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Medical Textile and Hydrogel Materials for Targeted Delivery of Drugs in Oncological Practice

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Abstract—Article is devited to the use of textile technologies for creation of new types of medical materials and textile-based hydrogels with drugs, secured their directed controlled and prolonged delivery to the site of lesions in cancer patients. The application of textile printing technology has been substantiated. The following aspects have been studied: the role of textile carrier – the matrix for the polymer and drug, teological characteristics of the polymers-thickeners, mass transfer of drugs into the environment, the antioxidant activity of the drugs used for the creation of medical materials to improve the efficiency of treatment during the radiation therapy.

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The use of textile technologies for preparation of new types of medical materials and textile-based hydrogels with drugs was described. These materials serve for targeted controlled and prolonged delivery of drugs to lesion sites in cancer patients. The application of textile printing technology was substantiated. The aspects examined include the role of textile carrier, a matrix for the polymer and the drug, as well as the rheological characteristics of the polymer thickeners, mass transfer of drugs into the external medium, and antioxidant activity of the drugs used in preparation of medical materials capable of improving the effectiveness of radiation therapy treatment.

Medical textile is a term covering a broad range of materials intended for application not only in medicine (in particular, for treatment of systemic diseases) but also in many other spheres of human activity (works under extreme conditions, sports, recreation, cosmetology, medical linen, doctor's cloth, etc.) [1].

Owing to their specific properties such as sorption capacity, air permeability, draping quality, etc., textile materials since distant times have been widely used as dressings, e.g., for closing wounds and cuts. A new generation of textile materials are suitable not only for closing wounds but also for treating lesions via placing thereon a textile bandage (application, napkin) with a drug impregnated [2–4]. Thus, a textile material can be considered as a matrix (or a "depot"), from which the drug is transported into the body to the lesion site.

Development of means for drug delivery directly to organs, tissues, and cells is the focus of ever-increasing specialists' attention. The use of systems of targeted transport of drugs gives huge health and economic benefits in terms of reduced side effects and much lower therapeutic doses of drugs. These factors are particularly important in treatment of cancer patients by using toxic drugs whose action is aimed at destruction of injured cells but which also adversely affect healthy organs and tissues and the circulatory system and depress the immune system. Hence, it is essential to deliver a drug in the desired concentration to the lesion site, while minimizing the exposure of healthy organs. Currently, medical textiles (napkins, applications, patches) are used for drug delivery to wounds as part of surgical treatment of diseases, as well as in dermatology for treatment of skin diseases, in endocrinology for "diabetic foot" treatment, and for first aid provision, in particular, with the use of hemostatic agents. At the same time, medical textiles suitable for application in oncology, an important area of medicine, are nearly lacking, although they are in great demand, e.g., for treatment of superficial tumors.

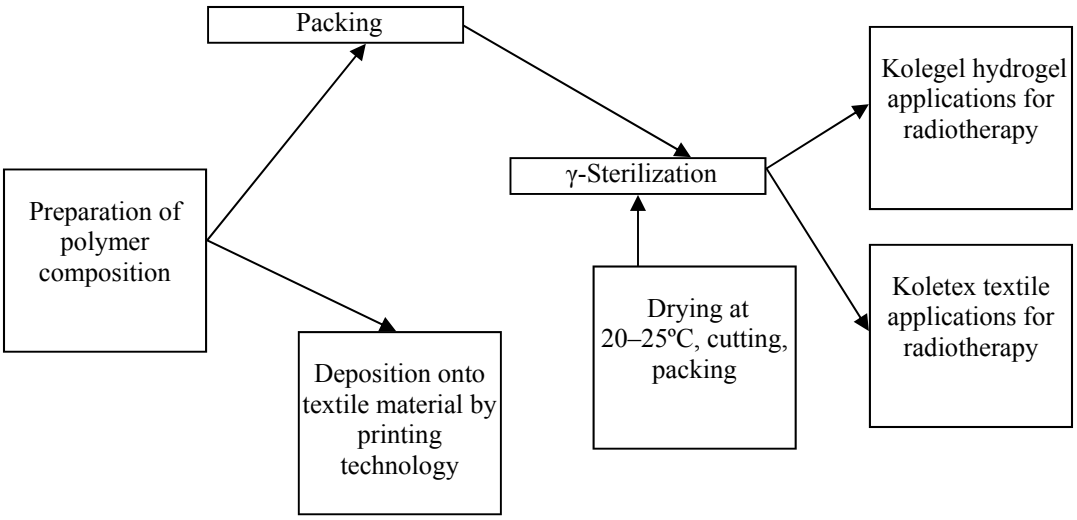

Fig. 1. Schematic of preparation of medical materials for radiation therapy.

It should be noted that the cancer incidence rates in Russia are stably high: Over 460 thousand new cases of cancer are diagnosed every year [5].

Technological Aspects of Preparation of Application Materials for Cancer Treatment

Cancer patients receive surgery, chemotherapy, and radiation therapy; 70% of them need radiation therapy. Specifically for this reason the development of new medical textile materials and means for cancer treatment, in particular, by radiation therapy, as well as of techniques for their application, is a task of much social and economic significance. The new assortment of application products (textiles, hydrogels) are intended for targeted delivery of drugs to the lesion site (e.g., to tumor tissues) in a strictly defined effective concentration, specific for each of the drugs, whose accumulation in intact tissues and organs is minimized.

