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Chemical Purity of PLA Fibres for Medical Devices

Abstract
The chemical purity of biodegradable poly(D,L-lactide) (PLA) fibres finished with various finishing agents was examined. Chemical purity parameters of aqueous extracts of the fibres were assessed, including turbidity, the content of sulphate and chloride ions, the content of water-dissolvable substances, the content of foaming agents, the content of heavy metal ions and pH. The content of organic solvent-leachable substances was also estimated according to the PN-EN ISO 10993-12:2009 standard. Tests under equal conditions were performed for PLA fibres spun without any spinfinish, PLA fibres with the spinfinish removed by extraction with organic solvents, and the raw material, PLA 6201D granulate. The certified fibre-grade polymer PLLA produced by Boehringer Ingelheim Pharma GmbH & Co KG (Germany) under the trade name Resomer L 207S served as the reference material and was analysed in the same way. In terms of chemical purity, PLA fibres finished with Estesol PF-790, pharmaceutical glycerol (glycerine), and PLA fibres after removal of the spinfinish were found to be suitable to use in hygiene and medical devices.

Key words: *biomedical polymers, PLA fibres, chemical purity, medical devices, sanitary articles, spinfinish, physical-chemical analysis, chemical contamination.*

Introduction

Synthetic and natural polymers find ever wider applications in pharmacy and medicine. The large family of so-called biomedical polymers includes materials used externally in direct or indirect contact with tissue or blood, materials in contact with mucous membranes and damaged outer tissues, and those that do not contact tissue. Polymers in medicine are used as permanent implanted materials like sutures, artificial cardiac valves, blood vessel prostheses, artificial corneas, and tendon prostheses. Many polymers are applied as components of medical devices such as dental prostheses, tissue glue, dental fillings, and in auxiliary medical equipment. Macromolecular compounds also have utility as pharmacological substances, blood substitutes, drug carriers, protective lacquers, auxiliary substances, and drug packaging materials [1 - 6]. Biodegradable and bioresorbable macromolecular compounds, introduced to the human organism along with an active substance, undergo decomposition as a result of metabolic processes, resulting in non-toxic and entirely disposable products.

Poly(lactic acid) is an innovative material with a wide range of applications; it is biodegradable, biocompatible, and thermoplastic. These features make it fit for use in medicine and pharmacy. The biocompatibility of PLA decomposition products underpins its medical application. As a result of decomposition, lactic acid is formed, which is a substrate of glucogenesis in the liver. This is a proof that the material is harmlessness to the organism [7]. Studies on the synthesis of biodegradable and bioresorbable aliphatic polyesters like poly(D,L-lactide) (PLA) and poly(L-lactide) (PLLA) have recently gained impetus. These polyesters are synthesised by a ring-opening reaction, mostly in the presence of tin octanate ($SnOct_2$) as the catalyst. This substance is approved in the USA and many other countries for the synthesis of macromolecular compounds intended for medical use. Discussions and investigations concerning the irritating and hazardous to human health effect of tin compounds caused that medical-grade PLA is specially purified by the producers in an expensive technological process [8, 9, 10]. Fibres made of PLA have utility in a variety of medical products like surgical sutures [11]. One very important application is in tissue engineering, e.g. in the preparation of bone scaffolds [10, 11]. An added value of the polymer is its synthesis from renewable raw materials and its ability to undergo hydrolytic self-degradation or biological decomposition after the required time of use [10, 11]. High demands are placed on medical-grade polymers concerning their physical-chemical properties, biocompatibility, and chemical purity. This is the reason why the chemical purity of polymeric medical devices must be examined to ensure safe use. This examination permits the assessment of the risk stemming from the profile of leachable substances which are analysed in terms of quality and quantity. The results form a basis for the assessment of safety in the testing of biocompatibility and clinical investigations. The examination of chemical purity comprises a number of physical-chemical analyses to straightforwardly characterise the tested product. Trace amounts of various harmful chemical compounds contained in the medical materials can be detected.

