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Sorption of isosorbide dinitrate to central venous catheters

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Abstract—As several studies demonstrated the sorption of isosorbide dinitrate (ISDN) to intravenous delivery systems, a study on the sorption of ISDN to several central venous catheters was performed. Fourteen different catheters were perfused during a 2 h period, under simulated infusion conditions, with ISDN (250 μg mL^{-1}) in 0·9% (w/v) sodium chloride. The drug loss to a polyethylene and a silicone catheter was 0·2 and 6·1%, respectively. The sorption to a polyvinylchloride heparin-coated thermodilution catheter was 1–6·9% depending on the length of the catheter. The drug loss to polyurethane catheters of different composition varied between 3·8 and 28·9%. For polyurethane catheters composed of cycloaliphatic polyurethanes an inverse relation was shown between Shore A hardness and sorption.

The influence of polymer composition, concentration of plasticizer, concentration of the drug and flow rate has been found to influence the extent of sorption of nitrates. In continuation of previous work (De Muynck et al 1988, 1991), the sorption of isosorbide dinitrate (ISDN), a drug widely used for prophylaxis of angina pectoris and for the treatment of congestive heart failure, to central venous catheters was investigated. This study reports on the sorption of ISDN to central venous catheters made of polyvinylchloride, polyurethane, polyethylene and silicone.

Materials and methods

Materials. Ampoules containing 10 mL ISDN (1 mg mL^{-1}) (Cedocard, Cedona, Haarlem, The Netherlands) were diluted in a glass infusion container with a 0·9% sodium chloride solution (saline) (Emmer Compascuum NPBI, The Netherlands) to obtain a concentration of 250 μg mL^{-1}.

The specifications as commercial name, supplier and composition, length, gauge diameter and Shore A or D hardness of the catheters used are shown in Table 1.

Analysis. The concentration of ISDN was assayed by HPLC (Gelber & Papas 1986). The HPLC system consisted of a UV detector (L-4000, Merck-Hitachi, Darmstadt, Germany) set at 215 nm, a pump (L-6000, Merck-Hitachi), a Chromato-Integrator (D-2000, Merck-Hitachi), with 20 μL injector loop, and a reversed phase column (Lichrospher RP-18, 5 μm particles, 125 mm × 4 mm, Merck). The mobile phase was 60/40 (v/v) methanol/water. The flow rate was 1 mL min^{-1}. Calibration curves showed linearity in a concentration range from 0 to 300 μg mL^{-1} by expressing peak height vs ISDN concentration ($y = 3{\cdot}87x + 0$, $r^2 = 0{\cdot}9991$). The standard deviation calculated on the slope of the calibration curve ($n = 6$) was 0·4% (inter-day) and 0·3% (intra-day).

Experimental. A polybutadiene tubing (Sureset A 261, Avon, Redditch, UK) was connected to a glass infusion container, containing 250 μg mL^{-1} ISDN. The flow rate of 20 mL h^{-1} was adjusted by an infusion pump (Model STC-503, Terumo, Tokyo, Japan). The catheter was connected to the tubing via a 3-way stopcock. The entire catheter, with the exception of the tip, was, from 15 min before the experiment, immersed in a water bath set at 37°C. Control samples were collected from the 3-way stopcock every 15 min and were taken into account to calculate the amount administered. Samples were collected at the catheter tip every 5 min during the first hour, and every 15 min during the second hour. Each catheter was tested three times. For the Secalon Hydrocath catheters the experiment was repeated after perfusion of the catheter, at 37°C, with saline (20 mL h^{-1}) during 7 days.

The amount of ISDN retained was calculated during the first 2 h of simulated administration and is expressed as the percentage of the amount administered.

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Results and discussion

In this study, catheters of four different groups of polymer were tested: polyurethane catheters with a different chemical composition, a polyvinylchloride, a polyethylene and a silicone catheter.

Polyurethanes are segmented or block copolymers, consisting of alternating hard (glassy or semicrystalline) and soft (elastomeric) chain segments (Lelah 1986). Polyurethanes are increasingly used as biomaterials in a broad variety of applications. They can be made durable enough to withstand continuous stress and flexing, they appear to be well tolerated in implant situations, and they can be readily synthesized from a variety of starting materials permitting a wide range of chemical and physical properties (Webster 1988). The primary advantages of polyurethane catheters are superior blood compatibility, improved stiffness for insertion, and softness after insertion reducing the vascular wall irritation and mechanically-induced phlebitis, better combination of fluid flow rates, stiffness and kink resistance, increased radio-pacity, wider applicability to a variety of catheters and reduced catheter assembly costs. Aliphatic polyurethanes have the advantage over aromatic polyurethanes in that they do not yellow upon exposure to UV light and that they do not decompose into carcinogenic products such as 4,4-methylene dianiline (Gogolewski 1988).