It was suggested [6–8] that the textile printing technology be used for preparation of application materials with drugs. This technique allows manufacture of two types of medical materials: textile-based materials for application to skin, breast, head-neck area, etc. and biopolymer-based materials comprised of polymer thickeners with a drug impregnated thereon (similar compositions for textile printing), intended for introduction into cavities: proctologic, gynecologic, etc. (see Fig. 1).

As already mentioned, the drug is introduced into the thickened composition by a procedure similar to that used in printing technology. However, by contrast to textile printing technology which comprises the dye fixing and washing stages, the manufacture of medical articles requires sterilization (in the presence of polymer thickeners, γ-sterilization is the only possible option), because the resulting applications will be placed onto injured tissues and mucous membranes, contact blood.

Thus, polymer thickeners loaded with drugs can serve a dual purpose, specifically, that of a means of drug impregnation onto the textile substrate and that of an independent therapeutic hydrogel composition. Clearly, polymers intended as thickeners for this dual designation should meet the printing technical requirements and, preferably, possess biological activity. The γ-sterilization procedure with finished products, conducted in special institutions with duly regulated radiation dose levels, can significantly affect the viscosity of the composition. Specifically, the viscosity can both decrease and increase, with the result being determined not only by the input dose and the exposure time but also by the drug used. Therefore, for each type of materials, depending on the drug and its concentration, it is necessary to select the initial viscosity of the composition (to be adjusted by varying the thickener concentration) such that the medical product could provide the desired effect.

Selection of drugs belongs with clinical oncologists, while technologists have to maintain the authenticity of the agent during the production process and ensure that the drug will be delivered to the lesion site in the medically required concentration.

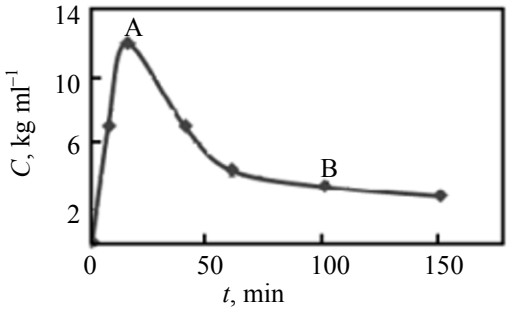

Fig. 2. Time variation of the 5-fluorouracil concentration in the external medium during desorption into water (the model includes the carryover effect). (A) loading drug dose and (B) equilibrium drug concentration. Sodium alginate thickener, knitted fabric base, bath module 10°C, kg ml^{-1}.

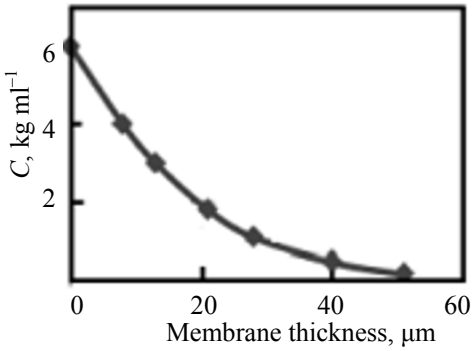

Fig. 3. Distribution of 5-fluorouracil over the collagen membrane layers. Experiment time 2 h. Sodium alginate thickener, knitted fabric base, 20-mesh screen.

Here, we report on preparation of medical materials destined to improve the effectiveness of radiation therapy. To this end, we used 5-fluorouracil, a cytostatic agent possessing radiomodifying properties, and metronidazole, a radiosensitizing agent, as well as of antioxidants mexidol, derinat, and propolis for prevention and treatment of radioreactions.

Textile Base and Thickeners Used for Preparation of Medical Materials

It would be inappropriate to treat textile materials exclusively as inert substrates onto which polymer compositions are to be deposited by the printing technology. Textiles largely determine the properties and quality of medical articles (napkins, applications) and affect not only the physicomechanical and hygienic characteristics of the article but also the mass transfer of the agent spread (impregnated) thereon into the external medium.

Textile materials intended for medical purposes should meet special requirements, both operational [smooth surface, high breaking (in particular, wet breaking) strength, ability to preserve strength properties, in particular, under γ-sterilization conditions, etc.) and hygienic (air permeability, water-yielding capacity, etc.). The mass transfer behavior of drugs released from textile material to external medium is strongly dependent on the material properties and structure. For example, the inter-phase mass transfer of a drug from a medical textile material to the lesion site needs a diffusion medium, for which purpose the napkin in a number of situations is to be premoistened. Therefore, of much importance are the water-absorption properties of the material. The use of the textile material in clinical practice needs authorization from the Ministry of Health and Social Development of the Russian Federation [7, 9, 10]. Our experience of preparation of medical materials, Koletex applications (napkins), by the printing technology suggests that the most suitable options are voluminous nonwoven stitched flax/viscose and cotton/viscose materials which are characterized by large internal surface area and high hydrophilicity, as well as cotton/polyester or cotton/polyamide knitted fabrics (material density 140–180 g m^{-2}). Woven materials are unsuitable for this technology, because they give hard and badly draped materials which do not allow the required high drug concentration to be achieved.

Medical application materials prepared by textile printing technology can be regarded as consisting of three functional layers formed during their preparation process. The first layer is a textile base manufactured from a material having large internal surface area and special structure, which coats the injured tissues. It not only provides air permeability, drainage properties, and good adhesion to the wound and has light weight, but also serves as carrier for the second layer, the polymer. The polymer layer, in turn, is composed of a natural polymer (or a mixture of polymers), a polysaccharide in our case (e.g., salts of alginic acids, chitosan), and the drug immobilized therein. Swelling of the polymer, either occurring under the influence of the wound effluent, blood, or artificially stimulated (in the liquid used for moistening the application), leads to formation of a hydrogel which imparts atraumatic properties to the resulting material owing to the soft layer located between the textile base and skin (or mucous membrane). The polymer layer acts as a "depot" for the drug introduced therein: Due to

unlimited swelling, it enables prolonged release of the required dose of the drug from the application to the lesion site (tumor, ulcer, etc.). The third layer consists of the drug spread over the surface of the medical application after drying. From this layer the first dose of the drug is delivered to the injured area, e.g., tumor, i.e., immediately after the napkin is adjusted [11].

