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MACROMOLECULAR CHEMISTRY AND POLYMERIC MATERIALS

Surface Immobilization of Indometacin for Preparing Polypropylene Materials Exhibiting Biological Activity

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Abstract—A procedure was proposed for the modification of the manganese-oxide catalyst hopcalite GFG allowing the new quality, water resistance of granules, to be reached. This procedure can be used for the reactivation of the exhausted catalytic contact.

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Development of combined materials exhibiting surface antimicrobial (bactericidal) and antiphlogistic properties is an urgent problem. Application of such materials makes less necessary the additional use of drugs, which decreases the risk of rejection and the level of allergic reactions in the body and increases the extent and rate of healing of wound tissues [1, 2]. Such materials are usually polymers modified with drugs.

The assortment of drugs suitable for imparting antimicrobials and antiphlogistic activity to polymers is very limited. Appropriate drugs should be primarily sought for among chemotherapeutical agents, antibiotics, and antiseptics. Within this group, only substances with sufficiently high thermal stability, high antimicrobial activity, and as low toxicity as possible can be chosen. In addition, the substances should have a broad spectrum of activity. Furthermore, because an antimicrobial or antiphlogistic agent should be immobilized on a polymeric support by chemical bonds, an additional requirement arises: The agent should contain specific active groups that can be involved in polymer-analogous transformations by reaction with functional groups of the support. It is desirable that such active groups may not inhibit the biological properties of the agent, otherwise its activity can be lost after the reaction with the polymer.

It is important that a drug should be immobilized on a fiber by a chemical bond or, at least, be incorporated in the fine structure of the fiber (similarly to inclusion compounds) if it is intended to fix it in the course of forming [3–5].

The problem of immobilization of antimicrobial substances on a fiber by a chemical bond involves two mutually contradicting, at first glance, conditions. On the one hand, it is necessary to prevent removal of groups responsible for the antimicrobial effect from the fiber in the course of operation of the material; on the other hand, it is necessary to provide transport (diffusion) of these groups to microbial cells, otherwise the main goal, remote killing of pathogenic microflora, will not be accomplished [4].

The solution is in the fact that chemical bonds, even covalent, can be weakened to certain extent, and under definite conditions the bound antimicrobial substance will be released, though in extremely small amounts. The loss of a small amount of the drug will not noticeably alter the properties of the fiber, including its antimicrobial activity, but the amount of the released drug may be sufficient to kill microorganisms.

EXPERIMENTAL

Because polypropylene contains virtually no active groups allowing chemical modification, i.e., is essentially inert, it is impossible to chemically immobilize biologically active substances on the polypropylene surface. Therefore, polypropylene should be preliminarily treated with aggressive substances to obtain functional groups on the polymer surface. This is, as a rule, a multi-stage procedure. Furthermore, cleavage of C–C bonds is inadmissible. Therefore, previously it was suggested to activate the polypropylene surface by plasmochemical

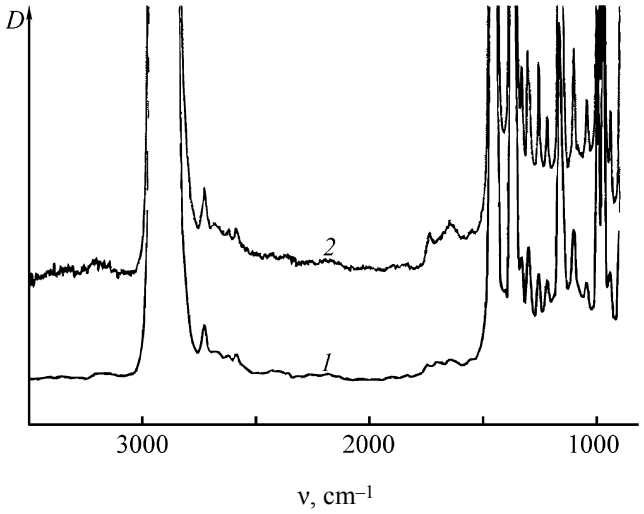


Fig. 1. MATIR IR spectra of a PP film in the range 3500–900 cm^{-1}: (D) absorption and (ν) wavenumber. Sample: (*1*) initial and (*2*) activated in a hydrogen peroxide solution.

