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Antibacterial Poly(ethylene terephthalate) Yarn Containing Cephalosporin Type Antibiotic

Abstract

An effective two-stage method for obtaining poly(ethylene terephthalate) yarn with antibacterial properties has been developed. The method consists of the incorporation of carboxylic groups into fibres by poly(acrylic acid) grafting polymerisation followed by impregnation of the fibres with an antibiotic which belongs to the cephalosporins with the Biotrakson trade name. The immobilisation of Biotrakson was due to ionic interactions. Drug loading was varied from 0.61 to 4.15% w/w. The modified fibres show effective biocide liberation into water. The release of Biotrakson from the modified PET fibres to water was monitored for 550 hours. Variations of Biotrakson concentration in water were approximated with a square equation. In vitro studies revealed that the drug-loaded fibres were bioactive against Gram-positive and Gram-negative microorganisms (Staphylococcus aureus ATCC 25923, Escherichia coli ATCC 25922, and Pseudomonas aeruginosa ATCC 27853). The presence of Biotrakson combined with the modified polyester yarn though chemical bonds has been proved by IR investigations.

Key words: *biocide poly(ethylene terephthalate) fibres, poly(acrylic acid), cephalosporin, Biotrakson, biocide immobilisation, biocide release.*

Introduction

Grafted copolymers containing poly(acrylic acid), (PAA) side chains as chain branches from the polymer main chain are considered interesting bio-compatible materials owing to their atrombogenic properties and their ability to be combined with appropriate antibiotics in the form of cations for the previously incorporated carboxylic groups. Polyester fibres modified in this way show antibacterial properties to Gram-positive and Gram-negative bacteria [1-10].

Fibres of this kind may be used in medicine as antibacterial surgical threads to protect patients against frequent post-surgery local perisutural infections. The presently accepted and compulsory procedure to treat patients and infection spots, as well as to protect implants against infection, includes the prophylactic administration of antibiotics within the near-surgery period [11-15]. In the general administration of antibiotics, important factors for an efficacious cure include the level of antibiotic in serum, blood supply to the tissue and antibiotic permeability of tissues. Thus, the use of antibiotics to fight against infection requires their presence in the infected tissue in a sufficient concentration to destroy the microorganisms that cause infection. This is impossible with their general application.

Orally or parenterally administrated antibiotics are dispersed in various tissues, often to no purpose, while their concentration in the site requiring treatment may be insufficient to play a positive part in combating pathogenic microorganisms.

An attempt to solve the problem of perisutural infections is the use of surgical threads and medical implants with antibacterial properties obtained by chemical or physical combination with antibiotics such as penicillin and aminoglucosides [2,3] or cephalosporines [9,10,16-18] as well as other biocide compounds [4,5,19].

The introduction of cephalosporines of the third generation is a great progress in the pharmacotherapy of infections. The group of cephalosporine antibiotics includes ceftriakson (formula in Figure 1), which shows a wide range of antibacterial effects towards Gram-positive and Gram-negative bacteria and anaerobes. It is worth mentioning its very high sensitivity to the examined antibiotic of anaerobic bacteria, which play an important part in the pathogenesis of surgical infections.

Biotrakson (an equivalent of *Longaceph*) is a safe medicine with no local or general side effects. No negative effects of *Biotrakson* on the functions of liver and kidneys were found. This antibiotic shows high prophylactic and therapeutic effectiveness. Due to its very wide range of antibacterial effects, it can be an antibiotic of choice, in case it is necessary to start the treatment before microbiological recognition. This medicine is very active against staphylococci, and is resistant to the action of staphylococcal penicillinase. It also shows better pharmokinetic properties, i.e., better tissue penetration [20]. Its mechanism of action consists in blocking the biosynthesis of bacteria cellular walls.

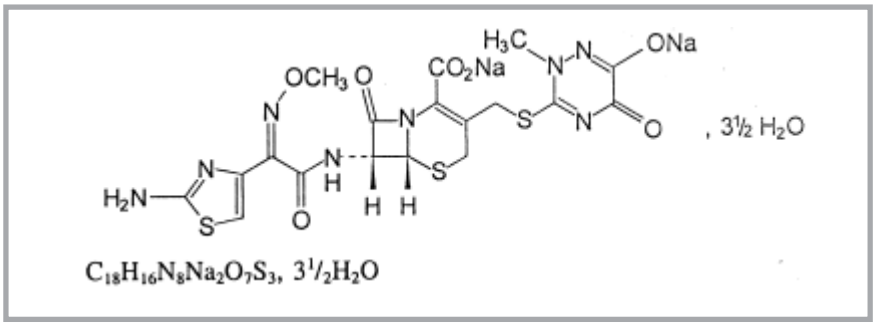

Figure 1. *Chemical formula of Biotrakson (the molecular weight Bx=661.61).*

The above considerations constitute the objectives for the present study, including the modification of polyester fibres to provide them with antibacterial properties, the examination of the antibiotic's release from fibres to water, and infrared measurements to confirm the chemical character of the antibiotic's addition to polyester yarn.

