperature for all three drugs after reconstitution in PVC bags and irrespective of the infusion solution (0.9 NaCl or 5% glucose).

In conclusion, the HPLC procedure described in this paper is rapid and reproducible for the determination of fluoroquinolones in parenteral solutions. The present study has examined the kinetics of pefloxacin, ofloxacin and ciprofloxacin concentration during simulated infusion using PVC infusion bags and administration sets. The results demonstrate satisfactory compatibility of fluoroquinolones with PVC infusion material over a 1 h infusion period. 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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