Disadvantages of catheters made of the polyolefin, polyethylene, are stiffness and higher thrombogenicity (Planck 1987).

A Swan Ganz catheter was also included in the study since such devices can be used for drug infusion next to their application as thermodilution catheters. Since the catheter was made of polyvinylchloride, with a heparin coating, a sorption study on this catheter was needed. Sorption of ISDN has been shown to be most pronounced to polyvinylchloride infusion tubings, depending on the Shore hardness (De Muynck et al 1991).

Silicone rubber is a polymer of repeating units that are polymerized and cross-linked to make a rubber-like material. The filler used to improve the mechanical property is silica powder, the higher the amount of filler, the harder the rubber is (Webster 1988). Silicone rubber is not often used because it is rather soft and mechanically weak (Planck 1987). However, this material is widely used for urethral catheters.

No sorption to the glass infusion container and minimal sorption to the polybutadiene tubing and the 3-way stopcock was observed. This confirms the data from previous experiments

Table 1. Specifications of the tested catheters and mean percentages (±s.d.) ISDN sorbed after 2 h.

Type of catheter and supplier	Composition	Shore hardness	Gauge size and catheter length (cm)	% Sorption mean (s.d.)
Nutricath "S" (cat. 2180.20) Vygon	Silicone	80 A	14	6·1
			25	(0·8)
LeaderCath (cat. 120.20) Vygon	PE	56 D	14	0·2
			25	(0·1)
Secalon Hydrocath (cat. 7510-1) Viggo	PU (aromatic polyether) (polytetramethylene glycol ether) (methylene di-isocyanate) PVP coated	100 A	16	6·9
			25	(0·6)
	After elution during 7 days*		16	7·0
			25	(0·5)
VygoflexOSpur (cat. 9154.520) Vygon	PU (cycloaliphatic polyether) (Flexane)	100 A	14	5·2
			25	(1·0)
Seldipur (cat. 128.456) Vygon	PU (cycloaliphatic polyether)	95 A	14	6·7
			25	(1·0)
Argon (cat. 497631) Weck	PU (aromatic polyester) (Estane 58092-45 D)	95 A	16	6·2
			20	(0·0)
LeaderFlex (cat. 1225.20) Vygon	PU (cycloaliphatic polyether) (Flexane)	93 A	14	8·5
			25	(0·6)
CVC set (cat. ES-04400) Arrow	PU (aromatic)	93 A	16	8·7
			25	(1·0)
Secalon Seldy (same composition as cat. 1845-7) Viggo	PU (aromatic polyether) (polytetramethylene glycol ether) (methylene di-isocyanate)	90 A	16	6·0
			25	(0·7)
Certofix (cat. 416501/2) Braun	PU (aromatic polyether)	90 A	16	6·0
			25	(0·3)
LeaderFlex** (cat. 1225.20) Vygon	PU (cycloaliphatic polyether) (Flexane)	85 A	14	28·9
			25	(0·9)
Hémocath (cat. 146.20) Vygon	PU (aromatic polyether)	55 D	14	3·8
			25	(0·4)
Viacath (cat. 39-734-7) Becton Dickinson	PU (aromatic polyether) (Vialon)	55 D	16	5·8
			25	(0·2)
Edwards Swan Ganz (93A-831H-7·5F) Baxter	PVC with AMC - Thromboshield	–	7·5 F(rench)	
			25*** and 110 cm	1 (4·1) 6·5 (2·5)

* This catheter was flushed during 7 days with saline 20 mL h^{-1}. ** Withdrawn from the market since 1990. *** The full length (110 cm) was reduced in order to compare catheters of the same length.
PU = polyurethane, PE = polyethylene, PVP = polyvinylpropylene, PVC = polyvinylchloride.

(De Muynck et al 1988, 1991). Samples drawn at regular intervals from the 3-way stopcock were taken as 100% values.

As shown in Table 1, the aromatic polyurethane Hémocath catheter showed the least sorption (3·8±0·4%). The greatest sorption (28·9±0·9%) was observed for a former type of LeaderFlex catheter with a Shore A hardness of 85. This catheter was withdrawn from the market in 1990 because of its high flexibility and was replaced by a new type of LeaderFlex catheter, made of the same block copolymers but mixed in different ratios (Shore A hardness of 93). This new type of catheter showed a significantly lower sorption (8·5±0·6%). The VygoflexOSpur and the Seldipur catheter, both cycloaliphatic polyethers, with a Shore A hardness of 100 and 95, respectively, showed a lower sorption (5·2±1·0 and 6·7±1·0%) than the new type of LeaderFlex. There is a trend indicating that an increase in the Shore hardness implies a decrease in ISDN sorption to polyurethane catheters with a similar chemical composition.

