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BIODEGRADABLE HOLLOW FIBRES FOR THE CONTROLLED RELEASE OF HORMONES*

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Poly(L-lactide), (PLLA), hollow fibres were prepared using a dry-wet phase inversion spinning process. The effect of several spinning parameters (i.e. bore medium flow rate, spinning dope extrusion rate, fibre take-up rate, and spinning height) on the hollow fibre dimensions is reported. The use of several spinning systems (i.e. different solvent/non-solvent pairs with or without additive) resulted in PLLA hollow fibres with varying asymmetric membrane structures, i.e. a porous matrix covered by an internal and external skin varying from very thick and dense to very thin and porous. Some of the differences in membrane structure were qualitatively explained on the basis of a model developed by Reuvers [52] for the formation of flat-sheet membranes by immersion precipitation. Release experiments were carried out using PLLA hollow fibres filled with a 25 wt.% dispersion of micronized ^{3}H-levonorgestrel in castor oil, and a receiving fluid consisting of 40 wt.% aqueous ethanol. The hollow fibre levonorgestrel release rates were found to be dependent on the membrane structure of the hollow fibre wall. For the different hollow fibre samples, zero-order levonorgestrel release rates were found, in the range of 0.1–10 μg/cm/day. Possible release mechanisms are discussed. Preliminary in vivo *(rabbit) release experiments showed that constant levonorgestrel blood plasma levels could be obtained for a period up to 210 days. It is concluded that the new biodegradable hollow fibre reservoir device shows very promising properties for possible application as a long-acting contraceptive delivery system.*

INTRODUCTION

The development of biodegradable drug delivery systems has received considerable attention during the last decade (reviews [1–8]). To achieve a zero-order drug release rate, reservoir devices may be used, provided that the activity of the drug in the reservoir remains constant and the polymeric membrane remains intact during drug delivery [9–12,13].

Biodegradable reservoir devices currently investigated include: (a) polyester microcapsules, prepared from L-lactide and D,L-lactide homopolymers or their copolymers with glycolide either by a coacervation [14–16] or an air suspension coating process [17,18]; (b) poly(α-amino acid) macrocapsules, prepared from L-glutamic acid/γ-ethyl-L-glutamate copolymers by a dip-coating technique [19–21]; (c) polyester macrocapsules, prepared from poly(ε-cap-

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rolactone) by polymer melt extrusion [22–24] and (d) polymer coating and drug containing core, usually employing poly(ϵ-caprolactone) containing dispersed drug as the core material with various biodegradable (co)polymers as the surrounding wall [25,26].

The systems mentioned above have some drawbacks such as not being removable in case of complications during treatment (a), require surgery or a large injection device (b, c), require the use of highly permeable polymers (b, c, d), are less suitable for polymers with low thermal stability (c, d) or require compatibility of the drug with the production process (a, d).

In this paper we will describe the development and characterization of a reservoir device based on biodegradable hollow fibres, which might overcome the limitations discussed above. The hollow fibers (diameter up to 1.5 mm and length up to 3 cm) are made of poly(L-lactide), PLLA using a phase inversion spinning process. Fibers with these dimensions can be applied subdermally with a simple injection device and are still large enough to allow removal by minor surgery when necessary. Using PLLA hollow fibres a sustained zero-order drug release-rate may be obtained because PLLA has a relatively low rate of biodegradation [27–29]. PLLA also has a low permeability for drugs [2,6,25,30] and a low thermal stability [31–33]. Application of the phase-inversion spinning process allows the preparation of asymmetric membranes with a reduced resistance for drug permeation. Furthermore the fabrication process is carried out at low temperatures thus preventing degradation of PLLA. Because the hollow fibres can be filled with drug after the spinning procedure, the production process is highly drug compatible.

Currently biodegradable polymeric rods or capsules [2,34–37] and intramuscular injectables based on biodegradable polymeric microcapsules [17] or microspheres [30,38] are being developed as long acting contraceptives. Only the injectable microspheres based on a copolymer of D,L-lactide and glycolide (85/15) designed to deliver the progestin norethindrone for 3 months [39] and the subdermal implant Capronor®, consisting of a poly(ϵ-caprolactone) capsule filled with a dispersion of levonorgestrel in ethyl oleate and designed to release the steroid for a period up to one year [23] have reached the stage of human clinical trials. Although devices based on biodegradable microspheres (and microcapsules) have the advantage of being injectable and easily administered [39] an important limitation mentioned by several investigators [1,6,40] is their lack of reversibility without extensive surgical intervention.

The Capronor® device is a reversible system, but requires surgical implantation under local anesthesia involving incision of the skin and insertion of the capsule through an 11-gauge needle using a trocar [23]. The dimensions of the Capronor® device, which contains a non-porous homogeneous capsule wall, are dictated by the desired steroid release rate and duration of action.

The biodegradable hollow fibre concept however aiming at a device with relatively small dimensions, possibly could result in a contraceptive delivery system which combines reversibility with subdermal injectability, thereby obviating the need for surgical implantation.

The *in vitro* and *in vivo* release of the contraceptive hormone levonorgestrel from PLLA hollow fibres prepared under different spinning conditions will also be discussed in this paper.

MATERIALS AND METHODS

Materials

Chloroform, dichloromethane, 1,4-dioxane and *N*-methyl-2-pyrrolidone (NMP) were of analytical grade. Ethanol and methanol were chemically pure. L-lactide was purchased from C.C.A. Biochem, Gorinchem, The Netherlands and was stored at −20°C in a dry nitrogen atmosphere. Stannous octoate (tin(II)-2-

ethylhexanoate) was obtained from Alpha Products, Danvers, MA 01923, U.S.A., and kept at room temperature under a dry nitrogen atmosphere. Poly(*N*-vinylpyrrolidone), PVP K-15, $\bar{M}_w = 10^4$ was obtained from GAF Corporation, Schiedam, The Netherlands. Tritium labeled and non-radiolabeled micronized ($< 3\mu$) levonorgestrel was obtained as a gift from Schering A.G., Berlin, Germany. The tritium-labeled (15,16-^{3}H) levonorgestrel had a specific activity of 0.25 mCi/g (5.50×10^8 dpm/g, or 9.17 MBq/g). Castor oil (Ph.Eur.) was purchased from Serva, Heidelberg, Germany.

Poly(L-lactide), PLLA, was synthesized at $T = 130\,^\circ$C by bulk ring-opening polymerization of L-lactide using stannous octoate as initiator [41]. Two batches of PLLA were prepared: PLLA-1 (600 g), monomer to initiator (M/I) molar ratio 150, $[\eta] = 2.4$ dl.g^{-1} (25 °C, $CHCl_3$), $\bar{M}_v = 1.3 \times 10^5$, $\bar{M}_w = 1.5 \times 10^5$, $\bar{M}_n = 9.5 \times 10^4$; PLLA-2 (1 kg), M/I = 5×10^4, $[\eta] = 6.3$ dl.g^{-1} (25 °C, $CHCl_3$), $\bar{M}_v = 4.75 \times 10^5$.

Methods

Infrared spectra were recorded on a Beckman IR-33 Infrared Spectrophotometer. Samples from the PLLA hollow fibres were prepared by casting thin films from chloroform solutions. ^{1}H-NMR spectra were recorded on a Nicolet 200 MHz NMR apparatus at ambient temperature using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference. UV spectra were recorded on a Unicam SD 800 UV Spectrophotometer. UV extinctions were measured using a Zeiss Spektral Photometer PM-6.

Polymer average molecular weights ($\bar{M}_w$, $\bar{M}_n$) were determined by combined high performance gel permeation chromatography (GPC) and low angle laser light scattering (LALLS). The GPC unit, consisting of a Waters model 6000A HPLC pump and a Waters U6K injector, was equipped with a Styragel (Waters, 500 Å; 37–75 μ) containing Waters guard column (cat. no. 84550) and four Waters μStyragel (10^6, 10^5, 10^4, 10^3 Å) GPC columns (7.8×300 mm) in series, and connected to a Chromatix KMX-6 LALLS apparatus ($\lambda = 633$ nm) and a Waters R401 differential refractometer. The overall column efficiency amounted to 20,000 theoretical plates. Elution was performed at room temperature at a flow rate of 2.0 ml/min using dichloromethane (p.a.) as eluent. PLLA solutions in dichloromethane were filtered before use, using a Millipore Fluoropore FHLP (0.5 μ) filter.

The refractive index increment (dn/dc) of PLLA in dichloromethane at 633 nm was determined at room temperature using a Brice Phoenix BP-2000-V differential refractometer. For the two PLLA samples the same value of $dn/dc = 0.032$ ml/g was found, which was thereafter taken as a constant independent of PLLA molecular weight.

A correction of the LALLS data for the second virial coefficient was necessary and performed as indicated by Ouano [42]. The second virial coefficient (determined by static LALLS measurements using the Chromatix KMX-6 apparatus; see e.g. Ref. 43) was assumed to be 0.003 mol·ml/g^2 for the whole range of molecular weights investigated. Correction for column dispersion (band-broadening) was found not to be necessary, as was determined from the GPC-LALLS data of narrow-MWD polystyrene standards (see also Refs. 42,44).