The antibacterial effects of modified fibres are microbiologically tested *in vitro* for the stunting of bacterial growth under hospital conditions, i.e., *Staphylococcus aureus* ATCC 25923 (*S. aureus*), *Escherichia coli* ATCC 25922 (*E. coli*) and *Pseudomonas aeruginosa* ATCC 27853 (*P. aeruginosa*).

The bacteria mentioned above are representative of the hospital environment and are very dangerous to the health and life of humans. The strains of these bacteria which we have been adhibiting in our studies are used throughout the world to control the quality and standardisations of methods in microbiological laboratories [23].

Polyester fibres and surgical threads are made antibacterial by a two-stage modification, including the incorporation of carboxylic groups into the polyester macromolecule by grafting acrylic acid followed by the antibiotic addition to those groups [2,3,7,16-19].

Experimental Part

Materials and methods

Poly(ethylene terephthalate), a (PET) multifilament yarn produced by Elana S.A. Toruń, was used in our studies. Before modification, the parent fibres were cleaned from a spin finish by heating at 333 K in aqueous soap solution (2 g · dm^{-3}) for 1 h, followed by extraction of methanol-soluble components in Soxhlet's apparatus for 2 h. Then, the fibres were dried at 323 K to a constant weight in presence of P_2O_5.

The following reagents were also used:

- Acrylic acid (AA) (FERAK, Germany) was purified from a stabiliser by distillation under reduced pressure. Before polymerisation, the AA was deoxygenated with nitrogen.
- Benzoyl peroxide (BP) (pure grade, Argon, Poland) was crystallised from a methanol-chloroform mixture.
- Toluene, diphenyl (DPh) (pure grade, POCh, Poland) and dispersing agent NNO (a mixture of salts of aromatic sulphoacids, ZPO-Rokita, Poland) were used without further purification.
- *Biotrakson* as disodium of salt of ceftriakson, Polish production (Instytut Biotechnologii i Antybiotyków, Warsaw, Poland), was used as received.
- Bacteria: *S. aureus* ATCC 25923, *E. coli* 25922, *P. aeruginosa* 27853 (Wytwórnia Surowic i Szczepionek, Warsaw, Poland).

Acrylic acid was grafted onto PET yarn, as described in [7]. Briefly, active centres on the PET yarn were formed by treatment with BP. 2 g samples of PET yarn were kept in 40 ml of 5.0% wt/v toluene solution for 30 min at 323 K. Next, the excess of the BP solution was squeezed out and traces of toluene were removed by evaporation for 15 min at 368 K. The pretreated yarn sample was placed into a 250 ml reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser, and nitrogen supply. Grafting was carried out at 368 K, under nitrogen in 100 cm^3 of aqueous solution containing AA (concentration was changed within the range of 2.5-10.0% wt/v), DPh (0.4% wt/v), and NNO (0.4% wt/v). Grafting time was 60 min for all samples. The unbonded PAA was removed by extraction with water. The amount of PAA grafted onto PET yarn was determined gravimetrically (the samples were dried at 323 K to a constant weight). Modified PET yarn samples with 17.00 to 37.80% wt/wt of poly(AA) were obtained.

Attachment of *Biotrakson* onto PET fibres modified with poly(AA) grafts.

The PET yarn and PET yarn samples with grafted poly(AA); X=22.3-31.6% wt/wt of poly(AA) were incubated with 20% wt/v solutions of *Biotrakson*. In each experiment, 0.6 g of the grafting yarn was incubated at 313 K with 12 cm^3 of the *Biotrakson* solution for a period of 1 h. The amount of attached drug was determined gravimetrically. Fibres containing 0.61-4.15% wt/wt were obtained. Information on the method of *Biotrakson* attachment was deduced from IR spectra of the poly(AA) modified PET fibres before and after attachment of the drug.

Biocide release from the modified fibres to water was carried out using gravimetric and spectrophotometric analysis. Applying the spectrophotometric method, measurements were executed at maximum absorption for *Biotrakson* λ=241 nm. The measurements were carried out on the UV-VIS Jasco spectrophotometer.

The kinetics of the *Biotrakson* release were monitored gravimetrically or spectrophotometrically for 550 hours. In a typical experiment, several samples (0.2 g each) of the PET yarn with immobilised *Biotrakson* were placed into flasks containing 100 cm^3 of water. At the required moments, the fibre samples were taken out and the remaining liquid was pressed off. Finally, in the gravimetrical method the remaining PET fibres were dried at 313 K to a constant weight. The weighed samples were immersed in water which had been changed every day. The measurements were repeated several times for each sample.

The quantity of released antibiotic B_τ in time τ was calculated from the difference:

$$B_\tau = m_a - m_\tau \qquad (1)$$

where:

m_a - the initial weight of fibre with added antibiotic (g),

m_τ - the weight of fibre with added antibiotic after releasing it into water for time τ (g).

The released quantity of the antibiotic calculated as above constitutes, at the same time, the approximate concentration of the given antibiotic (% by weight) in water [6].

