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Morphology of target drug delivery systems ($CaCO_3$ vaterites covered with dextran sulfate) in rat muscular tissue

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Summary

The present work is focused on the study of target drug delivery systems comprised of porous spherical calcium carbonate vaterites ($CaCO_3$) covered with the dextran sulfate protective shell. Behavior of the objects was investigated *in vivo*. The samples were implanted into rat muscular tissue and removed after different periods of exposure (3 days, 1, 2, 4, and 12 weeks after operation). It was shown that certain transformations in structure of the implanted carriers occurred over time, after which they underwent bioresorption. In 3 days after implantation, spherical vaterites degraded, and needle-like calcium carbonate objects were formed; during the following two weeks, these objects were completely resorbed in living tissues. Since no pathogenic influence of the samples on the surrounding tissues was revealed, we believe that $CaCO_3$ vaterites covered with protective shells are safe for potential medicinal applications and can be recommended for further studies as target drug delivery systems.

Keywords

Target drug delivery, calcium carbonate, dextran sulfate, bioresorption, muscular tissue, *in vivo* experiment.

Introduction

One of the main lines of development in modern medicine and pharmacology is design of the methods for target delivery of pharmaceutical preparations into the damaged area of a body. This approach enables researchers to (i) increase the dose of a preparation present in the damaged organ; (ii) achieve prolonged action of a drug; (iii) exclude or considerably reduce possibility of toxic action of a drug on healthy organs and tissues. As a rule, conventional treatment involves introduction of a preparation into systemic blood circulation, whereupon the substance is distributed by blood in the organism of a patient. Therefore, in order to reach sufficiently high (i.e., therapeutically effective) concentration of a drug in the damaged area, it is necessary to introduce intentionally high amounts of this drug [1, 2]. The situation is also complicated by the fact that the majority of pharmaceutical preparations possess considerable toxicity; besides, in many cases, multiple administrations (courses of therapy) are necessary. In particular, a major problem of treatment of patients with oncological diseases is related to high or extremely high toxicity of modern chemotherapy drugs [3, 4]. Therefore, development of systems and methods for target drug delivery is an especially important and actual task.

In general, the process of target delivery of medicinal preparations proceeds as follows: (i) the drug-containing carrier is introduced into systemic blood circulation; (ii) the carrier circulates within an organism and is selectively accumulated in the damaged area; (iii) low doses of a drug preparation are gradually released from the carrier [1, 2, 5, 6]. However, the

main disadvantage of this approach consists in the inability of carriers to be accumulated in a selected zone. Upon introducing into blood, carriers are distributed in the organism similarly to the conventional drugs [7]. An alternative procedure involves regional administration (for example, injecting drugs directly into the damaged area). This approach allows one to achieve predominant localization of carriers in the target provided that administration is performed with high accuracy.

Drug carriers are commonly designed on the basis of porous (hollow) micro- or nanospheres [8, 9]; however, particles without internal free volume can also be used (including liposomes, polymeric, oxide, metal particles, and the particles based on biocompatible non-toxic salts) [1, 2, 10-14]. Protective shells of various polymers are used to shield carriers and the enclosed drugs from the active internal media of an organism, and to provide prolongation of drug release. The polymers used to create these shells can be divided into two basic groups: synthetic (poly(acrylic acid) [15], polystyrene sulfonate [16], poly(ethylene oxide) [17]) and natural (carboxymethyl chitosan [18], alginate [19], hyaluronic acid [20], and dextran sulfate [21]).

The drug carriers used in the present work were based on porous microparticles of calcium carbonate ($CaCO_3$) covered with a layer of sodium salt of dextran sulfate; these objects meet the biological safety requirements and can be found in living organisms [22]. Spherical $CaCO_3$ porous vaterites (cores) were synthesized. Porous vaterite is one of three calcium carbonate polymorphs; other $CaCO_3$ modifications (cubic calcites and elongated aragonite crystals) do not possess porosity [23].