PLLA intrinsic viscosities were determined at 25 °C in chloroform using an Ubbelohde capillary viscometer. PLLA viscosity average molecular weights ($\bar{M}_v$) were calculated from a Mark–Houwink relationship established before [41]:

$$[\eta] = 3.48 \times 10^{-4}\ \bar{M}_v^{0.75}\ (\mathrm{dl \cdot g^{-1}}).$$

Differential scanning calorimetry (DSC) measurements were performed using a Dupont 910 DSC apparatus equipped with a Dupont 1090 Thermal Analyzer. The samples (ca. 2–5 mg) were heated in sealed aluminium DSC pans at a scan speed of 5 °C/min. After the first scan

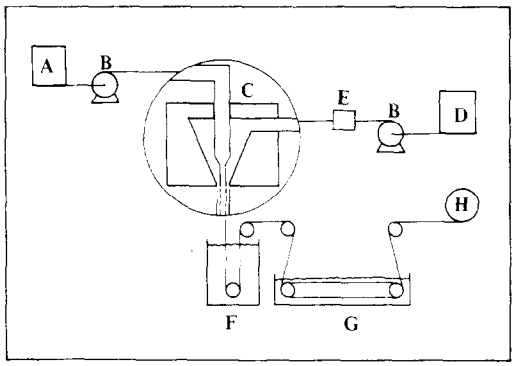

Fig. 1(a). Scheme of dry-wet spinning process: (A) bore injection liquid reservoir; (B) pump; (C) spinneret (enlarged); (D) spinning solution reservoir; (E) filter; (F) first coagulation bath; (G) second coagulation bath; (H) godet.

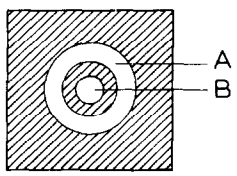

Fig. 1(b). Tube-in-orifice spinneret nozzle cross-section: (A) spinning solution; (B) bore injection fluid (internal coagulant).

(up to $T=200°C$), the samples were allowed to cool to room temperature and a second thermogram was recorded. The degree of crystallinity of the PLLA hollow fibres was calculated from the measured heat of fusion (ΔH_m) using the ΔH_m value for fully crystalline PLLA, $\Delta H_m=93.7$ J/g, given by Fisher et al. [45]. Melting points (T_g) were taken as the peak melting temperatures. Glass transition temperatures (T_g) were taken as the temperatures in the thermogram at the intersection of the extrapolation of the baseline with the extrapolation of the inflection.

Preparation of hollow fibres

The hollow fibre dry-wet phase inversion spinning process is schematically shown in Fig. 1a. The spinning dope (consisting of polymer, solvent and sometimes additive) was prepared directly in the spinning solution reservoir (D) of 0.7 liter capacity (usually at $T=50°C$). Part of the solution was temporarily removed to measure its viscosity (usually at $T=50°C$) with a Brookfield Synchro-lectric viscometer (model RVT). The viscous spinning solution was degassed and pumped (Elmekanics rotary gear precision metering pump) from the reservoir (which was kept at 1 bar nitrogen overpressure) through a heated tube (usually $T=50°C$) via a ca. 40μ cotton fabric filter (E; type KFW 6156, Merrem and Laporte, Zaltbommel, The Netherlands) into the spinneret (C).

The applied spinneret was a tube-in-orifice device (Fig. 1b) with an orifice diameter of 1.0 mm, an injection tube outside diameter of 0.6 mm and an inside diameter of 0.4 mm. The contents of the spinneret were not heated, except when processing PLLA solutions in NMP ($T=80°C$). The bore injection fluid (internal coagulant) was pumped (Perfusor®, Secura, Braun) from its reservoir (A) into the inner tube of the spinneret. The coagulation bath (F, external coagulant) was placed at a distance h under the spinneret. The length of the nascent fibre in the first coagulation bath (F) was 0.6 m. The nascent hollow fibre was passed several times through a second coagulation bath (G) containing the same (external) coagulant, resulting in a total fibre length in the second bath of 8.4 m. Both coagulation baths (F, G) containing polymer non-solvent (i.e. water or methanol) were kept at room temperature. After passing through the second coagulation bath, the hollow fibre was transferred onto a self-advancing godet (H). The godet speed determined the withdrawal rate of the yarn from the spinneret. The hollow fibre was collected and stored in a beaker with coagulant (water or methanol) for at least another day. The coagulant was refreshed several times. Finally, the bundles of hollow fibre were air dried.

After spinning, the hollow fibres were characterized with respect to PLLA molecular weight (viscometry and GPC-LALLS), residual additive content (IR, ^{1}H-NMR), crystallinity (DSC), dimensions (light microscopy)

and membrane microstructure (SEM).

Hollow fibre dimensions (inner and outer diameter) were determined by analysis of their cross-section by light microscopy using a Nikon Labophot Light Microscope, equipped with a Hitachi CCTV camera (magnification: 50×). The samples were prepared by cryogenic breaking (in liquid nitrogen).

To investigate the hollow fibre wall microstructure, cross-sections of the hollow fibres were examined by scanning electron microscopy (SEM) with a JEOL JSM 35 CF Scanning Electron Microscope. The samples were prepared by cryogenic grinding in liquid nitrogen followed by coating with a charge conducting layer of gold by means of a Balzer sputter unit.

Preparation of hollow fibre samples for release experiments

Hollow fibre samples were filled with a 25 wt.% dispersion of micronized ^{3}H-levonorgestrel in castor oil in the following manner: Pieces of hollow fibre were cut to the desired length (ca. 8 cm). To enable filling, both ends of each hollow fibre sample were first cemented into the lumen of a piece (ca. 1 cm) of silicone rubber (Silastic®) medical grade tubing (Talas, Ommen, The Netherlands; type SR 2HH: $d_i = 1.3$ mm, $d_o = 2.5$ mm) using a RTV silicone rubber adhesive sealant (General Electric, Waterford, New York). The hollow fibre samples were filled with the steroid dispersion using a syringe, which was introduced into the silicone rubber tubing. The filled hollow fibre was heat sealed at the desired length using a hot pair of pincers ($T \sim 140$–150°C), after which the remaining pieces of fibre including the silicone rubber tubing were cut away from both ends.

Determination of hollow fibre levonorgestrel content

The initial hollow fibre levonorgestrel content (expressed in μg steroid per cm hollow fibre length) was calculated from the total amount of radioactivity released from the hollow fibre during the *in vitro* release experiment, and the residual amount of radioactivity of the hollow fibre at the end of the release experiment (see below).

For hollow fibres filled with a dispersion of non-radiolabeled levonorgestrel in castor oil, the initial steroid content (core load) was determined by UV spectroscopy. A filled sample of the hollow fibre batch studied was dissolved in chloroform, and the amount of steroid determined spectrophotometrically ($\lambda = 247$ nm; $\epsilon = 17.200$ l/mol·cm).

TABLE 1

Solubility of levonorgestrel in ethanol-water mixtures

Ethanol/water (w/w)	Solubility[a] (mg/ml)
100/0	8.3 -8.6
70/30	4.1 -4.5
45/55	0.70–0.76
40/60	0.35–0.40
25/75	0.19–0.23
0/100	0.005[b]

[a]at $T = 37$°C, [b]Ref. 46.

Determination of levonorgestrel solubility

Solubilities of levonorgestrel in castor oil and ethanol-water mixtures at $T = 37$°C were estimated by adding small known amounts of castor oil (or ethanol-water mixture) to a suspension of solid (non-radiolabeled) levonorgestrel in the same medium, until a clear solution was obtained. Between the castor oil (or ethanol–water) additions, the suspension was equilibrated for 24 hours at $T = 37$°C in a shaking water bath. In this way, the solubility of levonorgestrel in castor oil was estimated to be in the range of 2.3–2.6 mg/ml. Solubilities of levonorgestrel in ethanol-water mixtures of various compositions are listed in Table 1.

In vitro release of levonorgestrel

The *in vitro* release of levonorgestrel from the hollow fibres was studied as follows: For each hollow fibre batch investigated, five filled hollow fibre samples of known length (ca. 5 cm each) were immersed in separate glass vials containing (usually) 40 wt.% aqueous ethanol ($EtOH/H_2O$: 40/60 w/w) as the receiving fluid (30 ml). The sealed vials were incubated at 37°C and agitated in a shaking water bath (Köttermann, Hänigsen, Germany; type 3047) at 135 cycles/min. Increasing the water bath shaking frequency to 190 cycles/min did not change the release rates. Periodically, aliquots (200 μl) were removed from the receiving fluid and assayed for ^{3}H-levonorgestrel by liquid scintillation counting (10 min; LKB-Wallac 1219 RackBeta Spectral Liquid Scintillation Counter, or Packard Tri-Carb Liquid Scintillation Spectrometer 3255). Lipoluma® (Lumac, Schaesberg, The Netherlands), resp. Plasmasol® (United Technologies Packard) were used as scintillation cocktail (4 ml). From the data of the five samples investigated for each hollow fibre batch, the average amount of levonorgestrel released was calculated. The receiving fluid of each vial was changed with such frequency that the concentration of levonorgestrel in the receiving fluid was maintained below 2% of its solubility ("infinite sink" conditions). At the end of the test period, the residual levonorgestrel content of the hollow fibres was determined by dissolving the samples in dioxane (30 ml) and counting an aliquot (200 μl) of this solution as described above.

