ELSEVIER

International Journal of Pharmaceutics 107 (1994) 111–119

international journal of pharmaceutics

Compatibility with medical plastics and stability of continuously and simultaneously infused isosorbide dinitrate and heparin

V. Sautou, J. Chopineau *, I. Gremeau, R. Chevrier, F. Bruneaux

Laboratoire de Pharmacie Clinique et Biotechnique, U.F.R. Pharmacie, 28 Place Henri Dunant BP 38, 63001 Clermont-Ferrand Cedex, France

(Received 13 October 1993; Accepted 13 December 1993)

Abstract

The compatibility and stability of continuously infused isosorbide dinitrate (ISDN) and heparin with medical plastics were investigated by simulating therapeutic conditions practiced in hospital. High-performance liquid chromatography (HPLC) with UV detection and C18 column was used to quantify the drugs. The results show that the compatibility of ISDN and heparin solutions with polypropylene syringes during a 12 h continuous infusion is good. Preparing the syringes 8 h in advance does not alter the stability of the drugs, as long as the ISDN is not refrigerated (at + 4°C). The stability of ISDN with PVC/PE tubing (polyvinyl chloride on the outside and polyethylene inside) is also satisfactory irrespective of whether it is administered alone or mixed with heparin. The behaviour of heparin with the PVC/PE tubing is more difficult to interpret, since the variations in concentration near 10% of the initial concentration of heparin. ISDN and heparin both have a compatibility problem with PVC tubing. ISDN is rapidly fixed on PVC and then released: it is released earlier when it is administered with heparin in the tube. Some heparin is lost in the PVC tubing. This loss is relatively stable with time and is similar and independent of the type of infusion solvent, or whether heparin is used by itself or in combination with ISDN.

Key words: Heparin; Isosorbide nitrate; Continuous infusion; Stability; Compatibility

1. Introduction

Various work has shown that there exists an interaction between certain drugs and plastics, especially polyvinyl chloride, PVC (Illum and Bundgaard, 1982; Allwood, 1983; D'Arcy, 1983; Arnaud et al., 1991). These interactions between drugs and plastics can have important clinical consequences, particularly if drugs are administered as a continuous infusion.

There have been many investigations of the behaviour of individual drugs with plastics, both static (in bags or flasks) or dynamic (during continuous infusion) studies. However, interactions that take place when drugs are administered simultaneously are far less well documented. Nonetheless, this is a situation that frequently arises in a clinical context. Drugs can often been infused using syringe pump systems: the drugs are not mixed in the syringes but are administered in

* Corresponding author.

SSDI 0378-5173(93)E0377-3

parallel. The drugs come into contact in the common tubing which leads into the vascular system of the patient.

Isosorbide dinitrate (ISDN) and heparin are two drugs that are often co-administered with syringe pump systems in the cardiology department. These two drugs, ISDN (Cossum and Roberts, 1981; Lee and Fenton-May, 1981; Remon and Bogaert, 1983; De Muynck et al., 1988, 1991) and heparin (Goodall et al., 1980; Tunbridge et al., 1981) have already been shown to react with plastics.

The aim of this study was to evaluate the behaviour of each of these drugs with polypropylene, polyethylene and polyvinyl chloride (and, in the case of heparin, according to the type of infusion solvent) whether they are administered alone or mixed in the infusion tubing.

ISDN and heparin were analysed using HPLC. The method used to quantify ISDN was based on the work of Olsen and Scroggins (1984). Fewer investigations have been performed on the methods of quantification for heparin (De Vries, 1989; Menzies et al., 1989; Pintabona et al., 1991). An HPLC method with UV detection was developed for quantifying sodic heparin.

2. Materials and methods

2.1. Materials

2.1.1. Drugs to be analysed

ISDN (Risordan®) was obtained from Theraplix SA-Rhone Poulenc (Paris, France) in 10 ml ampoules containing 10 mg of the product and sodic heparin (Heparine Sodique Leo®, ampoules of 5 ml (with 5000 IU/ml) from LEO laboratories (Saint-Quentin-Yvelines, France).

2.1.2. Chromatographic analysis

Apparatus. ISDN and heparin were analysed with the same HPLC system (Merck-Hitachi, Darmstadt, Germany) and column. This HPLC system consisted of the following units: L5000 LC Controller, 655A-11 pump, Model 7125 Rheodyne injection loop, and UV-Visible detector (LCM variable wavelength detector). The analytical column was a Lichrospher® C18 (125 × 4 mm i.d., 5 μm) RP 18 endcapped (Merck) preceded by a Lichrocart 4–4® 100 RP 18.5 μm (Merck) precolumn.

