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ORIGINAL RESEARCH

Polypropylene suture material with anti-inflammatory action

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Abstract

Polypropylene (PP) monofilament threads are widely used as surging sutures. Functionalization of their surface to impart new properties is of great importance and interest for medicine. This work provides an efficient approach for chemical activation of PP surface followed by anchoring of anti-inflammatory materials (aspirin and indomethacin). Two chemical routes for activation of PP surface and two anti-inflammatory substances were combined, giving a set of four different functionalized threads. Efficiency in terms of anti-inflammatory action of resultant hybrid materials was proved by ligation of wounds made along the spine of mice with further monitoring of inflammation process. In vivo test on mice showed the best healing of surgical skin wounds by means of suture activated by 45% H_2O_2 solution in the presence of $FeSO_4$ as catalyst at 60 °C for 2 h, which was then modified with aspirin. Plasma interleukin measurement and histological section experiment were performed to prove the efficiency of the threads used for tissue connection. Highest healing efficiency of the suture is obviously explained by higher containment of anti-inflammatory substance anchored on PP surface. The work provides data on a cheap and easy implementation method for novel hybrid materials in medical applications that are able to perform accurately on surgical intervention sites.

Keywords Polypropylene monofilament thread · Functionalization · Anti-inflammatory · Aspirin · Indomethacin

Introduction

The most widely used approach for tissue connection is by means of surgical suture [1]. The generally accepted characteristics of an ideal suture material contain superior tensile strength, sufficient knot reliability, excellent handling characteristics, minimal tissue reaction, absence of allergenic properties, resistance to infection, and eventual absorption when tissue repair has reached satisfactory levels. Except in a very few situations where permanent sutures are a necessity, such as anastomoses between prosthetic and host blood vessels, a satisfactory absorbable material would be desirable [2, 3]. An initial idea of surgery suture modification belongs to ab Aquapendente from Padua. He decided to use "flax imbued with gum". Lister suggested covering catgut with chrome to make it tougher [4]. Modification of surgery suture to impart new properties had been widely expanded further. At present, suture has been modified using various methods. Principally, polyfilament threads are being modified to improve biological properties and remove "sawing effect". Monofilament materials have certain advantages including weak traumatic effect upon pulling due to smooth surface of monofiber, high durability of the thread in tissues (PDS loses only 30% in the first month) [5, 6], and high bioinertness. There is almost no reaction of tissue toward polyolefins and thus they are used for infected tissues [4]; among them, polypropylene has a reliable knot (minimal number is four) [1, 4].

Functionalization of sutures is of great importance because it allows regulating threads' properties finely depending on the aim of surgical intervention. However, for the first time, activation of the material surface is needed for further anchoring of the active compound. There are different ways to realize it, e.g., by radiation [7], plasma assistance [8–10], chemical way [11–13], and mechanistic

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approach [14, 15]. Polymer materials are obtained by various methods, for example, ultrasonic treatment [16, 17]. The current work is devoted to chemically activating the PP surface and anchoring the anti-inflammatory drug substances (DS) of aspirin (Asp) and indomethacin (Ind) on the surface of monofilament suture to make novel hybrid materials for medical purposes.

To prove anti-inflammatory action, all hybrid samples were tested in vivo on inbred BALB/Lac mice (additional mice) and the comparison with non-treated thread was performed.

Experimental

Materials

Monofilament suture 3/0 PROLEN* No. 2 metric (ETHYCON, Great Britain) was purchased and used during experiment. Commercial drug substances such as aspirin ("Acros-Organics", Belgium, Geel) and indomethacin ("Molekula", UK, Newcastle) of 99% purity were used without additional purification. Commercial rectified ethyl alcohol of 96.6% (by weight) was purchased (OJSC Medkhimprom, Moscow, Russian Federation) and used for solution preparation of drug substances (DS). Anhydrous sodium hydroxide pellets of 98% purity (Sigma-Aldrich) were purchased and used for preparation of solution. Iron (II) sulfate heptahydrate of 99% purity (Sigma-Aldrich) was purchased and used as catalyst. Hydrogen peroxide solution of 50 wt% (ChemMedSynth, Russia) was purchased and used for activation of suture surface.

Methods

Commercial monofilament polypropylene sutures 3/0 PROLEN* No. 2 metric (ETHYCON) were used. Optimal conditions for activation of the polypropylene material and immobilization of DS were found, resulting from the external experiment given in Note S1 (Supplementary Material). Threads' surface was chemically activated by means of two methods. Method 1 (M1) treatment was conducted by immersion of a suture in a refluxing solution of 20% NaOH for 2 h, and method 2 (M2) was the treatment of the thread with a 45% H_2O_2 solution in presence of $FeSO_4$ as catalyst at 60 °C for 2 h.

