J. Pharm. Pharmacol. 1991, 43: 601–604
Received January 8, 1991

Influence of Intravenous Administration Set Composition on the Sorption of Isosorbide Dinitrate

C. DE MUYNCK, F. COLARDYN AND J. P. REMON

*Laboratory of Pharmaceutical Technology, State University of Gent, Harelbekestraat 72, B-9000 Gent, Belgium, and * Intensive Care Department, University Hospital, De Pintelaan 185, B-9000 Gent, Belgium*

Abstract—The influence of the composition of administration sets on the sorption of isosorbide dinitrate was investigated in-vitro. Isosorbide dinitrate solutions (250 $\mu g\ mL^{-1}$) in 0·9% NaCl or 10% glucose were stored in glass containers and administered at a flow rate of 20 mL h^{-1}. The influence of the concentration of different plasticizers (di-ethylhexylphthalate, tri-ethylhexyltrimelitate) in polyvinylchloride tubings was determined. Polybutadiene tubings of different mol. wt coextruded laminates of these polybutadienes with PVC of different composition and a polyethylene tubing were evaluated. The higher the Shore hardness of the PVC tubing, the lower the sorption. The infusion fluid played an additional role only for the tubings with high Shore hardness (> 70). The sorption of isosorbide dinitrate to polybutadiene tubings of different mol. wt was less than 2·5% after 5 h and was comparable with the sorption to the polyethylene tubing. When polybutadiene/PVC laminates were used, the sorption increased significantly and was in most cases dependent on the Shore hardness of the PVC (higher Shore hardness gave lower sorptions) and on the mol. wt of the polybutadiene (lower mol. wt resulted in higher sorption). Sorption was not dependent on the type of PVC plasticizer.

Nitrates are widely used in the therapy of angina pectoris and congestive heart failure. Different routes of administration and various formulations are available for this purpose (Parker 1987; Thadani 1987). Continuous infusion of nitrates (nitroglycerin and isosorbide dinitrate (ISDN)) is a mode of administration taking a prominent place in the treatment of the acute phase of myocardial infarction (Ebert et al 1982). A major problem concerning i.v. administration is the loss by sorption (ad- and absorption) of nitrates to the different parts of the administration sets. Extensive literature is available on this subject for both nitroglycerin (Boylan et al 1978; Cossum et al 1978; Baaske et al 1980; Roberts et al 1980; Remon & Bogaert 1983; De Rudder et al 1987) and ISDN (Cossum & Roberts 1981; Lee & Fenton-May 1981; Morrison et al 1982; Remon & Bogaert 1983; De Muynck et al 1988).

The sorption of ISDN is most pronounced when polyvinyl chloride (PVC) is used as a polymer material but the reason for some inconsistencies in the sorption data to PVC tubings remains unclear. It was the aim of this study to investigate the influence of the type and/or the amount of plasticizer on the ISDN sorption to PVC administration sets and to compare the sorption profiles of ISDN to polyethylene (PE) and different polybutadiene (PBD) tubing.

Materials and Methods

Materials

Cedocard IV ampoules (Cedona, Haarlem, Holland) containing 10 mg/10 mL ISDN in an aqueous solution were used. For all experiments these solutions were diluted in 500 mL glass infusion fluid containers containing 0·9% NaCl or 10% glucose (NPBI Emmer Compascuum, Holland). The final concentration of ISDN was 250 $\mu g\ mL^{-1}$.

Correspondence: J. P. Remon, Laboratory of Pharmaceutical Technology, Harelbekestraat 72, B-9000 Gent, Belgium.

Sixteen infusion tubings (Rehau AG & Co., Rehau, Germany) were tested. Three groups of PVC tubings were examined. The first two were different according to the plasticizer (di-ethylhexylphthalate (DEHP) and tri-ethylhexyltrimelitate (TEHTM)) and the concentration of plasticizer used. This latter variable reflected the hardness values. In a third group (PVC N88) no plasticizer, but only a stabilizer, epoxidized soya oil, was used. This stabilizer is present in all three groups of PVC tubing in order to reduce the decomposition of the PVC during extrusion or during γ-irradiation (Lemm & Bücher 1986).