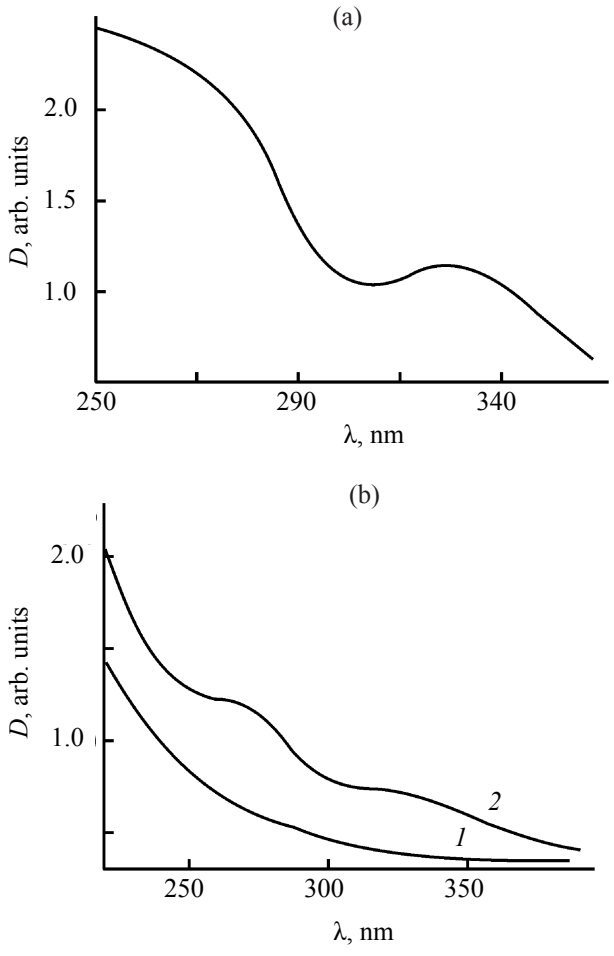


Fig. 2. Electronic absorption spectra: (*D*) absorption and (λ) wavelength. (a) Solution of indometacin in ethanol and (b) PP: (*1*) initial and (*2*) modified with indometacin.

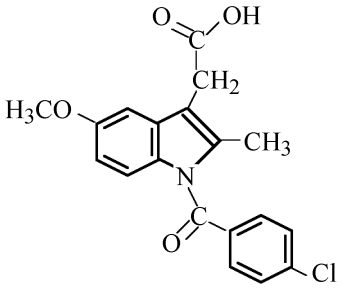
treatment [6–8]. Here we report that treatment with hydrogen peroxide is also a fairly efficient activation method.

In the experiments we used biaxially oriented 20-μm films of isotactic polypropylene (PP). As a drug we chose indometacin.

The surface activation of PP was performed as follows. PP samples of size 20 × 65 mm^2 were placed in weighing bottles containing a 37% aqueous solution of hydrogen peroxide. Activation was performed in the presence of an aqueous solution of iron(II) sulfate acting as a catalyst. Then the weighing bottles were placed in a thermostat and kept there at 60°C for 2 h. After the activation completion, the weighing bottles were removed from the thermostat and cooled in air at room temperature. Simultaneously we performed the blank experiments.

The composition of the surface layer of polypropylene after the chemical activation was examined by multiply attenuated total internal reflection (MATIR) IR spectroscopy. The measurements were performed with an Avatar 360 FT-IR ESP (Nicolet) IR Fourier spectrometer. 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. The signal was accumulated in 32 scans. The bands were assigned in accordance with [9]. The spectrum was recorded in the range 400–4000 cm^{-1}.

Indometacin [1-(*p*-chlorobenzoyl)-2-methyl-3-carboxymethyl-5-methoxyindole] chosen for polypropylene modification is one of the most active nonsteroid antiphlogistic agents [10]:



Immobilization of indometacin on the PP surface was performed from its 1% alcoholic solution at 20–80°C for 2–24 h. The state of the film was monitored by electronic absorption spectra in the UV range, which were recorded on a Lambda 20 spectrophotometer (Perkin–Elmer). To increase the level of the useful signal, we used stacks of 4–6 films. The spectra were recorded after immobilization of indometacin from its alcoholic solution and after

washing the samples with ethanol to remove weakly bonded (physically adsorbed) drug molecules.

Assuming that the photoabsorption cross sections of indometacin in solution and on the polymer surface are the same, we can estimate the surface concentration of the immobilized molecules and the degree of filling of the polymeric carrier surface with them. The area of indometacin molecules was calculated by the method of molecular mechanics (MM + force field) using the Hyper Chem program (version 7). To calculate the surface concentration NS of indometacin, we used the long-wave Soret band with $\lambda_{max} = 325$ nm, $\varepsilon = 2.52 \times 102$ l mol^{-1} cm^{-1}. The calculations showed that the degree of surface filling with the chemically bound drug can reach 40% of the monomolecular layer.

For the surface modification, polypropylene films were treated in a hydrogen peroxide solution. Under such conditions, chemical activation involves only the surface layers of the polymer. The bulk structure is not affected, and the physicomechanical characteristics of the starting material are virtually preserved. Modification of PP with hydrogen peroxide results in formation of various reactive functional groups (e.g., –OH, –C=O, –COOH, etc.), in formation or cleavage of chemical bonds, and in morphological and structural changes.