Sterilization of hollow fibres

To study the effect of sterilization by gamma irradiation on the hollow fibre release properties, some of the filled PLLA hollow fibres were exposed to a 2.5 MRad (=25 kGy) dose of gamma radiation from a cobalt-60 source (performed at Gammaster, Ede, The Netherlands). A number of other PLLA hollow fibre samples from the same batch were exposed to gamma radiation (2.5 MRad) prior to filling with the steroid dispersion.

Average PLLA molecular weights ($\bar{M}_w$, $\bar{M}_n$) of the latter irradiated hollow fibre samples were determined by GPC-LALLS as described before and compared to the values of the non-irradiated samples.

In vivo release of levonorgestrel

Preliminary *in vivo* levonorgestrel release experiments in rabbits, sponsored by the WHO (World Health Organization, Geneva, Switzerland), were carried out under the supervision of Dr. H.L. Gabelnick at the National Institute of Child Health and Human Development (NICHD), Bethesda, Maryland, U.S.A. In these experiments, two types of PLLA hollow fibres were used. The hollow fibres (length of each device: 3 cm), filled with a 25 wt.% dispersion of micronized non-radiolabeled levonorgestrel in castor oil, were implanted subcutaneously into the rabbit scapular region. Two (non-sterilized) devices of the same hollow fibre type were implanted into each rabbit. Daily blood plasma levels of levonorgestrel were determined by a radioimmunoassay.

RESULTS

Preparation of poly(L-lactide) hollow fibres

Several PLLA solvent/non-solvent pairs with or without additive in the spinning solution were used for spinning of PLLA hollow fibres. The different spinning systems investigated are summarized in Table 2. Polymer concentrations and temperatures of the spinning solutions were chosen to obtain spinning dope viscosities in the range of η=200–1000 Poise (20–100 Pa·s).

A PLLA concentration of 10 weight percent was regarded as the minimum polymer concentration necessary to obtain suitable hollow

fibres. Because of the very high viscosities of the PLLA-2 ($\bar{M}_v = 475{,}000$) dioxane and chloroform solutions ($\eta > 5000$ Poise for a 10 wt.% conc. at $T = 50°C$), only NMP was used as the solvent for spinning of PLLA-2 hollow fibres. In this case, relatively high temperatures ($T = 80°C$) had to be used to dissolve PLLA, and heating of the spinneret was necessary to prevent premature precipitation of PLLA. Viscosity measurements showed that for the PLLA-1 ($\bar{M}_v = 130{,}000$) concentrations of 15 wt.% PLLA could be used when operating at somewhat elevated temperatures (T = 45–50°C) to yield spinning solution viscosities in the desired range.

For practical reasons, water was chosen as the internal and external coagulant where possible, i.e. when using NMP or dioxane as the solvent. For the chloroform solutions, the external and the internal coagulant used were methanol and ethanol respectively.

In addition to the spinning systems mentioned above, PLLA hollow fibres were also prepared from dioxane and chloroform solutions containing low molecular weight poly(*N*-vinylpyrrolidone) as additive, PVP ($\bar{M}_w = 10^4$), and from a dioxane solution containing L-lactide as additive.

Effect of spinning conditions on hollow fibre dimensions

The effect of several spinning conditions on PLLA hollow fibre dimensions was investigated by determining the inside (d_i) and outside diameter (d_o), and thereby the wall thickness (d_w), by light microscopic analysis of the hollow fibre cross-sections. The spinning parameters investigated for each spinning system included the flow rate of the internal coagulant (bore medium) and the spinneret distance from the coagulation bath (spinning height). For some spinning systems, the flow rate of the spinning solution (extrusion rate) and the fibre withdrawal rate from the spinneret (take-up rate) was varied in addition. Typical results for the spinning systems H-146 and H-148 (see Table 2) are summarized in Tables 3 and 4. For the other spinning systems, similar results were found. The results show that PLLA hollow fibres with outside diameters in the range of $d_o = 600$–820 μm, inside diameters in the range of $d_i = 445$–640 μm, and wall thicknesses in the range of $d_w = 60$–125 μm were obtained.

From the results given in Tables 3 and 4 the following trends appear. With increasing bore medium (internal coagulant) flow rate, an increase of the hollow fibre inside and outside diameter was found, independent of the partic-

TABLE 2

Hollow fibre spinning systems investigated

System polymer code	Spinning dope		Temperature (°C)	η^a (Poise)	Internal coagulant	External coagulant
	Components	conc./ (wt.%)				
H-144 PLLA-2	PLLA/NMP	10/90	80	1800[b]	water	water
H-145 PLLA-1	PLLA/dioxane	15/85	50	400	water	water
H-147 PLLA-1	PLLA/$CHCl_3$	14/86	45	1000	ethanol	methanol
H-142 PLLA-1	PLLA/Lact/dioxane[c]	15/5/80	50	315	water	water
H-146 PLLA-1	PLLA/PVP/dioxane	15/5/80	50	285	water	water
H-148 PLLA-1	PLLA/PVP/$CHCl_3$	14/4.7/81.3	45	400	ethanol	methanol

[a]spinning solution viscosity, [b]at $T = 60°C$, [c]Lact = L-lactide.

TABLE 3

Effect of spinning conditions on hollow fibre dimensions for spinning system H-146[a]

Exp. no.	Spinning height (cm)	Extrusion rate (ml/min)	Take-up rate (m/min)	Bore medium flow rate (ml/h)	d_o (μm)	d_i (μm)	d_w (μm)
1	1	0.5	1	20	800	600	100
2	1	0.5	1	10	740	520	110
3	1	1.5	3	30	750	540	105
4	1	1.5	3	20	700	445	125
5	1	1.5	3	40	800	570	115
6	1	3.0	6	60	760	540	110
7	1	3.0	6	80	800	590	105
8	10	1.5	3	20	720	470	125
9	10	1.5	3	40	740	500	120

[a]spinning dope: PLLA/PVP/dioxane (see Table 2). d_o, d_i and d_w are outside diameter, inside diameter and wall thickness respectively.

TABLE 4

Effect of spinning conditions on hollow fibre dimensions for spinning system H-148[a]

Exp. no.	Spinning height (cm)	Extrusion rate (ml/min)	Take-up rate (m/min)	Bore medium flow rate (ml/h)	d_o (μm)	d_i (μm)	d_w (μm)
1	1	1.5	3	30	620	460	80
2	1	1.5	3	50	640	520	60
3	1	2.4	3	50	800	600	100
4	1	2.4	3	60	820	640	90
5	1	2.4	4	60	720	580	70
6	1	2.4	4	50	600	470	65
7	10	2.4	4	50	780	590	95

[a]Spinning dope: PLLA/PVP/$CHCl_3$ (see Table 2).

ular spinning height used. Usually, the hollow fibre wall thickness was not influenced very much by variation of the bore medium flow rate. With increasing spinning solution extrusion rate, the hollow fibre inside and especially outside diameter was increased, resulting in an increased wall thickness. When increasing the take-up rate (godet speed), a hollow fibre with smaller inside and outside diameter and smaller wall thickness was obtained. When increasing both the extrusion rate, take-up rate and bore medium flow rate simultaneously, a hollow fibre with the same dimensions was obtained. However, if the bore medium flow rate was not increased simultaneously with the extrusion rate and take-up rate, a hollow fibre with smaller inside and outside diameter resulted. Variation of the spinning height did not show a straightforward correlation with a change in hollow fibre dimensions.

Hollow fibre membrane structure

A number of hollow fibres were examined by SEM to investigate the structure of the hollow fibre wall. Representative macrostructures of PLLA hollow fibre cross-sections are shown in Figs. 2–4 for the products prepared by dry–wet

spinning of PLLA solutions in NMP (Fig. 2, spinning system H-144), dioxane (Fig. 3, spinning system H-146) and chloroform (Fig. 4, spinning system H-148). The cross-sections in Figs. 2–4 show that hollow fibres with various wall structures are obtained.

Typical membrane microstructures of the PLLA hollow fibres prepared using the different spinning systems investigated are shown in Figs. 5–10. The experimental preparation conditions and dimensions of the hollow fibre samples examined are summarized in Table 5.

Figure 11 shows that the porous sponge-like structured wall of the PLLA hollow fibre H-146-7 is covered by a dense external skin. A similar dense skin was also found to cover the internal surface of the hollow fibre wall (not shown). No SEM-observable pores were found in both the external and internal skin.

Figures 12 and 13 show the structure of a porous wall covered by an internal skin (ca. 0.3 μm) and external skin (ca. 0.3–0.4 μm), for fibre H-148-5. However, in this case the skins were not dense. Pores are found in both the internal surface (ca. 1–3 μm) and external surface (ca. 0.2–0.5 μm). For the PLLA hollow fibres prepared using the different spinning systems (see Tables 2 and 5), the thicknesses of the internal and external skins, and the diameters of the pores in the matrix of the wall are summarized in Table 6.

Further characterization of PLLA hollow fibres

PLLA hollow fibres obtained were also characterized with respect to average PLLA molecular weight, residual additive content, degree of PLLA crystallinity, glass transition and melting temperature. Average PLLA molecular weight ($\bar{M}_w$, $\bar{M}_n$) determinations by GPC-LALLS of the hollow fibres prepared from PLLA-1 (see Table 2) showed that no polymer degradation had occurred during spinning of the dioxane and chloroform solutions.

