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Morphology of hybrid doxorubicin delivery systems (dextran sulfate-coated $CaCO_3$ vaterites) in human blood plasma

Natalia N. Sudareva [1,2], Olga M. Suvorova [1], Natalia N. Saprykina [1], Vladimir V. Tomson [2], Dmitry N. Suslov [3], Oleg V. Galibin [2], Aleksandr D. Vilesov [1,2]

[1] Institute of Macromolecular Compounds RAS, St. Petersburg, Russia
[2] Pavlov University, St. Petersburg, Russia
[3] A. M. Granov Russian Research Center of Radiology and Surgical Technologies, St. Petersburg, Russia

Dr. Natalya N. Sudareva, Institute of Macromolecular Compounds, Bolshoy Ave 31, Vassilievsky Island, 199004, St. Petersburg, Russia
E-mail: nnsas@mail.ru

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Summary

In a number of cases, efficiency of cancer therapy may be enhanced by local administration of chemotherapeutic drugs into the tumor area. After regional injection, a drug, or appropriate delivery system is exposed to the interstitial fluid, which differs from blood plasma, mainly, in lesser protein amounts. In the present work, we studied the influence of human blood plasma upon structure and properties of hybrid drug delivery systems based on calcium carbonate ($CaCO_3$) vaterites coated with polyelectrolyte dextran sulfate (DexS). These delivery systems included anti-cancer drug doxorubicin (DOX). It has been shown that DexS-modified vaterites provided the prolonged release of DOX to blood plasma. SEM microphotographs revealed structural changes in hybrid delivery systems occurring in plasma and correlating with the DOX release profiles.

Keywords

Doxorubicin, drug delivery system, $CaCO_3$, dextran sulfate, blood plasma.

Introduction

Oncological diseases are among the main causes of death worldwide: cancer mortality reaches 20%. The World Health Organization predicts that in 20 years this value will double. In addition to existing methods of cancer treatment (surgery, radiotherapy, chemotherapy), a new method (targeted drug therapy) has been developed over last decade.

In many countries, doxorubicin monotherapy is considered to be the standard chemotherapy procedure [1]. DOX efficiently inhibits tumor growth by intercalation into DNA of cancer cells, which prevents replication process, thus leading to cell death. However, its clinical applications are limited by the dose-dependent cardiac toxicity. Moreover, this substance shows some disadvantages, i.e., short lifetime, accumulation in liver, and multidrug resistance of malignant cells [2]. Different delivery systems (DS) may be used in order to reduce these side effects. Prolongation of DOX release from DS can reduce probability of overdosage.

In the recent years, a large number of nano- and submicron-sized delivery systems for anti-cancer drugs have been developed [3]. The basic structure of carriers may vary; bio-organic objects are commonly used as carriers: exosomes [4], liposomes [5], dendrimers, macrophages [6], micelles [7], as well as inorganic substances, e.g., carbon nanotubes [8], calcium phosphates [9, 10], SiO_2 [11], and $CaCO_3$ [12]. It should be noted that manufacturing of most DS is rather laborious; in a number of cases, it is necessary

to synthesize complex polymers. Meanwhile, preparation of submicron-sized porous $CaCO_3$ vaterites is very simple, i.e., co-precipitation of $CaCl_2$ and Na_2CO_3 solutions [13]. Nanomicron-sized particles can be prepared by increasing viscosity of solutions [14] or changing ratio between concentrations of salts [15]. Of the three $CaCO_3$ polymorphs, porous vaterite is the least stable. Other forms (calcite and needle-shaped aragonite) are not porous. The $CaCO_3$ vaterites are biocompatible and biodegradable [16]. The particles have anti-cancer activity, even without encapsulated drugs, since $CaCO_3$ vaterites are shown to modulate local pH and inhibit tumor growth *in vivo* [17].