There are only few research papers concerning *in vivo* behavior of the $CaCO_3$-based drug carriers. In several works [21, 24], $CaCO_3$ vaterites containing various medicinal preparations were introduced to rats perorally and transdermally; their structures were studied after exposure to rat body for a certain time. The vaterites present in blood and plasma were destructed already in several hours after peroral administration [21, 25]. In the case of transdermal administration, vaterites underwent gradual bioresorption for one week without any morphological transformations [24]. In our earlier works, behavior of native $CaCO_3$-based carriers (without protective shells) in rat muscular tissue has been investigated [26]. It has been demonstrated that in 3 days after implantation of $CaCO_3$ cores into muscular tissue, structural transformation of calcium carbonate (from vaterite into aragonite) occurred; then, aragonite crystals were rapidly resorbed. In 2 weeks after operation, only traces of aragonite were found in tissues, and in 4 weeks, muscular tissue regained its normal state. No toxic action of the carriers on the surrounding tissues and the whole organism was revealed throughout the experiment.

We have found no papers describing *in vivo* behavior of $CaCO_3$-based carriers covered with dextran sulfate shells in muscular tissue.

The aim of the present work was to study *in vivo* behavior of porous spherical $CaCO_3$ vaterites (covered with protective shells of sodium salt of dextran sulfate) as components of target drug delivery systems in rat muscular tissue.

Materials and methods

Preparation of objects. Porous spherical vaterites ($CaCO_3$) were obtained by co-precipitation according to the technique described elsewhere [8] with several modifications [27]; namely, equal volumes of 1 M aqueous solutions of $CaCl_2 \times 2H_2O$ and Na_2CO_3 were poured together at stirring with an RW 20 anchor-type stirrer at 1 000 rpm. The mixture was stirred for 30 s. The suspension formed in 15 min was filtered with a Schott glass filter (#16); the precipitate was washed thrice with distilled water, then with aqueous solutions of acetone of increasing concentrations (30, 60, and 100%). The product was dried in thermostat at 40-50°C until a constant weight was reached. Diameters of the obtained cores varied from 1 to 4 μm. Then the cores were coated with polyanionic sodium salt of dextran sulfate (DexS) with MM=9-20 kDa (Sigma Aldrich, USA). Calcium carbonate cores (50 mg) were added to 0.001 wt.% aqueous solution of DexS (10 mL). The suspension was stirred using a Multi Bio RS-24 rotor (Biosan, Latvia) for 1 h; the solid fraction was filtered off using a Schott glass filter (#16), washed thrice with distilled water and dried at 20°C.

Scanning electron microscopy. The samples were studied with the aid of a Supra 55VP scanning electron microscope (Carl Zeiss, Germany) using secondary electron imaging. Before measurements, the samples were covered with thin platinum layer.

Experiments with animals. The *in vivo* experiments involved 25 white 3-month-old male rats of Wistar strain (5 animals *per* each series of experiments). Weight of the animals varied from 200 to 250 g. For the study of *in vivo* bioresorption, $CaCO_3$ cores covered with DexS were sterilized in autoclave at 110°C for 1 h. Each weighed amount of $CaCO_3$ (10 mg) was hermetically packed in aluminum foil. The animals were operated under general anesthesia (intraperitoneal injections of Zoletil 100 dissolved in 20 mL of physiological solution and Rometar (20 mg/mL), 0.1 and 0.015 mL of solutions *per* 0.1 kg of animal body mass, respectively). The samples were placed into thigh great adductor muscle (*musculus adductor magnus*) of one hind extremity (one sample *per* animal). Then the wounds in extremities were sutured layer by layer using atraumatic needles and Prolene 4-0 suture. After outer suturing, the rats were caged individually, were fed standard diet, and had free access to water. All animals were active after surgery; no inflammation in the implantation area was observed, which is indicative of the absence of detrimental effects of implantation.

Morphological studies of $CaCO_3$ vaterites covered with DexS implanted in rat muscle tissue. In 3 days, 1, 2, 4 and 12 weeks after operation, samples of muscle tissue containing $CaCO_3$ covered with DexS were removed from animals, fixed with 10% neutral formalin in phosphate buffer (pH=7.4) for not less than 24 hrs, dehydrated using a series of ethanol solutions with increasing concentrations, and enclosed in paraffin blocks according to the standard histological technique. The paraffin cuts (5 μm in width) transverse to muscular fibers were obtained with the use of an Accu-Cut SRT 200 microtome (Sakura, Japan) and stained with Mayer hematoxylin and eosin (BioVitrum, Russia). The connective

tissue was visualized according to the Mallory method (Bio-Vitrum, Russia). Microscopic analysis was performed using a Leica DM750 light microscope (Germany) with a 10× ocular and 4, 10, 40, and 100× objectives. Images were recorded with an ICC50 camera (Leica, Germany).