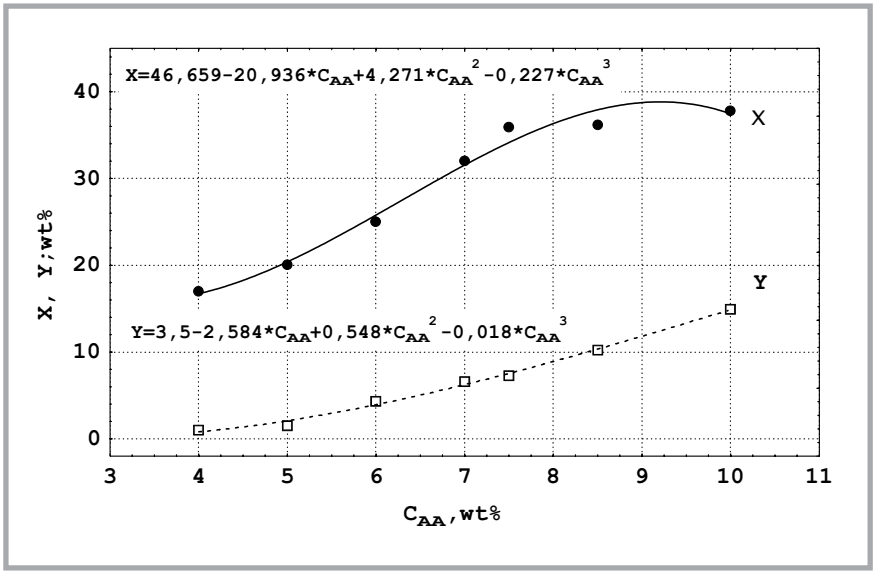

Figure 2. *Dependence of degree of grafting of poly(AA) on PET yarn (X, curve X •) and homopolymer content (Y, curve Y □) on concentration of acrylic acid in bath grafting, CAA (T=368 K, (τ=60 min).*

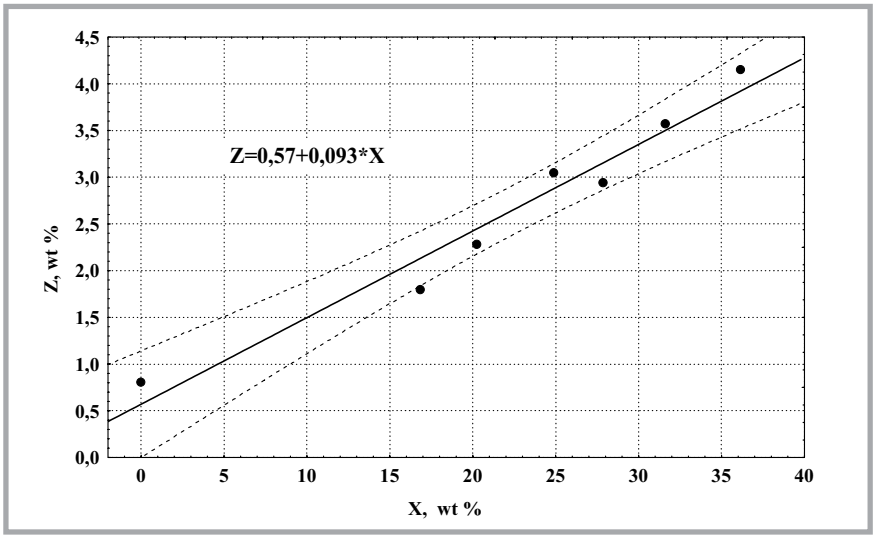

Figure 3. *Dependence of the Biotrakson concentration (Z) on the degree of grafting of poly(AA) of PET yarn (X). Limits of confidence = 95%.*

Antibacterial properties of PET fibres loaded with *Biotrakson*.

The samples of fibres, sealed in double-walled film packages, were sterilised by radiation (Co^{60} γ source, 25 kGy dose) at the Institute of Radiation Techniques, Technical University of Łódź.

The antibacterial properties of the fibres were assessed *in vitro* at 310 K using the direct and ring-diffusion methods [24]. The direct method consists in placing the fibre samples onto an agar support inoculated with tested bacteria and, after the required incubation time, measuring the dimensions of inhibition zones around the fibres. The ring-diffusion method consists in placing rings of blotting paper soaked with water suspensions of modified fibres onto an agar support inoculated with bacteria, and measuring the diameter of the inhibition zone around the paper sample. In each type of experiment, measurements of inhibition zones were carried out 20 h after applying the fibre samples onto the bacteria cultures.

The bacteria strains *S. aureus; E. coli,* and *P. aeruginosa* were used in these studies. All the bacteriological tests were carried out at the Copernicus Memorial Hospital, Łódź. The antibacterial properties of *Biotrakson* before and after irradiation were determined for bacteria mentioned above.

Infrared (IR) spectrophotometric measurements

IR measurements were conducted by use of an FTIR MATSON 1000 spectrophotometer within the range of frequency between 4000 and 500 cm^{-1}. The following samples were tested: initial PET yarn free from spin finish, PET yarn grafted with PAA (x=31.6% by weight), PET yarn grafted poly(AA) with *Biotrakson* fixed with the yarn (Z=4.15% by weight) and standard of *Biotrakson*. The samples of yarn cut with a microtom were prepared in the form of tablets. KBr was used as a standard reference.

