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SUSTAINED RELEASE OF VINCRISTINE FROM MICROPARTICLES OF CALCIUM ALGINATE GEL

Batyrbekov E. O., Rakhimbaeva D. Zh., Akylbekova T. N., Maishinova M., Musabekov K. B., Zhubanov B. A.

Bekturov A.B. Institute of Chemical Sciences, Al-Farabi Kazakh National University, Almaty, Kazakhstan, e-mail: erkeshbatyrbekov@mail.ru

The immobilization of anticancer drug vincristine on the microparticles of calcium alginate gel has been carried out. The dynamic of drug release from polymeric microparticles was investigated. The possobility of the use of alginate spheregels for the development of polymeric drug delivery systems with prolonged release of vincristine was shown.

Introduction

The modern chemotherapy of cancer demands application of high doses of the cytostatic drugs, frequently leading to the toxic effects. The existing arsenal of anticancer drugs is insignificant and also many of them possess small duration of anticancer action. The prolonged and controlled delivery of anticancer drugs represents great value at treatment of cancer diseases. The primary goal of tumor chemotherapy consists in selective suppression of malignant cells without damage of healthy tissue of organism [1,2].

One of ways of the decision of this problem is application of essentially new drug delivery systems in the form of the microparticles received on the basis of natural polymers. Such drug delivery systems reduce some potential disadvantages of cancer chemotherapy including toxicity, pain management, short in vivo half-lives and repeated administrations. The possibility of designing different drug delivery systems for a controlled and continuous release of the anticancer drug molecule has impact broadly the clinical application of the chemotherapies and improve the life-quality of the patients [3,4].

Among polymeric carriers, applied in pharmaceutical practice with the these purposes the alginic acid and its derivatives are of particular interest. These polymers are practically harmless, hydrophilic, able to form viscous water solutions and pastes, possess homogenizing, loosening and emulsifying properties. Alginic acid presents a polysaccharide, obtained from seaweed (laminaria) and consisting of repeated links of β-D-mannuronic and α-L-guluronic acids, interconnected with glucosidic bonds [5,6].

Alginic acid and its sodium and potassium salts have already found a wide application in pharmaceutical practice as loosening and binding remedies upon the production of tablets and preparation of ointments and pastes. In the presence of two-valency cations the alginic acid forms gels, built from guluronic acid with the participation of a cation [7]. A strong structure of alginate

gel and big sizes of pores allow one to easily immobilize large quantities of different physiologically active compounds, proteins, enzymes and even cells.

The purpose of the present work was the development of new drug delivery system based on microparticles of calcium alginate gel, containing immobilized anticancer drug vincristine.

Experimental

Sodium alginate, molecular weight 75-100 000 from *Macrocystis pyrifera* were purchased from Sigma Chemicals, St.louis, USA. Vincristine was used pharmaceutical grade.

Microparticles were obtained in the following way: at the first stage a solution of drug in 2,5% solution of sodium alginate was prepared, then the obtained solution was filtered and syringed dropwise into 0,1 M calcium chloride at a constant dropping rate of 1,0 ml/min. The obtained microparticles of calcium alginate were treated by the solution of calcium chloride for 30 min, washed with distilled water and physiological solution. As a result microparticles of calcium alginate containing immobilized drug were obtained [8,9].

For the determination of kinetics of drug release from alginate microparticles a special device was applied, consisting of a metallic basket, a thermostatic glass and a mechanic mixer. The release of drug was studied under conditions *in vitro* at 37°C. With this purpose a definite quantity of alginate particles was placed in a metallic basket, immersed in 300 ml of physiological solutions at pH 7,1. A constant rate of mixing of the released medium (100 turns/min) was ensured with the help of a magnetic mixer, thermostating was maintained with the help of a running cell. After definite time intervals 2 ml of the solution was selected for the determination of the content of drug with the help of the ultraviolet spectroscopy. Release of drugs was controlled each minute for the first 10 minutes, each 2 min for the following 100 minutes.

UV-spectra of drug were detected on a spectrophotometer Jasco UV/VIS 7850, Japan, in 10 mm quartz cuvette at 220 nm. SEM-photos were received on scanning electron microscopy Superprobe733, Russia, equipped energy dispersion spectrometer Inga Energy. Dry microparticles were sputter coated with gold using Fine Coat equipment and imaged at 20 kV at regime of secondary electrons.