Viscometric analysis of the hollow fibres pre-

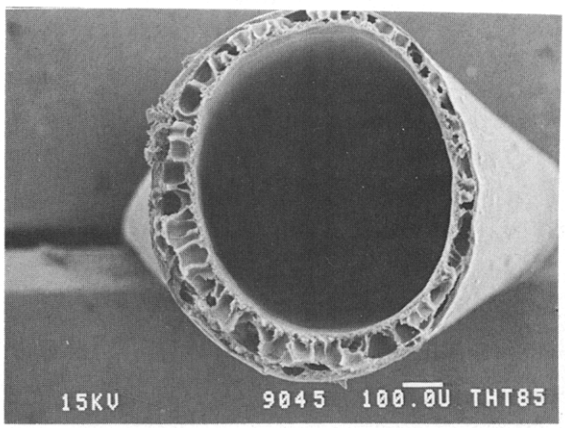

Fig. 2. SEM micrograph of PLLA hollow fibre cross-section. Spinning dope: PLLA/NMP, 10/90 (wt.%). Spinning system H-144 (see Table 2).

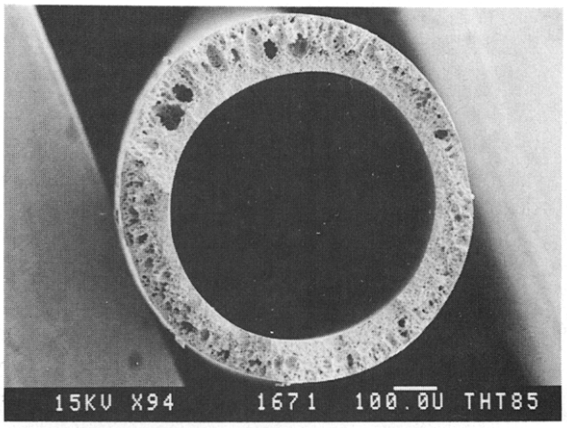

Fig. 3. SEM micrograph of PLLA hollow fibre cross-section. Spinning dope: PLLA/PVP/dioxane, 15/5/80 (wt.%). Spinning system H-146 (see Table 2).

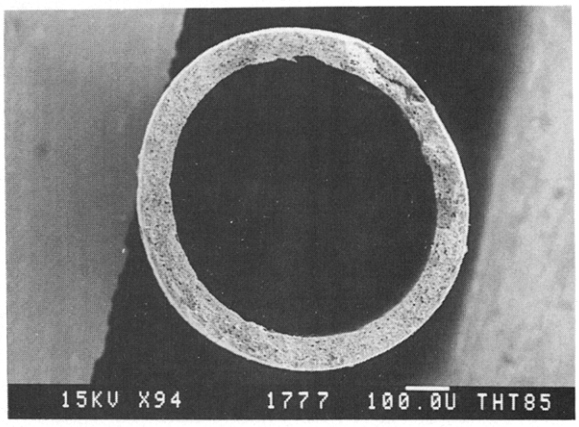

Fig. 4. SEM micrograph of PLLA hollow fibre cross-section. Spinning dope: PLLA/PVP/$CHCl_3$, 14/4.7/81.3 (wt.%). Spinning system H-148 (see Table 2).

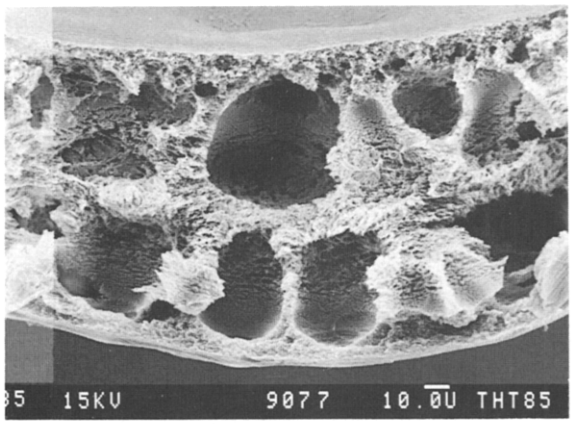

Fig. 5. Cross-section of PLLA hollow fibre wall. Spinning dope: PLLA/NMP, 10/90 (wt.%). Spinning system: H-144-1 (see Table 5). Internal surface is facing up.

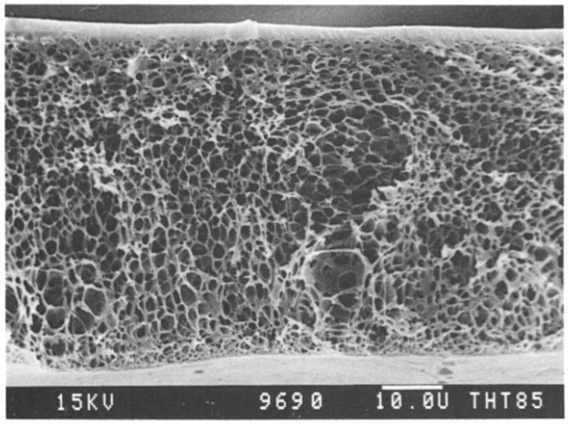

Fig. 6. Cross-section of PLLA hollow fibre wall. Spinning dope: PLLA/dioxane, 15/85 (wt.%). Spinning system: H-145-4 (see Table 5). Internal surface is facing up.

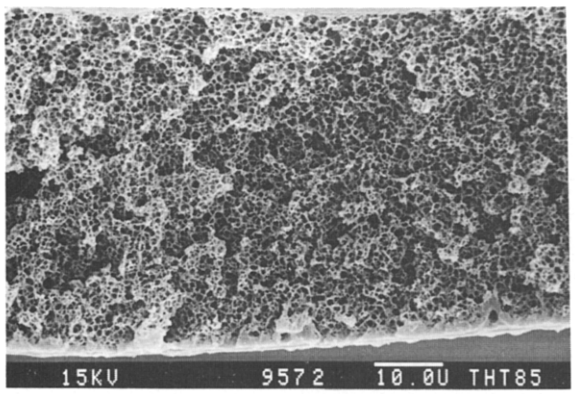

Fig. 7. Cross-section of PLLA hollow fibre wall. Spinning dope: PLLA/$CHCl_3$, 14/86 (wt.%). Spinning system: H-147-1 (see Table 5). Internal surface is facing up.

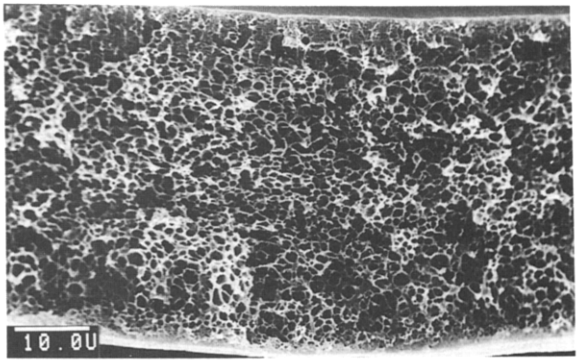

Fig. 8. Cross-section of PLLA hollow fibre wall. Spinning dope: PLLA/Lact/dioxane, 15/5/80 (wt.%). Spinning system: H-142-8 (see Table 5). Internal surface is facing up.

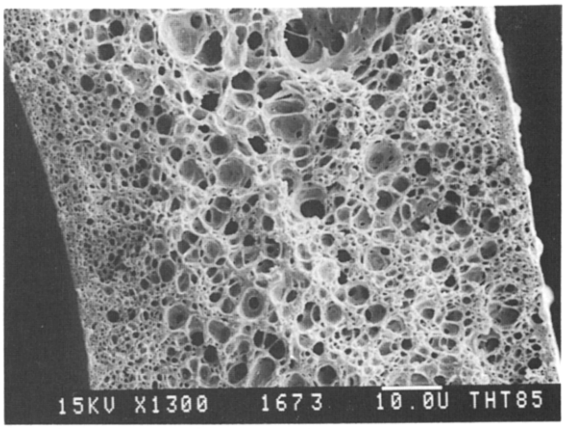

Fig. 9. Cross section of PLLA hollow fibre wall. Spinning dope: PLLA/PVP/dioxane, 15/5/80 (wt.%). Spinning system: H-146-7 (see Table 5). Internal surface is facing to the left.

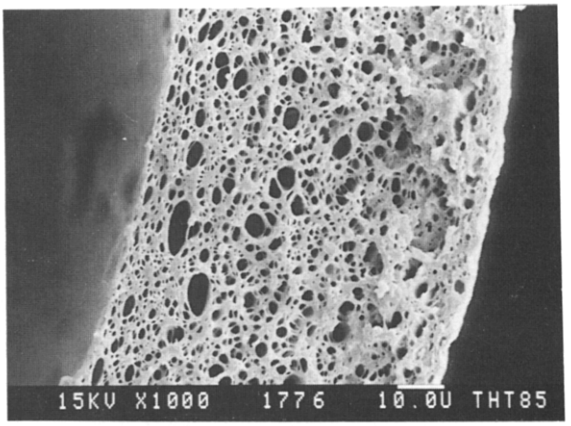

Fig. 10. Cross-section of PLLA hollow fibre wall. Spinning dope: PLLA/PVP/$CHCl_3$, 14/4.7/81.3 (wt.%). Spinning system: H-185-5 (see Table 5). Internal surface is facing to the left.