Results and Discussion

The attempts to immobilise antibiotics in polyester yarn by impregnating the yarn with biocide solutions have found no practical application, since these agents are quickly and easily washed out in tissues. On the other hand, the combination of an antibacterial agent with the PET polymer via chemical bonds is found to be difficult, due to the lack of suitable functional groups capable of forming chemical bonds with the antibacterial agent.

Hence, it was necessary to graft acrylic acid onto PET yarn to incorporate carboxylic groups, and to add the antibacterial agent to them. The results of dependence of degree of grafting poly(AA) on PET yarn (X) and homopolymer content (Y) on the monomer concentration in aqueous solution (CAA) are presented in Figure 2. Samples of this series of experiments were used as material for loading with *Biotrakson*.

Modified fibres with appropriate functional groups (acidic, amine or other) have ion-exchange properties. Depending on whether these groups are free or substituted, the fibres may assume various properties, including antibacterial effects, as was found in previous studies [16-19]. The choice of the antibiotic used in this study was preceded by tests in vitro for the sensitivity of bacteria under hospital conditions, i.e., *S. aureus, E. coli* and *P. aeruginosa*, to the examined antibiotic. From this analysis it resulted that the mentioned bacteria were sensitive to *Biotrakson*. Thus, it should be expected that fibres containing this antibiotic will also have antibacterial properties.

To examine these properties, polyester yarn grafted with poly(AA) was impregna-

ted with *Biotrakson* solutions. The effect of the impregnating bath's parameters on the degree of fibre impregnation with the antibiotic was examined. Figure 3 shows, as an example, the results of the dependence of the degree of impregnation with *Biotrakson*, on the degree of fibre grafting with poly(AA), X [wt%]. The ordinate also shows the value of Z for untreated fibres after their impregnation with *Biotrakson* under the same conditions as grafted fibres.

From Figure 3 it is seen that the antibiotic is added to the untreated polyester fibres only to a very low extent (0.614% by wt.). This is due to the fact that these fibres contain low quantities of functional groups which can combine the antibiotic. On the other hand, polyester yarn grafted with a polymer containing appropriate functional groups can effectively combine the medicine, as shown in Figure 3.

The amount of antibiotic added to polyester yarn depends on the presence of functional groups both in the fibre and the antibiotic. The antibiotic used contains in its structure amine, acidic, amide and hydroxyl groups as well as an aromatic ring with nitrogen, which provides good conditions for the formation of strong chemical bonds, such as ionic or co-ordination bonds, and weaker hydrogen bonds or van der Waal's forces. It is also possible that the above mentioned polymer-antibiotic interactions result in the formation of complex compounds.

Biocide release from the modified fibres

If the antibiotic added to fibres is to play its positive part, it must be released from the fibres into its environment within a definite period of time, maintaining its activity towards pathogenic microorganisms. In order to examine such possibilities, trials of controlled release of the antibiotic from the modified fibres to water were carried out, and the results obtained are shown in Figure 4.

It was found that after a prolonged (550 hs) release of the antibiotic into water, the yarn still contained some amount of it (about 20-30% on average), this amount being dependent on the initial quantity of the antibiotic in the yarn. The unmodified yarn containing a low amount of *Biotrakson* (0.61%) loses its total antibiotic content after only one hour of releasing into water.

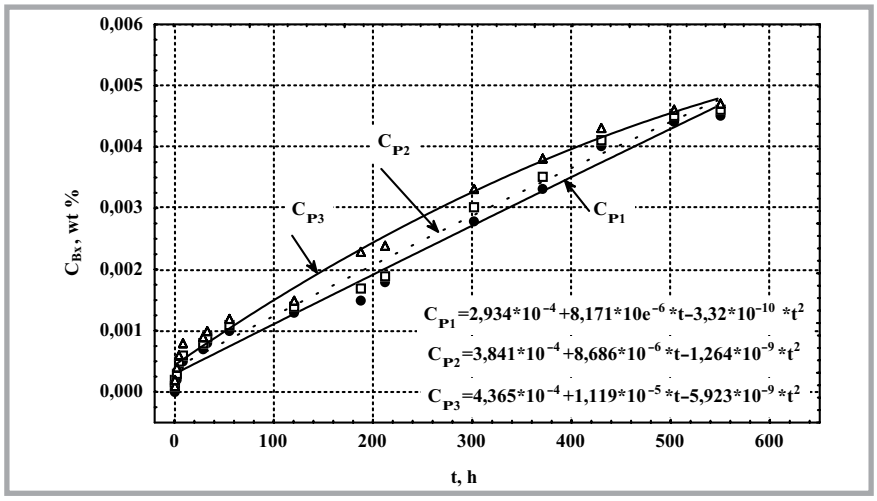

Figure 4. *Dependence of the Biotrakson concentration C_{Bx} on the time of liberation t from modified PET yarn to water (CBx Biotraxon concentration in water). Samples: P1 (X=22.3%, Z=2.94%), P2 (X=27.8%, Z=3.57%), P3 (X=31.6%, Z=4.15%), t=550 hs.*