Results and Discussion

One of ways of increase of efficiency of cancer chemotherapy is immobilization of drugs in structure of the polymeric microparticle, selectively absorbed by malignant cells that allows to create high concentration of drugs in a zone of a cancer cells for a long time. The encapsulation of the drugs can improve drug solubility and stability as well as reduce other disadvantages of cancer chemotherapy including toxicity, pain management, short in vivo half-lives and repeated administrations. Among polymeric microparticles, applied for anticancer drug carriers, alginic acid and its derivatives have already found a wide application.

One of the effective anticancer drugs widely used at treatment of cancer is vincristine. However along with many advantages this drug possesses short-term pharmaceutical action. Therefore in the given work the researches for development of new drug delivery system based on vincristine-loaded microparticles of calcium alginate gel are conducted.

From the literary data it is known that at formation of alginate gels a dominant role play blocks of guluronic acids where everyone calcium cation coordinates with 10 oxygen atoms of four residues of L-guluronate. Thus a polymeric chain get the original cellular-extended form in which each cell has a certain orientation of atoms of oxygen to calcium ions, forming conformation-correct links. The model of this coordination is popularly known as the «eggs in box».The scheme of coordination of calcium ion with blocks of guluronic acids at formation of «eggs in box» model in alginate gels is presented in Figure 1.

Microparticles were obtained by syringed dropwise of drug-containing solution of sodium alginate into a solution of calcium chloride. It is shown that alginate particles with optimum diameter about 0,8-1,0 mm formed under following conditions: an initial sodium alginate concentration 2 % (20 ml), temperature of full dissolution 40°C, time of dissolution 1-1,5 ч, dropping rate of 1,0 ml/min, concentration $CaCl_2$ - 0,1 M (100 ml). The spherical microparticles received thus had average diameter 1,0±0,05 the mm measured for 5 samples.

Scanning electron micrographs of air dried alginate microparticles were illustrated in Fig. 2. Apparently from drawing the microparticle has the correct spherical form in diameter 400-600 microns, the surface of microparticles has friable fibrous structure. The surface morphology of Ca-Alg microparticles improved by increasing alginate concentration whereas increasing alginate concentration above 3% made preparation of the beads difficult.

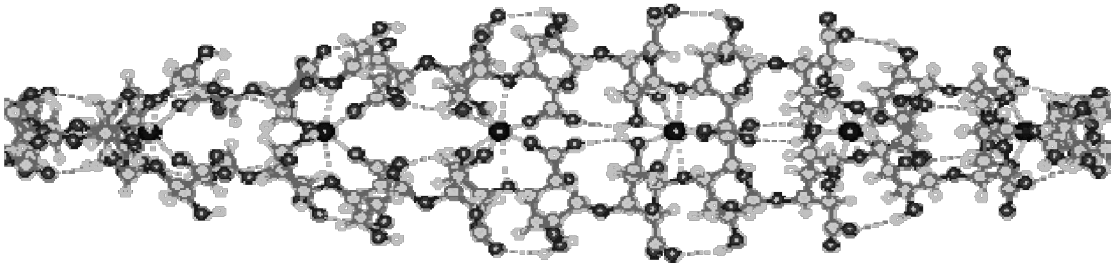

Figure1. Coordination of calcium ion with blocks of guluronic acids in the alginate microparticles

At IR-spectra of sodium and calcium alginate intensive bands in the field of 1690-1650 sm^{-1} corresponded to valency carbonyl groups were observed. Thus for calcium alginate in comparison with linear alginate sodium alginate reduction of intensity in the field of 1100-1200 sm^{-1}, characteristic for simple ether groups, were observed. This testifies to association hydroxyl groups at coordination. The band in the field of 3450-3500 sm^{-1}, characteristic for associated hydroxyl groups, in alginate particles has more expressed character.

