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$CaCO_3$ vaterites as components of target drug delivery systems

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Summary

Successful treatment of the majority of oncological diseases that affect solid organs is related to appropriate use of potent and (to varying degrees) toxic antitumor drugs. In a number of cases, chemotherapy requires the maximum localized action of a drug in the tumor area. The most efficient methods of drug administration are introducing medicinal compounds (MC) directly into the tumor or use of target drug delivery systems. The second method makes it possible to decrease general toxicity of MC, and to reach prolonged therapeutic action due to uniform and time-controlled release of a MC into tumor tissue.

In the present work, we studied behavior of porous spherical $CaCO_3$ vaterites (components of delivery systems for antitumor drugs) in various environments (human blood plasma, rat muscle tissue). It was demonstrated that the studied drug carriers undergo morphological transformations and are destructed with time. In blood plasma, due to ion exchange reactions, vaterites are transformed into gradually disintegrating needle-like structures (as shown by scanning electron microscopy and energy dispersive spectroscopy). Similar processes were observed in muscle tissue: in three days, spheres were transformed into needle-like structures and then underwent complete bioresorption.

Keywords

Anticancer drugs delivery systems, $CaCO_3$ vaterites, blood plasma, intramuscular administration, bioresorption.

Introduction

Target drug delivery systems find increasingly wide application in medicine. Use of these systems requires high stability of encapsulated MC, low dosage and toxicity, prolonged therapeutic action. Porous vaterites (one of three calcium carbonate polymorphs) have been used as carriers in delivery systems (DS) for biologically active compounds and medicinal compounds since 2004 [1]. In many research works, they were used as "sacrificed" matrices. Porous carbonate cores were saturated with biologically active compounds using different methods, then their surface was coated layer-by-layer with polyelectrolytes; polymers with opposite excess charges were applied by turns. After dissolution of $CaCO_3$ cores in the presence of chelate compounds (e.g., ethylenediaminetetraacetic acid), these multilayered shells were used as capsules for delivery of biologically active compounds [2]. In some cases, carbonate cores were not dissolved, but used together with their PE shells [3-5]. Since one of the objectives of employing delivery systems is to provide prolonged release of an encapsulated MC, preservation of the porous core increases resistance of the structure against external influence and thus helps attain this goal. Another way of using $CaCO_3$ as a component of DS consists in including carbonate cores into alginate granule, which significantly simplifies DS preparation [6].

A number of research papers [7-9] report preparation of DS with $CaCO_3$ in combination with various polymers; antitumor drug doxorubicin was used as an active substance. *In vitro* experiments demonstrated prolonged pH-dependent release of the drug.

Note that synthesis of $CaCO_3$ cores is relatively simple. It is believed that they are completely biocompatible and biodegradable; they show neither toxicity nor immunogenicity, and thus are well tolerated by a recipient organism [10]. This opinion was confirmed by the studies of behavior of $CaCO_3$-based delivery systems in various model environments as well as upon administration of these DS into living rabbits, rats and mice by various methods. Configurations of DS based on $CaCO_3$ cores depend on the method used for their administration. The influence of various environments on the DS containing $CaCO_3$ cores is described in the papers that are quoted below.

In water or physiological solution (0.9% NaCl), $CaCO_3$ vaterites undergo morphological transformations [11]. At medium temperatures, porous vaterites turn into calcites (which are more thermodynamically stable), and at elevated temperatures (above 37-40°C), they are transformed into aragonites [12]. Since these polymorphs are not porous, recrystallization is accompanied by release of drugs encapsulated in vaterites. The drug release profiles correlate with percentages of calcites formed [13].

Oral administration is the most convenient method for patients. However, vaterite cores dissolve in acidic medium of a stomach; therefore, the cores with encapsulated MC should be protected. This protection can be provided both by PE shells (on condition that their components are stable in acidic stomach environment) and alginate granules surrounding $CaCO_3$ cores. Since it is necessary to provide penetration of MC from intestinal tract into main blood flow, a polymer shell should swell or dissolve in the middle division of intestinal tract, thus releasing $CaCO_3$ with MC. Model experiments involving 0.15 M phosphate buffer with pH=7.4 (model intestinal fluid) demonstrated that $CaCO_3$ enters into ion-exchange reaction with phosphate ions; as a result, rather compact porous vaterites are transformed into loose macroporous $CaHPO_4$ structures. This process facilitates release of the encapsulated MC. Scanning electron microscopy (SEM) and energy-dispersive spectroscopy (EDS) studies revealed structural changes in $CaCO_3$ vaterites [14]. Similar transformation also occurs with time in the case of two-level DS that consist of alginate granules and carbonate cores. The presence of fragments of $CaCO_3$ cores in blood and plasma of experimental animals (rats) was confirmed by elemental analysis of the samples [15].

