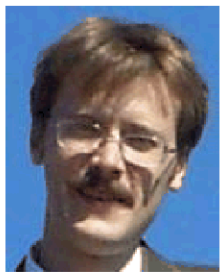
Alginate matrices ultrasonic modification for the develop the drug delivery systems



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Introduction

The most important advantage of the alginate matrix is that it is stable in a stomach acid medium. In an intestine alkaline medium alginate matrix dissolves. Thus, controlling the rate of the matrix dissolving it is possible to control the rate of the drug delivery to the organism. The most effective method to influence the rate of alginate matrix dissolving is ultrasound. Treatment by ultrasound causes destruction of macromolecules (Margulis M.A., 1995, Mason T.J. et al., 1988). On the basis of the obtained alginate samples with known molecular weight it is possible to develop drug delivery systems with the set properties, able to be dissolved on narrow sites of a gastroenteric path.

Material and methods

Sodium alginate was obtained from ZAO "ArialBio" (Moscow, Russia). All other reagents used were of analytical grade.

In this work ultrasound generator IKASONIC U50 control (Germany) was used with US 50-3 Sonotool nozzle which allows treating liquids and solutions of the volume of up to 100 cm^3 and ultrasound intensity in the range of 92 up to 460 W/cm^2. The viscosity of alginate aqueous solutions was determined at a temperature of 35° C using Ubbelohde viscosimeter with the capillary tube inside diameter of 0.73 mm.

Result and Discussion

In recent years the practical interest to drug delivery systems (DDS) on the basis of polymer matrices has increased. Such systems have much more advantages comparing with traditional medicinal preparations. They are close to real food objects, have prolonged effect, are capable of the selective release of the drug on different parts of intestine and allow decreasing doses of drugs.

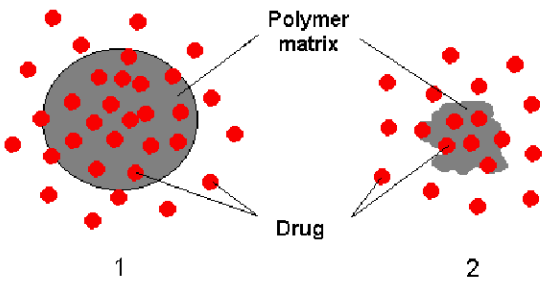

Fig. 1 Two groups of DDS

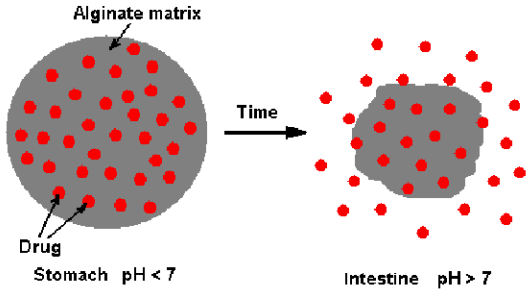

Fig.2 Schematic representation of biodegradable alginate DDS

The important condition of such systems development is the control of the drug outlet from the matrix-carrier. Drug delivery systems can be divided into two groups (fig. 1):

- systems where the drug yield is limited by the diffusion processes (1),

- systems where the drug yield is limited by the process of the polymer matrix destruction (2).

The most promising carrier for such systems development is matrices on the basis of alginates. The formation of an alginate matrix resulted from the interaction of sodium alginate and bivalent Ca^{2+} cations. Due to physical and chemical properties alginates are most often applied to the development of drug delivery systems. They are biodegradable, non-toxic and are not antigens. The most important advantage of the alginate matrix is that it is stable in a stomach acid medium and it protects the medicinal substance it contains. In an intestine alkaline medium alginate matrix dissolves (fig. 2). Thus, controlling the rate of the matrix dissolving it is possible to control the rate of the drug delivery to the organism.