TABLE 5

Spinning conditions of hollow fibres examined by SEM[a]

System code	Spinning dope[b]	Spinning height (cm)	Extrusion rate (ml/min)	Take-up rate (m/min)	Bore medium flow rate (ml/h)	d_o (μm)	d_i (μm)	d_w (μm)
H-144-3[c]	PLLA/NMP	10	1.5	3.0	50	930	680	125
H-145-4	PLLA/dioxane	10	1.5	4.5	40	630	530	50
H-147-1	PLLA/$CHCl_3$	1	0.5	1.5	20	700	580	60
H-142-8	PLLA/Lact/dioxane	0.5	0.5	1.0	20	720	620	50
H-146-7	PLLA/PVP/dioxane	1	3.0	6.0	80	800	590	105
H-148-5	PLLA/PVP/$HCHl_3$	1	2.4	4.0	60	720	580	70

[a]see also Table 2, [b]for concentrations: see Table 2, [c]using PLLA-2.

pared from the PLLA-2 solution in NMP (see Table 2), however, revealed that in this case significant polymer degradation had taken place during spinning. The PLLA intrinsic viscosity was reduced from 6.3 to 3.8 $dl \cdot g^{-1}$, indicating a 50% decrease in $\bar{M}_v$, i.e. from 4.7×10^5 to 2.4×10^5.

^{1}H-NMR and infrared spectroscopic analysis of PLLA hollow fibres H-142-8, H-146-7 and H-148-5 (see Table 5) did not show the presence of residual additive (L-lactide or PVP) in the hollow fibres, provided the samples had been thoroughly washed with non-solvent as described in the Experimental Section. This implies that the residual additive content of the hollow fibres was less than ca. 2.5 wt.%, being the additive detection limit of the methods used.

The PLLA hollow fibres (H-145-4, H-147-1, H-146-7 and H-148-5) were analyzed by DSC measurements for their glass transition temperature (T_g), melting temperature (T_m) and degree of crystallinity. All samples examined showed a value of $T_g \sim 60°C$ and $T_m \sim 176°C$, which are identical to the values commonly reported for PLLA [32,47,48]. No heat event attributable to the possible presence of PVP (Ref. 49: $T_g \sim 100°C$) could be detected in the samples H-146-7 and H-148-5. All samples examined, including the ones prepared from a spinning solution containing PVP, showed a degree of crystallinity around 50%. The second DSC thermogram, recorded after the samples had been allowed to cool to room temperature, showed the same values for T_g and T_m as found in the first scan. Slightly higher degrees of crystallinity (54–58%) were calculated from the second thermogram for all samples investigated.

In vitro release of levonorgestrel

The *in vitro* release of levonorgestrel from PLLA hollow fibres filled with a 25 wt.% dispersion of micronized ^{3}H-levonorgestrel in castor oil was investigated, using a receiving fluid consisting of 40 wt.% aqueous ethanol ($T = 37°C$).

Figure 14 shows the plots of the cumulative amount of levonorgestrel released from the PLLA hollow fibres listed in Tables 5 and 6 as a function of time. The results show a very fast release of levonorgestrel from PLLA hollow fibre H-144-3 (spinning dope: PLLA/NMP), which had released its total drug load within 3 days. Only very small amounts of levonorgestrel were released from PLLA hollow fibres H-145-4 (spinning dope: PLLA/dioxane), H-147-1 (spinning dope: PLLA/$CHCl_3$) and H-142-8 (spinning dope: PLLA/Lact/dioxane). These samples had released only ca. 3–5% of their drug load in 200 days (release rate ca. 0.1 μg/cm/day).

Constant (zero-order) intermediate release

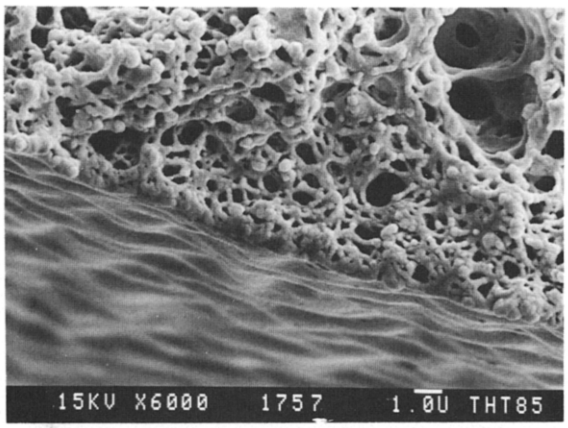

Fig. 11. External surface and wall cross-section at external surface of PLLA hollow fibre H-146-7. Spinning dope: PLLA/PVP/dioxane, 15/5/80 (wt.%). Spinning conditions: see Tables 2 and 5.

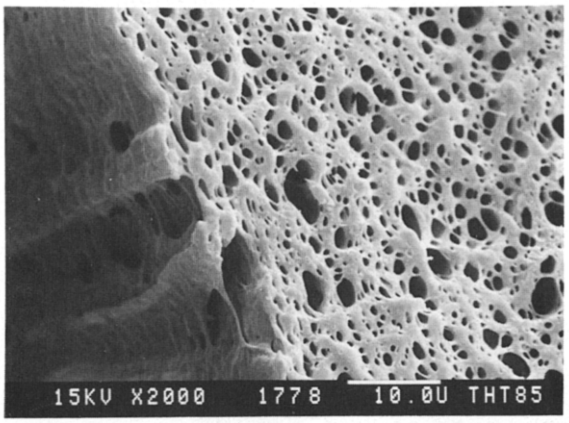

Fig. 12. Internal surface and wall cross-section at internal surface of PLLA hollow fibre H-148-5. Spinning dope: PLLA/PVP/$CHCl_3$, 14/4.7/81.3 (wt.%). Spinning conditions: see Tables 2 and 5.

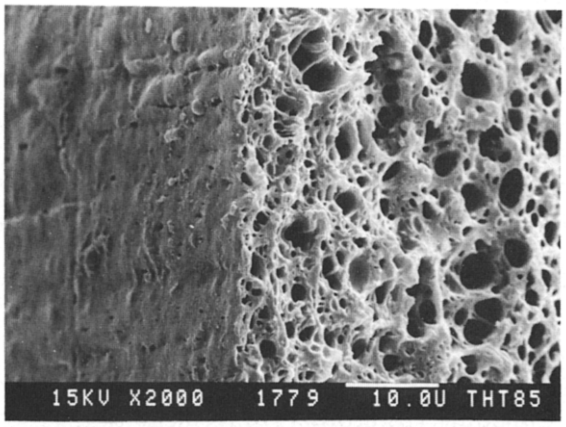

Fig. 13. External surface and wall cross-section at external surface of PLLA hollow fibre H-148-5. Spinning dope: PLLA/PVP/$CHCl_3$, 14/4.76/81.3 (wt.%). Spinning conditions: see Tables 2 and 5.

rates were found for PLLA hollow fibres H-146-7 and H-148-5. Samples H-146-7 (spinning dope: PLLA/PVP/dioxane) had released their drug content in ca. 70 days, while samples H-148-5 (spinning dope: PLLA/PVP/$CHCl_3$) still contained ca. 50% of their initial steroid load after ca. 180 days.

Figure 15 and 16 show the daily amounts of levonorgestrel released from PLLA hollow fibres H-146-7 and H-148-5, respectively, which were calculated by dividing the amount of steroid measured in the receiving fluid by the duration of release since the last change of the receiving fluid. For PLLA hollow fibre H-146-7 (spinning dope: PLLA/PVP/dioxane), a constant release rate of 10 ± 1 μg/cm/day was found for a period of 60 days, after which the release rate rapidly decreased to zero within another 10–20 days (Fig. 15). For PLLA hollow fibre H-148-5 (spinning dope: PLLA/PVP/$CHCl_3$), also a constant but much lower release rate was found, which amounted to 1.7 ± 0.2 μg/cm/day and continued up to the end of the release experiment, i.e. after ca. 180 days (Fig. 16). In addition, to the release experiments described above, also the effect of gamma sterilization (2.5 MRad) of PLLA hollow fibres (batch H-146-7), before or after filling with the steroid dispersion, on the hollow fibre release properties was investigated. GPC-LALLS measurements of the hollow fibre samples which were gamma irradiated *before* filling indicated that PLLA average molecular weights were substantially decreased during gamma irradiation (i.e. from $\bar{M}_w = 1.5 \times 10^5$ and $\bar{M}_n = 9.5 \times 10^4$ to $\bar{M}_w = 5 \times 10^4$ and $\bar{M}_n = 2.5 \times 10^4$).