Two PBD tubings were used one with high (PBD H) the other with low (PBD L) mol. wt. These tubings were used as such or as laminates with an outer PVC layer having a different plasticizer composition and hardness. A PE tubing was also included in the study. All the tubings were 180 cm in length, had an internal diameter of 3·0 mm and a wall thickness of 0·55 mm. The main specifications of the tubings are given in Table 1.

Hardness determination

The hardness of all tubings was tested following the Shore hardness testing procedure (DIN 53505-ISO R 868) using a hardness meter Härteprüfer HP-AR (Bareiss, 7938 Oberdischingen, Germany). The hardness values are shown in Table 1. For the tubings made from two different polymers, the Shore hardness value of the inner part is given followed by the value of the outer part.

Simulated infusion

The infusion of ISDN was simulated in the laboratory. Administration sets were connected to the infusion fluid containers and the infusion rate was adjusted to 20 mL h^{-1} by a roller clamp. Samples were taken at the end of the administration set at regular time intervals over 5 h. The samples were collected in borosilicate tubes with rubber stoppers and were analysed the same day.

Table 1. Specifications of the tested administration sets and mean percentages (±s.d.) ISDN sorbed after 5 h.

Code	PVC plasticizer	Shore hardness	% Sorption (± s.d.) after 5 h 0·9% NaCl	10% Glucose
PVC D 65	DEHP	A 65	35·2±0·7	34·2±0·3
PVC D 70	DEHP	A 70	27·1±1·9	24·2±2·3
PVC D 75	DEHP	A 75	20·7±1·4	14·4±2·0
PVC D 84	DEHP	A 84	12·9±1·8	8·9±0·5
PVC D 90	DEHP	A 90	8·9±0·2	4·4±1·0
PVC N 88	—	A 88	8·9±2·7	5·5±0·4
PVC T 75	TEHTM	A 75	15·7±2·3	11·5±1·5
PVC T 90	TEHTM	A 75	9·3±2·5	5·3±1·2
PBD H	—	A 90	1·6±0·3	1·9±0·8
PBD H/PVC D 65	DEHP	A 91/A 65	8·1±3·4	8·8±0·9
PBD H/PVC D 70	DEHP	A 91/A 70	7·6±0·7	5·6±0·3
PBD H/PVC D 80	DEHP	A 91/A 80	7·7±2·0	4·0±1·3
PBD H/PVC T 80	TEHTM	A 91/A 80	8·9±2·7	3·3±0·5
PBD L	—	A 79	1·8±0·1	1·1±0·1
PBD L/PVC D 70	DEHP	A 79/A 70	11·5±1·0	16·1±4·0
PE	—	D 45	1·6±0·3	1·9±0·2

Each code gives: the polymer name (PVC, PBD or PE), the plasticizer for the PVC tubing: D (di-ethylhexylphthalate), T (tri-ethylhexyltrimelitate) or N (no plasticizer). The mol. wt of the PBD tubing H(high) or L(low), the Shore A hardness.

All experiments were performed three times and the study was carried out at room temperature (21±1°C).

Calculation

The area under the ISDN recovery-time curve was determined and the percentage ISDN sorbed was calculated. Non-parametric statistics were performed by the Mann-Whitney U-test and Kruskal-Wallis one-way analysis of variance by rank. $P < 0.05$ was considered to be statistically significant.

Analysis

An HPLC method described by Gelber & Papas (1983) was used for the ISDN analysis. The system consisted of an HPLC pump (Merck-Hitachi L-6000 pump, E. Merck, Darmstadt, Germany), a reversed phase column (5 μm particles Lichrospher RP-18; 125 mm × 4 mm, E. Merck, Darmstadt, Germany), a variable wavelength UV-Vis detector (Merck-Hitachi UV-Vis detector, E. Merck, Darmstadt, Germany) set at 215 nm, an integrator (Merck-Hitachi D-2000, E. Merck, Darmstadt, Germany) and a septumless syringe-loaded injector loop of 50 μL (Valco Instruments Corporation, Houston, USA). The mobile phase consisted of methanol-water (40:60, v/v). The flow rate was 1·0 mL min^{-1}.

Several calibration curves were prepared in a concentration range of 0 to 300 μg mL^{-1}. Linearity was obtained in this concentration range by expressing peak height vs ISDN concentration ($y = 3{\cdot}33x + 0{\cdot}28$ with $r^2 = 0{\cdot}9979$). The standard deviation calculated on the slope of the calibration curve (n = 5) was 0·4% (inter day CV) and 0·2% (intra day CV).