The requirements for size of DS intended for *parentheral* administration are more rigid, but in this case the carrier should not be necessary protected (unlike the systems used in oral delivery). The $CaCO_3$ vaterites that were synthesized according to the technique described in [1] have sizes of 3-5 μm. Diameter of cores may be reduced by various methods: change in the basic synthesis conditions – increasing concentration of the initial solutions of salts (Na_2CO_3 and $CaCl_2$), and stirring intensity [16]; increase in viscosity of starting solutions by adding ethylene glycol [17]; addition of a polyelectrolyte during co-precipitation of the salts [18-20]. Unfortunately, the latter method gives low yield of the final product and requires monitoring interaction between MC and polymer.

The authors of [21] used *intratracheal* administration of $CaCO_3$ cores that contained BSA protein labeled with Cy7 fluorophore. It was demonstrated that efficiency of penetration into lungs for carriers of various diameters decreased with increasing core size from 0.65 to 3.15 μm. Penetration of the labeled protein into lungs with the aid of $CaCO_3$ vaterites of different sizes was confirmed by confocal microscopy of mouse lung cryocut sections. The lower DS size, the deeper they penetrate into lung tissue. Confocal microscopy makes it possible to localize $CaCO_3$ carriers in a sample. Recrystallization of vaterites was observed in the model environment that included physiological solution and bronchoalveolar lavage (containing proteins and surfactants). It was shown that the components of lavage covering vaterite surface protect them from recrystallization.

The authors of [22] demonstrated possibility of penetration of $CaCO_3$ vaterites with encapsulated loperamide through blood-brain barrier of rats after *intranasal* administration. In order to enhance mucoadhesion, $CaCO_3$ cores were covered with mucoadhesive polymers (hyaluronic acid or poly-L-lysine).

It was suggested [10] to use $CaCO_3$ cores with encapsulated superoxide dismutase enzyme as an ophthalmic delivery system. According to the authors, no undesirable effects were observed after injections of vaterite microcrystals (concentration 10 mg/mL) into eye tissues of rabbits.

In vivo transdermal administration of $CaCO_3$ particles (diameter: 4 μm) to a depth of 200 μm was performed *via* laser ablation followed by massage. These relatively large particles did not penetrate into the underlying derma. In 1 week after beginning of the experiment, $CaCO_3$ particles dissolved in rat body and released the encapsulated compound [23].

It was revealed [24] that porous $CaCO_3$ cores degraded completely in three months after introducing them into rat *bone tissue*.

Along with other calcium-containing inorganic nanostructured materials, $CaCO_3$ vaterites find increasing applications in regenerative medicine and tissue engineering [25].

To summarize, all methods for introducing DS based on $CaCO_3$ vaterites are aimed at providing absorption of cores by cells. The influence of size and shape of $CaCO_3$ particles on cell uptake was studied in [26]. It was demonstrated that internalization is more effective for spherical particles with the lowest volume, and for elongated particles.

Currently, there are no literature data on the studies of behavior of vaterite-based DS in human blood plasma and upon their *intramuscular* administration. When using the majority of the above-mentioned methods, it is necessary to study transformations of DS in blood plasma. The second method may be efficient when DS with MC are introduced directly into tumor tissue. Thus, the goal of the present work was to study behavior of spherical $CaCO_3$ vaterites (compo-

nents of target delivery systems for antitumor drugs) *in vitro* (in human blood plasma) and *in vivo* (in rat muscle tissue).

Abbreviations: *DS, delivery systems; MC, medicinal compounds; EDS, energy dispersive spectroscopy; SEM, scanning electron microscopy; EDTA, ethylenediaminetetraacetic acid; BSA, bovine serum albumin.*

Materials and methods

Synthesis of carbonate cores

Porous vaterites ($CaCO_3$ cores) were prepared by co-precipitation according to the technique described in [1] with some modifications. Equal volumes of 1 M aqueous solutions of $CaCl_2 \times 2H_2O$ and Na_2CO_3 were rapidly mixed at stirring with an RW 20 anchor-type mechanical stirrer (Kika-Werk, Switzerland) (1000 rpm). The mixture was stirred for 30 s. Then the suspension was filtered through Schott filter glass (#16), washed thrice with distilled water, then with acetone/water mixtures with increasing acetone concentrations (33%, 50%, and 100%). The precipitate was dried in thermostat at 40-50°C until a constant weight was achieved. Diameter of the obtained cores varies from 1 to 3 μm.