The results of the *in vitro* release experiments shown in Fig. 17, however, indicate that the release properties of these samples were not changed after gamma irradiation. An average levonorgestrel release rate of ca. 10 μg/cm/day was found, which is identical to that found for the non-irradiated samples (cf. Fig. 14). On the other hand, different release characteristics were found for the PLLA hollow fibre samples that were gamma irradiated *after* filling with the steroid dispersion. In this case a declining levonorgestrel release rate was found. Initially,

TABLE 6

Pore diameters and skin thicknesses of PLLA hollow fibres[a]

System code	Spinning dope		Matrix pore size[b] (μm)	Skin thickness[b] (μm)	
	components	conc. (wt.%)		internal	external
H-144-3	PLLA/NMP	10/90	25 -50	ND	ND
H-145-4	PLLA/dioxane	15/85	1 - 3	2.5	<0.5
H-147-1	PLLA/$CHCl_3$	14/86	0.5- 1	0.2	1 -2
H-142-8	PLLA/Lact/dioxane	15/5/80	0.5- 2	1-2	0.5
H-146-7	PLLA/PVP/dioxane	15/5/80	0.5- 5	0.2-0.3	0.3-0.4
H-148-5	PLLA/PVP/$CHCl_3$	14/4.7/81.3	0.3- 8	0.3[c]	0.3-0.4[c]

[a]for spinning conditions: see Tables 2 and 5, [b]estimated from SEM micrographs, [c]porous skin, ND: not determined.

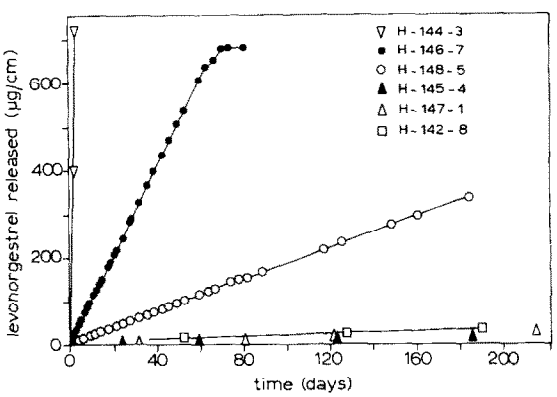

Fig. 14. Cumulative amount of levonorgestrel released *in vitro* from PLLA hollow fibres (see Tables 5 and 6), filled with a 25 wt.% dispersion of ^{3}H-levonorgestrel in castor oil, into a receiving fluid consisting of 40 wt.% aqueous ethanol maintained at 37°C. Each point represents the average value for five samples.

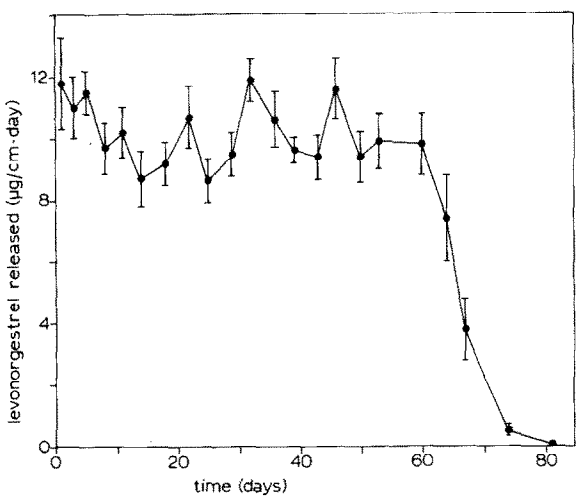

Fig. 15. Daily amounts of levonorgestrel released *in vitro* from PLLA hollow fibre H-146-7 (spinning dope: PLLA/PVP/dioxane; see Tables 5 and 6). Initial steroid content: 680 μg/cm. Each point represents the average value ($\pm$S.D.) for five samples. For experimental data: see legend of Fig. 14.

a release rate of ca. 25 μg/cm/day was found, which decreased to ca. 10 μg/cm/day in a period of 30–40 days, and to even lower values thereafter.

Release experiments were also carried out with (non-sterilized) PLLA hollow fibres of bath H-146-7 using a different receiving fluid composition, i.e. 25 wt.% aqueous ethanol. The results represented in Fig. 17 show that in this case a much lower levonorgestrel release rate (ca. 4 μg/cm/day) was found compared to that using a receiving fluid consisting of 40 wt.% aqueous ethanol (cf. Fig. 14 and 17).

The results of the *in vitro* levonorgestrel release experiments from PLLA hollow fibres are summarized in Tables 7 and 8. In Table 7 also the (initial) steroid core loads of the hollow fibres are listed. The initial hollow fibre levonorgestrel content was found to agree very

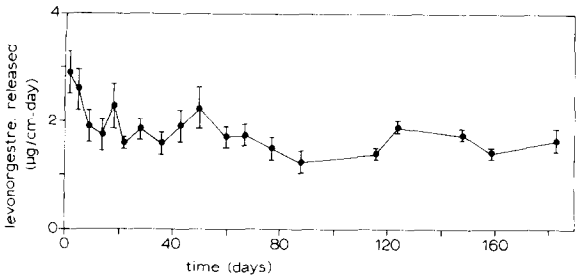

Fig. 16. Daily amounts of levonorgestrel released *in vitro* from PLLA hollow fibre H-148-5 (spinning dope: PLLA/PVP/$CHCl_3$; see Tables 5 and 6). Initial steroid content: 670 µg/cm. Each point represents the average value (±S.D.) for five samples. For experimental data: see legend of Fig. 14.

well with the steroid load calculated from the core volume of the hollow fibre and the density of the steroid dispersion (1.0 g/ml).

In vivo release of levonorgestrel

The *in vitro* release properties of the hollow fibres used for the *in vivo* experiments (rabbits) are listed in Table 9.

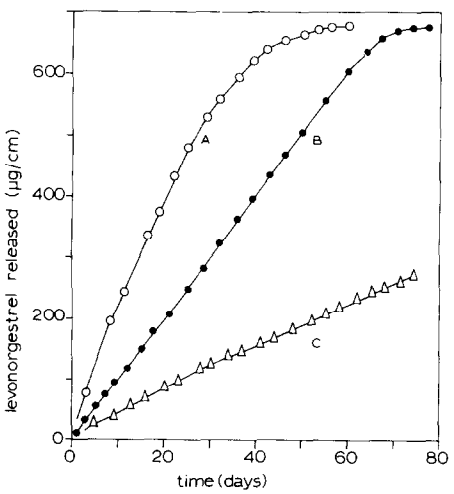

Fig. 17. Cumulative amount of levonorgestrel released *in vitro* from PLLA hollow fibre H-146-7 (for experimental data: see legend of Fig. 14): (A) sample gamma irradiated (2.5 MRad) after filling (○); (B) sample gamma irradiated (2.5 MRad) before filling (●); (C) sample not irradiated, receiving fluid 25 wt.% aqueous ethanol (△). Each point represents the average value for three samples.

TABLE 7

In vitro release rates of levonorgestrel from PLLA hollow fibres[a]

Batch code	Internal diameter (µm)	Steroid load (µg/cm)		Levonorgestrel release rate[d] (µg/cm/day)
		calc.[b]	found[c]	
H-144-3	680	910	900	(300)
H-145-4	530	550	540	0.10±0.05
H-147-1	580	660	600	0.10±0.05
H-142-8	620	775	760	0.15±0.05
H-146-7	590	680	680	10.0 ±1.0
H-148-5	580	660	670	1.7±0.2

[a]for experimental conditions: see legend of Fig. 14, for data on hollow fibres: see Tables 5 and 6; [b]calculated from core volume of hollow fibre and density of steroid dispersion (=1.0 g/ml); [c]determined as described in Experimental Section; [d]average value (±S.D.) for five samples.

The results of the *in vivo* release experiments are represented in Fig. 18. The release of levonorgestrel from PLLA hollow fibres H-146-8 resulted in very constant blood plasma levels (ca. 0.2 ng/ml) for a period up to ca. 210 days. A very peculiar levonorgestrel blood level profile, however, was found for the rabbits implanted with PLLA hollow fibre H-149-4. After ca. 60 days, the steroid blood level

TABLE 8

In vitro levonorgestrel release rates from PLLA hollow fibre. H-146-7[a]

Sample	Levonorgestrel release rate[b] (µg/cm/day)
normal[c]	10
gamma irradiated before filling[d]	10
gamma irradiated after filling[d]	25-5
in 25 wt.% aqueous ethanol	4

[a]for experimental conditions: see legend to Fig. 14 for data on hollow fibre: see Tables 5 and 6; [b]average value for five, resp. three samples; [c]non-irradiated; receiving fluid: 40 wt.% aqueous ethanol; [d]dose of 2.5 MRad (2.5×10^4 m^2/s^2).

TABLE 9

PLLA hollow fibres used for *in vivo* release experiments

Batch code	Spinning dope composition	Outside diameter (μm)	Inside diameter (μm)	Steroid load (μg/cm)	In vitro ^{3}H-levonorgestrel release rate[c] (μg/cm/day)
H-146-8	PLLA/PVP/dioxane[a]	720	470	435	10 ±1
H-149-4	PLLA/PVP/$CHCl_3$[b]	840	575	645	2.5 ±0.2

[a]identical to H-146-7; [b]identical to H-148-5 (see Tables 5 and 6); [c]experimental conditions: identical to as described above (see legend of Fig. 14). Average value (±S.D.) for five samples.