Guidelines for the selection of methods to analyse the profile of leachable substances and for the assessment of an acceptable profile in medical materials based on the conditions of their clinical use are contained in the standards PN-EN ISO: 10993-12:2009 "Biological assessment of medical devices" – Part 12; "Preparation of the sample and reference materials", 10993-17:2009 Biological assessment of medical devices – Part 17; "Determination of allowable limits of leachable substances", 10993-18:2009

*Table 1. Characteristic of the spinfinishes used; * certificate approving contact with food, cosmetics and use in toys (FDA CFR 21 as well as Directive 2002/72/EC and Directive 2009/48/EG of the European Parliament and Council). ** certificate permitting sales of pharmaceutical raw materials issued by the Ministry of Health, approval No. IL-3940/LN. *** 15% [v/v] aqueous solution of the starting spinfinish.*

Trade name	Source	Chemical composition	Concentration of emulsion or solution, %	Recommended deposition on the fibre, %	pH***
Estesol TXB	Bozzetto Group (Italy),	blend of synthetic ester oil, mineral oil, non-ionic emulsifier, and antistatic agent	15	0.6 - 1.2	7.6
Estesol PF 790*	Bozzetto Group (Italy),	poly-ethylene-glycolester	13	0.4 - 1.0	7.1
Lurol PT - L216	Goulston Technologies Inc. (USA),	ethoxylated surfactan	8	0.35 - 0.40	5.5
Lurol PL - 801	Goulston Technologies Inc. (USA),	n.a.	5	0.3 - 0.5	5.9
Stantex S 6457	Pulrachem,	blend of polyglycolethers	10	n.a.	6.5
Pharmaceutical glycerine (glycerol)**	Pharma-cosmetics	85% glycerol	15	-	5.2

Biological assessment of medical devices – Part 18: Chemical characteristic of materials [17 - 19].

The aim of the present work was the assessment of the chemical purity of PLA fibres designed for the preparation of flat textiles for hygiene and medical uses.

Materials and methods

Experimental fibres were made at IBChF from the fibre-grade polymer PLA type 6201D, supplied by NatureWorks LLC, USA. The fibres were prepared in the framework of the key project POIG.01.03.01-00-007/08 "Biodegradable textile products" (BIOGRATEX). The characteristics of the used PLA were: density 1.24 g/cm^3, isomer D content 1.4%, MFI_{210^oC} 15 - 30 g/10 min, melting temperature 160 - 170 °C, and glass transition temperature 55 - 60 °C.

Undrawn yarn (as spun) with a linear mass of 400 dtex was investigated. It was spun at 240 °C with a throughput of 30 g/min and speed of 760 m/min through a spinneret with 24 holes. A spinfinish in the form of an emulsion or aqueous solution was applied to the fibre in the course of spinning.

Table 1 shows the characteristics of the spinfinishes used (manufacturer's data).

Extraction of chemical substances from the PLA fibres

Chemical substances were extracted from the fibre with purified water in a dynamic mode according to standard PN-EN ISO 10993-12:2009 [16]. The extraction was carried out at 37 ± 1 °C (temperature of the human body) and 50 ± 1 °C for 24 ± 2 h. Mixtures containing 10 g of the fibre and 100 cm^3 of purified water were prepared for the extraction which was carried out in a water bath shaker (ELPIN Co., Poland) at 150 r.p.m.

To estimate the leachable substances, the fibres were also subjected to exhaustive extraction with organic solvents according to methodology described in standards PN-P-04607:1983 and PN-EN ISO 10993-18 [18, 20]. The extraction was performed in a Soxhlet apparatus for 1 h after which time the initial content of the leachable substance was estimated in the tested sample. The same sample was put in the Soxhlet apparatus again and extracted for 1 h. The extraction cycle was repeated as many times as necessary to attain no more than 10% of the leachable substance in the extract in relation to the first run. Two samples of the PLA fibre were extracted in parallel. Petroleum ether was used for the Estesol TXB spinfinish, diethyl ether for Lurol PT-L216 and methanol for the remaining ones.

Estimation of the chemical purity of the aqueous extracts from PLA fibres

The following parameters of chemical purity were estimated in two parallel tests: turbidity, content of sulphate and chloride ions, content of water-soluble substances, content of foaming agents, content of heavy metal ions, and pH.

The pH was measured by means of a pH meter (Schott Instruments, Germany) and Blue Line 14pH electrodes (Schott Instruments, Germany) according to standard PN-EN ISO 3071:2007 [21] with a measuring accuracy of 0.1 pH units.