Experiments confirmed that the application depot materials prepared by screen printing technology provide for prolonged mass transfer of drugs spread within the textile and biopolymer depot into the external medium under which conditions high drug doses (according to medical prescriptions) and predicted concentrations can be achieved in the external medium. This effect can be observed in the case of 5-fluorouracil cytostatic (Fig. 2). Examination of 5-fluorouracil desorption from the application revealed escape of a part of the external liquid medium from the bath (the wound is a bath with a small module; the module is the ratio of the mass of the liquid in the wound to that of the medical material). This phenomenon is typical for biological objects: A part of the drug is carried away into lymph and bloodstream and is replaced by a new portion of the body fluid. A similar situation was observed in examination of the mass transfer of the drug from the textile application to a multilayer collagen membrane simulating the intact skin (Fig. 3). It should be kept in mind that, under the experimental conditions, the drug is carried away much faster than under real conditions of a body.

In our experiments we used the multilayer membrane comprised of collagen films, to which the textile impregnated with the drug was applied, as the model protein substrate (collagen is the basis of connective tissue). Thereby, the resistance of intact skin to drug penetration was simulated, and comparative data were provided on how the rate of penetration into the membrane varied with the properties of thickeners, drug, experimental conditions, etc.

The plots in Figs. 2 and 3 are indicative of a mass transfer of the drug from the textile depot material (into which it was introduced by screen printing) to the external medium, where its equilibrium concentration is attained. Figure 3 confirms the drug accumulation in the collagen membrane layers, thereby suggesting the possibility of targeted delivery of the drug to the tumor tissues.

Selection of polymer thickeners was dictated by the need to satisfy both the technological (relating to printing technology) and medicinal requirements. Specifically, the medicinal use of the selected polymer needs authorization and the polymer desirably exhibits an independent medical effect or biological activity, like, e.g., in the case of prodrug sodium alginate [12–14]. Naturally, we selected a polymer from among those used in textile industry as thickeners and (which concerns selected commercially available items) in medicine.

Along with sodium alginate, we used water-soluble chitosan succinate as biopolymer for preparation of hydrogel compositions. Chitosan succinate possesses unique properties (exhibits antioxidant and film-forming activity and perfect ingredient compatibility, lacks toxicity and allergenicity, is capable of biodegradation, etc.). We assessed its suitability as thickener, both individually and in combination with sodium alginate (we presumed that this would affect the rate and extent of mass transfer of the drug impregnated into the polymers).

Because of the lack of data on the use of chitosan succinate for textile printing applications and for manufacture of medical articles, we had to choose the concentration of this polymer in the composition such that optimal rheological and printing technical properties of the composition can be achieved, i.e., the desired viscosity, thixotropy (no less than 65%), storage stability, etc. Also, we have to examine how the rate and extent of the drug mass transfer are affected by the formulation of the composition. The experimentally determined viscosity satisfied the requirements relating both to printing technology and clinical use of the application.

To optimize the chitosan succinate concentration, we examined the rheological behavior of the compositions differing in the polymer content (on a dry weight basis). To this end, we carried out the viscosity measurements on a Rheotest-2 instrument at 1.5–1312 s^{-1} shear rates. Chitosan succinate-based compositions are characterized by abnormal viscosity and behave like pseudoplastic liquids (their effective viscosity tends to decrease with increasing shear rate). A sig-nificant characteristic of the system is its thixotropy; it has great importance in screen printing of the composition and even greater importance in inde-pendent introduction of viscous hydrogel composition into a patient's body cavity. In the former case, the

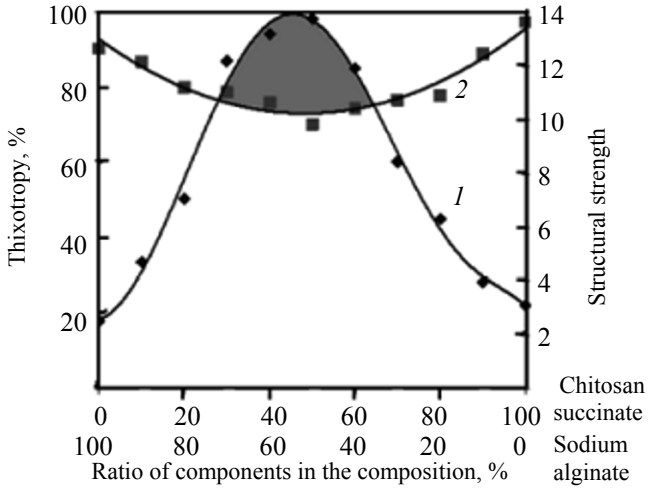

Fig. 4. (*1*) Structural strength and (*2*) thixotropy of the sodium alginate–chitosan succinate bicomponent mixtures vs. mixture component ratio.