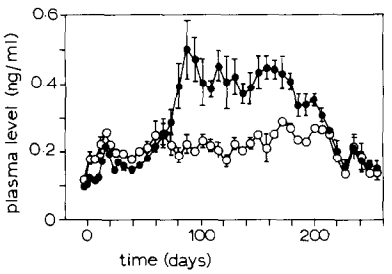

Fig. 18. Daily rabbit blood plasma levels of levonorgestrel released from PLLA hollow fibres (L=3 cm) filled with a 25 wt.% dispersion of levonorgestrel in castor oil: ○ = H-146-8; ● = H-149-4. Two devices were implanted into each rabbit. Each data point represents the average value (±S.D.) for five samples.

increased and thereafter remained reasonably constant for another 100 days at a value which was ca. 2 times that found for rabbits implanted with PLLA hollow fibres H-146-8.

DISCUSSION

Mechanism of membrane formation

Dry–wet phase inversion spinning is a well-known method for obtaining hollow fibres with various isotropic or anisotropic membrane structures [50]. In general, the mechanism of formation of hollow fibre membranes is closely related to that of flat-sheet membranes produced by immersion precipitation [50,51]. A model for the mechanism of formation of flat-sheet membranes by immersion precipitation which has recently been developed by Reuvers [52–55] will be used to qualitatively explain the membrane structure of PLLA fibres obtained by phase-inversion spinning using different conditions. Six different spinning dope compositions were used for fabrication of the PLLA hollow fibres (see Table 3).

The results presented in Tables 3 and 4 for two spinning systems (H-146 and H-148; see Table 2) show the effect of variation of some of the spinning parameters on the dimensions of the extruded hollow fibre. An increase in hollow fibre dimensions was found in case of (a) an increase in bore medium flow rate ("blowing-up" of fibre from core), (b) an increase in spinning solution extrusion rate (predominantly increasing the outside diameter and wall thickness), and (c) a decrease in the hollow fibre take-up rate. When increasing these three spinning parameters simultaneously and proportionally, the hollow fibre dimensions were found to remain constant. Similar effects of these spinning parameters on the dimensions of polysulfone hollow fibres spun from a solution in *N,N*-dimethylacetamide (DMAc) containing PVP were reported by Cabasso et al. [56].

Variation of the spinning height did not show a straightforward correlation with a change in hollow fibre dimensions. In a recent report on the dry–wet spinning of polysulfone hollow fibres from DMAc solutions containing PVP, Aptel et al. [57] could also not find a correlation between the spinning height and hollow

fibre dimensions. These authors suggested that an exact theoretical analysis of the dry–wet phase inversion spinning process would also have to take into account the die-swell phenomenon, which is the swelling of the extrudate as it emerges from a capillary, in order to explain the effect of the different spinning parameters on the hollow fibre dimensions [57].

The effect of each of the six different spinning systems used on the PLLA hollow fibre membrane structure was investigated by SEM analysis of hollow fibre cross-sections (see Table 5 for samples investigated).

Figures 5–10 show that in all cases a PLLA hollow fibre with an asymmetric membrane structure was obtained, consisting of a porous matrix covered by a more or less dense internal and external skin. Figures 2 and 5 show the wall structure of the hollow fibre spun from the PLLA solution in NMP (Table 6: system code H-144-3). The structure shows the presence of large macrovoids surrounded by very loosely connected material covered by a thin more dense internal and external skin. This indicates that at the internal as well as the external surface of the hollow fibre wall instantaneous onset of demixing caused by the high degree of miscibility of water and NMP occurs upon contacting the polymer solution with the coagulant [52]. In addition to liquid–liquid phase separation in the matrix, probably also aggregates of PLLA were formed, PLLA being insoluble in NMP at temperatures below 50°C. Aggregates are formed by nucleation and growth of the polymer-rich phase, which leads to a "porous" structure in which the dilute solvent/non-solvent forms the continuous phase [52,53]. An indication that such aggregate formation occurred is obtained from the presence of the loosely connected material surrounding the macrovoids. The hollow fibre (code H-144-3) was mechanically very weak. Further characterization of the fibre showed that degradation of PLLA had taken place during spinning, resulting in a 50% reduction in $\bar{M}_v$. Based on these findings, this spinning system using NMP as the solvent was considered unsuitable for the preparation of hollow fibres of the high molecular weight PLLA-2.

Figure 6 shows the wall structure of the hollow fibre spun from the PLLA solution in dioxane (Table 5: system code H-145-4). In this case, a porous spongelike matrix, on both sides covered by a dense skin was found. A much thicker internal skin was observed as compared with the external skin (see also Table 6). This possibly could be caused by the fact that this hollow fibre was spun at a relatively large spinning height (10 cm; see Table 5) taking a longer time before the external surface of the nascent hollow fibre contacts the coagulant compared to the internal surface. During this period, some (internal) coagulant can penetrate from the bore towards the external surface [51]. In addition, the external surface might pick up some moisture during passage through air. As a result, the external periphery already will contain some non-solvent when it contacts the coagulation bath. This promotes the onset of liquid–liquid demixing to be instantaneous upon contacting the external surface of the nascent hollow fibre with the water bath, resulting in a thin external skin [52]. The thick internal skin might be a result of delayed onset of liquid–liquid demixing, because dioxane and water are only poorly miscible [52].

Figure 7 shows the asymmetric wall structure of the hollow fibre spun from the PLLA solution in chloroform (Table 5: system code H-147-1), containing a very thin internal skin and a thicker external skin (see also Table 6). The presence of a thick external skin possibly resulted from evaporation of the highly volatile chloroform from the external surface of the nascent hollow fibre during passage through air. The solvent evaporation would increase the polymer concentration at the external surface, resulting in a thick toplayer. Use of an additive in the spinning dope will influence the membrane formation mechanism, as the phase inversion process is changed from a ternary to a quaternary system. For such a four-compo-

nent system containing two types of polymers, the phase inversion process is not yet fully understood [52]. L-lactide was used as additive in the PLLA dioxane spinning solution (Table 5: system code H-142-8). L-lactide dissolves in the polymer solvent (dioxane) and does not precipitate from this solution when contacted with the polymer nonsolvent (water). No residual L-lactide was found in the resulting PLLA hollow fibre. Substitution of part of the solvent for L-lactide did not have a very large effect on the structure of the resulting hollow fibre wall. A very similar membrane structure (Fig. 8) to that obtained when using the dioxane solution without L-lactide was found (cf. Fig. 6), with a somewhat thinner internal skin.

Use of a low molecular weight water-soluble polymeric additive (PVP, $\bar{M}_w = 10^4$) however, did show a significant effect on the hollow fibre membrane structure. Substitution of part of the dioxane solvent in the spinning dope for PVP (Table 5: system code H-146-7) resulted in a PLLA hollow fibre wall structure (Figs. 9, 11) with a matrix containing larger interconnected pores and, especially for the internal surface, a much thinner skin (cf. Fig. 6). Still, both the internal and external skin appeared to be dense, with no SEM-observable pores (see e.g. Fig. 11). However, it cannot be excluded that the skins contain very small pores not observed by SEM, i.e. smaller than ca. 5×10^{-3} μm). Substitution of part of the chloroform solvent in the spinning dope for PVP (Table 5: system code H-148-5) also resulted in a PLLA hollow fibre wall structure (Figs. 10, 12, 13) containing larger pores in the matrix and, especially on the external surface in this case, a much thinner skin. However, both the internal and external skin were not dense, but obtained SEM-observable pores (Figs. 12 and 13).

It should be noted that, although the PVP used was soluble in dioxane and chloroform (cf. Ref. 49), a cloudy spinning dope was obtained on combining the PLLA and PVP dioxane or chloroform solutions. Possibly, interaction of PLLA and PVP by complex formation (see e.g. [49,58]) caused the presence of PLLA-PVP aggregates in the spinning dope, which was found to have a decreased viscosity compared to the PLLA dioxane or chloroform solution without PVP (see Table 2: spinning system H-146 vs. H-145; H-148 vs. H-147). At this moment, however, it is not clear in what way the occurrence of this type of microphase separation influences the hollow fibre membrane formation mechanism.

Although no residual PVP was found in the resulting PLLA hollow fibres (sample code H-146-7, resp. H-148-5) and no difference in the DSC data was found between the samples spun in the absence or presence of PVP, it cannot be excluded that traces of PVP are present in the hollow fibre, entrapped between the PLLA segments. However, the presence of small amounts of residual PVP will not cause a problem for possible use of the PLLA hollow fibre in controlled release applications. The low molecular weight PVP used ($\bar{M}_w = 10^4$) has molecular dimensions small enough to be excreted by the kidneys [49], is reported to be non-antigenic in man [59], and already is being used extensively for various applications in the pharmaceutical and food industry [49,60].

Levonorgestrel release rates from the hollow fibres

For the PLLA hollow fibres used in this study, large differences in levonorgestrel release rates were found (see Table 7, and Fig. 14), which were shown not to be caused by differences in hollow fibre dimensions. Therefore, the differences in release rates must have resulted from variations in the PLLA hollow fibre membrane structures. The thicknesses of the internal and external skins of the PLLA hollow fibres, which were estimated from SEM micrographs of hollow fibre cross-sections, together with the average levonorgestrel release rates, are combined in Table 10.