Results and discussion

Fig. 1 presents SEM images of surfaces of $CaCO_3$ cores covered with DexS. It is seen that the cores are homogeneous in size; the average diameter of the majority of particles varies from 1 to 4 μm. The core surface is rough; nanometer-sized pores are observed. This structure is convenient for medicinal applications: the loaded substances can freely penetrate into the internal volume of a core, and prolonged release in the damaged area is facilitated. Besides, due to high porosity, transport of high amounts of a preparation is possible, which also contributes to therapeutic effect.

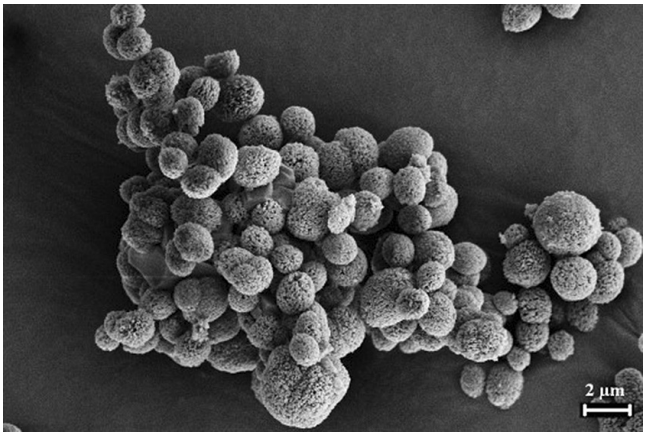

Figure 1. SEM image of $CaCO_3$ cores covered with DexS

$CaCO_3$ cores covered with DexS in muscular tissue in 3 days after implantation. In 3 days after operation, in 1 of 5 operated animals, round plicated cavity was observed visually; this cavity contained transparent viscous liquid (apparently, DexS) and was surrounded by a thin $CaCO_3$ rim. High amount of leukocytes was found in the formed cavities (mainly neutrophiles and eosinophiles). In 4 of 5 cases, no cavities were revealed, and $CaCO_3$ was localized in muscular tissue in the form of round aggregates and whitish streaks (Fig. 2a). Histological studies showed that calcium carbonate was mainly present in the form of elongated crystals 40-120 μm long and 10-20 μm wide assembled in bundles and surrounded by rather wide cellular shaft. This "mound" or wall consisted of loose lying cells (mainly macrophages, little amounts of segment-nuclear leukocytes (neutrophiles, eosinophiles), single lymphocytes, and few fibroblasts (Fig. 3 a, b)). The vessels surrounding this cellular mound were varicose and plethoric; erythrocyte sludges (stacks of aggregated erythrocytes) were observed. Pronounced edema appeared between muscle fibers near implantation site. High amounts of macrophages were found in endomysium; the vessels were dramatically exaggerated and plethoric. No necrotic damage was revealed in the surrounding tissues.

The proposed mechanism of formation of cavities in muscular tissue involves the reaction between $CaCO_3$ cores and