The next step was immersion of threads treated by methods 1 and 2 into a 1% alcohol solution of aspirin and holding it at 60 °C for 4 h. Indomethacin-containing threads were obtained by a similar technique, in which a 0.8% alcohol solution of indomethacin was used instead of aspirin. All samples were washed three times with double distilled water after immobilization. In this way, polypropylene suture surgical threads functionalized by aspirin and indomethacin were obtained. Summary of all methods and DS used is given in Table 1. To maintain constant concentration of DS, the flask, where activation was performed, was equipped with a reflux condenser.

Investigation of healing dynamics of surgical skin wounds on mice under ligation by threads of various functionalization approaches was performed according to a general procedure. Twenty inbred BALB/Lac mice were put to sleep. The operation area was shaved and treated with ethanol (70%). The skin was cut along the spine. The edges of the incision were connected with four nodal sutures by means of 26 mm needle and threads 0, 1, 2, 3, 4. The sutures did not go under additional treatment thereafter. Mice were monitored every day. Sutures with surrounding tissue were cut off on days 3, 5 and 7, fixed in 12% buffered formalin and then embedded with paraffin. Histological sections were prepared according to the generally accepted method, stained with hematoxylin and eosin (magnification of the images is standard; 100×).

Plasma IL-6 was assayed using high-sensitivity ELISA available from R&D Systems (Minneapolis, MN, USA). Quality assessment samples (concentration: 2.47 pg mL^{-1}) were determined with intra- and inter-assay CVs of 3.3 and 8.9%, respectively.

Characterization of surface property

Composition of polypropylene surface layer before and after chemical activation was examined by multiply attenuated total internal reflection (MATIR) IR spectroscopy. The MATIR prism was made of crystalline zinc selenide. The incidence angle of the beam relative to the phase boundary was 45°, with 12 reflections.

A FTIR spectrometer Avatar 360 (Nicolet, USA) was employed to characterize the functional groups on the diverse PP surface. The FTIR spectra were recorded at room temperature in the range of 4000–400 cm^{-1} at a resolution of 2.0 cm^{-1} and the background spectra were recorded in air.

Electron absorption spectra (UV–Vis) were registered by means of a Unico 2800 (USA) spectrophotometer in

Table 1 Characteristics of experimental sutures functionalization

No.	Treatment			
	Activation method	Solution	Temperature (°C)	Immobilization time (h)
0	Control thread	–	–	–
1	M1	1% alk.sol. (Asp)	60	4
2	M1	0.8% alk.sol. (Ind)	60	4
3	M2	1% alk.sol. (Asp)	60	4
4	M2	0.8% alk.sol. (Ind)	60	4

the spectral range of 200–1000 nm. Quartz optical cell was used for the measurements. UV–Vis spectra were recorded at 298.15 ± 0.03 K.

Scanning electron microscope micrographs were obtained by means of a Vega 3 SBH scanning electron microscope (TESCAN, Czech Republic) at an acceleration energy of 5 kV. Contact angle measurements were performed in accordance with the method described in [18].

Results and discussion

Chemical activation

Figure S1a (Supplementary Material) shows the MATIRIR spectra of chemically activated PP and corresponding non-activated PP sample. The spectral data show that chemical activation has led to the formation of aldehyde groups. This is indicated by the presence of bands at 1700 cm^{-1} characterizing C=O stretching vibrations and the bands in the range of 2800–2900 cm^{-1} responsible for stretching vibrations of functional C–H group formed on the surface of PP [19]. The difference in band intensity of M1 and M2 is caused by various activation efficiencies that are supported by SEM micrographs (Figure S2).

The contact angle measurements (Table S1) indicate a decrease in surface-free energy (γ) after performing both activation methods, which support successful activation accompanied by surface hydrophobicity development.

Though the most prominent benefit of monofilament sutures compared to multifilament threads is their lower surface roughness, the SEM micrographs (Figure S2) indicate an increase in roughness after activation of material surface. However, there were no tissue drag and interstices observed upon ligation of mice.