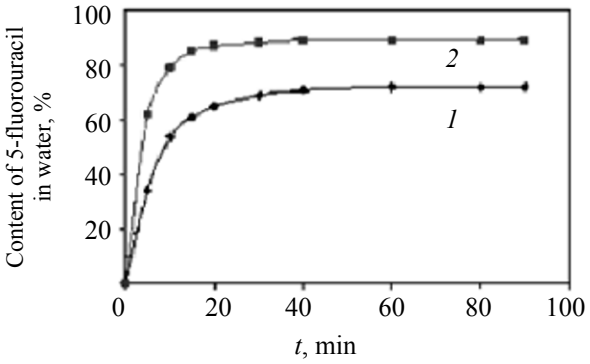

Fig. 5. Kinetic curves of 5-fluorouracil desorption into distilled water from the textile material surface: (*1*) nonwoven cotton/viscose fabric and (*2*) PF-2 knitted fabric. Bath module 250.

thixotropy should be no lower than 60–65%, and in the latter case it should be higher and strictly follow the medical prescriptions: When a composition is injected, e.g., by Janet's syringe (under load), low thixotropy of the composition will result in its flowing out of the cavity, whereas too high thixotropy will cause pains in patients. Therefore, we selected the thixotropy level experimentally, on a specially designed instrument, with which it was possible to adjust the viscosity level to the medically prescribed time and amount of the composition injected. Study of the rheological characteristics of the compositions with different chitosan succinate concentrations (ranging from 4 to 10%) revealed nearly 100% thixotropy level, which means that the inner structure was virtually completely regained after the load was removed.

The compositions containing 4 and 6% chitosan succinate sodium salt fail to provide the viscosity level required for printing, i.e., do not support an even and clear contour, whereby a large amount of the drug may be lost. At 10% concentration, the polymer composition has an excessively high viscosity, which can lead to blind spots due to screen clogging. The most acceptable concentration of the solution of chitosan succinate sodium salt is 8%. It is important to note that, throughout the concentration range examined, the viscosity of the chitosan succinate-based thickening agents remained virtually unchanged within 3 days of storage at 20°C.

The use of thickening agents comprised of chitosan succinate solely leads to significantly increased cost of the product. To examine the possibility of using bicomponent systems consisting of sodium alginate and chitosan succinate, which can exert a combined effect, we studied the rheological and printing technical characteristics of these biopolymer systems with different ratios of the components (Fig. 4). We found that, with decreasing thixotropy, the strength of the system structure tends to increase and reaches a maximum at a 50:50 ratio of the mixture components. The monocomponent system with 100% chitosan succinate exhibits nearly 100% thixotropy level, and that with 100% sodium alginate is less capable of regaining its inner structure under steady-flow conditions at high velocity gradients, but nevertheless it preserves a very high thixotropy level.

Thus, it is reasonable to use mixtures of chitosan succinate with sodium alginate taken in a 30:70 ratio (see Fig. 4).

Mass Transfer of the Drug from Medical Textile and Hydrogen Materials to the External Medium

The first phase of preparation of the application materials consisted in examining how the textile material affected the mass transfer of the drug, exemplified by a cytostatic and radiomodifier 5-fluorouracil (2,4-dioxo-5-fluoropyrimidine), to the external medium, distilled water. As textile printing substrate for thickening agent–drug compositions served PF-2 knitted fabric and nonwoven cotton/viscose stitched material (Fig. 5).

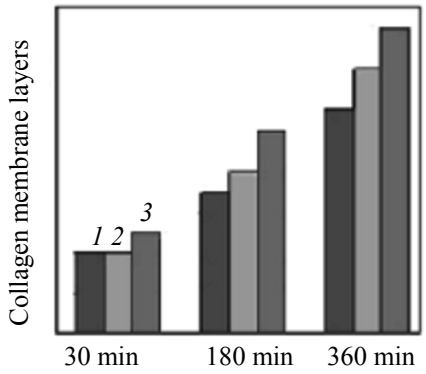

Fig. 6. Depth of penetration of 5-fluorouracil into collagen membrane layers in relation to the nature of the drug carrier and duration of the experiment: (*1*) textile material with deposited polymer composition based on sodium alginate (100%), (*2*) hydrogel based on sodium alginate, and (*3*) hydrogel composition based on sodium alginate and sodium salt of chitosan succinate, taken in the 70:30 ratio.

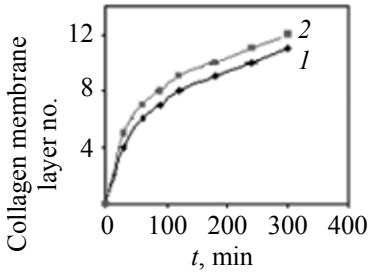

Fig. 7. Assessment of the intensity of mass transfer of 5-fluorouracil from hydrogel based on (*1*) sodium alginate and (*2*) 70:30 (per cent) sodium alginate–chitosan succinate mixture into collagen membrane.

The desorption rate and the amount of the drug transferred to the external medium from PF-2 knitted fabric exceeded those for the nonwoven cotton/viscose fabric. This difference is associated with the specific structure of the textile material: In knitted fabrics the composition is spread mostly over the surface, and in nonwoven cotton/viscose fabrics characterized by higher hydrophilicity, in the bulk. This feature is characteristic for all the application materials with different drugs that we examined.

To assess the effect of the substrate on the mass transfer of the drug, we examined the inter-phase mass transfer of 5-fluorouracil (1%) from the polymer thickeners and compositions thereof to collagen membranes. We took into account the fact that, if the tumor is located in a body cavity (e.g., in the rectum), the only reasonable choice is hydrogel composition, while for skin tumors the preferred option is textile napkin.