Turbidity (NTU, nephelometric turbidity units) was estimated using a turbimetric method according to FP VII [20] with the use of a Unicam 5625 UV/VIS spectrophotometer (ATI Unicam, UK).

The method of estimating sulphate ions in the aqueous extracts was performed based on the standard PN-P-04781/04:1987 [21]. This method consists of precipitation of sulphate ions with $BaCl_2$ under standard conditions and comparing the turbidity of the tested extract with the turbidity of a reference solution containing a known amount of $[SO_4]^{2-}$ ions. The measurement was performed with a Unicam 5625 UV/VIS spectrophotometer. The limit of detection of the method is 0.001 mg of $[SO_4]^{2-}$ ions per 1 g of the medical device.

Estimation of the chloride ion [Cl$^-$] content was performed according to standard PN-P-04895:1984 [24]. The method employs argentometric titration of aqueous solutions with an $AgNO_3$ solution with a concentration of 0.01 mol/dm^3 in the presence of chromate ions and diluted H_2O_2. The limit of detection of the method is 0.003 mg $[Cl]^-$ ions per 1 g of the medical device.

The content of water-soluble substances was determined according to standard PN-P-04781/06:1988 [23]. The amount of dry residue in the water extract is estimated in this method. The residue is the sum of water-soluble and insoluble matter (turbid extracts).

Detection of foam-forming agents in the PLA water extracts was done according to standard PN-P-04781/14:1989 [26].

Determination of the heavy metal ion content, including Cd, Cr (sum of all oxidation states), Pb, Zn, Hg, and Sn was done in accordance with procedures applied in the accredited Laboratory of Paper Quality of IBWCh by the atomic absorption spectrometry method using a SCAN-1 spectrometer (Thermo Jarrell ASH Co., USA). The method is described elsewhere [27].

Table 2. *Main chemical purity parameters of the aqueous extracts of the starting material PLA 6201D, fibres without a spinfinish, and the reference material PLLA. Dynamic extraction was performed at 37 °C and 50 °C.*

Tested sample	Temperature, °C	Content of foaming agents, NTU	Content of ions, mg/g product		pH	Dry residue of aqueous extract, %wt	Turbidity, NTU
			$[SO_4]^{2-}$	$[Cl]^-$			
PLLA medical-grade	37	none	0.001	0.003	5.8	0.02	0.5
	50		0.002	0.004	6.4	0.02	0.5
PLA yarn no spinfinish	37		0.030	<0.003	7.1	0.04	4.2
	50		0.040	<0.003	7.0	0.04	3.5
PLA 6201D granulate	37		0.003	<0.003	6.1	0.02	1.8
	50		0.004	<0.003	6.2	0.02	2.9

The content of Sn in the PLA 6201D granulate was determined by the mineralisation of a 0.5 g sample in 5 cm^3 70% HNO_3 in a microwave oven MOS 200 (CEM Co., USA). The Sn content in the mineralised sample was determined by the ASA method with electro-thermal atomisation (ETAAS) with the following parameters: $\lambda = 235.5$ nm, max temperature of pyrolysis 900 °C, temperature of atomisation 2350 °C, in a platinum cuvette with a platform modifier matrix of 100 mg/dm^3 Pd+200 mg/dm^3 $Mg(NO_3)_2$. The limit of determination was 0.005 mg/ dm^3 for aqueous extracts and 0.25 mg/kg for the mineralised part.

The content of water-soluble substances was determined according to standards PN-P-04781/06:1988 [23] and PN-EN ISO 10993-12:2009 [19] both in the spinfinish-containing PLA fibres and fibres without the spinfinish.

Results and discussion

The determination of substances extracted from fibres made of Nature Works PLA 6201D was performed. PLA fibres were equipped with various spinfinishes indispensable in spinning and further processing. Only two of the auxiliary agents used, Lurol PT-L216 and Lurol PL-801, were specifically prepared by the manufacturer for use with PLA. Medical certificates are not available for either of the spinfinishes used. The concentration of the aqueous emulsion or solution of the spinfinish varied in the range of 5 - 15wt.% depending on the on-fibre deposition degree recommended by the manufacturer.