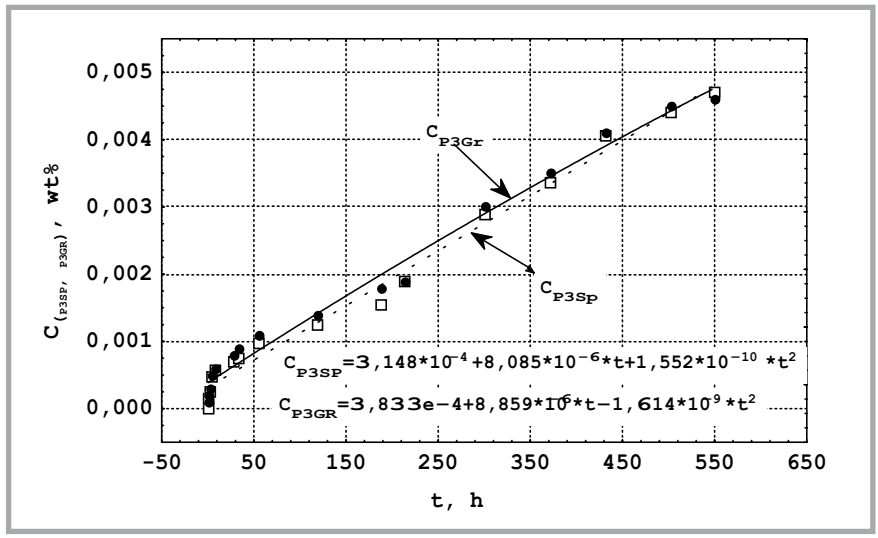

Figure 5. *Dependence of Biotrakson concentration C_{P3SP} and C_{P3GR} (spectrophotometrically and gravimetrically) on the time of liberation t from modified PET yarn. Samples: P3 (X=31.6%, Z=4.15%), t=550 hs.*

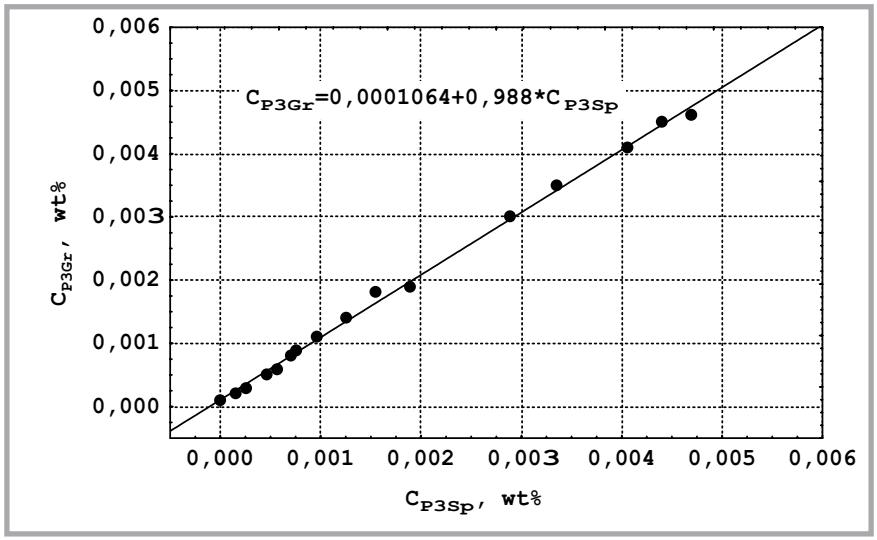

Figure 6. *Dependence of Biotrakson concentration measured gravimetrically C_{P3Gr} on concentration measured spectrophotometrically C_{P3Sp}.*

Table 1. *Antibacterial activity (expressed as thickness of the inhibition zone) of polyester fibres (parent and with immobilised Biotrakson, Z_{Bx}=4.15 wt%, determined by the direct method) and of the drug itself (determined by the ring-diffusion method).*

Strain of bacteria	Time of monitoring days	Thickness of the zone with inhibited bacterial growth, mm			
		Direct method		Ring-diffusion method	
		Parent fibres	Fibres with Biotrakson	Reference solution of Biotrakson	
		After irradiation		Before irradiation	After irradiation
S. aureus	1	0.0	28.0	27.0	27.0
	5	0.0	28.0	28.9	28.0
E. coli	1	0.0	37.0	37.0	37.0
	5	0.0	37.0	37.0	37.0
P. aeruginosa	1	0.0	25.0	25.0	25.0
	5	0.0	24.0	24.0	24.0