Interaction between $CaCO_3$ and human blood plasma

Interaction between carbonate cores and human blood plasma was performed at continuous stirring of the suspension. When the reaction was complete, the cores were centrifuged (5 min at 3000 rpm); the supernatant was poured out and substituted for distilled water. The procedure was performed twice. The cores were dried at 40°C until a constant weight was achieved.

Scanning electron microscopy (SEM)

SEM microphotographs of $CaCO_3$ cores were obtained with the help of a Supra 55VP scanning electron microscope (Carl Zeiss, Germany) using secondary electron imaging; before the experiments, the samples were coated with thin platinum layer.

Energy dispersive spectroscopy (EDS)

Elemental compositions of the samples were determined by energy-dispersive spectroscopy (EDS) using an X-Max 80 detector (Oxford Instruments, UK).

Experiments with animals

The experiments involving animals were performed according to the laboratory animal welfare policy accepted in Russian Federation and European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (ETS 123, Strasbourg, 1986).

In vivo experiments involved 10 male Wistar rats (weight: 200-250 g, age: 3 months). Before studies of bioresorption *in vivo*, $CaCO_3$ cores were sterilized in autoclave at 110°C for 1 h. Each weighed amount of $CaCO_3$ (10 mg) intended for an experiment in each of two locations in one animal was carefully hermetically packed in aluminum foil. The animals were operated under general anesthesia (intraperitoneal injections of Zoletil 100 (0.1 mL) and Rometar (20 mg/mL) solutions, 0.0125 mL *per* 0.1 kg of animal body mass). The samples were placed into thigh great adductor muscles (*musculus adductor magnus*) of both hind extremities. Then the wounds 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.

Histological studies

In 1 and 2 weeks after operation, samples of muscle tissue containing $CaCO_3$ were 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 (Bio-Optica, Italy). The connective tissue was visualized according to the Mallory method (BioVitrum, 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

Influence of human blood plasma on the structure of $CaCO_3$ cores

Blood plasma contains phosphate ions, which enter into reaction with $CaCO_3$ vaterites; as a result, macroporous $CaHPO_4$ structures are gradually formed [14]. It is seen in the SEM images of $CaCO_3$ vaterites (Fig. 1) that the objects with increasingly loose structure are formed with time; they consist of needle-like subunits less than 1 μm in diameter.

Phosphorus content in the studied structures was determined by energy-dispersive spectroscopy (see Table 1).

The EDS data show that phosphorus content in transformed structures increases with time; this result confirms that ion exchange reaction indeed occurs in $CaCO_3$ vaterites.

Table 1. Phosphorus content (P) in $CaCO_3$ samples that contacted with blood plasma for various periods of time

Sample	P (wt. %)
Plasma	0.10±0.07
$CaCO_3$ 2 hours in plasma	0.30±0.11
$CaCO_3$ 24 hours in plasma	0.38±0.16
$CaCO_3$ 50 hours in plasma	1.92±0.50