Reagents. The following reagents with a high degree of purity (> 99.9%) were used: methanol (Carlo-Erba, Milan, Italy), acetonitrile (Prolabo, Paris, France), dipotassium hydrogenophosphate (Merck), potassium dihydrogenophosphate (Merck) and 0.1 N chlorhydric acid (Titrisol®, Merck).

ISDN was assayed using an internal standard: nitroglycerine (1% Nitroglycerine EN Solution®, Merck).

2.1.3. Continuous infusion

Apparatus. Two ID2S (Allegre Biomedical, Saint-Etienne, France) syringe pump systems with adjustable flow rate were used.

The infusion material consisted of the following: 50 ml polypropylene (PP) syringes; Plastipak Luer-Lock® (Beckton-Dickinson, Dublin, Ireland); two tap ramp with a 50 cm M/M prolongation (reference 9744–51, Plastimed, Saint-Leu La Forêt, France) in polyvinyl chloride (PVC); Prolongation Biocath® made of both polyvinyl chloride and polyethylene (PVC/PE); PE on the inside of the tube; the tubing has a diameter of 3

Table 1
Analytical conditions used

Drugs to be analysed	Mobile phase	Rate (ml/min)	Injected volume (μl)	Wavelength (nm)	Standard
Isosorbide dinitrate	methanol/water (55 : 45 v/v)	0.8	20	220	internal (nitroglycerin)
Sodic heparin	phosphate buffer (0.01 M) pH 4/acetonitrile (65 : 35 v/v)	1.3	20	220	external

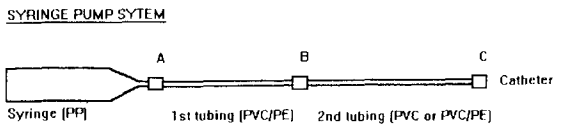

Fig. 1. Diagram of the experimental unit for infusing a single drug (ISDN or heparin). A–C are the points where samples were taken.

Table 2
Infusion protocols

Drugs	Rate (ml/h)	Concentration in the syringe (mg/ml)	Solvent of dilution	Time of perfusion
ISDN	4	10	no solvent	12
Heparin	4	3	5% glucose or EPPI	12

mm over a length of 150 cm (reference PC 3315 M, Care L.G.L., Tarare, France).

Solvents. Heparin solutions for infusion were preapred in 5% glucose (Biosedra, Louviers, France) or in water for injectable preparations (EPPI), (Bruneau, Boulogne-Billancourt, France).

2.2. Methods

2.2.1. Preparation of standard solutions

Working solutions were obtained by diluting the ISDN and heparin in water. Standard curves were established for ISDN concentrations from 100 to 1000 μg/ml and heparin concentrations from 1.25 to 5 mg/ml (i.e., 125–500 IU/ml).

2.2.2. Chromatographic conditions

Table 1 summarises the analytical conditions used for each active substance tested.

The standard curves represent the peak surface as a function of the heparin concentration. ISDN was quantified by taking the ratio between the peak surfaces (ISDN peak surface/peak surface of internal standard) as a function of ISDN concentration. The ISDN or heparin concentration of a sample was calculated by interpolation from the linear equation $y = ax + b$ of the standard.

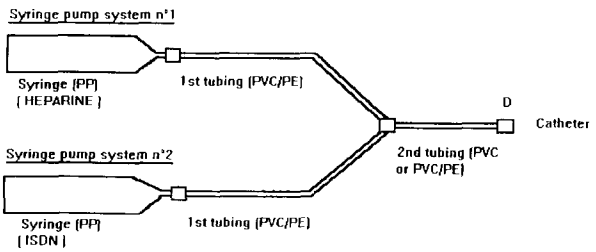

Fig. 2. Diagram of the experimental unit for infusing simultaneously ISDN and heparin. D is the point where samples were taken.