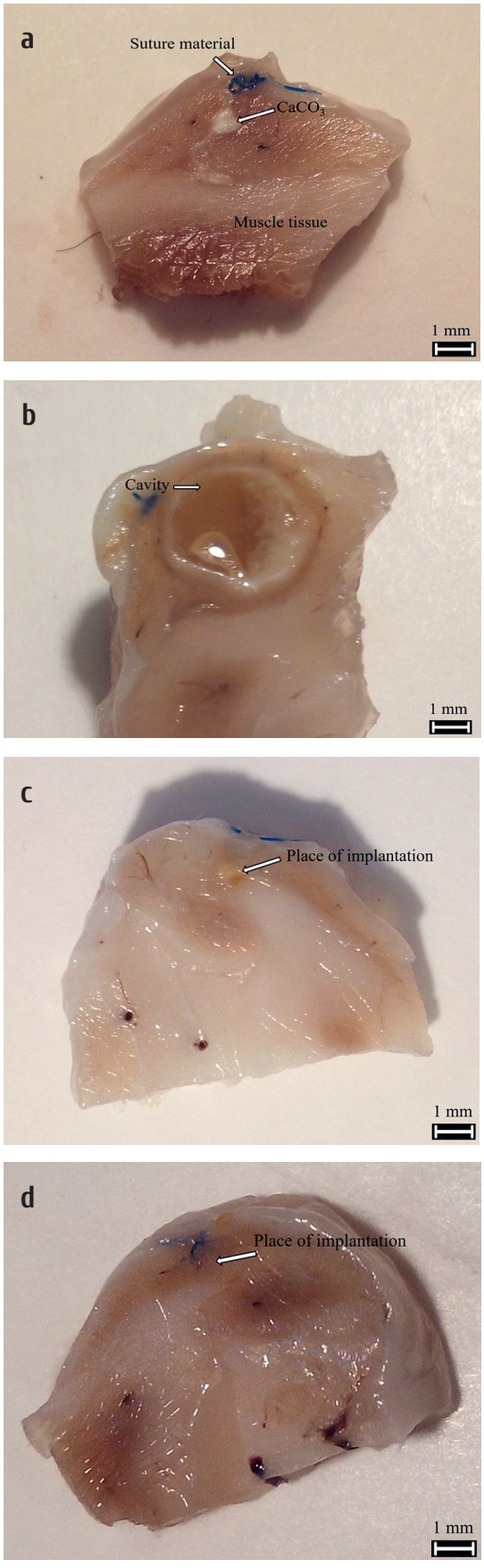

Figure 2. Images of cross-sections of muscles after implantation of $CaCO_3$ cores covered with DexS. a – in 3 days after implantation; b – in 1 week after implantation; c – in 2 weeks after implantation, d – in 4 weeks after implantation. The samples were fixed in neutral 10% formalin for not less than 48 h.