Results and Discussion

Preliminary tests revealed that no ISDN was lost to the glass and rubber from the infusion fluid containers over 5 h. Table 1 indicates the mean percentages ISDN (±s.d.) sorbed to the different tubings over 5 h, for both infusion solutions. The amount of plasticizer played an important role in the sorption process. The higher the amount of plasticizer the higher the sorption. Fig. 1 shows typical sorption profiles of ISDN, diluted in 10% glucose, to PVC tubings plasticized with different amounts of DEHP. The sorption profile can be divided into two phases: an initial adsorption of ISDN to the polymer surface resulting in a significant decrease in available ISDN and a second phase due to adsorption of ISDN in the polymer (De Muynck et al 1988) (Fig. 1). The amounts of ISDN sorbed to PVC tubings with different concentrations of DEHP (PVC D group) were significantly different ($P < 0.05$ Mann-Whitney U-test) for both infusion fluids.

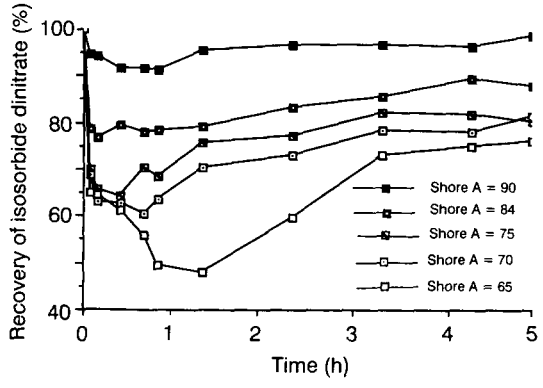

FIG. 1. Mean % ISDN recoveries of to PVC D tubings, of different Shore A hardness, from 10% glucose over 5 h (n = 3).

The values for Shore A hardness (amount of plasticizer) and the percent sorption are given in Table 1. When the sorption of ISDN diluted in 0·9% NaCl or 10% glucose was compared, no significant difference was found for the tubings with the highest amount of plasticizer (PVC D 65 and PVC D 70) in contrast to the PVC D 75–84–90 tubings where the

sorption was significantly higher from 0·9% NaCl ($P < 0·05$; Mann-Whitney U-test). The higher sorption from 0·9% NaCl solutions was previously attributed to a difference in hexane-water phase partition coefficient (De Muynck et al 1988). Sturek et al (1978) observed greater loss of nitroglycerin from 0·9% NaCl than from 5% glucose. Loucas et al (1990) recently reported a lower initial adsorption of nitroglycerin from 0·9% NaCl solution while after this initial period the opposite effect occurred. Pikal et al (1977) found that non-polar solutes could be salted out by electrolytes. Our results indicate that care should be taken in using partition coefficients for the prediction of sorption of drugs from different infusion solutions to polymer tubings. Sorption of ISDN from 0·9% NaCl and glucose solution to PVC tubing was dependent on the amount of plasticizer.

Although DEHP is still the most widely used plasticizer in PVC tubings, there is an increasing interest in other plasticizers such as tri-ethylhexyltrimelitate (TEHTM). This is because DEHP has been shown to migrate easily from PVC into fluids such as fat emulsions (Mazur et al 1989) or blood products (Jaeger et al 1972). The use of other plasticizers seems justified since DEHP is a suspected hepatotoxin, carcinogen and teratogen (Daniel 1978; Gray et al 1982). Although being structurally related to DEHP, TEHTM is reported to migrate from PVC to a much lesser extent that DEHP (Lemm & Bücher 1986).

In this study the sorption of ISDN to PVC tubings with different amounts of TEHTM was also determined (PVC T tubings). The results (Table 1) show that, as for the PVC-DEHP tubings, the sorption was dependent on the amount of plasticizer and on the infusion fluid used. There was a significantly higher sorption to the PVC T 75 than to the PVC T 90 tubing for both infusion fluids ($P < 0·05$; Mann-Whitney U-test). The sorption to both tubings was higher when 0·9% NaCl was used. ($P < 0·05$; Mann-Whitney U-test). No significant difference in sorption to tubings with a different plasticizer (DEHP or TEHTM) but with the same Shore hardness (A75 or A90) was found. This indicates that the Shore hardness more than the type of plasticizer used was the determining factor for ISDN sorption. The influence of the type and amount of plasticizer as well as the influence of the infusion fluid on the sorption of ISDN was confirmed by comparing the PVC N 88 the PVC D 90 and the PVC T 90 tubing ($P < 0·05$; Kruskal-Wallis test). The sorption of ISDN was significantly higher when 0·9% NaCl was used. ($P < 0·05$; Mann-Whitney U-test).