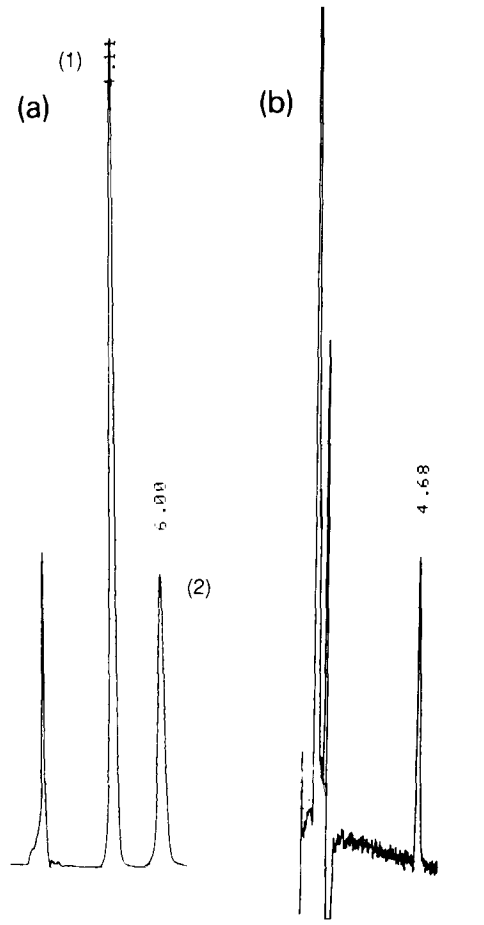

Fig. 3. (a) Chromatogram of a 500 μg/ml ISDN solution (1) and 400 μg/ml of trinitrine, internal standard (2); (b) chromatogram of a 2.5 mg/ml heparin solution.

Table 3
Precision and linearity of HPLC methods

Drugs	Concentration added (mg/l)	Intra-day variability		Inter-day variability		Linearity	
		Concentration found (mg/l)	Coefficient of variation (%)	Concentration found (mg/l)	Coefficient of variation (%)	Equation	Correlation coefficient
ISDN	100	99.6 ±2.1	2.1	101.0 ± 3.4	3.4	$y = 0.00433x + 0.0257$	0.9999
	500	496.0 ±6.7	1.4	507.2 ±18.3	3.6		
Heparin	1.25	1.24±0.08	6.3	1.24± 0.04	3.1	$y = 9989x + 5$	0.9999
	2.5	2.50±0.07	2.8	2.51± 0.08	3.2		
	5	4.91±0.13	2.6	5.00± 0.04	0.8		

2.2.3. Infusion protocol

The conditions used in a hospital service (Cardiology Department, Hospital G. Montpied, Clermont-Ferrand, France) were followed.

Clinical conditions were simulated in the laboratory. This study was aimed at the evaluation of not only the compatibility of ISDN and heparin with plastics (PP, PVC, PE) but also their behaviour when administered as a mixture and the influence that they have on each other (in the final tubing before entering the vascular system of the patient).

The experimental unit and points of sampling are illustrated in Fig. 1 and 2. Sampling at points A–C allowed each drug (ISDN and heparin) to be evaluated separately as regards their compati-