There are few studies on usage of different drug delivery systems based on $CaCO_3$ for tumor suppression, e.g., the pH dependence of $CaCO_3$ may control release of photosensitizer leading to cancer cell apoptosis [14]. The review [18] gives several examples of applications for $CaCO_3$ nanoparticles as carriers for various anti-cancer drugs, including DOX.

Various methods have been proposed to increase efficiency of delivery systems. Modification of polymer particles with polyelectrolyte coating leads to prolonged drug circulation time [19]. Similar effect can be expected upon treatment of $CaCO_3$ carriers with polymers. Special study concerned behavior and fate of hybrid phospholipid-treated $CaCO_3$ nanoparticles without drugs *in vitro* and in tumor-bearing mice [20]. Their uptake, penetration and distribution in tissues were investigated. It was demonstrated that the hybrid nanoparticles showed almost no cytotoxicity *in vitro* or *in vivo* and had high biocompatibility. The lipid-coated $CaCO_3$ cores saturated with DOX help to overcome chemoresistance in hepatocellular carcinoma [21]. In our earlier works, it has been demonstrated [12] that the properties of $CaCO_3$-based delivery systems for DOX may be improved. In particular, the drug load can be increased, the carrier morphology can be stabilized, and drug release can be prolonged by covering the cores with polyelectrolytes (dextran sulfate, polyacrylic acid, and polyvinyl sulfonate). In our recent works [22, 23], behavior of the DS based on submicron-sized $CaCO_3$ particles in mouse muscle tissue was studied for the first time. We have revealed that the DS based on parent porous vaterites and the vaterites coated by DexS undergo complete bioresorption in mice within, respectively, 2 and 3 weeks after administration. This process involves the stage of transition to needle-shaped aragonite structures. No pathological effects of the carriers on the surrounding tissues have been observed.

Anti-cancer therapy involves different ways of drug administration, including local introduction of DS containing active drugs [22]. For example, during treatment of hepatocellular cancer, the drug is introduced intraperitoneally. In this case, the DS will be exposed to interstitial fluids, which differ from blood plasma, mainly, in lesser protein contents.

Thus, the goals of the present work were: (i) to study *in vitro* structural changes in hybrid DOX delivery systems (based on porous $CaCO_3$ vaterites modified with DexS) in human blood plasma; (ii) to assess correlation between DOX release profiles from these DS into human plasma, and concomitant structural changes of the carrier substance.

Materials and methods

Reagents

Doxorubicin hydrochloride under the brand name of Sindroxocin, which contains 17% of doxorubicin (DOX) and 83% of lactose, was purchased from Actavis (Hafnarfjordur, Iceland). In experimental studies, doxorubicin salt with protonated amino group ($-NH_3^+$) was used. Inorganic salts ($CaCl_2 \times 2H_2O$, Na_2CO_3), acetone, and dextran sulfate, Mw=9-20 kDa were purchased from Sigma-Aldrich (St. Louis, MO).

Synthesis of carbonate cores

Porous vaterites ($CaCO_3$ cores) were prepared by co-precipitation according to the technique described in [13], with some modifications. Equal volumes of 1 M aqueous solutions of $CaCl_2 \times 2H_2O$ and Na_2CO_3 were rapidly mixed with stirring (1000 rpm) for 30 s, using RW 20 anchor-type mechanical stirrer (Kika-Werk, Switzerland). The resulting suspension was then filtered through Schott glass filter (#16), washed thrice with distilled water, then with acetone/water mixtures at increasing acetone concentrations (33%, 50%, and 100%). The precipitate was dried in thermostat at 40-50°C, until achieving constant weight.

Modification of carbonate cores with DexS and preparation of hybrid DS

The carbonate cores were coated with polyanions (sodium salt of dextran sulfate). $CaCO_3$ cores (50 mg) were added to 1 mg/mL aqueous solution of DexS (10 mL). The suspension was stirred using a Multi Bio RS-24 rotor (Biosan, Latvia) for 1 h. Solid fraction was filtered off using a Schott glass filter (#16), washed thrice with distilled water and dried at 30°C.