The chemical purity was also examined with respect to the fibre made of PLA 6201D under the same conditions, without a spinfinish, and the raw material, PLA 6201D polymer. The certified medical-grade PLLA polymer (Resomer L 207 S, made by Boehringer Ingelheim Pharma GmbH & Co. KG) was chosen as the reference material.

In ***Table 2***, the main chemical purity parameters of the aqueous extracts are presented, including the reference material, medical-grade PLLA, PLA yarn without a deposited spinfinish, and the PLA 6201D granulate ground to a particle size of 0.5 mm in a liquid nitrogen-cooled 6770 Freezer/Mill® cryogenic grinder (SPEX Sample Prep Co., USA).

The medical-grade PLLA had the lowest values of the chemical purity parameters tested. The content of leachable contamination was higher for the PLA 6201D polymer, which may contain various additives like stabilisers and antioxidants. The highest contamination level was seen with the PLA yarn without spinfinish, which may be explained by the influence of the spinning process.

Chemical purity was also examined in fibres from which the spinfinish was removed by an exhaustive extraction process using an organic solvent in a Soxhlet apparatus. The spinfinish was applied to the fibre to provide a smooth run in the spinning process. Depending upon the application of the PLA fibre, the deposited spinfinish was removed according to the recommendations of the manufacturer using organic solvents or detergents. Exhaustive extraction was investigated in this work for the purpose of determining the amount of leachable substances and the level of other impurities remaining after the removal of the spinfinish with organic solvents.

The results of the determination of the amount of spinfinish deposited on the tested PLA fibres are shown in ***Figure 1***.

The highest concentration of the deposited spinfinish was found for EstesoTXB.

This agrees with the recommendation of the manufacturer to assure proper processability of the polyester fibre.

The content of Lurol PT L-216, Lurol PL-801, and pharmaceutical glycerol was in the 0.4 - 0.5 wt.% range. A 4 h extraction time appeared to be sufficient for all the spinfinish agents, since after a repeated 1 h extraction, the content of the leachable substances did not exceed 10% of the amount determined after the 4 h extraction [19]. The effective removal of the spinfinish provided a purified PLA fibre that could be further used in the analysis of chemical purity. The impact of the type of spinfinish on the chemical

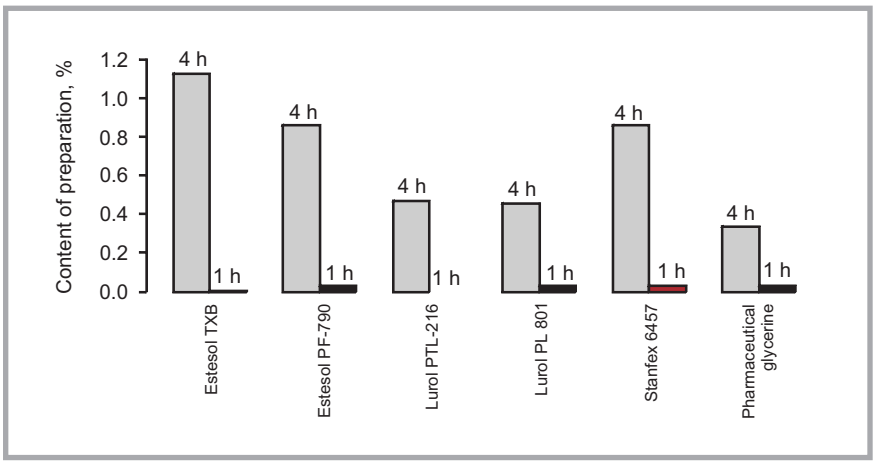

Figure 1. *Content of spinfinish (oily phase) deposited on the PLA fibre after 4 and 1 h of extraction.*