Our choice of the time of the experiment was dictated by relevant physicians' data, specifically, the exposure time of 300–360 min for the material impregnated with the drug to be introduced (rectally). We found that PF-2 cotton/polyester material has little effect on the drug release into the collagen membrane; the desorption rate is determined exclusively by the rate of the polymer swelling and dissolution and by the drug solubility (Fig. 6). The penetration depth of 5-fluorouracil into the collagen membrane from the textile material and the hydrogel composition varies with time: Within 30 min the agent reaches the 4th layer, within 180 min, the 7th layer, and within 360 min, the 11th layer (the multilayer membrane with up to 40 layers, that we used, can be considered as being infinite). Over the exposure time indicated, the drug penetrates the material to the calculated depth and, which is essential, resides there in a high concentration, i.e., the textile material and the polymer composition successfully perform their function of a "depot" for the drug. We found that, under identical initial application conditions (identical initial concentrations of the drug in the textile material and in the hydrogel composition), 5-fluorouracil from the hydrogel composition consisting of sodium alginate and chitosan succinate taken in a 70:30 (per cent) ratio penetrates the collagen membrane faster than from sodium alginate gel (Fig. 7). This finding correlates with the swelling rates of these polymers.

Having analyzed the depths of penetration of the drug into the collagen membrane simulating the tissue, that we determined, and on the results of comparison of the effects exerted on this process by the biopolymers, sodium alginate and chitosan succinate, we concluded the following. The drug is desorbed in a larger amount and at a higher rate from the polymer composition comprised of a mixture of sodium alginate and chitosan succinate sodium salt. Hence, the rate and extent of desorption of the drug can be varied by changing to another biopolymer or by varying the proportions of the biopolymers in the composition.

In selected cases, when textile napkins are applied for a prolonged time (for up to 24 h), they need to be additionally moistened, because the mass transfer of drugs occurs from moist napkins solely. The rate of mass transfer of the drug depends on the technique by which the napkin is used (i.e., how a textile application is placed): If it gets dry, it needs additional moistening (Table 1).

Table 1. Assessment of the influence of additional moistening of applications on mass transfer (K_M coefficient of 5-fluorouracil) from the textile material into the multilayer collagen membrane

Experimental conditions (initial 5-fluorouracil concentration on the textile material = const)	K_M, 10^{-7} cm^2 s^{-1}
Textile material is applied to collagen membrane	0.65
Textile material is applied to membrane and coated with polyethylene film	0.80
Textile material is applied to membrane and additionally moistened after 15 min	1.30

Study of the mass transfer of the drug from the applications into the external medium, especially under real conditions, is an extremely difficult task from the methodological viewpoint. In our experiments we took the following approach to studying the mass transfer of the drug from napkin. Initially, we used water and some other liquids (e.g., saline, lipovenos solution) for simulating the external medium. Next, we examined the mass transfer into collagen membranes and, further, into biological tissues (in experimental animals). This was followed (after an appropriate toxicological study was carried out) by clinical tests in patients (as authorized by the Ministry of Health and Social Development of the Russian Federation). Examination of the mass transfer of the cytostatic drug 5-fluorouracil from the textile applications into tumor tissues of different histogeneses, regrafted to laboratory animals (mice, rats), confirmed that targeted delivery of the drug from textile applications into tumors and its accumulation therein can be achieved, as suggested by effectiveness of the cytostatic action (tumor regression was observed). The napkins did not cause any serious manifestations of local or general toxicity effects in tumor-bearing animals.

Preparation of Medical Textile and Hydrogen Applications with the Use of 5-fluorouracil

The above-described experiments validated the concept of development of textile applications with 5-fluorouracil impregnated thereon to be used for local targeted delivery of the drug to the tumor tissue and demonstrated their effectiveness in treatment of tumors in various stages and convenience in use. Through application of Koletex napkins for delivery of high doses of cytostatic agent and prolonged transport of the drug to the external medium (injured tissue, tumor) it is possible to achieve tumor regression, while preserving patients' quality of life. To this end, not only clinical but also outpatient treatment can be provided, in particular, in periods between radiotherapy treatment sessions.

For treatment of intracavitary tumors (e.g., in larynx, rectum, and large intestine, as well as in gynecological organs, etc.), in which case the use of textile napkin applications for drug delivery is unacceptable, physicians recommended an independent use of a hydrogel composition printed onto a textile material. Printed hydrogel compositions comprising 5-fluorouracil should meet specific technological and medical requirements. It was suggested that the polymer substrate have thixotropy of no less than 75–98% and viscosity of 7.0–720.0 Pa s (depending on the application area: proctology, urology, gynecology, etc.). The use of compositions with optimized characteristics for targeted drug delivery allows the drug doses received by patients to be significantly reduced relative to those used in drug delivery by standard routes (oral administration, injection) due to directed delivery of the composition which is locally positioned with respect to the lesion. We undertook joint experiments with Blokhin Russian Oncological Scientific Center, Russian Academy of Medical Sciences, Federal State Institution, in which a large number of compositions with identical drug concentrations though with different viscosities (different percent content of polymer thickener) were analyzed. Based on the experimental results, we selected a viscosity level, compliant with appropriate technological and medical requirements, to be adjusted by varying the thickener concentration. It should be noted that the desired viscosity of the composition is to be selected experimentally for each batch of the natural biopolymer (sodium alginate).