DOX loading and release

Loading of hybrid DS with DOX was performed by continuous stirring of the mixture of DSs suspension and DOX solution (C=2 mg/mL) for 24 hours. The DOX/($CaCO_3$+DexS) ratio was 0.4. After mixing, the suspension was centrifuged at 8000 rpm for 3 min, and DOX amounts were determined in supernatants.

DOX loading (L) was calculated by the following equation: $L = (m_i - m_s)/mp$, where m_i is initial amount of DOX (mg); m_s, the amount of non-encapsulated DOX in supernatant solution (mg); mp, amount of particles (mg). DOX concentrations were determined using the calibration curves obtained from optical density values, using appropriate solvents (λ = 480 nm). The measurements were carried out using SF-2000 spectrophotometer (LOMO, St. Petersburg, Russia).

In vitro release of DOX from hybrid DSs was analyzed in human blood plasma obtained from the Department of Blood Transfusion, Pavlov University. Incubation of DS in plasma was carried out at 20°C, with constant mixing. Aliquots were collected from incubation mixtures every 1-2 hours after centrifugation of core suspension at 3000 rpm for 3 min. The DOX contents in aliquots were determined by spectrophotometry. The supernatants obtained for similarly incubated DOX-free hybrid $CaCO_3$ cores were used as a reference