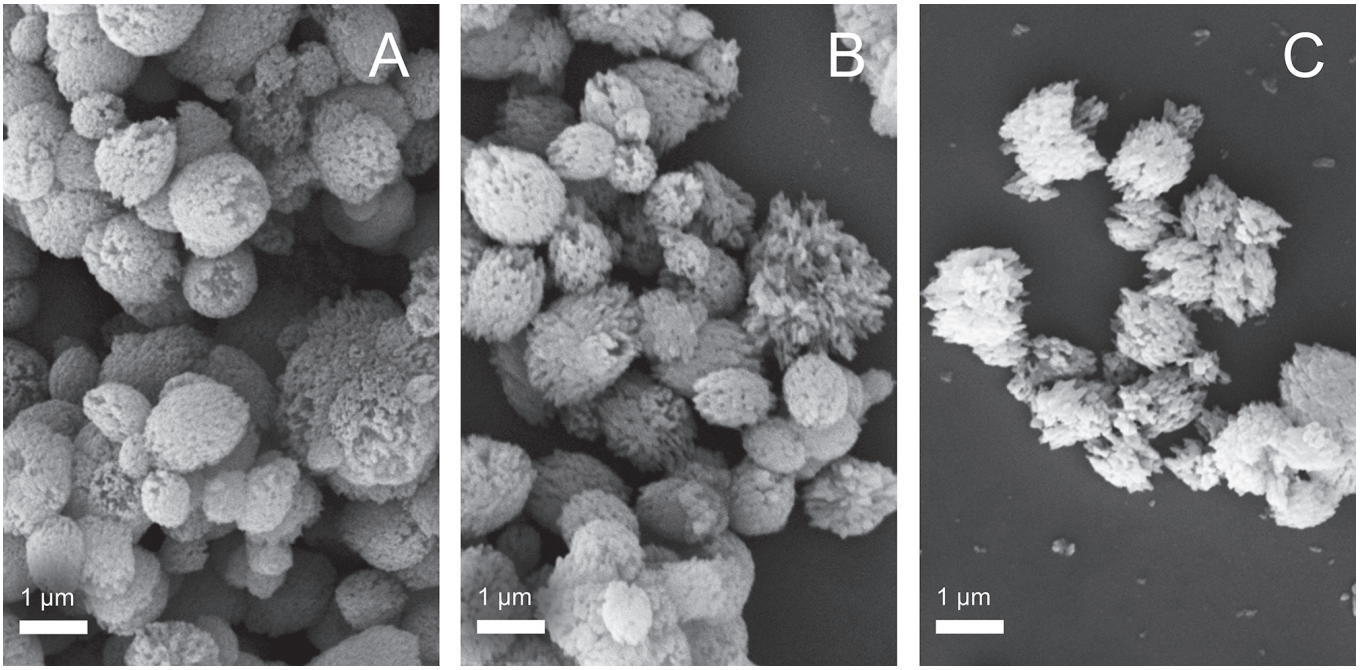

Figure 1. Microphotographs of $CaCO_3$ vaterites taken upon interaction with human blood plasma for various periods of time: A – 2 hrs; B – 24 hrs; C – 50 hrs

Transformation of $CaCO_3$ vaterites upon intramuscular administration

After injection of $CaCO_3$ vaterites into thigh great adductor muscles (*musculus adductor magnus*) of both hind extremities in rats, needle-like structures were formed (Fig. 2) and then gradually disappeared in two weeks due to bioresorption. Presumably, these needles are aragonites (one of three $CaCO_3$ polymorphs). Fig. 2B presents the magnified image of the area where vaterites were introduced and then transformed into aragonites (1 week after operation). As was mentioned in Introduction, aragonites (non-porous elongated structures) are one of three morphological modifications of calcium carbonate, along with non-porous (usually cubic) calcites and porous spherical vaterites (which are used as components of target drug delivery systems). Transformation of vaterites during their use in delivery systems into calcites is frequently observed [13]. Formation of aragonite-like structures in the process of bioresorption of $CaCO_3$ vaterites was revealed in the present work for the first time.

Discussion

The reason for transformation of porous $CaCO_3$ vaterites (diameter: 1 – 3 μm) into needle-like aragonites (length: 30 – 150 μm, width: 10 – 40 μm) in muscle tissue still remains unclear. It may be suggested that morphological transformation of vaterites is influenced by the following factors. First, there is a difference between pH values of muscle tissue and blood or its components (pH of muscle tissue is lower). The second factor involves peculiarities of metabolic processes, mainly, exchange of carbon dioxide. Upon interaction with water,