Coating of the Secalon Hydrocath catheter did not cause a relevant change in sorption. Elution of a part of the polyvinylpropylene coat (Jansen & Brim 1987) by flushing the catheter during 7 days with saline did not alter the sorption of ISDN.

Although the contact surface of the catheters was different because of different gauge diameter and different wall thickness or surface smoothness, the amount of ISDN retained by the other catheters was between 5·8 and 8·7% of the amount of ISDN administered.

Sorption to the Swan Ganz thermodilution catheter was low and depended on the catheter length. The mean ISDN sorption

value for the short length (25 cm) catheter was lower than for the polyurethane catheters, but the standard deviation was higher.

Of all catheters tested the polyethylene catheter showed the lowest drug sorption: only $0{\cdot}2 \pm 0{\cdot}1\%$ (mean $\pm$ s.d.) of the amount of ISDN administered was sorbed. The sorption to the silicone catheter was $6{\cdot}1 \pm 0{\cdot}8\%$ and was similar to values observed for polyurethane catheters with a similar Shore hardness.

For all catheters a similar sorption profile was observed. During the first 10 min a sharp decrease in the amount of ISDN available was seen, probably caused by adsorption of the ISDN to the catheter wall. Afterwards, the amount of ISDN available increases towards the original level.

In conclusion, the sorption of ISDN to central venous catheters is low compared with the sorption observed for polyvinylchloride tubings. Polyethylene catheters showed the lowest sorption followed by the polyvinylchloride thermodilution catheter. Within the cycloaliphatic polyurethanes an inverse relation between Shore hardness and sorption was observed.

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A comparison of the incorporation of model steroids into non-ionic micellar and microemulsion systems

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Abstract—The incorporation of testosterone and two of its esters, and progesterone and one of its esters (log P_{oct} varying from 3·3 to 6·9) into 2% w/w soybean oil/Brij 96 microemulsions and Brij 96 surfactant systems has been examined. Possible sites of incorporation have been investigated. The drug carrying improvement of an oil-in-water microemulsion over a micellar system appears to depend on the solubility of the drug in the dispersed oil phase and is significant only for very lipophilic drugs.

Non-ionic oil-in-water (o/w) microemulsions represent an interesting prospect for the development of formulations suitable for the incorporation of poorly water soluble drugs. Such systems are transparent, easy to prepare, thermodynamically stable and may be sterilized by filtration.

It has previously been suggested that unless the drug has significant solubility in the dispersed oil phase, the increase in drug loading in these systems, compared with a micellar solution will be small (Malcolmson & Lawrence 1990).

In this study we report on the level of incorporation of five poorly water soluble, structurally related steroids, of varying log P_{oct} in surfactant systems of the non-ionic surfactant Brij 96, and 3-component o/w microemulsions produced from Brij 96 and containing 2% w/w soybean oil.

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Materials and methods

Materials. All chemicals were used as received. Testosterone, testosterone propionate, testosterone enanthate, soybean oil, 1-octadecene, polyoxyethylene-10-oleyl ether (Brij 96) and dimethoxytetraethylene glycol (DMTG) were obtained from Sigma Chemical Co. (Poole, UK). Methanol (HPLC grade) was obtained from FSA Laboratory Supplies (Loughborough, UK). Progesterone was a gift from Cox Pharmaceuticals (Barnstaple, UK) and medroxyprogesterone acetate a gift from Upjohn Ltd (Crawley, UK). Triple-distilled water, obtained from a well-seasoned all-glass still, was used throughout.

Sample preparation. The microemulsions and surfactant solutions were prepared by adding the required weight of each ingredient, heating to 343 K for 5 min and returning to room temperature (294 K), with constant stirring. The area of existence of 3-component o/w microemulsion systems composed of soybean oil, Brij 96 and water, which remain stable at ambient conditions for at least one month, was determined by producing a large number of individual samples. Oil-in-water microemulsions consisting of 2% w/w soybean oil and either 10, 15 or 20% w/w Brij 96 (testosterone, testosterone proprionate and testosterone enanthate) or 15 or 20% w/w Brij 96 (progesterone and medroxyprogesterone) were used to test drug incorporation compared with micellar solution or equivalent Brij concentration.

Drug incorporation. The levels of incorporation of each drug were determined by introducing a known excess of drug to