PBD tubings were introduced to solve the sorption problems of drugs. Lee (1986) and De Muynck et al (1988) described the negligible or low sorption of chlormethiazole, nitroglycerin, diazepam and ISDN to PBD tubings.

The results obtained with the different PBD tubings and the PE tubing are shown in Table 1. PBD tubings of two different mol. wt (PBD H(high mol. wt) and PBD L(low mol. wt) were used. For both PBD tubings the sorption was lower than 2·5% after 5 h and comparable with the sorption observed for PE tubing. The disadvantage of the PBD H and PE tubings is the difficulty in accurate adjustment of flow rates by peristaltic infusion pumps, due to the high Shore A hardness of these tubings. The error in the delivered volume by a peristaltic infusion pump was less than 5% for the PBD L tubing and about 25% for the PBD H tubing. Therefore, the PBD L tubing seems a suitable alternative to PVC tubings.

To obtain tubings of better pumping characteristics, especially for the PBD H, several tubings have been developed with an inner PBD wall and an outer PVC wall. Three additional groups of tubings were tested: the PBD H/PVC D or T laminates and PBD L/PVC D laminates. The use of PVC D outer wall induced a significant increase in sorption of ISDN to the PBD H tubing, for both infusion fluids. The sorption to the PBD H/PVC D tubings was not influenced by the concentration of plasticizer for the experiments with 0·9% NaCl in contrast to the experiments with 10% glucose where the sorption of ISDN was proportional to the amount of plasticizer in the PVC. This dependence of sorption on the amount of plasticizer has already been noted for the PVC tubings without PBD inner wall. This phenomenon can probably be explained by migration of plasticizer into the PBD matrix. The sorption was significantly lower than for the PVC tubing without the PBD inner wall (PVC D 65 vs PBD H/PVC D 65; $P < 0·05$ Mann-Whitney U-test). No influence of the type of plasticizer (DEHP or TEHTM) on the sorption to PBD H/PVC was seen. This was rather surprising since TEHTM has been proposed as a plasticizer having a reduced affinity for migration from PVC tubings (Lemm & Bücher 1986).

The use of a laminate composed of a lower mol. wt PBD L and PVC D 70 resulted in significantly higher sorption of ISDN than observed for the PBD tubing of a higher mol. wt surrounded by the same PVC tubing (PBD H/PVC D 70) ($P < 0·05$; Mann-Whitney U-test). The sorption was significantly lower than for the PVC D 70 tubing without PBD inner wall ($P < 0·05$; Mann-Whitney U-test), for both infusion solutions. The lower mol. wt probably allows an easier and higher migration of the plasticizer to the PBD part of the laminate. In contrast to the PBD H/PVC D 70 tubing no significant difference was found between the percentages of ISDN sorbed from the two infusion solutions.

In conclusion we can say that the sorption to PVC tubings was dependent on the Shore hardness of the tubing and that the infusion fluid plays an additional role only for the tubings with a Shore hardness higher than 70. The sorption of ISDN to PE and to PBD tubings of different mol. wt is less than 2·5% after 5 h of infusion and comparable with the polyethylene tubing. When PBD/PVC laminates were used the sorption increased significantly, was dependent on the mol. wt of the PBD and on the Shore hardness of the PVC laminate (except for PVC D tubings and 0·9% NaCl) but was not dependent on the plasticizer used in PVC. Clinically, PBD or PE tubings in combination with syringe pumps or PBD L tubing for peristaltic infusion pumps are recommended for the i.v. administration of ISDN.

Acknowledgements

The authors wish to thank Rehau Ag & Co. (Rehau, Germany) for the supply of all tubings, the Belgian Hospital Supplies (Wilrijk, Belgium) for the assemblation of the administration sets and the Belgian Association of Hospital Pharmacists.