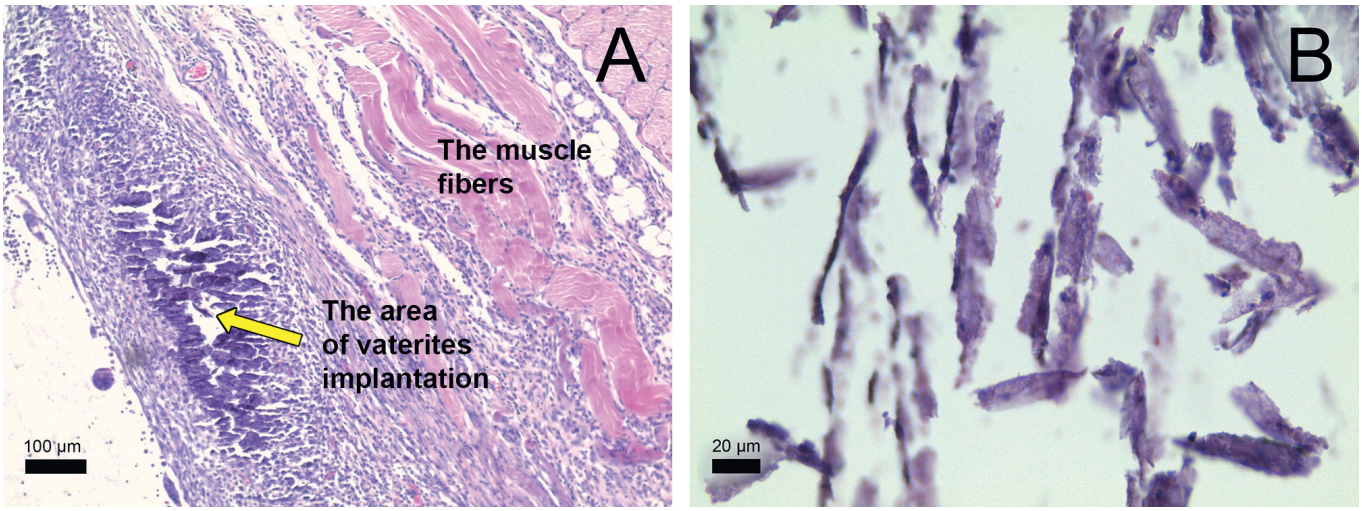

Figure 2. Histological cuts of rat muscle tissue obtained in 1 week after implantation of $CaCO_3$ vaterites. Staining with hematoxylin and eosin; objectives 10× (a), 40× (b)

carbon dioxide forms carbonic acid, which reacts with calcium carbonate. Among other factors are intensive action of immune cells, and, finally, mechanic action related to muscle contraction. This issue should be investigated further.

The comparison between our results and the literature data on transformation of $CaCO_3$ vaterites with encapsulated Fe_3O_4 nanoparticles (which occurred after shallow transdermal injection into rat body [23]) shows that no vaterite modification in muscle tissue was observed. The histological sections prepared in one week after transdermal administration show spherical structures almost similar to the initial cores. In two weeks after operation, vaterites underwent bioresorption, and Fe_3O_4 nanoparticles were released. These data may indirectly confirm our hypothesis concerning the influence of the above factors on transformation of $CaCO_3$ vaterites in muscle tissue.

Bioresorption of vaterites in blood plasma *in vitro* is also completed in relatively short period of time (several weeks), while plasma composition remains mostly unchanged.

The main advantage of the DS based on $CaCO_3$ vaterites intended for intramuscular administration of antitumor preparations is the fact that modified carbonate cores undergo complete bioresorption in 2 weeks *in vivo* and exert no negative influence on the surrounding tissues. The fact that aragonites are formed in the muscles once again indicates the ambiguity of applying the conclusions obtained from *in vitro* experiments to the *in vivo* behavior of the studied objects.

The obtained results confirm ability of porous calcium carbonate cores for bioresorption and their safety for medicinal use, which allows us to recommend porous $CaCO_3$ vaterites for further experimental studies as components of target drug delivery systems.

Conflict of interests

None declared.

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Ватериты $CaCO_3$ как компоненты системы направленной доставки лекарственных препаратов

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Резюме

Успехи в лечении большинства онкологических заболеваний связаны с применением действенных и в различной мере токсичных противоопухолевых препаратов. Во многих случаях химиотерапия требует максимальной локализации препарата в зоне опухоли. Поэтому наиболее эффективным методом является введение медицинских препаратов (МП) непосредственно в опухоль или применение таргетных систем их доставки. Второй из этих методов дает возможность снизить общую токсичность МП и достичь пролонгированного терапевтического эффекта из-за равномерного, контролируемого по времени выхода МП в опухолевую ткань.

В данной работе мы исследовали поведение пористых сферических частиц ватерита $CaCO_3$ (компонентов системы доставки противоопухолевых препаратов) в различных средах (плазма крови человека, мышечная ткань крыс). Было показано, что исследуемый носитель МП подвергается морфологической трансформции и со временем разрушается. В плазме крови, благодаря ионному обмену, ватериты превращаются в постепенно распадающиеся иглоподобные структуры, что показано с помощью сканирующей электронной микроскопии и энергорассеивающей спектроскопии. Сходные процессы наблюдались в мышечной ткани: в течение 3 дней сферические частицы превращались в иглоподобные структуры и затем подвергались полной биологической резорбции.

Ключевые слова

Противоопухолевые препараты, системы доставки, $CaCO_3$, ватериты, плазма крови, внутримышечное введение, биорезорбция.