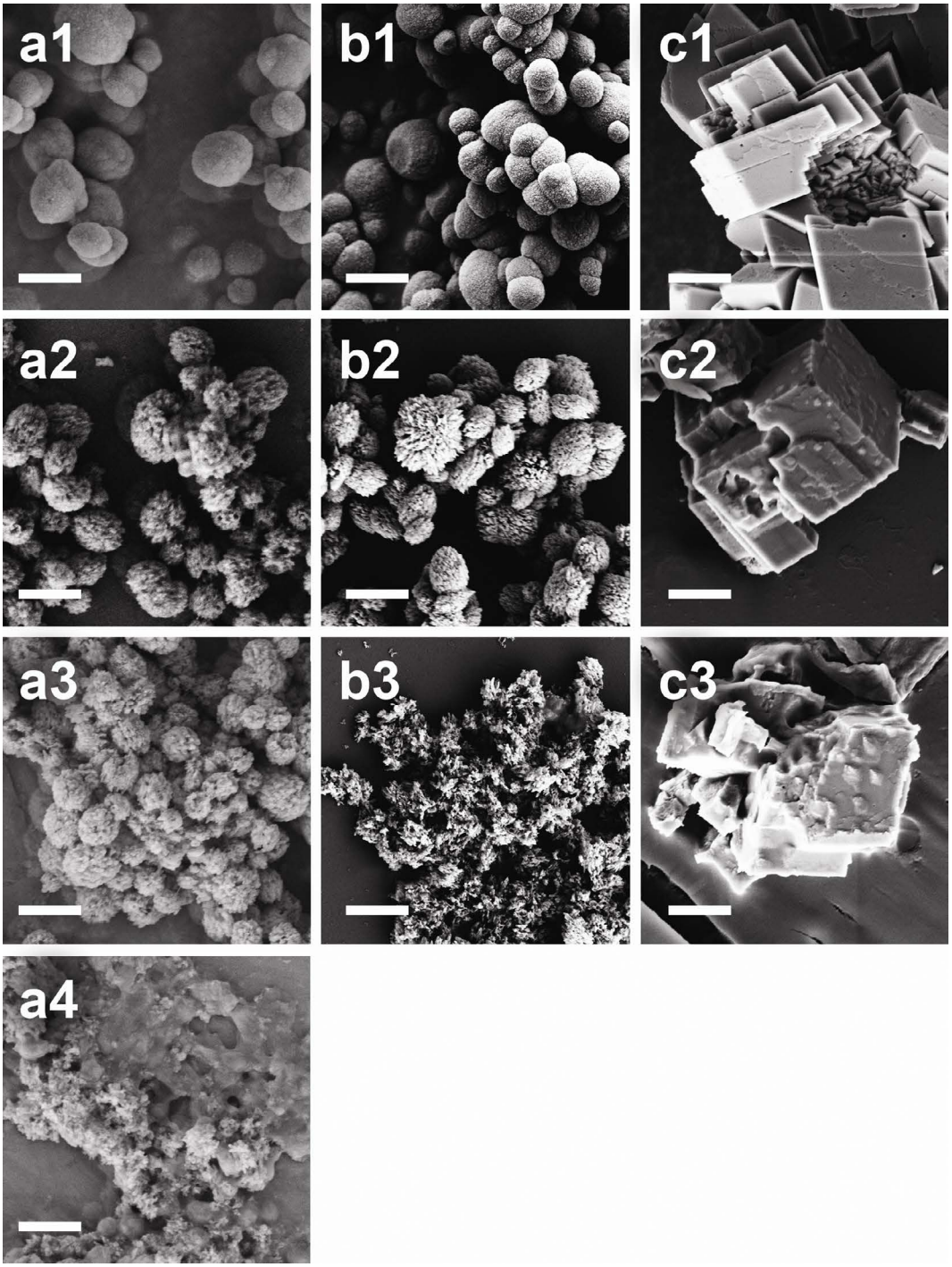

Figure 1. SEM micrographs of $CaCO_3$ vaterites coated with DexS (a), non-coated vaterites (b), and calcites (c). Images of the initial cores (1) were made upon interaction with human blood plasma for various periods of time: 1 day (2); 4 days (3); 7 days (4). Magnification: 20x. Marker size: 2 μm.

solution. The cumulative release was determined as percentage of DOX amounts loaded into the initial cores.

All the measurements were carried out in triplicate.

Interaction between DexS-modified $CaCO_3$ and human blood plasma

The interaction between hybrid carbonate cores and human blood plasma occurred in suspension at continuous stirring for different periods of time. Upon completion of the reaction, the cores were centrifuged (5 min at 3000 rpm), the supernatant was discarded and substituted by blood plasma. The procedure was performed twice. The cores were dried at 40°C until constant weight was achieved.

Scanning electron microscopy (SEM)

SEM micrographs of DexS-coated $CaCO_3$ cores were obtained by means Supra 55VP scanning electron microscope (Carl Zeiss, Germany) using secondary electron imaging. Before imaging procedure, the samples were coated with a thin platinum layer.

Results and discussion

Efficiency of the therapy with encapsulated drugs and various methods of administration (intravenous, intramuscular, etc.) depends on interaction between delivery systems and media of an organism, thus resulting into the drug release. In the case of local administration of chemotherapeutic preparations into tumor area, the drug and a delivery system are exposed to the interstitial fluid, which, unlike blood plasma, contain lesser protein amounts. In the present work, we studied structural and functional characteristics of hybrid delivery systems for DOX based on $CaCO_3$ vaterites modified with DexS polyanions. Porous vaterite is the least stable of three $CaCO_3$ polymorphs, whereas calcite and needle-shaped aragonite are not porous. In our previous publications [12, 22], it has been shown that the exposure of vaterites to blood plasma led to gradual destruction of calcium carbonate cores. This destruction may be caused, e.g., by interaction between vaterites and phosphate ions present in blood plasma, thus causing gradual development of macroporous $CaHPO_4$ structures [24].

Structural changes of $CaCO_3$ vaterites coated with DexS upon exposure to blood plasma for various periods of time (1, 4 and 7 days) are presented in Fig. 1. SEM micrographs of non-coated vaterites and calcites in plasma are also provided [12].