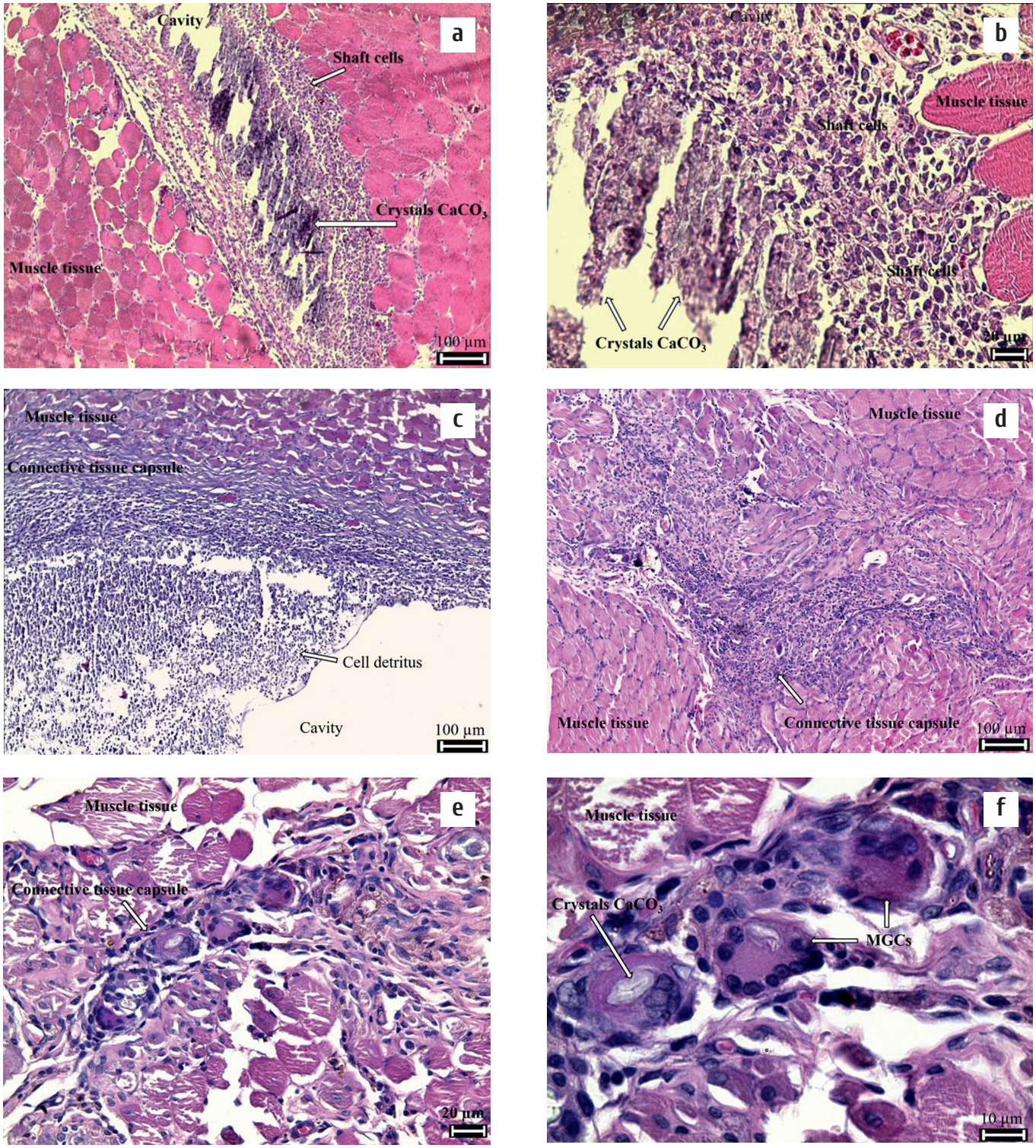

Figure 3. Histologic sections of rat muscular tissues made in 3 days (a, b), 1 week (c), 2 weeks (d), and 4 weeks (e, f) after implantation of $CaCO_3$ cores covered with DexS. The samples were stained with hematoxylin and eosin. Magnification: 10× (a, c, d), 40× (b, e) and 100× (f).

carbonic acid (the product of interaction between carbon dioxide and water, which is present in intercellular fluid). Carbon dioxide, in turn, is formed in the process of cellular respiration; however, it is mainly released by cells in the form of carbonic acid. The acid and the products of its dissociation exist in equilibrium. In addition, carbonic acid is included into the bicarbonate buffer system of blood plasma and intercellular fluid, which accounts for more than 50% of total buffer capacity [28]. The reaction between carbonic acid and $CaCO_3$ cores gives calcium hydrocarbonate $Ca(HCO_3)_2$, an unstable compound, which dissolves well in water. Decrease in carbonic acid concentration in the reaction zone leads to beginning of decomposition of the salt to $CaCO_3$, carbon dioxide and water already at 15-20°C [29].

The average body temperature of rats is 38°C. Decrease in carbonic acid concentration in the implantation zone is caused by formation of a connective tissue capsule, which

forms an impenetrable boundary between the reaction zone and intercellular fluid (containing buffer systems and products of muscle cell respiration). Consequently, $CaCO_3$ precipitates in the form of crystals (and not in the form of cores), and carbon dioxide that is released during decomposition forms a cavity. The most probable morphological modification of the appearing crystals is aragonite, which is formed at similar temperatures [30]. The main reaction equations can be written as follows:

$CaCO_3 + CO_2 + H_2O \rightarrow Ca(HCO_3)_2$,

or: $CaCO_3 + H_2CO_3 \rightarrow Ca(HCO_3)_2$;

$Ca(HCO_3)_2 \rightarrow CaCO_3\downarrow + CO_2\uparrow + H_2O$

The above reactions can proceed repeatedly and cease gradually as the interacting compounds are absorbed by the surrounding tissues and removed from the reaction zone.

$CaCO_3$ cores covered with DexS in muscular tissue in 1 week after implantation. In one week after operation, round cavities were detected in the implantation site in all cases; their sizes were larger than those formed in 3 days (Fig. 2 b). These cavities were also filled with a transparent viscous liquid; no $CaCO_3$ particles were visible. Microscopy studies revealed low amounts of calcium carbonate crystals accumulated at the periphery, on the inner surface of cavities. High amounts of cellular detritus and neutrophiles were present in the cavities (Fig. 3c). The cavities were surrounded with macrophage wall and a wide connective tissue capsule, in which fibroblasts were localized between young loose collagen fibers; macrophages, single segment-nuclear leukocytes and lymphocytes were also revealed. Many macrophages and lymphocytes penetrated into the cavity and were located inside it. The vessels in the forming capsule were exaggerated and plethoric; erythrocyte sludges were visible in some of them. Muscular tissue around the cavity was edematous; increased amounts of macrophages and lymphocytes were present in endomysium. The vessels in connective tissue interlayers were dramatically expanded and plethoric. No necrotic damage in the surrounding tissues was revealed.

$CaCO_3$ cores covered with DexS in muscular tissue in 2 weeks after implantation. In 2 weeks after implantation, macroscopic cavities were visible in the form of narrow fissures only in 1 animal; no cavities were observed in the remaining rats (Fig. 2 c). Capsules consisting of loosely arranged collagen fibers were revealed around fissure-like cavities. The capsules consisted of fibroblasts, macrophages, and lymphocytes. When a cavity was absent, a wide connective tissue interlayer was found in its place; this interlayer contained high amounts of cells, mainly fibroblasts, macrophages, lymphocytes, and multinucleated foreign body giant cells (MFBGC) arranged around isolated crystals of $CaCO_3$ (Fig. 3 d).