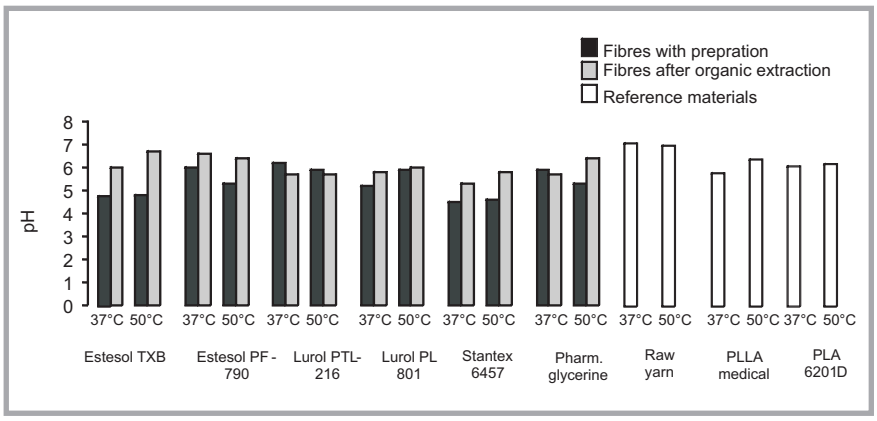

Figure 2. *The pH of aqueous extracts of the PLA fibre, the starting polymer PLA 6201D, and the reference material medical-grade PLLA.*

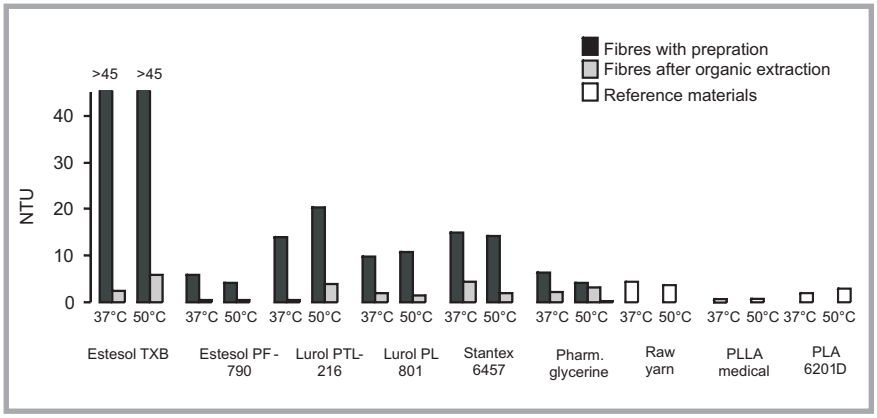

Figure 3. *Turbidity of aqueous extracts of the PLA fibres, the PLA 6201D polymer, and the reference material medical-grade PLLA.*

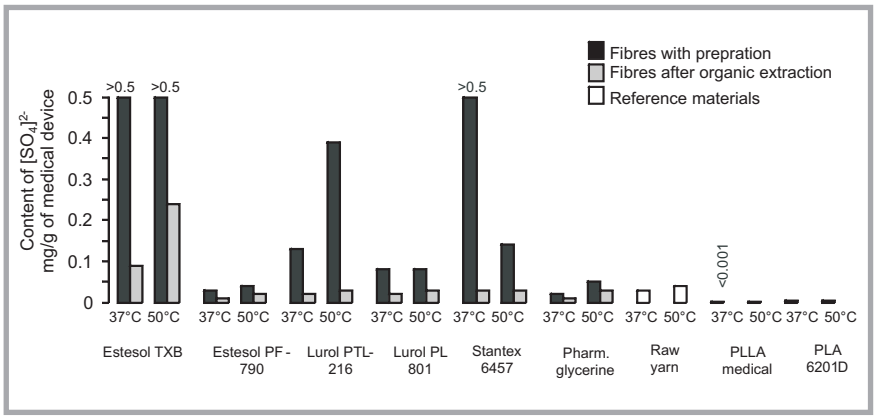

Figure 4. *Content of sulphate ions in aqueous extracts of the PLA fibres, the PLA. 6201D polymer and the reference material medical-grade PLLA.*

purity of the PLA fibre was assessed by parameters such as the pH of the aqueous extracts, turbidity, the content of sulphate and chloride ions, the content of water-soluble substances , the content of foaming agents, the content of heavy metals, and the content of substances leachable with organic solvents.

In further steps, the pH of the aqueous extracts of the PLA fibre with spinfinish and after its removal at 37 °C and 50 °C was measured; the results are presented in ***Figure 2***.

