ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Encapsulation of Antitubercular Drugs by Biopolymers and Polyelectrolyte Multilayers.

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ABSTRACT

The encapsulation of oral antitubercular drugs (ATDs) pyrazinamide, moxifloxacin and isoniazide by polyelectrolytic multilayers from a cationic polyelectrolyte chitosan and an anionic polyelectrolyte dextransulfate with use as a matrix of biopolymers - gellan, pectin and sodium alginate is carried out. The prepared capsules were studied by SEM analysis. The encapsulation efficiency and in vitro drug release were studied. It is shown that capsules possess prolonged action.
Keywords: antitubercular drugs, capsule, biopolymers, polyelectrolytic multilayers, controlled release.

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ISSN: 0975-8585

INTRODUCTION

The problem treatment of drug resistant tuberculosis (DR-TB) is difficult and actual. The standard of treatment of DR-TB has provided reception by the patient of 6 antibiotics, i.e. 20 tablets each day. It causes heavy side effects because of the formation of toxic products in organism as a result of drugs interaction. It is important that any drugs were dissolved in a gastric, and others were soaked up in intestines that leads to the increase of bioavailability, reduction of a dosage, and decrease in toxicity [1].

Recently, the possibilities of the usage of different drug delivery systems (DDS) for ATDs has been more studied: polymeric composites, microparticles, nanoparticles, liposomes, the hollow and filled capsules [2-12].

As a model ATD rifampicin has been more studied [5-8, 11-12].

Evaluation of three first-line antituberculosis drugs (rifampicin, isoniazide, and pyrazinamide) co-encapsulated in PLGA NPs was carried out by Pandey et al [10]. Authors [11] have prepared the chitosan-alginate microcapsules containing ATD rifampicin, isoniazide or pyrazinamide in the ratio drug: alginate: chitosan 1:2:2. They have shown that drug release from microcapsules happens within 72 hours.

In the literature some results of the inclusion of ATDs in multilayer capsules are described. So, rifampicin was included in multilayered capsules at pH=2 to the capsules of polyvinylpirrolidone and poly(methacrylic) acid formed by 8 layers having several microns size. In neutral media, up to 90% of the preparation was released [8]. Note, that this system is stabilized by H-bonds, not by ion pares between the polysaccharides.

However, there are very few literary data on encapsulation of antitubercular drugs by polyelectrolytic multilayers. In [12] chitosan-dextran sulfate hollow capsules were prepared by LbL-technique using silica particles. After five bilayers were adsorbed, the coated particles were subjected to treatment with 1 M HF to remove silica cores. Anti-tubercular drug, rifampicin encapsulated into prepared hollow capsules. The microcapsules exhibited sustained release of rifampicin over 72 hours at pH=1.2 and pH=7.4.

The aim of this work are encapsulation of antitubercular drugs in the biopolymers coated with polyelectrolytic multilayers, and evaluation of drug release at values pH, modeling various sites of a gastrointestinal tract (GIT).

MATERIALS AND METHODS

The natural polymers: low-acetylated gellan (China producted), LM (low methoxyl) pectin, and sodium alginate (Sigma-Aldrich) were used as the containers for capsules. For preparation multilayers cationic polyelectrolyte chitosan (Hit) water-soluble, ≥ 8000 Da (Bioprogress, Moscow), anionic polyelectrolytes sodium dextran sulphate (DS), 500 kDa (Sigma-Aldrich) were chosen.

Substances of antitubercular drugs isoniazide and pyrazinamide (Shanghai International Pharmaceutical Co producted), a moxifloxacin hydrochloride (Pavlodar Pharmaceutical Plant, Kazakhstan producted.

Drug containing capsules were prepared by ionotropic gelation. Biopolymer solution (gellan, pectin or sodium alginate) was heated with drug solution to 90 °C. The prepared mix on drops was brought in calcium salt solution.

The encapsulation efficiency was determined by Pharmacopoeia methods: pyrazinamide and moxifloxacin on the spectrophotometer (Specord 210, Germany) at 268 nm and 295 nm, isoniazide by a bromatometric method [13].