Anchoring of DS

Anchoring of indomethacin (Fig. 1a) and aspirin (Fig. 1b) on the activated PP surface is confirmed by UV spectra (Fig. 2), in which the bands at 230 and 278 nm are characteristics of aspirin, and at 273 and 320 nm those of indomethacin. UV spectra were registered after washing. In addition, Fig. S1b contains IR spectra of the activated PP samples modified with Asp and Ind, and Fig. S1c represents DS IR spectra. By comparing the corresponding IR spectra, one can conclude that the immobilization has been successful. The characteristic bands of Asp and Ind at about 1700 cm^{-1} indicate that C=O stretching became more intensive after immobilization. In addition, there is a characteristic band at 1200 cm^{-1}, indicating asymmetrical C–O–C vibrations. Valent vibrations of aromatic C–C bonds are observed near 1600 cm^{-1}. The

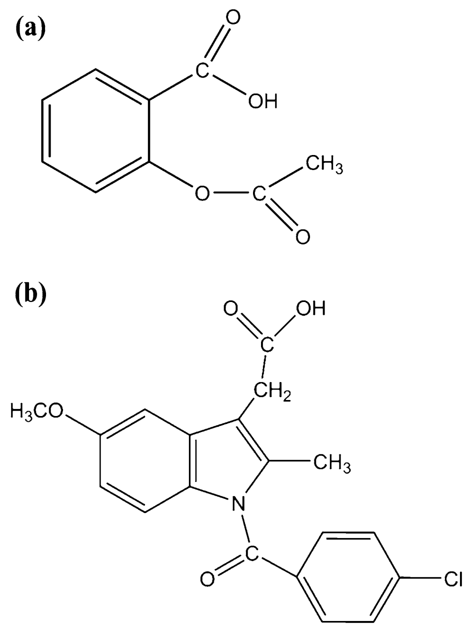


Fig. 1 Anti-inflammatory compounds **a** aspirin (acetylsalicylic acid), and **b** indomethacin (2-[1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid)

spectra of indomethacin-modified materials have a signal at 670 cm^{-1}, indicating C–Cl stretching vibrations.

Surface concentrations of anti-inflammatory compounds were calculated based on UV spectra (Table 2). Anchoring mechanisms on the surface of PP, activated according to methods 1 and 2, are the same due to the formation of similar functional groups. The difference is in the group concentration and amount of residual reagents on the surface. There are much more oxygen-containing groups on the surface upon alkali activation, and hence surface concentration of DC is higher. However, the activation based on both methods did not lead to deep destruction of polymer, because only surface layers were involved. Thus, there is no violation of the plasticity and durability of surgical sutures.

The mechanism of aspirin anchoring is double point-to-point (Scheme 1). Indomethacin realizes immobilization through one functional group (Scheme 2).

In vivo test

The wound channel after 3 days from ligation was filled with tissue detritus. Derma had a diffuse serous-inflammatory infiltration. Accumulation of cells (neutrophils and macrophages) was found in deep layers of dermis closer to the subcutaneous tissue. All mice demonstrated severe hyperemia of capillaries and proliferative processes in the epidermis. The diffuse serous-inflammatory infiltration of dermis was stronger in the ligation by sutures No. 2 and No. 4 than that by No. 1 and No. 3. The dermal inflammatory