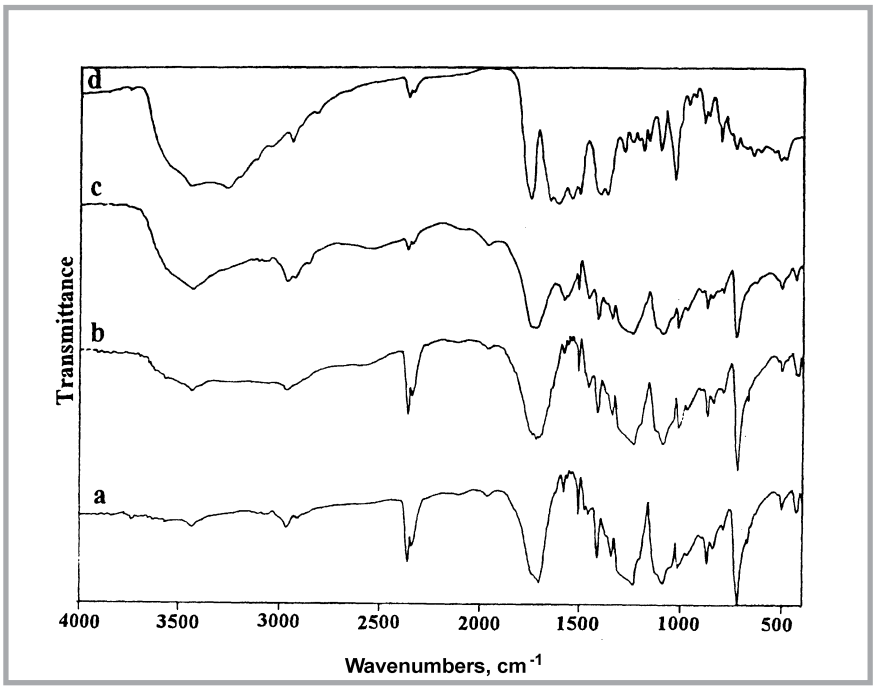

Figure 7. *IR Spectra of PET- fibres parent (a), PET-poly(AA) (b), Biotrakson loaded PET - poly(AA) fibre (c), standard of Biotrakson (d).*

For the interpretation of the antibiotic release within the specified period of time, equations (2) to (4) were used as model equations [26,27].

$$C_1 = C_\infty \cdot [1 - e^{-(k \cdot t_b - b)}] \quad (2)$$

$$C_2 = C_\infty \cdot k \cdot t_b^{\,w} \quad (3)$$

$$C_3 = k \cdot \sqrt{t_b} + b \quad (4)$$

where:

$C_{1\text{-}3}$ - concentrations of the antibiotic in solution after time t_b,

C_∞ - concentration of the antibiotic in the state of equilibrium,

k, b - characteristic constants of the system;

w - exponent.

Analysing equation (2) and approximating it to experimental data, it was found that for the yarn with the degree of grafting X=31.6% and the impregnation degree Z=4.15%, the correlation coefficient is r_{C_3}=0.9782, with the remaining parameters of the equation being k=0.0046, b=0.0178.

The fitting of the curves of linear and square regressions to the experimental data was also checked. It was found that the correlation coefficient r and the determination coefficient r^2 were slightly higher in the case of the linear fitting than that in the square fitting, which means better representation of the experimental data by the linear function.

For the linear regression we have the correlation coefficients of r_{C_3}=0.9997; r_{C_2}=0.9926; r_{C_1}=0.9923 and determination coefficient: $r^2_{C_3}$=0.9795; $r^2_{C_2}$= 0.9853; $r^2_{C_1}$=0.9865 at the significance level p<0.00005 (the probability of error for the approximations of the linear regression equation).

The above values were calculated by means of a statistical computer program. From the data in Figure 4, it follows that the increase in the degree of polyester yarn impregnation with *Biotrakson* also brings about an increase in its concentration of the aqueous extract of the soaked yarn.

In order to estimate the exactitude of gravimetric analysis in comparison with spectrophotometric analysis, the measurements of releasing *Biotrakson* from modified fibres were executed using gravimetric and spectrophotometric methods. The results of these measurements are illustrated in Figure 5. These results of drug release from fibres to water in both analyses were approximated by square equations.

To convince how strongly the results of gravimetric (concentration C_{P3Gr}) and spectrophotometric analyses (concentration C_{P3Sp}) were correlated, we made the graphs of dependence of concentration of releasing the drug using the gravimetric method, and compare it with the concentration of the measured drug by the spectrophotometric method. These dependences are illustrated in Figure 6.

On the basis of these graphs, it was possible to introduce the following equation of regress:

$$C_{P3Gr} = 0.000106 + 0.988\, C_{P3Sp} \quad (5)$$

which defines the dependence between these methods.

From the statistical analysis carried out, it results that the degree of adjustment of the course of C_{P3Gr} as a function of time (in the shape of a straight line) is high and adequate to the results of C_{P3Sp}, as the coefficient of correlation equalled 0.999, while the error of estimation of the straight line was 0.00008 (concentration C_{P3Gr}=C_{P3Sp}) with the level of significance p≤0.00000. The assessed determination coefficient which estimates the measure of the adjustment accuracy of the regression line to the empirical data is also high and testifies that one quantity well reflects the other. The dependencies are practically proportional.

Testing *in vitro* the antibacterial effects of the modified polyester yarn

The antibacterial effects of modified yarns were tested *in vitro* using samples of untreated yarn, modified yarn containing *Biotrakson* and the standard of the antibiotic already mentioned. The results obtained are given in Table 1, where standard deviation was equal to 0.513 mm, the level of trust of measurements carried out β=95%, the average relative error of the measurement carried out was 1.68%, and the precision of the measurement method carried out was 1.72% [25].

From the data in Table 1, it follows that the untreated yarn is inactive towards Gram-positive and Gram-negative bacteria used in the tests, while the modified polyester yarn containing *Biotrakson* is active to a large extent towards *S. aureus, E. coli* and *P. aeruginosa,* which is shown by large zones of bacteriostasis.