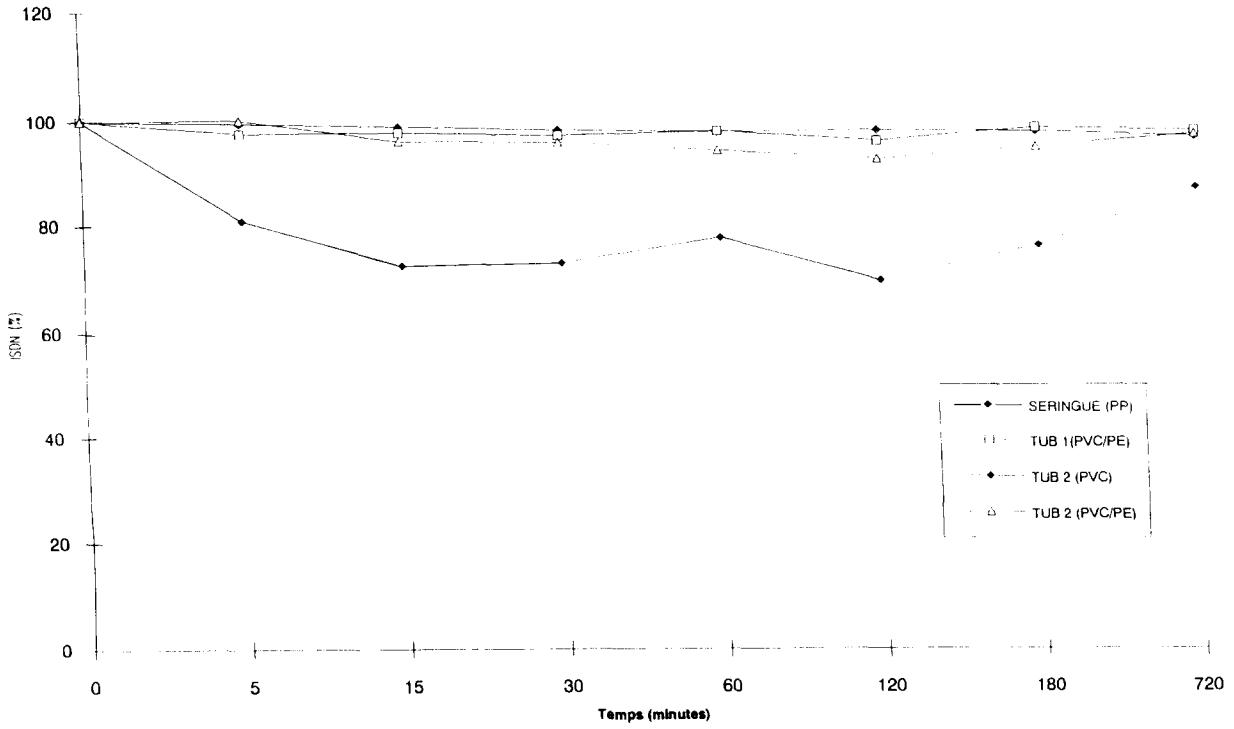

Fig. 4. Stability of ISDN alone during continuous infusion: compatibility with PP, PVC/PE and PVC.

bility with the PP syringe, the first PVC/PE tubing and the second PVC or PVC/PE tubing. The sample taken at point D investigated the compatibility of a combination of ISDN and heparin which entered simultaneously and was mixed in the final tubing of PVC or PVC/PE.

Samples were taken at set times during the infusion procedure: the first samples were removed at A–D when purging the system before infusion was started. These were samples T_0. Samples were then taken after intervals of 5, 15, 30 min and then at 1, 2, 3 and 12 h. Infusions in clinical practice do not last more than 12 h for either heparin or ISDN.

The above investigation was carried out at room temperature. No particular conditions of light were specified.

The samples were analysed immediately by HPLC.

The parameters adopted for the therapeutic protocol and the infusion were representative of the situations most frequently found in hospital and are given in Table 2.

Before HPLC injection, the ISDN samples were diluted with an equal volume of water containing a fixed quantity of internal standard, since the undiluted concentrations were too high for the range of standards.

A substance was considered as stable if the variations observed did not exceed 10% of the initial concentration.

Nurses often prepare the syringes several hours before the infusion is due to begin. It was necessary therefore to investigate the stability of both ISDN and heparin in PP syringes left for 8 h under different conditions: for heparin, at room temperature and in the refrigerator (+4°C); for ISDN, at room temperature under light, at room temperature in the dark, in the refrigerator (+4°C).