The very high release rate found for PLLA hollow fibre H-144-3 (spinning dope:

TABLE 10

PLLA hollow fibre skin thicknesses[a] and levonorgestrel release rates

Batch code	Spinning dope composition	Skin thickness (μm)		Levonorgestrel release rate (μg/cm/day)
		internal	external	
H-144-3	PLLA/NMP	ND	ND	(300)
H-145-4	PLLA/dioxane	2.5	< 0.5	0.10
H-147-1	PLLA/$CHCl_3$	0.2	1 -2	0.10
H-142-8	PLLA/Lact/dioxane	1 -2	0.5	0.15
H-146-7	PLLA/PVP/dioxane	0.2-0.3	0.3-0.4	10.0
H-148-5	PLLA/PVP/$CHCl_3$	0.3[b]	0.3-0.4[b]	1

[a]average value; [b]porous skin; ND: not determined.

PLLA/NMP) indicates that the hollow fibre membrane caused only very little or no diffusional resistance for levonorgestrel. Probably, the hollow fibre skins consisted of a highly porous and loosely connected structure. Obviously, this type of PLLA hollow fibre is unsuitable for long term controlled release applications for low molecular weight compounds.

The very low levonorgestrel release rates of PLLA hollow fibres H-145-4 (spinning dope: PLLA/dioxane), H-147-1 (spinning dope: PLLA/$CHCl_3$) and H-142-8 (spinning dope: PLLA/Lact/dioxane) probably are the result of the presence of a relatively thick and dense internal or external hollow fibre membrane skin (ca. 2 μm; see Table 10). Permeation of levonorgestrel through the membrane skin may be of the solution–diffusion type. The low levonorgestrel release rates for these hollow fibres would agree with such a mechanism, since PLLA is reported to have a very low permeability for steroids (e.g. [25,61]).

As shown in Figs. 14 and 15, a constant (zero-order) and much higher levonorgestrel release rate was found for PLLA hollow fibre H-146-7 (spinning dope: PLLA/PVP/dioxane). The higher release rate, however, cannot only be explained by the smaller thickness of the hollow fibre skin. Compared to PLLA hollow fibre H-145-4 (spinning dope: PLLA/dioxane), for example, a hundred times higher steroid release rate was found for PLLA hollow fibre H-146-7, while in case of a membrane skin controlled permeation process only a ten times higher release rate would be expected on the basis of the ten times smaller skin thickness (see Table 10). Although it is realized that estimations of hollow fibre skin thicknesses by SEM are not very accurate, it is not expected that this can explain the factor 10 difference.

A 2.5 times lower levonorgestrel release rate from PLLA hollow fibre H-146-7 was found when using 25 wt.% aqueous ethanol instead of 40 wt.% aqueous ethanol as the receiving fluid (see Fig. 17 and Table 8). One of the possible explanations for this result could be that in the solution–diffusion mechanism the steroid release rate is controlled by the rate of diffusion of the steroid from the hollow fibre into the receiving fluid (diffusion layer- limiting partition-controlled process). In such a case, the release rate would be proportional to the solubility of the steroid in the receiving fluid. Table 1 shows that the solubility of levonorgestrel in 25 wt.% aqueous ethanol is about half of that in 40 wt.% aqueous ethanol. This agrees very well with the difference in release rates, especially when considering that the method used to determine the steroid solubilities only gives a rough estimation. A method to investigate whether the release is controlled by a boundary layer-limiting diffusion process is to increase the agitation intensity of the receiving fluid [40,56]. However, increasing the water bath shaking frequency (from 135 to 190 cycles/min) in this study did not change the steroid release rates. Therefore, a diffusion layer-limiting partition-controlled release mechanism is considered not very likely for PLLA hollow fibre H-146-7. Instead, a pore-diffusion mechanism could be operative for release from PLLA hollow fibre H-146-7, in which the steroid release rate is controlled by the partitioning of the steroid from the core vehicle into the receiving fluid in the pores of the membrane skin. This mechanism also would account for the dependence of the release rate on the steroid solubility in the receiving fluid observed. The presence of pores

in the skins of this type of PLLA hollow fibre is not very unlikely, since the hollow fibre was spun from a spinning dope containing PVP. Use of PVP as an additive in the spinning dope is a well-known method for preparing hollow fibres with microporous skins [51,57]. The fact that no SEM-observable pores were found in the skins of PLLA hollow fibre H-146-7 indicates that, if pores are present, they are smaller than ca. 5×10^{-3} μm, which is the detection limit of the SEM method used. Such pores could still be large enough for diffusion of the small steroid molecules, which have a minimal cross-sectional area of ca. 40 Å^2 [62].

Figures 14 and 16 show that also for PLLA hollow fibre H-148-5 (spinning dope: PLAA/PVP/$CHCl_3$) a constant levonorgestrel release rate was found, which however was lower than that for follow fibre H-146-7 (see Table 10). In this case, the steroid release rate probably will not be determined by the permeability of the hollow fibre membrane skins, which were found (see Figs. 12 and 13) to contain SEM-observable pores (>0.1 μm). More likely, the release rate will be mainly controlled by the rate of steroid diffusion through the hollow fibre matrix, which was found to contain pores showing only a limited degree of interconnection. In this case, a pore-diffusion mechanism can also be imagined, in which the lower levonorgestrel release rate compared to that of hollow fibre H-146-7 could be explained by the larger part of the membrane thickness showing hindered diffusion and the increased tortuosity. The results obtained in this explorative study show that the PLLA hollow fibre levonorgestrel release rates could be varied over a wide range (i.e. 0.1–10 μg/cm/day) by variation of the hollow fibre spinning conditions.

Of the different PLLA hollow fibres investigated (excluding sample H-144-3), the highest (zero-order) levonorgestrel release rates were found for the samples that were prepared using a spinning dope containing PVP as an additive (H-146-7, H-148-5). The results of the *in vitro* levonorgestrel release experiments suggest that these higher release rates might be the result of a change in release mechanism from a solution-diffusion type through the skin for the samples spun in the absence of PVP to a pore-diffusion type for the ones prepared in the presence of PVP. However, more experiments are necessary to verify this hypothesis.

The possible use of the PLLA hollow fibre device as a long-acting contraceptive delivery system

Assuming a constant levonorgestrel release rate for PLLA hollow fibre H-146-8, an average *in vivo* release rate of 2 μg/cm/day is calculated for this type of PLLA hollow fibre by dividing the initial steroid load (435 μg/cm) by the duration of release (210 days) (Fig. 18). This value is one fifth of that found for the *in vitro* release rate (see Table 9). As already discussed above, the *in vitro* levonorgestrel release rate from this type of PLLA hollow fibre (H-146-7) was found to be dependent on the steroid solubility in the surrounding receiving fluid (see Fig. 17 and Table 8). The fact that *in vivo* a lower release rate was found might therefore be explained by the lower solubility of levonorgestrel in the fluid surrounding the hollow fibre *in vivo* than in the 40 wt.% aqueous ethanol used as receiving fluid in the *in vitro* release experiments.

Based on these results, it appears necessary to increase the *in vivo* levonorgestrel release rate by a factor 5 to obtain a value of ca. 10 μg/cm/day (i.e. a device of 3 cm length releasing 30 μg/day). This could be accomplished in part by increasing the hollow fibre dimensions by a factor 2 to an outer diameter of ca. 1.5 mm and inner diameter of ca. 1.0 mm, which would increase the steroid release rate by a factor 2. Further increase of the steroid release rate possibly can be accomplished by variation of the spinning conditions to influence the structure of the hollow fibre membrane. Increasing the hollow fibre dimensions will also increase the duration of release. A device with an inner

diameter of 1.0 mm, filled with a 25 wt.% dispersion of levonorgestrel in castor oil, will contain enough steroid (ca. 2 mg/cm) to release 10 μg/cm per day for a period of 6 months. Further increase of the duration of release, if desired, could then be accomplished by increasing the concentration of levonorgestrel in the core vehicle.

An important aspect in the development of the hollow fibre controlled release device is the method of sterilization. In this study, sterilization of PLLA hollow fibres (H-146-7) by gamma irradiation (2.5 MRad) after filling with the levonorgestrel dispersion in castor oil was found to have a significant effect on the steroid release rate (see Fig. 17 and Table 8). An initially much higher and thereafter declining rate of steroid release was found for the sterilized devices. An explanation for these phenomena, however, is not available at this moment. Possibly, an adverse effect of the gamma radiation on levonorgestrel could be involved [63,64]. Also, an effect of the sterilization method on the castor oil can not be excluded. In contrast, the release properties of the PLLA hollow fibres that were gamma irradiated before filling were not changed (see Fig. 17). This implies that gamma sterilization of the empty PLLA hollow fibres, followed by filling under aseptic conditions, could be a possible method to obtain sterile devices.

The useful lifetime of this new device will be determined by the *in vivo* degradation rate of the PLLA hollow fibres. PLLA usually is considered to be a very slowly degrading material [27–29], with reported *in vivo* degradation times up to 4 years [65]. It should be noted, however, that the actual degradation rate of the PLLA hollow fibre device will depend on the polymer molecular weight, degree of crystallinity, size and shape of the device, and especially its porosity, in addition to the particular animal species and implantation site used [29,66]. The *in vivo* rate of degradation of the hollow fibres as well as the histocompatibility are currently investigated.

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