The hydrogel material (hydrogel napkin) with 5-fluorouracil (under the trade name Kolegel with 5-fluorouracil) has successfully passed toxicological and technical tests. Thereupon it was subjected to clinical tests with the aim to assess the effectiveness of the hydrogel composition in treating patients with malignant tumors in cavities (rectal, in particular). Specifically, the possibility of 5-fluorouracil accumulation in tumor tissues in amounts required for achievement of the known medically effective concentration was assessed. In parallel, the concentrations of the drug delivered to tumors by different routes were determined. To this end, the 5-fluorouracil concentration was estimated in tumor tissues of

patients treated with this drug by standard methods, orally (Xeloda pellets, Switzerland) or by injection. The concentrations were determined by the technique developed by us in collaboration with the Institute of Carcinogenesis, Blokhin Russian Oncological Scientific Center, Russian Academy of Medical Sciences, Federal State Institution. Examination of samples of surgically removed tumor tissues validated the targeted mass transfer of the drug from the hydrogel composition to biological tissues. The concentration of 5-fluorouracil delivered with the use of the hydrogel composition is comparable to that achieved via standard delivery routes, but the latter entail worsening of the patients' quality of life due to increasing toxicity: blood counts change, nausea, vomiting, etc.

The above-said suggests opening up a possibility for using gels loaded with 5-fluorouracil, which acts both as cytostatic drug and cell cycle radiomodifier (making cells most vulnerable to radiation harm), for effective, less toxic cancer treatment by radiation therapy and chemotherapy methods.

Preparation of Applications with the Use of Radiosensitizer Metronidazole

Another drug that we used for development of medical materials capable of improving the radiation therapy effectiveness was radiosensitizer metronidazole [(1-β-hydroxyethyl)-2-methyl-5-nitro-imidazole]. This is an electron-accepting compound which, while imitating the action of oxygen, undergoes slow metabolism and diffuses into all segments of tumor, including those devoid of blood vessels (this feature is specific of tumor tissues) and reaches more distant hypoxic (oxygen-depleted) zones. This leads to formation of free radicals and singlet oxygen which destroy the tumor cells.

The desired effect can be achieved at no lower than 150–200 μg g^{-1} metronidazole concentrations in tumor tissues. This level may be exceeded (in tumor), but the concentration should not be high in blood (and urine) in order to avoid toxic effect of the drug in patients. In this context, the knowledge of how long the required concentration will be maintained is essential (this is the factor deciding the possibility of radiation therapy treatment and also, to a large extent, the irradiation procedure). The required concentration level can be achieved by oral administration of up to 40–60 drug pellets, but this treatment technique is poorly tolerated by patients because of toxicity, and its application results in the need for antiemetics, reduced quality of life, and high drug concentrations in blood (up to 50%).

We have to accomplish the following task: to select a drug concentration in the textile material such that it will allow the desired concentration level (no lower than 150–200 μg g^{-1}) to be achieved in tumor tissues within a certain period of time since the napkin was applied. This level should be maintained over the required period so as to "prepare" the tumor to radiation treatment and bring cancer cells to the condition most vulnerable to destruction.

To estimate the effectiveness of metronidazole-impregnated napkins, we determined the rate of mass

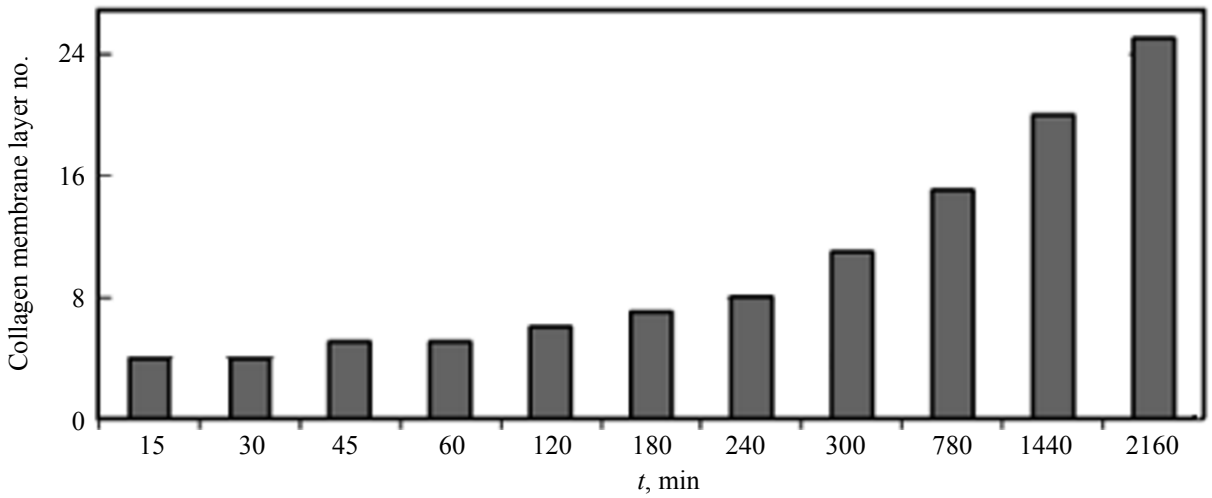

Fig. 8. Assessment of the intensity of mass transfer of metronidazole from knitted fabric into collagen membrane. Sodium alginate polymer, screen printing (20 mesh).