The coating of capsules by polyelectrolytic multilayers was carried out by LbL-technique, consistently immersing them in water solution of a chitosan and in dextran sulphate solution in sodium chloride. After

immersion in each polyelectrolyte capsules twice washed distilled water. This procedure was repeated by 5 or 10 times. Thus, 5 or 10 bilayers of oppositely charged polyelectrolytes have been formed.

Dzeta-potential of each polyelectrolytic layer was measured by dynamic laser light scattering method on the Malvern Zetasizer Nano ZS90 (Great Britain).

The surface morphology of the capsules was studied by scanning electronic microscopy on a low-vacuum raster electronic microscope of "JEOL" of JSM-6390 LV (Japan).

In vitro drug release studies carried out according to Pharmacopoeia requirements [13], using the dissolution apparatus (Erweka, Germany) at temperature (37 ± 0.5) ºC and the rotation speed 100 rpm. The tests were performed at gastric pH (0.1N HCl, pH=1.2) and intestinal pH (phosphate buffer, pH=7.4). Pyrazinamide, moxifloxacin and isoniazide concentration were determined by UV-Visible spectrophotometric method at 268, 295 and 263 nm.

All quantitative analyses were repeated 3 times.

RESULTS AND DISCUSSION

Optimum concentrations of drugs, biopolymers and polyelectrolytes are picked up. For encapsulation 0,01 g/ml solution of pyrazinamide, 0,02 g/ml solutions of a moxifloxcin and isoniazid are used. Optimum concentration of biopolymers are: 1% and 3% gellan solution, 1% and 2% pectin solution, 2% and 3% sodium alginate solution. 0,5% water solution of a chitosan, 0,5% dextran sulphate, 0,5% eudragit solution in sodium chloride were used.

It is known that ionotropic gelation happens in the presence of metal salts. It is revealed that the optimum environment for capsules preparation is the solution of bivalent metal salt. We have chosen 1% solution of calcium chloride.

It is found that alginate capsules need to be prepared only at pH =5, at other pH values the prepared capsules were unstable.

Drug containing spherical capsules of size around of 1,5-2,0 mm were prepared. Capsules were kept within 10 min in calcium salt solution, then passed through a sieve and washed twice in the distilled water and dried on air at the room temperature. The solution was used for determination of encapsulation efficiency.

In fig. 1 the SEM microphotographs of the capsule are presented. On the right, the border between gellan and polyelectrolytic multilayers is clearly visible.