The staring polymer PLA 6201D and the medical-grade reference material PLLA showed pH values close to that of purified water (pH 5.96, according to Quality Certificate QC/2/0072/10 for Baxter injection water) both at 37 °C and 50 °C. Values were higher for the extract of the fibre prepared without a spinfinish (pH 7.1). In fibres from which the spinfinish was removed, the pH values were in the 6.0 - 6.5 range. Lowest pH values, below 5, were found for fibres coated with Estesol TXB and Stantex 6457. When the spinfinish was removed, the pH rose to about 6 due to the acidic components in Estesol TXB and Stantex 6457. A pH level below 5 may render the two spinfinishes unsuitable for medical use.

The turbidity (in nephelometric turbidity units, NTU) of the aqueous extracts (37 °C and 50 °C) was measured; the results are presented in ***Figure 3***.

In accordance with the recommendations of the Polish Pharmacopeia (VII edition) [20] for medical devices, a solution is regarded transparent if turbidity falls below a value of 3 NTU. The turbidity of the aqueous extracts of the fibre coated with the water-insoluble spinfinish Estesol TXB used in a water suspension surpassed by many times the allowable limit of 3 NTU. The turbidity of Estesol PF-790 and glycerol-coated PLA fibre extracts had a value of 5, while the remaining extracts showed values of 10 NTU. The turbidity of the extracts of PLA fibres dropped to 5 NTU after the removal of the spinfinish. The low turbidity of the extracts of PLA fibres were comparable with those of medical-grade PLLA after the removal of the Estesol PF-790 spinfinish. These results demonstrate the effective action of methanol as a solvent for that spinfinish.

The content of sulphate ions ($[SO_4]^{2-}$) in the aqueous extracts (37 °C and 50 °C) was analysed; the results are presented in ***Figure 4***.

The content of sulphate ions in the extracts of medical-grade PLLA and PLA 6201D were close to each other and fell into the 0.001-0.004 mg/g range, while for the PLA fibres spun without a spinfinish the content was about 10 times higher. It may be therefore concluded that the spinning process influences the $[SO_4]^{2-}$ ion content in the extracts. This could have been caused by the use of sulphate ions in water as an auxiliary agent, thereby replacing the spinfinish to reduce friction during spinning. The content of sulphate ions in the extracts from fibres with the spinfinish Estesol PF-790 and glycerol were at a similar level and close to that of the PLA fibres without a spin-

finish, i.e. in the range of 0.03-0.05 mg/g. In the extracts of fibres after the removal of Estesol PF-790 and medical-grade glycerol prepared at 37 °C, the content of sulphate ions matched that of medical-grade PLLA.

Figure 5 shows the level of dissolvable matter in extracts prepared at 37 °C and 50 °C of PLA fibres spun with a spinfinish and after its removal, of the starting polymer PLA 6201D, and of PLLA reference material.

The aqueous extracts of PLA fibres with a deposited spinfinish contained a considerable amount of water-dissolvable matter when compared with those of the PLA 6201D starting material, the PLLA reference material, and fibres spun without a spinfinish. Extracts of fibres with deposited glycerol revealed the lowest amount of water-soluble substances, comparable with that of the reference material medical-grade PLLA. In the extracts of PLA fibres devoid of the Estesol PF-790 or Lurol PL-801 spinfinish and glycerol, the content of dissolved substances was lower than that of the medical-grade PLLA.

Figure 6 shows the content of chloride ions in aqueous extracts prepared at 37 °C and 50 °C of PLA fibres spun with a spinfinish and after its removal, fibres spun without a spinfinish, the starting polymer PLA 6201D, and the PLLA reference material.

The aqueous extracts of fibres with a deposited spinfinish showed a much higher content of chloride ions than those of the fibres after organic solvent extraction, in which the content was below the limit of detection. The highest chloride ion content was measured for the Santex 6457 spinfinish and the lowest was found for Estesol PF-790, which was comparable with that of medical-grade PLLA.

Figure 7 presents the content of foaming agents in the aqueous extracts prepared at 37 °C and 50 °C of PLA fibres spun with a spinfinish and after its removal, fibres spun without a spinfinish, the starting polymer PLA 6201D, and the reference material PLLA.

A considerable amount of foaming agents was found in the fibres with an Estesol TXB or Lurol PTL-216 spinfinish. After the removal of these substances by means of organic solvent extraction, the amount of foaming agents was greatly reduced.