$CaCO_3$ cores covered with DexS in muscular tissue in 4 and 12 weeks after implantation. In 4 weeks after operation, the connective tissue interlayer (Fig. 2d) was revealed visually and with the aid of a microscope in the place where $CaCO_3$ cores have been implanted. Collagen fibers were completely formed; high amounts of cells were found. Fibroblasts, macrophages, MFBGC localized around isolated crystals of $CaCO_3$, and leukocytes were revealed (Fig. 3 e, f). The vessels in the connective tissue interlayer and in endomysium were slightly expanded. The morphology (structures of muscular tissue, endomysium and perimysium) observed in the implantation zone in 12 weeks after the operation was almost similar to normal.

Thus, it was demonstrated that in 3 days after implantation of $CaCO_3$ cores covered with DexS into muscular tissue, they were basically transformed into aragonite crystals, while cavities were formed in muscles in 1 of 5 cases; the cavities contained viscous liquid (obviously, solution of DexS). The cellular composition in the implantation zone indicated aseptic medium-grade inflammation. In 1 week after implantation, cavities filled with viscous liquid were observed in all cases. Note that this liquid is apparently solution of DexS (a natural bioresorbable polymer). $CaCO_3$ cores were not revealed visually. The light microscopy data showed that the amount of calcium carbonate crystals decreased considerably as compared to the case observed in 3 days after operation, which indicates active bioresorption of the cores. Cellular detritus was visible in the cavities, and macrophage shafts were formed around them. The connective tissue started to form; it contained increased numbers of macrophages and leukocytes, which is an indication of a chronic inflammation process. However, bioresorption of vaterites was ahead of formation of the connective tissue capsule, and already in 2 weeks after the beginning of the experiment, only traces of $CaCO_3$ were visible. In 4 weeks after operation, isolated $CaCO_3$ inclusions surrounded with MFBGC were visible. At the same time, the state of muscular tissue became normal again, which is a favorable outcome. In 12 weeks after beginning of the experiment, no $CaCO_3$ inclusions were found. It is important to note that no toxic (damaging) action of $CaCO_3$ cores on the surrounding tissues and the whole organism was revealed at any stages of the experiment. However, appearance of cavities at the early stages of the experiment should be taken into account; tumors should be treated carefully, since the above-mentioned cavities may facilitate formation of metastases.

Conclusion

The obtained data indicate that porous $CaCO_3$ vaterites covered with DexS are safe for medicinal use and capable of bioresorption; thus, they are promising materials for use as target drug delivery systems. The results of this study allow us to recommend the described systems as objects for further *in vivo* studies.

This work is a continuation of studies on the behavior of targeted drug delivery systems based on $CaCO_3$ vaterites in living systems, published earlier [25, 26].

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Compliance with ethical standards

The experiments involving animals were performed according to European Convention for the Protection of Vertebrate

Animals used for Experimental and other Scientific Purposes (Strasbourg, 1986) and WMA Declaration of Helsinki concerning welfare of laboratory animals (1996).

Conflict of interests

The authors declare no conflict of interests.

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Морфология систем адресной доставки лекарственных препаратов (ватеритов $CaCO_3$, покрытых сульфатом декстрана) в мышечной ткани крыс

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Резюме

В настоящей работе изучено поведение пористых сферических ватеритов карбоната кальция ($CaCO_3$) покрытых защитной оболочкой из сульфата декстрана – систем адресной доставки лекарственных препаратов – в мышечной ткани крыс на сроках 3 сут., 1, 2, 4 и 12 нед., после имплантации. Было показано, что с течением времени происходит структурная трансформация и биорезорбция изучаемых носителей. Через 3 сут наблюдается преобразование сферических структур в игольчатые с последующей их биорезорбцией в течение 2 нед. При этом патологического воздействия на окружающие ткани выявлено не было, что подтверждает безопасность применения покрытых защитной оболочкой $CaCO_3$ ватеритов и позволяет рекомендовать их для проведения дальнейших исследований в качестве систем адресной доставки лекарственных препаратов.

Ключевые слова

Адресная доставка лекарственных препаратов, карбонат кальция, сульфат декстрана, биорезорбция, мышечная ткань, эксперимент *in vivo*.