SEM micrographs demonstrate that delivery systems of various structures have different resistance upon incubation with blood plasma. DexS coating protects $CaCO_3$ vaterites from aggressive medium. Comparison of SEM micrographs of hybrid $CaCO_3$ and non-coated vaterites following exposure to blood plasma for 4 days (Figures 1a3 and 1b3) shows a more pronounced destruction of non-coated vaterites.

After 1 week of exposure to blood plasma, the hybrid delivery systems were also destroyed to a large degree (Fig. 1, a4). The DexS coating was partially separated from $CaCO_3$ cores, and the exposed vaterites are strongly damaged. Non-porous calcites do not undergo any significant structural changes under the contact with blood plasma. Thus, they are not suitable for use as delivery systems.

An important question arises concerning relations between structural characteristics of DOX delivery systems and their functional characteristics, i.e., DOX loading and time-dependent release profile of the drug? The process of DOX loading into various $CaCO_3$-based DS involves sorption, diffusion, and ionic interactions. Calcites interact with DOX mainly *via* sorption mechanism. The vaterite loading proceeds via sorption and diffusion interactions between DOX and porous core matter. When hybrid delivery systems ($CaCO_3$ vaterites coated with DexS polyanions) are used, additional ionic interaction takes place between DOX cations and excess negative charges present on the cores covered with polyanions (non-compensated charges). Thus, one may expect that, all other factors being equal, loading of DOX into hybrid DSs will be the highest of these three systems. Loading values (L) of non-coated and hybrid $CaCO_3$ cores were 370 and 400 μg/mg, respectively. Loading of calcites was about 100 μg/mg. Fig. 2 presents the DOX release profiles from $CaCO_3$-based DS of various structures.

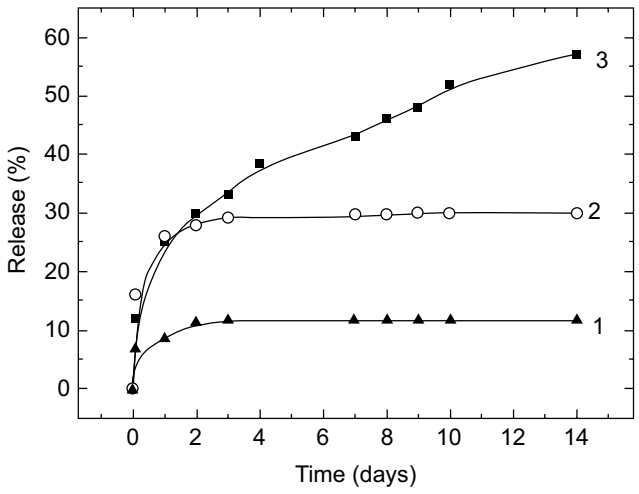

Figure 2. Release of DOX into blood plasma from $CaCO_3$ cores of different morphologies: calcites (1); vaterites (2); vaterites coated with DexS (3). Abscissa, incubation terms, days; ordinate, DOX release, %

For comparison experiments, DS of various structures, however, with similar DOX loading values were selected.

Release of DOX from hybrid cores was delayed, but more intensive as compared to those for the non-coated cores (curves 3 and 2). Therefore, one may expect that the amount of drug entering the bloodstream will be higher in the first case. The cumulative release of DOX from $CaCO_3$ coated with DexS into plasma was 55% in 2 weeks. For comparison, we now give the data on DOX release into model media from the delivery systems prepared with layer-by-layer coating of $CaCO_3$ vaterites with polyelectrolytes, followed by dissolution of carbonate cores [25]. During first 24 h of the experiment, 60% of DOX was released from these DS, and no increase in cumulative drug release was observed in the next 10 days. These results indicate more efficient prolongation of drug release from the DS based on hybrid $CaCO_3$ vaterites.