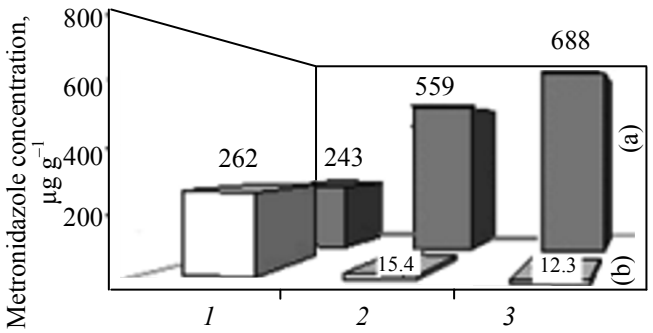

Fig. 9. Metronidazole concentration in tumor (III-IV stage tongue squamous cell carcinoma) and in blood serum in relation to the administration route: (*1*) oral (pellets), (*2*) intratumoral injection, and (*3*) Koletex napkin with metronidazole application. (a) ^{T}umor, μg g^{-1} and (b) blood serum, μg g^{-1}.

transfer of the drug from the napkin to the external medium, i.e., simulated drug desorption into the lesion, and identified factors affecting this characteristic (textile material properties, polymer type, etc.).

Mass transfer of metronidazole from textile application into skin and deeper-lying segments of tumor was studied with the use of collagen membranes. Dimethyl sulfoxide, which is known to facilitate penetration of certain substances (in particular, drugs, biologically active substances) through the skin, was additionally introduced into the medical composition.

The diagram in Fig. 8 shows that, within 24 h, metronidazole (drug concentration on napkin 10 mg cm^{-2}) was detected in the 20th membrane layer (~1.4 cm), and within 36 h, in the 25th layer (~1.75 cm). Hence, metronidazole is capable in principle of penetration even into intact skin and of accumulation in tumor. This effect was confirmed by medicobiological tests (upon surgical removal of tumor tissue after a textile napkin with metronidazole was applied, the drug concentration in the removed tissue was determined spectrophotometrically).

It is essential that the drug is delivered from the textile material and retained in tumor tissues for up to 3 days since the application was placed (after 3 days the metronidazole concentration was 274 μg g^{-1}), thereby simplifying the radiation treatment procedure (Fig. 9). This effect cannot be achieved by injections and oral administration. Specifically, when metronidazole pellets are administered, the drug is present in blood serum in even larger amounts than in the tumor cells. In the case of drug injection directly into the lesion, the metronidazole concentrations at the initial moment of time are comparable with those achieved with the use of applications, but already after 30–60 min the drug is released from the tumor into the bloodstream. As a result, the drug effect cannot to be prolonged to the extent required for covering the period needed for radiation therapy treatment [15].

It was suggested that a printed composition deposited onto the textile material be used for metronidazole delivery to body cavities. The medical composition is comprised of a sodium alginate-based gel and metronidazole drug. Compared to the case of Koletex napkins applied onto the skin or mucous membranes, the mass transfer of the drug from the gel (at identical drug concentrations) proceeds at a higher rate and to a larger extent, because the inhibiting action from the textile material is lacking and the rate of mass transfer of the drug is governed by the polymer swelling and biodegradation. This finding was validated by experiments in which, within 300 min, the drug immobilized in the napkin and in the gel penetrated 11 and 14 layers, respectively. The same effect was achieved through the use of Koletex napkins with metronidazole in medicobiological examinations conducted by us jointly with the Department of Proctology, Blokhin Russian Oncological Scientific Center, Russian Academy of Medical Sciences, Federal State Institution [supervised by Prof. Yu.A. Barsukov, Dr. Sci. (Med.)].

Based on the joint studies with clinicians, we developed a polymeric hydrogel composition with metronidazole, possessing the desired properties. The use of this composition afforded the required drug concentration (no lower than 150–200 μg g^{-1}) in tumor tissues.

The textile material and hydrogel composition thus developed (known under trade name Koletex with metronidazole and Kolegel with metronidazole, respectively) have successfully passed medicobiological, toxicological, and technical tests. The Blokhin Russian Oncological Scientific Center, Russian Academy of Medical Sciences, Federal State Institution, has developed a program for treatment of patients with colorectal cancer. In this program, the preoperative irradiation scheme includes the use of the developed polymer material with metronidazole to be introduced rectally. Thus, combined treatment

procedure, in which Kolegel with metronidazole serves as radiomodifier, for radiation therapy allowed the five-year disease-free survival rate to be reliably improved to 92.2% against 67.4% for patients receiving thermoradiotherapy solely.

Development of Medical Textile Materials with the Use of Antioxidant Drugs

The injury inflicted by radiation therapy treatment to tumor-adjacent healthy tissues causes a frequently occurring associated disease. As a result, not only the patients' quality of life is reduced and special medical treatment is required, but in some cases radiation therapy should be terminated, despite the fact that the dose received by the patient is still lower than that necessary for the treatment. Thereby, the treatment results and prognosis for recovery are adversely affected. In this context, much significance is attached to development of medical materials capable of prevention and treatment of radiation injuries (and also of post-radiation injuries occurring within 6 months after the radiation exposure), as well as of the methods for drug delivery directly to lesions, especially for targeted (e.g., into cavity) local (e.g., in treatment of breast cancer) drug delivery. Account should be taken of the localization of radiation injury, high abundance of medicines administered, and weakened immune system of cancer patients.

Considering the fact that the radiation therapy procedure is associated with development of processes involving free radicals in the body, it was recommended that radiation injuries (in particular, burns) be treated with the use of antioxidants. Also, there is a need in regeneration of tissues and, in some cases, in analgesics to relieve pains. Three domestic agents exhibiting antioxidant properties were selected for development of a new medical textile material: derinat (sodium deoxyribonucleate) extracted from sturgeon soft roe, mexidol (3-hydroxy-6-methyl-2-ethylpyridine succinate), and propolis, natural antioxidant. Also, we used lidocaine having an analgesic effect. The antioxidants were responsible for radioprotective properties of the materials developed, and alginate (owing to its specific curative properties), for the regenerative ability. The textile matrix should coat the injured surface area without sticking thereto (due to antiadhesion properties of the biopolymer, sodium alginate, acting as thickener in the composition). Moreover, when used as hydrogel, alginate coats the injuries in cavities, penetrates the tissues, and smoothens out their uneven texture.