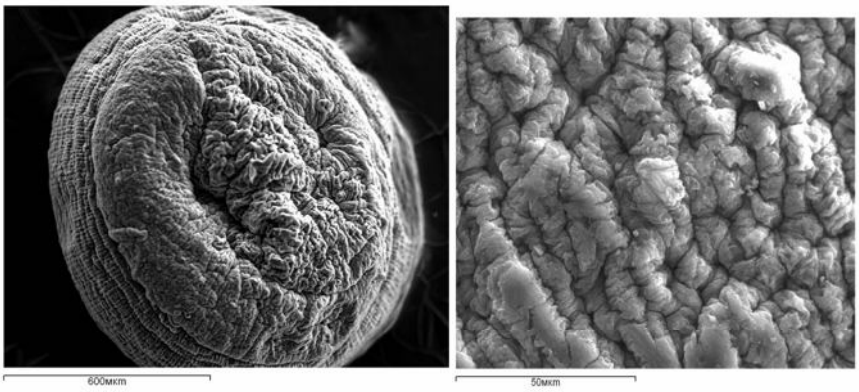

Figure 2. SEM micrographs of the dried vincristine-loaded alginate microparticles and surface of microparticles.

One of the main characteristics of drug delivery systems is the program of drug release in an organism. It is necessary to notice that in the majority of researches rate of release in experiments *in vitro* as in experiences *in vivo* the drug release is influenced by various factors essentially complicating the adequate description of the mechanism of process. In the present work the release of vincristine from alginate microparticles in physiological solution in conditions *in vitro* was investigated.

Results of experiences were presented in Figure 3. It was established that the greatest rate of release is observed for the swollen samples. So, the release of 50 % drug from the swollen microparticles is observed for 15-18 min whereas the same quantity of drug from completely dried samples occurs for 30-35 min. Full release of cytostatics on 90-95 % from the swollen samples occurs during 80-100 min, and from the dried samples within 140-160 min. All the release data show the typical pattern for a matrix controlled mechanism. The cumulative amount of drug released from alginate gels was linearly related to the square root of the time and the release rate decreased this time. The use of such systems makes it possible to develop systems with sustained release of anticancer drugs.

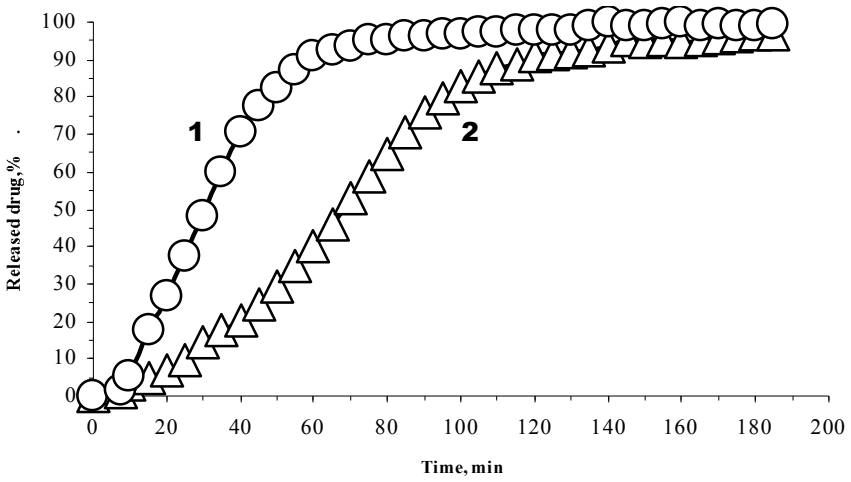

Figure 3. Vincristine release from alginate gel microparticles into physiological solution. 1- swollen, 2 – dried

Thus, the obtained data testifies to possibility of use of alginate microparticles of calcium alginate gel for development of drug delivery system with sustained release of anticancer drug vincristine.

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АНТИБАКТЕРИАЛЬНАЯ АКТИВНОСТЬ 2,6-ДИАРИЛЗАМЕЩЕННЫХ ПИПЕРИДИН-4-ОНОВ И ИХ ПРОИЗВОДНЫХ (обзор)

Бортникова К.А., Асылханов Ж.С., Ратникова И.А., Курманкулов Н.Б., Ержанов К.Б.
АО «Институт химических наук им. А.Б. Бектурова», Алматы,

В статье приводится краткий обзор отечественной и зарубежной литературы по биологической активности 2,6-диарилзамещенных пиперидин-4-онов и их производных.

Благодаря интенсивным исследованиям в области химии пиперидинсодержащих соединений, получены существенные результаты по методам синтеза, физико-химическим