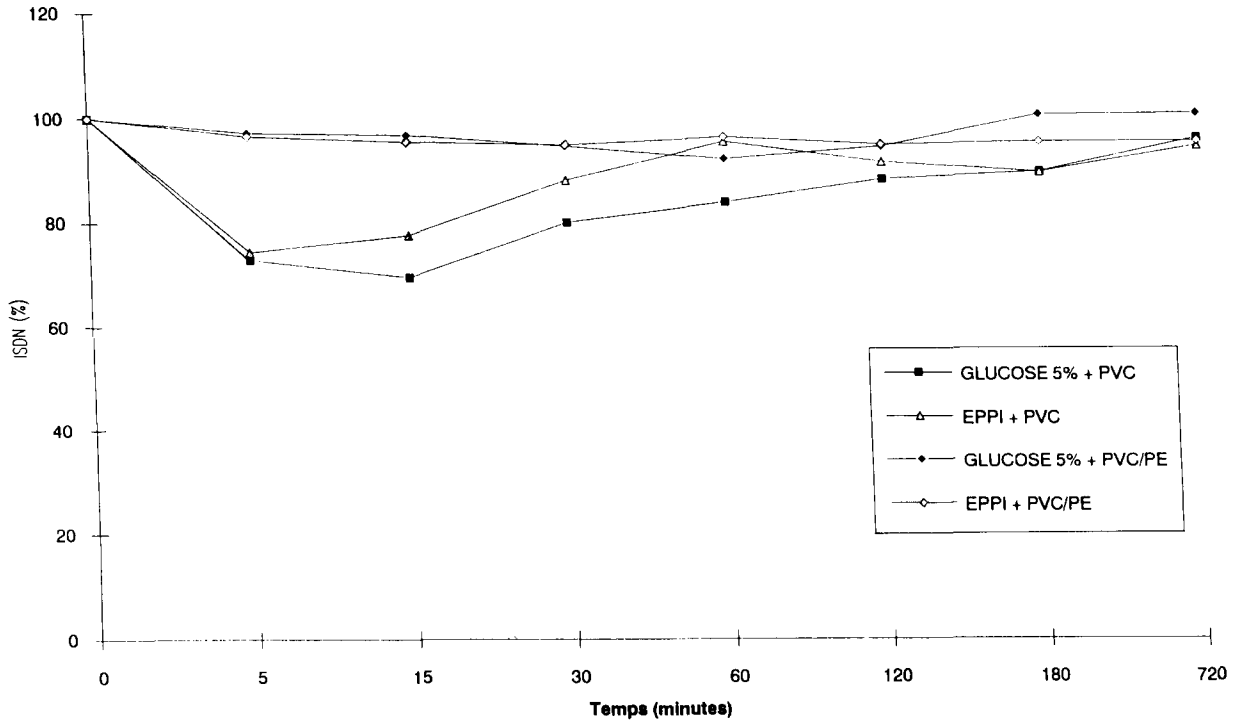

Fig. 5. ISDN stability in second tubing during a simultaneous infusion with heparin.

3. Results and discussion

3.1. Chromatographic analysis

The techniques for quantifying ISDN and heparin were found to be valid: the precision (intra-day and inter-day variabilities) and the linearity (equation and correlation coefficient) are given in Table 3. For studying intra-day and inter-day variabilities, 10 measurements were made for each of the concentrations analysed.

Chromatograms a and b in Fig. 3 show, respectively, the results obtained after injection of a 500 μg/ml ISDN standard (with trinitrine as internal standard) and a 2.5 mg/ml (i.e., 250 IU/ml) heparin standard.

3.2. Continuous infusion stability studies

The quantification of the different samples is presented as a kinetic plot over 12 h. The amounts are expressed as a ratio of the initial value at T_0. The percentages given are the average of five different repetitions ($n = 5$).

3.3. ISDN stability during continuous infusion (ISDN alone) (Fig. 4)

ISDN was stable in PP syringes and in PVC/PE tubing. The variations were lower than 10%. However, the loss of this product could be as much as 30% in PVC tubing. This loss decreased after 12 h, therefore, it can be supposed that the ISDN fixed on the PVC is eventually released.

Various studies have shown that nitrate compounds are fixed by plastics in two ways: adsorption and absorption (Yuen et al., 1979; Roberts et al., 1983): the nitrate compounds undergo an initial rapid phase of adsorption (a surface phenomenon) and a slower second phase of absorp-