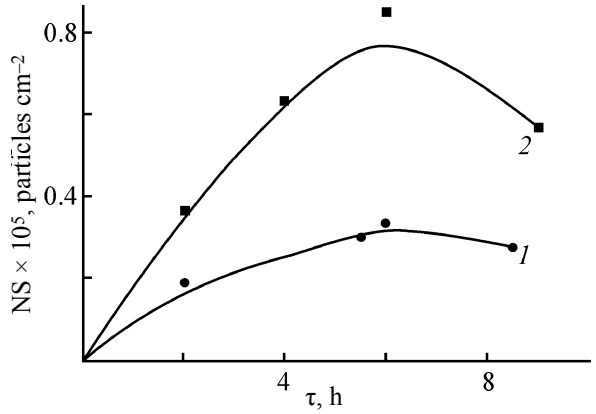


Fig. 3. Surface concentration NS of indometacin as a function of immobilization time τ. Temperature, °C: (*1*) 60 and (*2*) 80.

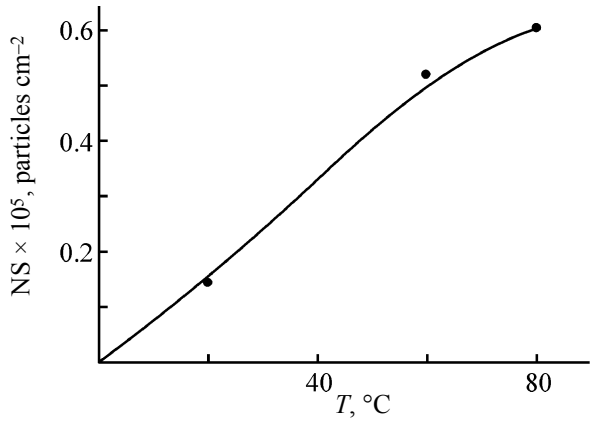


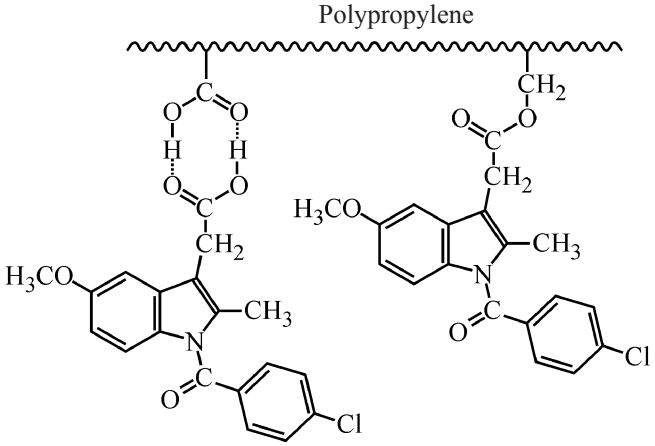
Fig. 4. Surface concentration NS of indometacin as a function of sorption temperature *T*. Immobilization time 6.5 h.

Figure 1 shows the MATIR IR spectra of a chemically activated PP film and a reference PP sample. The spectra show that the chemical activation leads to the formation of primary alcoholic groups. This is indicated by enhancement of the intensity of the absorption bands in the range 1020–1400 cm^{-1} belonging to OH bending and C–O stretching vibrations. In addition, chemical activation of PP leads to an increase in the intensity of absorption bands at 1560–1580, 1600–1680, and 1710–1740 cm^{-1}, belonging to stretching vibrations of the C=O bond in various functional groups in the surface layer of the modified polymer [6].

The results obtained show that such chemical activation allows grafting of indometacin to the PP surface.

Binding of indometacin with activated PP is confirmed by the presence in the electronic absorption spectrum of the modified film of absorption bands at 270 and 325 nm (Fig. 2). According to the electronic absorption spectrum (Fig. 2), indometacin immobilized on the PP surface is in the nonaggregated and nonassociated form.

It should be noted that the grafted biologically active substance is only partially removed from the film by washing with water and/or alcohol. This fact suggests formation of relatively strong bonds between the polymeric support and immobilized compound, probably of cyclic hydrogen bonds and covalent bonds, e.g.:



We performed experiments to optimize the conditions of indometacin immobilization on the chemically activated PP surface. The results are given in Figs. 3 and 4. It can be seen that the optimal conditions of indometacin immobilization are 6.5 h, 60°C (at higher temperatures, the drug starts to decompose).

CONCLUSIONS

(1) Chemical activation of the surface of a polypropylene film provides conditions for surface immobilization of indometacin. The optimal immobilization conditions are 6.5 h, 60°C.

(2) The suggested procedure for polypropylene modification is promising for the development of medicinal materials with antimicrobial action.

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