We may correlate the DOX release profiles (Fig. 2) with SEM micrographs of hybrid DS (Fig. 1a) and non-coated $CaCO_3$ vaterites (Fig. 1b). Exposure to blood plasma causes similar structural changes in hybrid and non-coated vaterites (Fig. 1, a2 and Fig.1, b2). Release profiles of DOX from hybrid and non-coated vaterites (Fig. 2, curves 3 and 2) are also similar for both DS exposed to blood plasma for 1 day. Similar results were obtained in experiments with $CaCO_3$ calcites. The structure of non-porous calcites virtually does not change even upon prolonged exposure to blood plasma (Fig.1, c1 to c3). The DOX release profile from calcites increases up to 11% in the first 2 days, then the release is ceased (Fig. 2, curve 1). Hence, we have shown that DOX release profiles correlate with structural changes of the tested delivery systems.

Conclusion

This work is a continuation of the research concerning the *in vitro* and *in vivo* behavior of targeted drug delivery systems based on $CaCO_3$ vaterites and carrying anti-cancer drug

doxorubicin as described in our earlier publications [12, 22, 23]. Our previous results suggest that porous $CaCO_3$ vaterites coated with DexS may be safe for medicinal use and undergo bioresorption in a living organism. In order to model behavior of the developed DOX-containing delivery systems in the interstitial fluid after intraperitoneal administration, we assessed structural and functional changes in these DS occurring during interaction with human blood plasma. Ionic composition of a medium is an important characteristic when degradation processes of different DS based on $CaCO_3$ cores are concerned. Treatment of $CaCO_3$ vaterites with DexS polyanion allowed us to obtain the delivery systems that provide a prolonged release of 55% of encapsulated anti-cancer drug DOX, with increased terms of drug release by more than 2 weeks. Using DS of various structures as examples, a correlation between functional characteristics of delivery systems (DOX release profiles into human blood plasma) and their structural changes was demonstrated. DOX is excreted from bloodstream very rapidly upon intravenous administration. According to chromatography data [26], DOX concentration in plasma becomes 100 times lower in 40-60 min after a single drug injection into mice (7 mg/kg). Since achievement of prolonged drug release is one of the main goals in DS development, our further studies will be focused on determination of DOX concentrations released into blood from DS of various structures.

Acknowledgement

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Conflict of interest

The authors declare no conflict of interest.

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Морфология гибридных систем доставки доксорубицина (ватериты $CaCO_3$, покрытые декстран-сульфатом) в плазме крови человека

Наталья Н. Сударева [1,2], Ольга М. Суворова [1], Наталья Н. Сапрыкина [1], Владимир В. Томсон [2], Дмитрий Н. Суслов [3], Олег В. Галибин [2], Александр Д. Вилесов [1,2]

[1] Институт высокомолекулярных соединений РАН, Санкт- Петербург, Россия

[2] Первый Санкт-Петербургский государственный медицинский университет им. акад. И. П. Павлова, Санкт-Петербург, Россия

[3] Российский научный центр радиологии и хирургических технологий им. А. М. Гранова, Санкт-Петербург, Россия

Резюме

Регионарное введение химиотерапевтических препаратов в область опухоли может во многих случаях повысить эффективность лечения злокачественных опухолей. После введения в организм, лечебный препарат или система доставки препарата могут подвергаться воздействию внутритканевых жидкостей, которые отличаются от плазмы крови тем, что они содержат меньше белков. В настоящей работе мы изучали влияние плазмы крови человека на структуру и свойства гибридной системы доставки, основанной на кальций-карбонатных ватеритах ($CaCO_3$), покрытых полиэлектролитом декстран-сульфатом (DexS). Эти системы доставки содержали противораковый препарат доксорубицин.

Было показано, что ватериты, модифицированные DexS, обеспечивали пролонгированный выход доксорубицина в плазму крови. Сканирующие микрофотографии выявили структурные изменения гибридных систем доставки, возникающие при контакте с плазмой и коррелирующие с профилем высвобождения доксорубицина.

Ключевые слова

Доксорубицин, система доставки препаратов, $CaCO_3$, декстран сульфат, плазма крови.