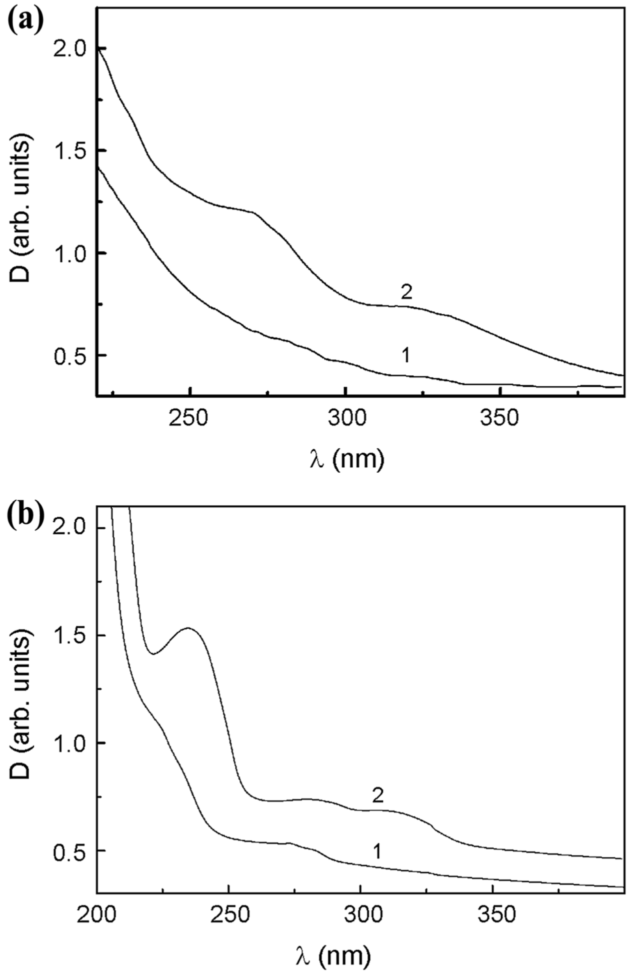
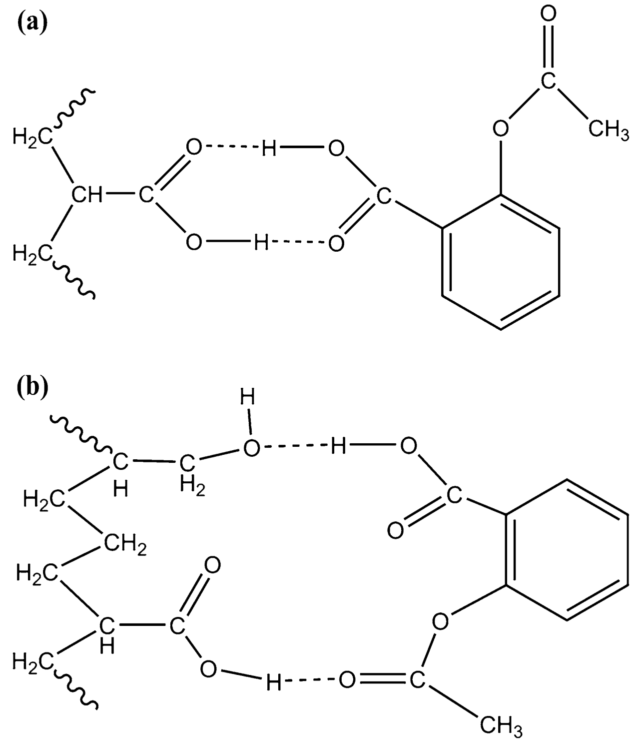


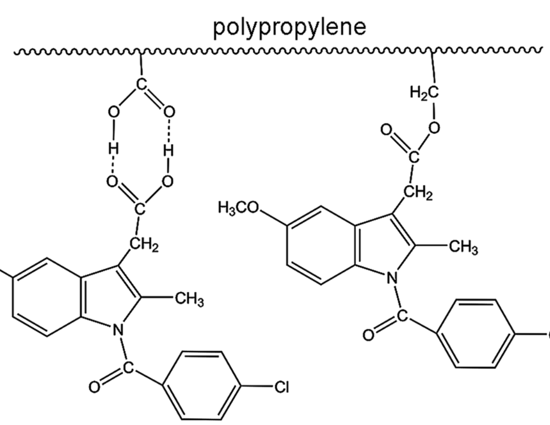
Fig. 2 UV spectra of PP: 1—initial; 2—functionalized with **a** indomethacin, and **b** aspirin

Table 2 Surface concentrations of anchored DS

No.	Activation method	Immobilized DS	Surface concentration $N_S \times 10^{-16}$ particles cm^{-2}
Immobilization of DS at room temperature			
1	M1	Aspirin	2.43
		Indomethacin	0.26
2	M2	Aspirin	0.52
		Indomethacin	0.19
Immobilization of DS at $T=60$ °C, $\tau=4$ h			
3	M1	Aspirin	2.55
		Indomethacin	1.46
4	M2	Aspirin	0.98
		Indomethacin	0.20



Scheme 1 Anchoring mechanisms for Asp: **a** through one functional group, and **b** through two functional groups



Scheme 2 Anchoring mechanism for Ind

reaction of mice with suture No. 3 was weaker than that with control and sutures Nos. 1, 2 and 4. Visual micrographs are presented in Fig. 3a1–a5.

Compared to resluts obtained on a third day, neutrophil infiltration as well as vascular hyperemia decreased after five days in all the testing mice except those with the suture No. 1. Proliferation of the epithelium along the edges of the wound is pronounced. Fibroblasts are at majority among the infiltrate cells; signifying proliferation of connective tissue cells aimed to heal the wound. In this way, the exudative