The antioxidant activity of the chosen drugs in the external medium (wound), as well as the rate of their mass transfer from the textile and polymer matrix, were estimated from the content of free radicals in the external medium (other properties were not analyzed in this experiment).

The total concentration of free radicals in the external medium (wound) was derived from the change in the content of endogenous antioxidants in blood plasma of 25 patients, regarded as the dose exposure response, which was determined by chemiluminescence analysis technique. The normal level of endogenous antioxidants is 18.6×10^{-6} mol (blood plasma ml)$^{-1}$ on the average. In pathology the content of antioxidants decreases by two–three orders of magnitude. Under presumption that, in pathology, the endogenous antioxidants go entirely for suppression of spontaneous release of radicals into the wound exudate, the quasistationary concentration of pathogenic radicals in wound can be estimated at 10^{-6}–10^{-9} mol l^{-1}, which value has the same order of magnitude as do the values reported in literature.

The antioxidant activity of the drugs impregnated onto textile base was determined in a model experiment. As the model reaction simulating the radical process proceeding in the "wound" served low-temperature (37°C) oxidation of cumene, initiated by α,α-azo-bis-isobutyronitrile (AIBN); the process was monitored by the chemiluminescent kinetic method (chemiluminescent model). The generation of cumene peroxide radicals in this reaction corresponds to the generation of pathogenic radicals in the "wound" in response to radiation injury. Acetonitrile and chlorobenzene taken in a 1:1 ratio served as the solvent. Acetonitrile acted as wound exudate which promoted swelling of the biopolymer (sodium alginate, a drug composition component) on the textile material sample and mass transfer of the drug from the textile application into the external medium. The mass transfer is controlled by the rate of swelling of the material and sodium alginate, i.e., like in all the above-described situations, by the concentration gradient of the drug in the textile material–external medium system, as well as by the solubility of the drug and the rate of its carryover into the external medium (blood, lymph). This results in shifting of the concentration equilibrium of the drug between the external medium (wound) and the drug remaining on the material and in desorption of the drug into the external medium.

Table 2. Indicator of antioxidant activity of drugs. The chemiluminescent method was applied for a model reaction of initiated oxidation of cumene (50%)

Drug	$K_7\times10^{-4}$, ms^{-1}
Mexidol	2.8
Derinat	1.3–1.5
Propolis	0.9–1.4

Interaction of cumene perioxide radicals with mexidol and their consumption lead to additional desorption of the drug from the napkin into the bulk of the model system (along with the above-described action produced by the drug in the wound). In this feature, the chemiluminescent model is qualitatively different from other models which neglect the kinetics of drug consumption in the "wound" by a radical mechanism and take into account only the properties of the medium and the carryover of the drug and alginate from the wound with lymph and blood. In our experiment we deliberately neglected the influence exerted on mass transfer by a number of characteristics, e.g., the actual composition of the external medium, in particular, the protein composition, viscosity, etc. Our study was focused exclusively on the antioxidant properties exhibited by the system after a napkin with mexidol was placed into the wound.

Samples (0.5×0.5 cm^2) of napkins with mexidol deposited by the printing technology were placed into a temperature-controlled bubbler-type cell filled with the reaction mixture: cumene (50%), acetonitrile (25%), chlorobenzene (25%), and AIBN. As the textile samples were kept at 37°C, we measured the residual mexidol content in the samples in 0.5-h intervals. Using the kinetic curve, we calculated after each measurement the effective rate constant of interaction of mexidol with cumene peroxide radicals K_7 characterizing the antioxidant activity of the drug.

The K_7 constant and the content of antioxidant mexidol in the napkin, measured simultaneously, suggest that, within 700 min (over 11 h) of keeping of the samples in the model (wound), K_7 remained virtually unchanged, $(1.3–2.3)\times10^{-4}$ ms^{-1}. Hence, the antioxidant activity of mexidol was preserved during the period indicated, which finding is of decisive importance for determining how often the napkins should be changed.

The antioxidant properties of mexidol impregnated into the polymer, and subsequently into the textile matrix, remained at the clinically effective level. The established fact that the antioxidant is released into the external medium by the exponential law, depending on the exposure time of the medical material, allows prediction of how the therapeutic effect will be affected by varying the mexidol concentration in the textile napkin. The introduction of alginate into the system has a negligible effect on K_7 (2.50×10^{-4} against 2.48×10^{-4} ms^{-1}). Similar results were obtained in examinations of the possibility and advisability of the use of other drugs possessing antioxidant properties (Table 2).

Our studies have culminated in development of Koletex medical textile napkins with antioxidant drugs mexidol and propolis, as well as with derinat both with and without lidocaine addition, and also of Kolegel gels with derinat and propolis. These agents have shown a good therapeutic effect consisting in the prevented/significantly delayed development of radioreactions, as well as in the enabled continuous radiation treatment until the required dose was achieved and in reduced pains.

Thus, we demonstrated the suitability of textile technologies for preparation of new types of medical materials capable of improvement of the effectiveness of radiation therapy in oncological practice, as well as of prevention and treatment of post-radiation injuries in cancer patients.

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