References

Baaske, D. M., Amann, A. H., Wagenknecht, D. M., Mooers, M.,

Carter, J. F., Harvey, J. H., Stoll, R. G. (1980) Nitroglycerin compatibility with intravenous fluid filters, containers and administration sets. Am. J. Hosp. Pharm. 37: 201–205

Boylan, J., Robinson, R., Terill, P. (1978) Stability of intravenous nitroglycerin solutions in viaflex plastic containers. Ibid. 35: 1031

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

Cossum, P. A., Roberts, M. S., Galbraith, A. J., Boyd, G. W. (1978) Loss of nitroglycerin from intravenous infusion sets. Lancet ii: 349–350

Daniel, J. W. (1978) Toxicity and metabolism of phthalate esters. Clin. Toxicol. 13: 257–268

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

De Rudder, D., Remon, J. P., Neyt, E. N. (1987) The sorption of nitroglycerin by infusion sets. Ibid. 39: 556–558

Ebert, W., Menke, G., Engelhardt, W., Rietbrock, N. (1982) Löslichkeit und Adsorption von nitroglycerin und nitraten des isosorbids in polypropylen-, polyäthylen-, polyurethan- und polyvinylchloridschläuchen. Probleme bei intravenöser application von nitraten. Nitrattherapie Heute. Friedr. Vieweg & Sohn Braunschweig/Wiesbaden, Germany, pp 53–61

Gelber, L., Papas, A. N. (1983) Validation of high-performance liquid chromatographic methods for analysis of sustained-release preparations containing nitroglycerin, isosorbide dinitrate, or pentaerythritol tetranitrate. J. Pharm. Sci. 72: 124–126

Gray, T. J., Beamand, J. A., Lake, B. G., Foster, J. R., Gangolli, S. D. (1982) Peroxisome proliferation in cultured rat hepatocytes produced by clofibrate and phthalate ester metabolites. Toxicol. Lett. 10: 273–279

Jaeger, R. J., Rubin, R. J. (1972) Migration of phthalate ester plasticizer from PVC blood bags into stored human blood and its localization in human tissues. New Engl. J. Med. 287: 1114–1118

Lee, M. G., Fenton-May, V. (1981) Absorption of isosorbide dinitrate by PVC infusion bags and administration sets. J. Clin. Hosp. Pharmacy 6: 209–211

Lee, M. G. (1986) Sorption of four drugs to polyvinylchloride and polybutadiene intravenous administration sets. Am. J. Hosp. Pharm. 43: 1945–1950

Lemm, W., Bücher, E. S. (1986) Was ist medizinisches no-DOP-PVC? Kardiotechnik 9: 39–42

Loucas, S. P., Maager, P., Mehl, B., Loucas, E. M. (1990) Effect of vehicle ionic strength on sorption of nitroglycerin to a polyvinyl chloride administration set. Am. J. Hosp. Pharm. 47: 1559–1562

Mazur, H. I., Stennett, D. J., Egging, P. K. (1989) Extraction of diethylhexylphthalate from total nutrient solution-containing polyvinylchloride bags. J. Parent. Enter. Nutr. 13: 59–62

Morrison, R. A., Fung, H. L., Hohmann, D., Meimertz, T., Jahnchen, E. (1982) Isosorbide dinitrate: pharmacokinetics after intravenous administration. J. Pharm. Sci. 71: 721–723

Parker, J. O. (1987) Nitrate therapy in stable angina pectoris. New Eng. J. Med. 316: 1635–1642

Pikal, M. J., Biber, D. A., Rutherford, B. (1977) Polymer sorption of nitroglycerin and stability of molded nitroglycerin tablets in unit dose packaging. J. Pharm. Sci. 66: 1293–1297

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

Roberts, M. S., Cossum, P. A., Galbraith, A. J., Boyd, G. W. (1980) The availability of nitroglycerin from parenteral solutions. J. Pharm. Pharmacol. 32: 237–244

Sturek, J. K., Sokoloski, T. D., Winsley, W. T., Stack, P. E. (1978) Stability of nitroglycerin injection determined by gas chromatography. Am. J. Hosp. Pharm. 35: 537–541

Thadani, U. (1984) Current status of nitrates in angina pectoris. Mod. Concept Cardiovasc. Dis. 56: 49–54