The experiments showed that the most effective and simple method to influence the rate of alginate matrix dissolving is ultrasound. Ultrasound causes destruction of sodium alginate macromolecules the degree of which depends on the time of treatment and intensity of ultrasound. The depth of destruction was controlled over the change of macromolecules molecular weight (MW). It was determined from the Mark - Kuhn -Houwink equation relating molecular weight to the solution viscosity: $[\eta] = KM^{\alpha}$, where K = 0.002 and α = 1.0 (Smitsrod O. et al., 1971) – are constants for the sodium alginate – water system. The intrinsic viscosity was determined from the Solomon – Snuth equation: $[\eta] = \left(\sqrt{2}/c\right) \cdot \sqrt{\eta_r - 1 - \ln \eta_r}$, where η_r – is relative viscosity, c – concentration, g/cm^3. The viscosity of alginate aqueous solutions was determined at a temperature of 35^0 C using Ubbelohde viscometer.

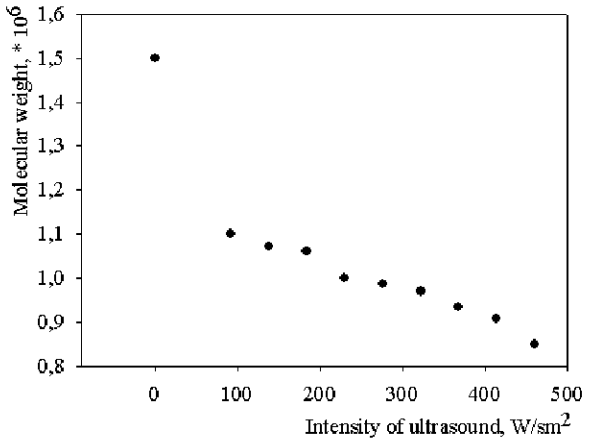

Fig. 3 The dependence of values of sodium alginate macromolecules MW on the intensity of ultrasound

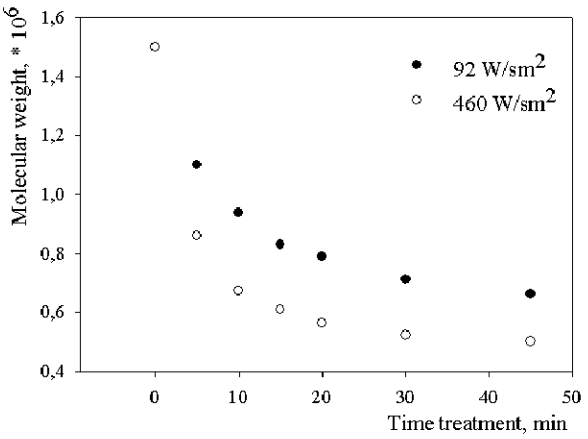

Fig. 4 The dependences of values of sodium alginate macromolecules MW on the time of ultrasonic treatment

In this work sodium alginate water solution with concentration of $1.5 \cdot 10^{-3}$ g/ml was used. The alginate of the indicated concentration is in the form of spherical Gartly micelles (Oberuhtina I. et al., 2001). To study the influence of ultrasonic intensity on sodium alginate macromolecules destruction a series of solutions (volume of 25 ml) was treated at various intensity of ultrasound. Time of ultrasonic treatment is 5 minutes.

The decrease of molecular weight occurs practically linearly, it is proportional to the increase of ultrasonic processing capacity (fig. 3). It confirms the fact, that the minimal molecular weight of polymer macromolecules for each intensity has definite value. Macromolecules with such molecular weight are not exposed for destruction any more. This fact proves to be true also by results of the experiments on the influence of the of time of ultrasonic processing on the viscosity of water solutions of sodium alginate.

Two series of sodium alginate solutions were exposed to ultrasonic treatment for the various time periods. The first series of solutions was treated by ultrasound with the intensity of 92 W/sm^2, the second - 460 W/sm^2. After this for each sample molecular weight was defined. In figure 4 the dependences of values of sodium alginate macromolecules molecular weight on the time of ultrasonic treatment are presented. After the 30-th minute the value of molecular weight practically does not change. Macromolecules with molecular weight of 0,662 · 10^6 and 0,502 · 10^6 at the intensity of ultrasound, accordingly, of 92 and 460 W/sm^2 are not exposed to destruction any more.