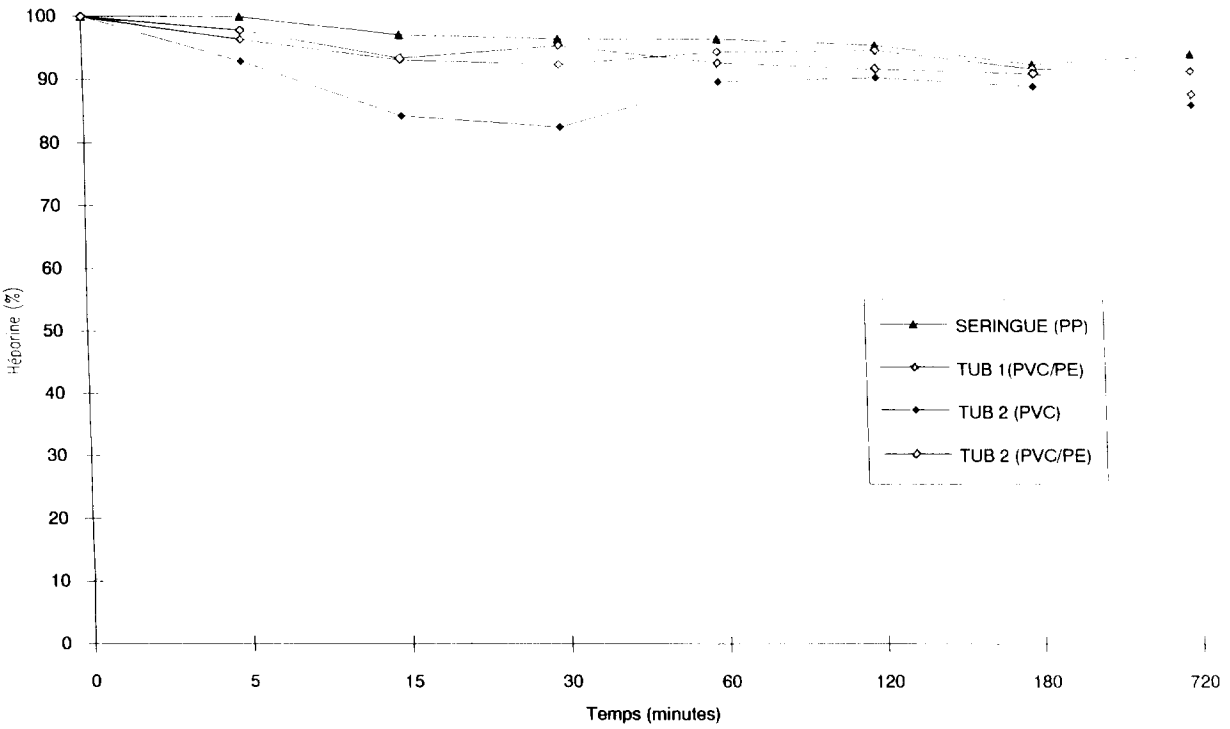

Fig. 6. Stability of heparin administered alone during continuous infusion in 5% glucose.

tion (the products diffuse inside the polymer). These ISDN/PVC interactions are reversible as shown by the release of ISDN after fixation on PVC.

3.4. ISDN behaviour in the second tubing (sample D) during continuous infusion in association with heparin (Fig. 5)

The behaviour of ISDN in two different situations was studied: the heparin was either diluted in 5% glucose or in a preparation of injectable water (EPPI). When the second tubing was PVC/PE the results were similar for the two solvents: the variations were less than 10%. However, in the case of PVC tubing, ISDN was released after about 15 or 30 min when administered simultaneously with heparin in comparison to a much longer time when administered alone.

3.5. Heparin stability during continuous infusion when in 5% glucose (Fig. 6) or in EPPI (Fig. 7) (heparin alone)

The stability of heparin with plastics as well as the influence of solvent type on this stability was studied.

Heparin was stable in PP syringes irrespective of the solvent used. However, heparin was lost as it passed through PVC tubing. The variation in heparin concentration was relatively stable with time (20–25% in 5% glucose and 10–15% in EPPI).

The behaviour of heparin in PVC/PE tubing was more difficult to evaluate because the variations were near to 10%.

There was no statistically significant difference between the stability of continuously infused heparin in 5% glucose or in EPPI.

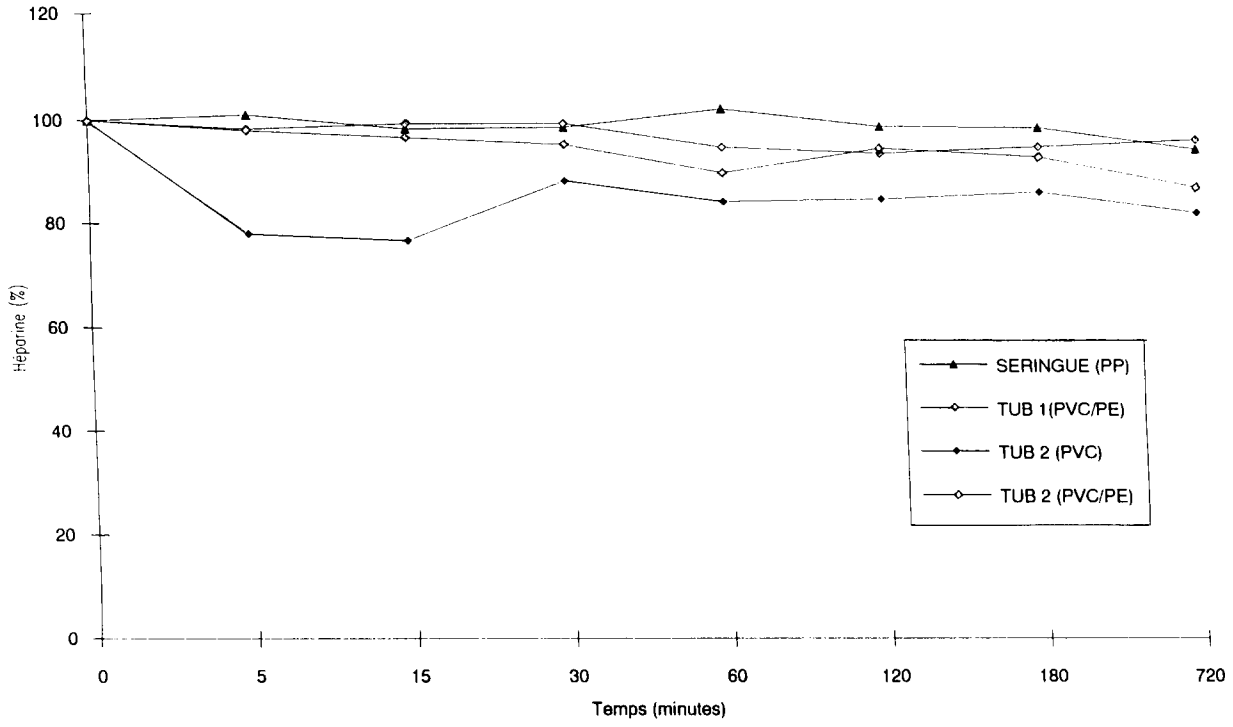

Fig. 7. Stability of heparin administered alone during continuous infusion in EPPI.