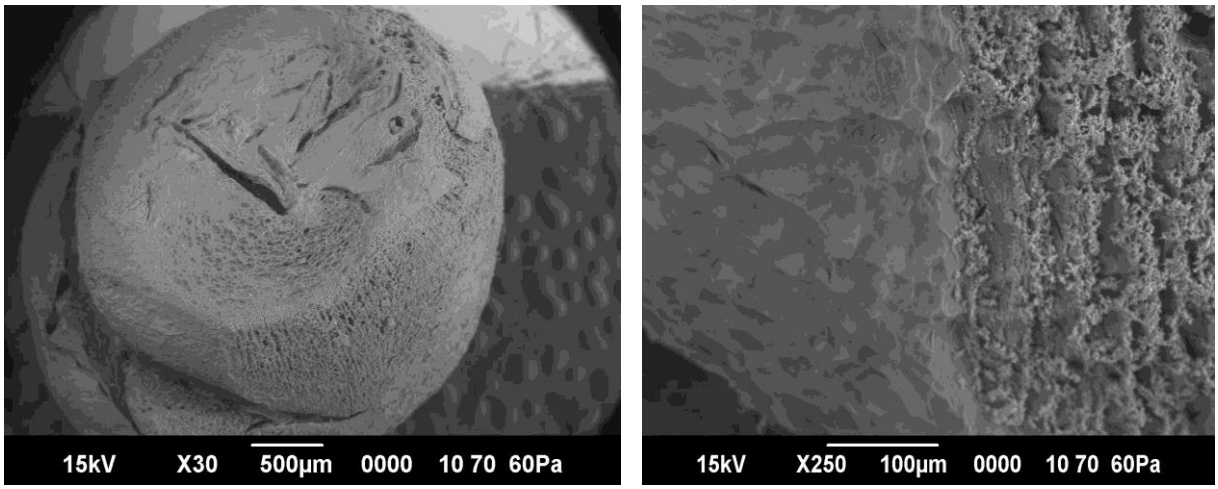

Fig. 1: Gellan-isoniazide capsule is coated by polyelectrolytic multilayers of chitosan and dextran sulfate

ISSN: 0975-8585

Results of encapsulation efficiency determination are given in table 1.

Table 1: Encapsulation efficiency (%)

Capsule matrix	Drug		
	pyrazinamide	moxifloxacin	isoniazide
1% gellan	22,67 ± 1,44	31,00 ± 2,49	26,33 ± 1,44
3% gellan	25,00 ± 2,49	49,67 ± 1,44	22,00 ± 2,49
1% pectin	17,00 ± 3,05	39,00 ± 2,49	35,33 ± 1,44
2% pectin	46,33 ± 1,44	51,67 ± 1,44	35,67 ± 1,44
2% alginate	24,33 ± 4,54	30,07 ± 2,61	13,72 ± 4,41
3% alginate	26,53 ± 3,09	50,60 ± 1,64	19,43 ± 2,93

Apparently from the table 1, generally encapsulation efficiency increases with the increase of biopolymer concentration. Encapsulation efficiency increases among isoniazide<pyrazinamide<moxifloxacin.

At pH =1.2 within 2 hours drugs weren't released from the capsules. At pH =7.4 extent of drug release (%) without coating polyelectrolytic multilayers has made of capsules in 4 hours about 30% of active agent, in 8 hours – about 50%, for 12 hours – more than 80% (pH =1,2, pH =4,5 and pH =6,8). Prolongation has made 12 hours. The drugs stated above are applied daily once a day. The therapeutic dose remains in an organism of patients within 12 hours. Prolongation of 12 hours provides presence of therapeutic doses within a day. However such extent of prolongation is insufficient for ATDs as they are very toxic.

In case of the capsules coated with polyelectrolytic multilayers (5/10 bilayers of each polyelectrolyte) at pH =7.4 more prolonged release was observed: in 6 hours is released by 34/30% of active agent, in 12 hours – 55/50%, in 18 hours – more than 87/80%. In this case prolongation is over 18 hours, 1,5 times more, than without multilayers. The prolongation is longer if more number of bilayers.

Initial active ingredients pyrazinamide, moxifloxacin and isoniazide are quickly dissolved and quickly soaked up in GIT and also quickly removed from an organism. Therefore, patients are forced to accept them daily. The developed prolonged shape will be kept by therapeutic concentration a long time, so it is possible to reduce the frequency of drugs, using that will lead to decrease in toxic effects.

CONCLUSIONS

Thus, encapsulation of ATDs by biopolymers and polyelectrolytic multilayers by LbL-technique was carried out for the first time. The safe biodegradable and biocompatible polymers were used for encapsulation.

Successive absorption of the oppositely charged polyelectrolytes from the solutions yielding polyelectrolyte multilayers, so-called Layer by Layer deposition, or LbL-technique, has led to the encouraging results. Encapsulation was performed in aqueous solutions at room temperature without costly or special apparatus.

Encapsulation efficiency is 20-50%, the greatest encapsulation efficiency is found for a moxifloxacin. Studying ATDs pyrazinamide, moxifloxacin and isoniazide controlled released at intestinal pH.

It is shown that polyelectrolytic encapsulation leads to the creation of the prolonged forms of ATDs for oral use.

ACKNOWLEDGEMENTS

This study was performed with the financial support of the Ministry of Education and Science of the Republic of Kazakhstan, grant №0794/ GF4.

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