Thus, using ultrasound of a definite intensity, changing the time of treatment, sodium alginate with a definite molecular weight of macromolecules can be obtained. As alginate matrices properties directly depend on the properties of their structural parts, it is possible to obtain the matrices with definite characteristics.

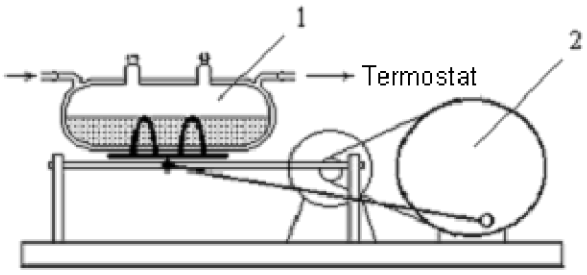

Fig. 5 Setup use for beads dissolving process studying (1 – reactor, 2 – stirring mechanism)

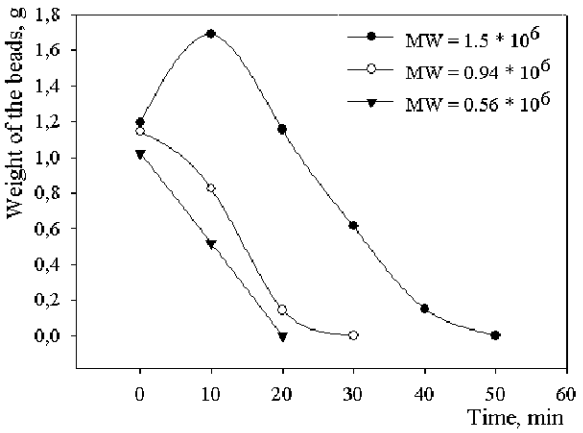

Fig. 6 Dissolving of beads on alginate basis with the different molecular weight

For studying the influence of ultrasound on alginate matrixes solubility three groups of beads on the basis of the sodium alginate treated by ultrasound with various intensity and time of treatment were prepared. The first group of beads was prepared from the raw sodium alginate solution. The time of ultrasonic treatment of the solution for the second group of beads was 10 minutes at the intensity of 92 W/sm^2, for the third group - 20 minutes at 460 W/sm^2. Thus, the molecular weight of alginate macromolecules is 1.5 · 10^6; 0.94 · 10^6 and 0.56 · 10^6, accordingly (table 1).

Group	Intensity of ultrasound	Time of ultrasonic treatment	Molecular weight
I	-	-	1.50 · 10^6
II	92.0 W/sm^2	10 min	0.94 · 10^6
III	460.0 W/sm^2	20 min	0.56 · 10^6

Table 1.

The research of beads dissolving process was carried out in the environments simulating stomach and intestine conditions. In the beginning beads were placed in 0.1 M solution of a hydrochloric acid (pH 1.0), at a temperature of 37^0 C for 1.5 h. After that, beads were plunged into the phosphatic

buffer (pH 7.4) (Dong L. et al., 1991). The rate of dissolving was controlled over the change of beads weight. To study the beads dissolving process the setup presented in figure 5 was used.

It is clear from the data presented in figure 6 that the beads obtained from alginate treated by ultrasound dissolved more quickly in comparison with the control samples. Full dissolving of beads on alginate basis with the molecular weight of $1.5 \cdot 10^6$ occurs by the 50^{th} minute, with the molecular weight of $0.938 \cdot 10^6$ - by the 30^{th} minute, and with the molecular weight of $0.565 \cdot 10^6$ - by the 20^{th} minute.

Conclusions

Thus, treatment by ultrasound causes destruction of polysaccharide macromolecules the degree of which depends on intensity and time of treatment. On the basis of the obtained alginate samples with known molecular weight it is possible to develop drug delivery systems with the set properties, able to be dissolved on narrow sites of a gastroenteric path and providing effective therapeutic effect.

Acknowledgement

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