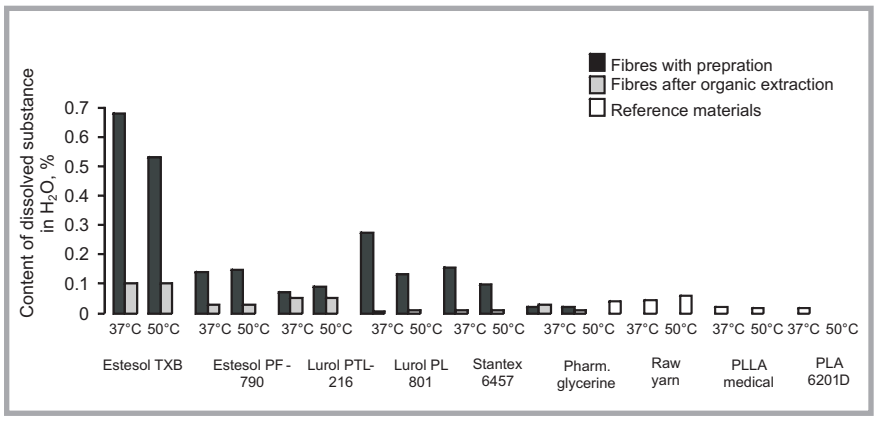

Figure 5. *Content of dissolvable matter in extracts of the PLA fibres, the starting polymer PLA 6201D, and the PLLA reference material prepared at 37 °C and 50 °C.*

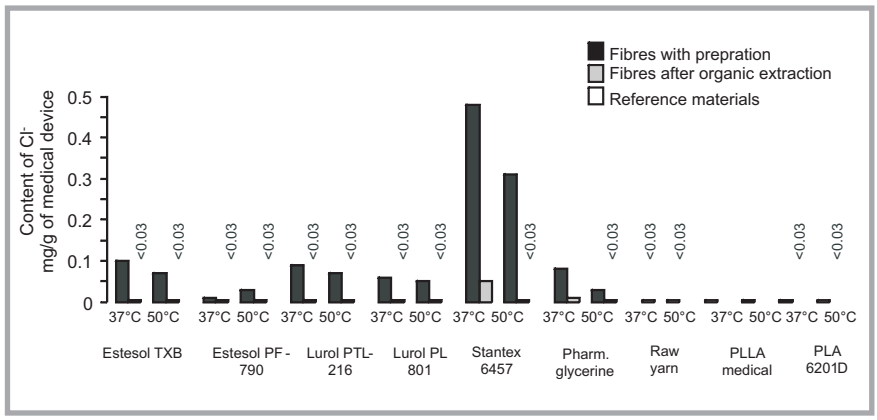

Figure 6. *Content of chloride ions in aqueous extracts of the PLA fibres, the starting polymer PLA 6201D, and the PLLA reference material.*

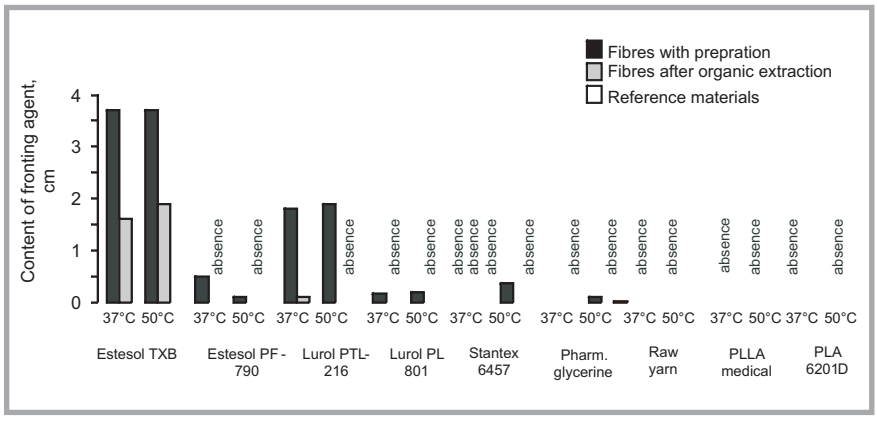

Figure 7. *Content of foaming agents in the aqueous extracts of PLA fibres, the starting PLA 6201D polymer and the reference medical PLLA.*

Fibres with other spinfinishes showed an insignificant amount of foaming agents. Foaming agents were not detected in the aqueous extracts of the fibres devoid of the spinfinish.