The sensitivity of the bacteria used for testing to the modified yarns containing *Biotrakson* is consistent with the sensitivity of these bacteria to the standard of this antibiotic as seen in Table 1. From Table 1 it also follows that the antibiotic standard is equally active both before and after irradiation, which may be of importance in the sterilisation of surgical threads by this procedure.

Infrared spectrophotometric measurements. Mechanism of *Biotrakson* addition to PET yarn

Chemical changes in the PET yarn due to the grafting process were examined by infrared spectroscopy. The absorption signals in spectrograms at appropriate wavelengths were ascribed to appropriate atom groups on the basis of data entered into a computer.

The measurements comprised the following samples: a - untreated PET yarn, b - PET yarn grafted with poly(AA), c - grafted PET yarn containing *Biotrakson*, d - the standard of *Biotrakson*. The spectrograms of the samples mentioned are shown in Figure 7.

The spectrogram of the untreated PET yarn shows characteristic bands at the wavelengths of 3432 cm^{-1} corresponding to the vibration of free -OH groups in the end groups of PET, 2966 cm^{-1} due to methylene groups in PET molecules, 1716 cm^{-1} corresponding to strong valence vibration of C=O groups, and at 1015, 871 and 720 cm^{-1} corresponding to the vibration of benzene rings of PET.

The grafting of the PET yarn resulted in significant changes, which are seen in the spectrogram of these fibres. There is a broadening of the absorption band at λ=1734 cm^{-1} corresponding to C=O vibration, and of the band at λ=1086.7 cm^{-1} corresponding to COOH vibration. This confirms the increased content of carboxyl groups in the modified PET derived from the grafted poly(AA). The intensity of bands at λ=2073 cm^{-1} in the spectrogram of the grafted PET yarn is also increased.

Biotrakson standard shows the following characteristic bands:

at λ=3744.14 cm^{-1}
corresponding to -CONH vibration;
at λ=3462.58 cm^{-1}
corresponding to -OH and -NH vibration;
at λ=1737.6 cm^{-1}
corresponding to -CO vibration;
at λ=1620.9 cm^{-1} and 1544.4 cm^{-1}
due to the vibration of heterocyclic structures;
at λ=1537.0 cm^{-1} and 1499.4 cm^{-1}
corresponding to the vibration of aromatic rings;
at λ=1648.9 cm^{-1}
due to the presence of the -C=N group;
at λ=1252.6 cm^{-1}
due to the presence of the -COOH group;
at λ=682.7 cm^{-1}
due to the presence of $-NH_2$;