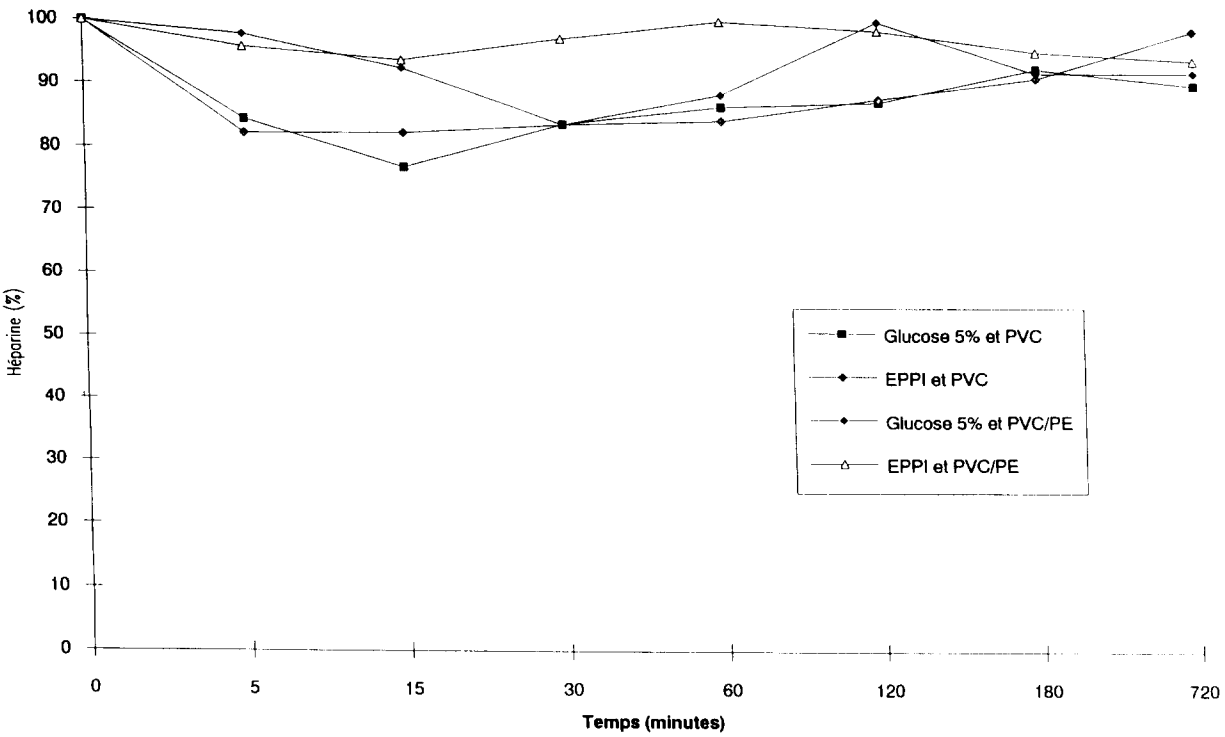

Fig. 8. Heparin stability (in glucose or EPPI) in the second tube during simultaneous administration with ISDN.

3.6. Heparin behaviour in the second tubing (sample D) during continuous infusion in association with ISDN (Fig. 8)

This study evaluated the stability of heparin diluted either in 5% glucose or EPPI with PVC or PVC/PE when infused simultaneously with ISDN in the same tube.

Heparin loss in PVC tubing was similar to that which occurred when the drug was infused alone.

The results with PVC/PE tubing were very variable. These variations seemed greater with 5% glucose. A 16% loss after 30 min was observed and 11–12% after 1 h. However, the variations did not exceed 10% whether the infusion solvent was 5% glucose or EPPI.

3.7. Stability studies of heparin and ISDN in PP syringes prepared in advance

Heparin solutions (3 mg/ml) were stable for 8 h in PP syringes regardless of the solvent used (5% glucose or EPPI) or conditions under which the syringes were kept (room temperature or in the refrigerator at 4°C).