Table 3 (see page 140) shows the content of heavy metal ions in the aqueous extracts prepared at 37 °C and 50 °C of PLA fibres spun with a spinfinish and after its removal, fibres spun without a spinfinish, the starting polymer PLA 6201D, and the PLLA reference material.

The heavy metal ion content in the aqueous extracts of PLA fibres with a spinfinish and after its removal by organic solvent extraction as well as in the medical-grade PLLA was below the determination limit. The content of Zn ions in the aqueous extracts of fibres with a spinfinish and after its removal was in the range

Table 3. *Content of heavy metal ions in extracts of the PLA fibres, the PLA 6201D polymer, and the reference material medical-grade PLLA.*

Symbol of sample		Content of heavy metal ions, mg/100cm^3 of the aqueous extract									
		Cd		Cr		Zn		Pb		Hg	
		Extraction temperature, °C									
		37	50	37	50	37	50	37	50	37	50
Fibre without spinfinsh		<0.002	<0.002	<0.020	<0.020	0.004	0.010	<0.020	<0.020	<0.0002	<0.0002
Medical-gradePLLA .						0.006	0.007				
PLA 6201D						0.013	0.008				
Estesol TXB	with spinfinish					0.020	0.020				
	spinfinish removed										
Estesol PF-790	with spinfinish										
	spinfinish removed										
Lurol PL 801	with spinfinish										
	spinfinish removed										
Stantex 6457	with spinfinish										
	spinfinish removed										
Glycerol pharmaceutical	with spinfin										
	spinfinish removed										

of 0.02 mg/100 cm^3. The Zn content was 0.004 and 0.006 mg/100 cm^3 in extracts of the as-spun fibre and medical-grade PLLA, respectively.

Table 4 presents the contents of Sn in aqueous extracts prepared at 37 °C and 50 °C of PLA fibres spun with a spinfinish and after its removal, fibres spun without a spinfinish, the starting polymer PLA 6201D, and the reference material PLLA.

Table 4. *Content of Sn in aqueous extracts of the PLA fibres, the PLA 6201D polymer, and the reference material medical-grade PLLA (ppm).*

Symbol of sample		Tin content, mg/1000 cm^3 aqueous extract	
		Temperature of extraction, °C	
		37	50
PLA fibre, Estesol PF 790	With spinfinish	0.0160	0.013
	Spinfinish removed	< 0.005	0.007
PLA fibre without spinfinish			<0.005
PLLA medical grade			
PLA 6201D			

The Sn content in the PLA 6201D granulate and in the reference material medical-grade PLLA is given in ***Table 5***.

The Sn concentration in the aqueous extracts of PLA fibres with the Estesol PF-790 spinfinish and after its removal as well as in the extracts of the reference material did not exceed a value of 1 ppm (***Table 4***). The Sn content in the PLA 6201D granulate was distinctly lower than the concentration in the medical-grade PLLA provided by the manufacturer.

Table 5. *Content of Sn in the tested materials; * Value provided by the manufacturer in the analysis certificate.*

Symbol of sample	Tin content in the polymer, mg/kg (ppm)
PLA 6201D granulate	14.5
PLLA medical grade	23.0*

Conclusions

The results obtained in the examination of the chemical purity of PLA fibres revealed that the spinfinish Estesol TXB shows the highest level of the estimated parameters; thus, it does not meet the requirements placed on medical devices. It may be concluded that the unfavourable level of the chemical purity parameters in this case was caused by the higher on-fibre deposition degree of the spinfinish.

Among all tested spinfinishes applied on the PLA fibre, Estesol PF-790 and pharmaceutical glycerol showed the best results, comparable with those of the reference material medical-grade PLLA.

The allowable content of tin in polymeric medical products has not yet been defined in Polish law. The European Pharmacopeia [28] defines 20 ppm of tin as the upper allowable limit for materials in contact with blood or its constituents.

It was documented in the present investigation that the PLA 6201D polymer fulfils all demands concerning chemical purity, inclusive of the tin content. It may therefore be concluded that fibres made of this material can be used in medical devices. The methods of sample preparation used here and the range of examination were adequate for the assessment of products concerning chemical purity.

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