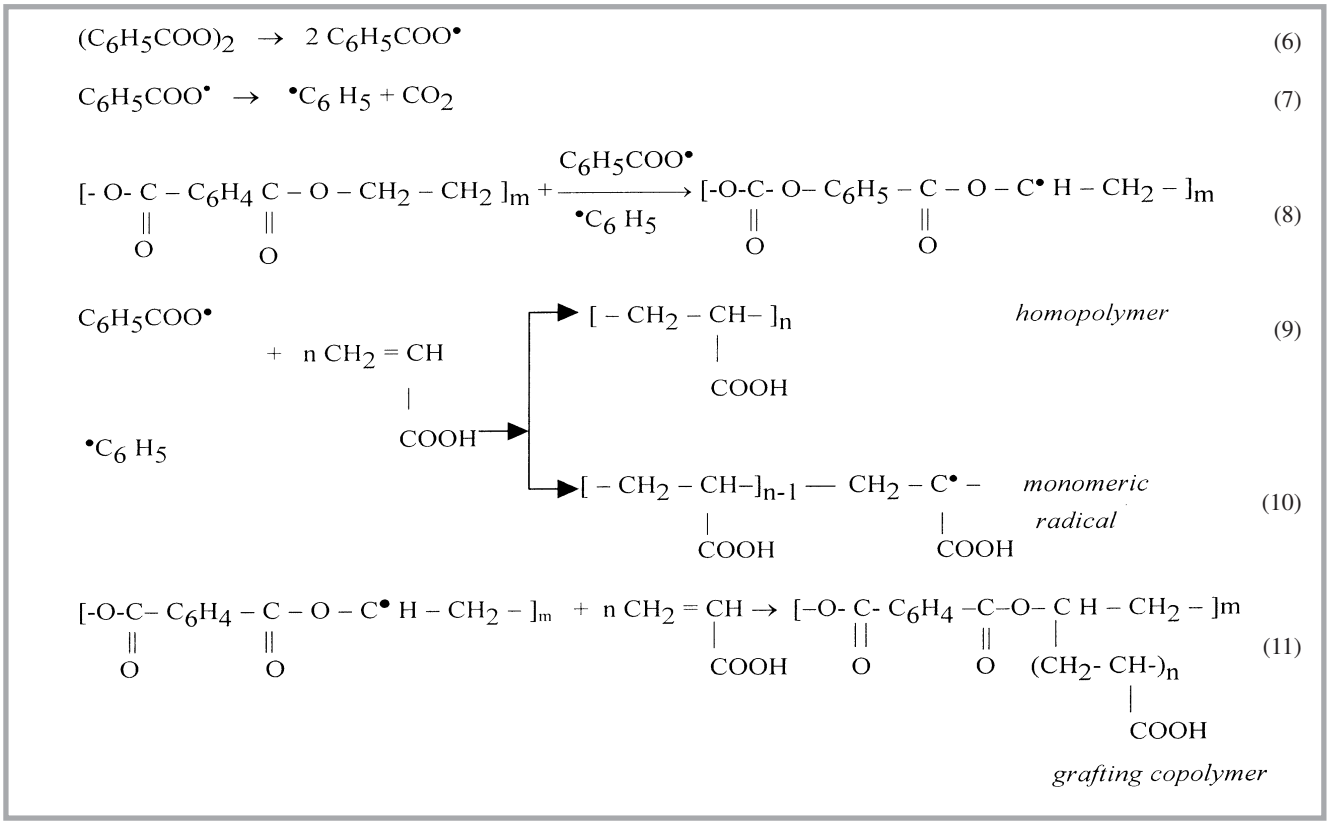

Figure 8. *The initiate and grafting PET- yarn of PAA.*

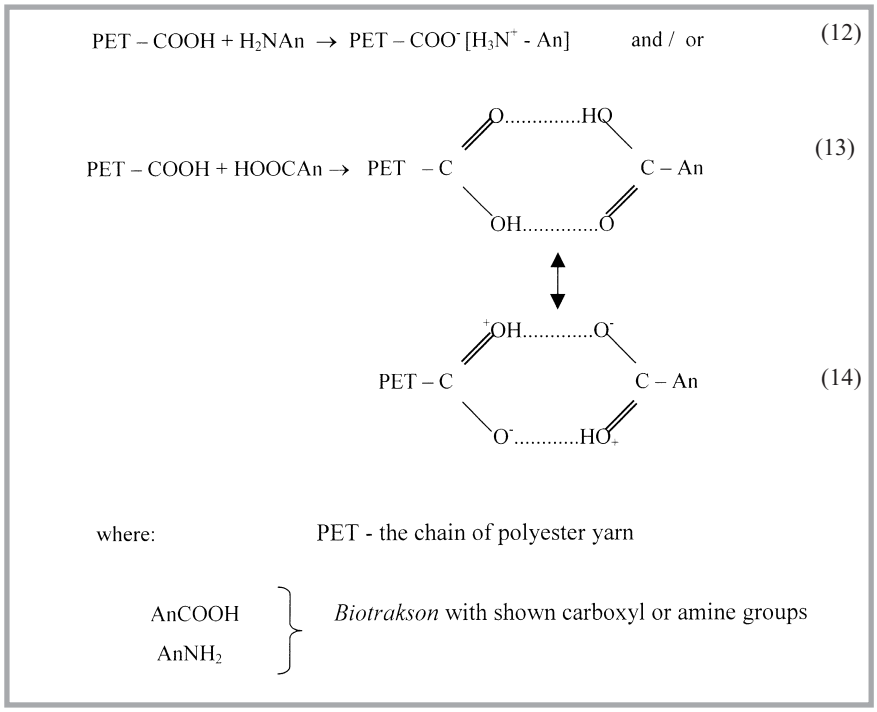

Figure 9. *Attachment of Biotrakson onto grafting PET yarn.*

at λ=820.6 cm^{-1} derived from the vibration of benzene rings;
and at λ=509.1 cm^{-1}
due to the presence of -CS group in the *Biotrakson* structure.

The PET yarn grafted with poly(acrylic acid) and containing *Biotrakson* also shows, in addition to the characteristic bands derived from the grafted PET and the antibiotic, a strong band near 1600-1500 cm^{-1}, and a weaker absorption at about 1400 cm^{-1} corresponding to carboxyl ions and ammonium ions at λ=3346.9 cm^{-1}. The latter were not observed in the spectrograms mentioned previously. This would suggest that the -NH_2 groups of *Biotrakson* and the -COOH groups of the grafted PET formed ionic bonds. Absorption bands at about 3000 cm^{-1} and 1400 cm^{-1} are also seen, which may be interpreted as dimers of the -COOH group.

It may be concluded that the appearance of carboxylate and ammonium ions, as well as of -COOH dimers at appropriate wavelengths, confirms the formation of ionic and other bonds between the antibiotic and the grafted polyester yarn. The processes taking place during grafting and the bonds formed between the antibiotic and the modified yarn may be suggested as in Figures 8 and 9.

Conclusions

- A two-stage modification of polyester yarn has been developed to provide the yarn with antibacterial properties to Gram-positive and Gram-negative bacteria (*S. aureus, E. coli, P. aeruginosa*),
- Unmodified polyester yarn is inactive to the above mentioned bacteria.
- The polyester yarn containing *Biotrakson* is very active to the tested bacteria, as is shown by large zones of bacteriostasis.
- The sensitivity of the bacteria used in testing to the modified yarn containing *Biotrakson* is consistent with the sensitivity of these bacteria to the standard of this antibiotic.
- The antibiotic standard is equally active before and after irradiation, which may be of importance in the sterilisation of surgical threads by this procedure.
- Testing the antibiotic release from modified fibres to water, one may foresee their activity towards the tested bacteria.

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