ISDN solutions (10 mg/ml) in PP syringes were stable for 8 h whether or not they had been exposed to light. However, with refrigerated syringes there was a variation of approx. 10% of the initial concentration of ISDN. Hence, it is not advisable to keep syringes in the refrigerator.

4. Conclusion

The behaviour of two drugs frequently administered with syringe pump systems and which are mixed in a common prolongation tube before entering the vascular system of the patient has been assessed. After investigating the compatibility of each of these drugs with plastics during a 12 h continuous infusion, their stability when mixed in a common tubing was studied. The results show that absorption or adsorption and release of

the drugs are very random phenomena. This implies that the administration to the patient of these drugs must be variable, even discontinuous. This work will be pursued further by a pharmacokinetic study of ISDN and an assessment of heparin activity in vivo with the patient.

Acknowledgements

The authors wish to thank F. Picq, H. Confolent and M.T. Groueix for cooperation in the analysis of isosorbide dinitrate and heparin

References

Allwood, M.C., Sorption of drugs to intravenous delivery system. *Pharm. Int.*, 4 (1983) 83–85.

Arnaud, Y., Dauphin, A. and Mignot, A., Interactions matières plastiques/médicaments. In *Les Matières Plastiques à Usage Pharmaceutique*, E.M. Inter, 2nd Edn, 1991, pp. 302–355.

Cossum, P.A. and Roberts, M.J., Availability of isosorbide dinitrate, diazepam and chlormethiazole from i.v. delivery systems. *Eur. J. Clin. Pharmacol.*, 19 (1981) 181–185.

D'Arcy, P.F., Drug interactions with medical plastics. *Drug. Intell. Clin. Pharm.*, 17 (1983) 726–731.

De Muynck, C., Colardyn, F. and Remon, J.P., Influence of intravenous administration set composition on the sorption of isosorbide dinitrate. *J. Pharm. Pharmacol.*, 43 (1991) 601–604.

De Muynck, C., Remon, J.P. and Colardyn, F., The sorption of isosorbide dinitrate to intravenous delivery system. *J. Pharm. Pharmacol.*, 40 (1988) 601–604.

De Vries, J., Analysis of heparins by size-exclusion and reversed-phase high performance liquid chromatography with photodiode-array detection. *J. Chromatogr.*, 465 (1989) 297–304.

Goodall, K.T., Chooi, C.C. and Gallus, A.S., Heparin stability: effects of diluent, heparin activity, container and pH. *J. Clin. Pathol.*, 33 (1980) 1206–1211.

Illum, L. and Bundgaard, H., Sorption of drugs by plastic infusion bags. *Int. J. Pharm.*, 10 (1982) 339–351.

Lee, M.G. and Fenton May, V., Absorption of isosorbide dinitrate by PVC infusion bags and administration sets. *J. Clin. Hosp. Pharm.*, 6 (1981) 209.

Menzies, A.R., Benoliel, D.M. and Edwards, H.E., The effects of autoclaving on the physical properties and biological activity of parenteral heparin preparations. *J. Pharm. Pharmacol.*, 41 (1989) 512–516.

Olsen, C.J. and Scroggins, H.S., High performance liquid chromatographic determination of the nitrate esters isosorbide dinitrate, pentaerythritol tetranitrate and erythrityl tetranitrate in various tablet forms. *J. Pharm. Sci.*, 73 (1984) 1303–1304.

Pintabona, A., Bottazzi, A. and Capra, R., Analisi biologica e HPLC di eparina trattata termicamente. *Boll. Chim. Farm.*, 130 (1991) 439–442.

Remon, J.P. and Bogaert, M.G., Loss of glyceryl trinitrate and isosorbide dinitrate during infusion: a literature survey and practical recommendations. *Acta Clin. Belg.*, 38 (1983) 328–334.

Roberts, M.S., Cossum, P.A., Kowaluk E.A. and Polack, A.E., Factors affecting the availability of organic nitrates, from plastic infusion systems: structure of organic nitrate, nature of plastic and effect of temperature. *Int. Pharm.*, 17 (1983) 145–159.

Tundridge, L.G., Lloyd, J.V. and Penhall, R.K., Stability of diluted heparin sodium stored in plastic syringes. *Am. J. Hosp. Pharm.*, 38 (1981) 1001–1004.

Yuen, P.H., Denman, S.L., Sokoloski, T.D. and Burkmann, A.M., Loss of nitroglycerin from aqueous solution into plastic intravenous delivery systems. *J. Pharm. Sci.*, 68 (1979) 1163–1166.