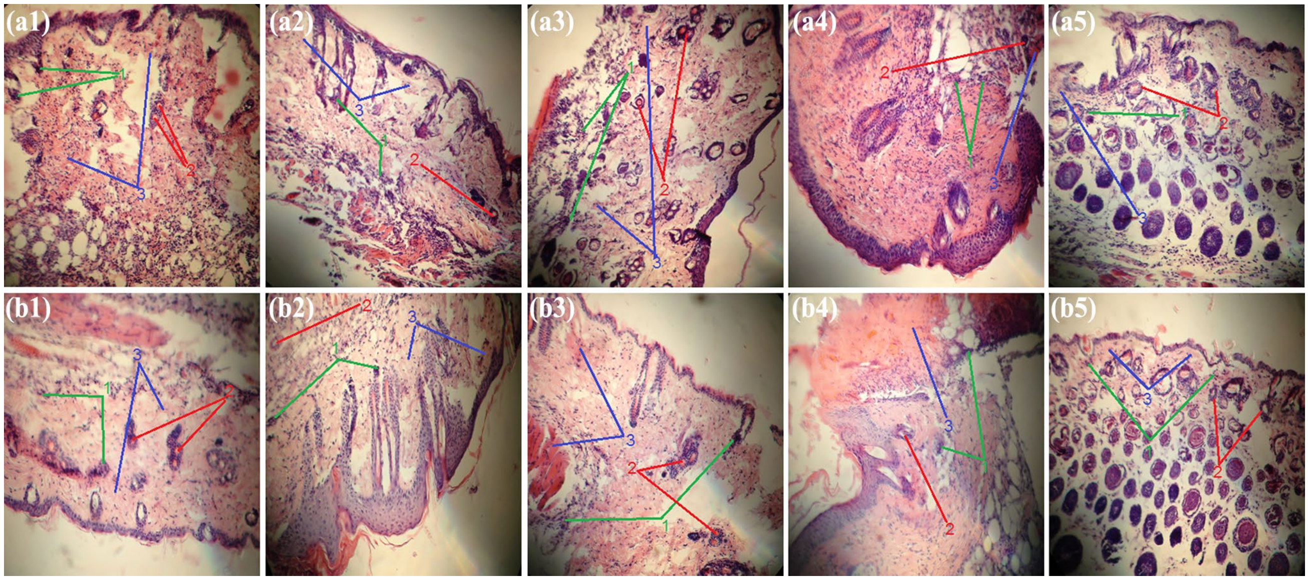


Fig. 3 Histological sections of mice derma after ligation by threads Nos. 1, 2, 3 and 4, and control one (0) at magnification of × 100 on **a** 3rd day, and **b** 7th day, where (1) green is areas of infiltration of inflammatory cells; (2) red is blood vessels; (3) blue is fragments of fibrous connective tissue

Table 3 IL-6 test data (in pg mL^{-1})

Thread	Control value	Day 3	Day 5	Day 7
0	40	271	190	116
1	37	215	125	82
2	42	249	168	90
3	47	188	110	69
4	40	236	157	85

component of the inflammatory reaction weakens and the proliferative one begins to dominate.

There was no wound healing on day 7 after ligation. Tissue detritus was maintained in the wound. Exudative component of inflammatory reaction was noticed to be weaker among all testing mice. The neutrophil infiltration has been decreased. Proliferation of connective tissue continued to increase. Amount of fibroblasts and macrophages was increased along the edges of the wound channel, and further away there was increase in number of fibrocytes. Transitional forms from fibroblasts to fibrocytes are presented. Epithelium proliferation along the edges of the wound was well-pronounced. Mice with ligation No. 3 demonstrated the best healing, where exudative reaction was weaker and the proliferative one was stronger than those of other tested mice. Histological sections on day 7 after incisions are presented in Fig. 3b1–b5.

IL-6 test was performed to approve the histological experiments. Table 3 provides corresponding data. Value is an average quantity of IL-6 found in blood serum of four mice treated with the same type of thread. Control value was measured right before the incision made. Interleukin 6 is a response of living organism toward a stress, for example, during infection and after trauma, especially burns or other tissue damages leading to inflammation.

Presented data correspond to the lowest value of IL-6 within mice treated with thread No. 3 after the incision was made. This fact proves the highest anti-inflammatory effect of the thread that correlates with the histological sections tested.

Conclusion

This work is comprised of an approach to functional hybrid materials for medicinal applications. In sum, the monofilament polypropylene suture 3/0 PROLEN* No. 2 metric was chemically activated and functionalized with drug substances of an anti-inflammatory action. The obtained sutures were tested in vivo, and the results demonstrated the best performance of ligature No. 3, which was activated by a 45% H_2O_2 solution in the presence of $FeSO_4$ as catalyst at 60 °C for 2 h and then modified with aspirin. The main advantages of such treatment are cheapness and ease of implementation, which give the possibility to obtain functional materials right in the place of surgical intervention, in a medical institution. All chemicals used were widely available and no additional equipment was necessary. Depending on the type of surgical intervention, other drug substances also may be anchored on the surface of a suture. Thereby, the current work provides simplification and further improvement on suture materials applied in surgery.

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