Macromol. Symp. **127**, *251–256 (1998)*

SYNTHETIC AND NATURAL POLYMERS AS DRUG CARRIERS FOR TUBERCULOSIS TREATMENT

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Abstract Drug forms based polymer carriers of prolong action were created for toxicologic effect of drug to be reduced in spite of long treatment of diseases. In present work a number of synthesis and natural polymers have been studied as carriers of antituberculous drugs for controlled delivery application. Following as drugs as isoniazid and ethionamide were incorporated into polymeric matrix (segmented polyurethanes, polyvinyl alcohol) and chemically bound with the polymer chain by covalent or electrostatic forces (aldehyde- and carboxymethylderivatives of polysaccharides). Biodegradation of polymeric systems and the release of drugs were studied by various physico-chemical methods. It was shown that the drug release depends of method of the immobilization, type of the drug/polymer bonding, drug loading. The bacteriostatic activity of obtained systems was determined. The possibility of tuberculosis treatment was proved in experiments of animals.

INTRODUCTION

The traditional treatment of chronic microbial tuberculous disease extends over long period and requires administration of large doses of chemotherapeutic drugs [1]. Thus are lead to develop microbial drug resistance and toxico-allergic side effects.These drawbacks can be remove by the use polymeric drug delivery systems [2,3]. Controlled release drug delivery systems attempt to alter drug absorbtion and subsequent drug concentration in blood by modifying the drug release rate from the device. This leads to reduce fluctuations in the plasma drug concentration, sustained drug effects with less side effects and increased patient compliance [4,5].

Controlled release dosage forms are consisted of the pharmacological agent and the polymer carrier that regulate its release. In general two types of drug delivery systems have been used: diffusion-controlled systems and dissolution-controlled systems [5]. In the

 CCC 1022-1360/98/$ 10.00

first case the drug is usually dispersed or dissolved in the solid reservoir or membrane and the kinetics of drug release are generally controlled by diffusion through the polymer. In the second case the drug are generally incorporated into a water-soluble or water-swellable polymer and the release of drug are controlled by swelling and dissolution of polymer. In the both cases polymer function is a principal component which controls the transport and the release rate of drug molecule [5].

A wide variety of natural and synthetic polymers have been used as carriers of pharmaceutical agents. To be a useful drug carrier, a polymer needs to possess certain features. The polymeric carrier has to be non-toxic, non-immunogenic and biocompatible; the carrier must contain an effective dose of active agent; the material of system must biodegradable and/or form biologically acceptable degradation products; the rate of drug release from the carrier must occur at an acceptable rate; the carrier must be able to be easily sterilized. A number of natural polymers like polysaccharides and synthetic polymers like segmented polyurethanes has been successfully used as polymeric drug carriers [6-8].

The objective of this paper is evalution of some natural and synthetic polymers as carriers of antituberculous drugs for controlled delivery application. The drug used in the investigation were isoniazid, kanamicin and ethionamide. The mechanism of drug release from polymeric systems based on natural polysaccharides and some synthetic polymers such as polyurethanes and polyvinyl alcohol have been also studied. Some medical-biological test of obtained polymeric drug delivery systems were carried out.

RESULTS AND DISCUSSION

Among many natural polysaccharides using as drug carriers pectin and its derivatives has considerable interest [6]. Pectin are colloidal polygalacturonic acids in which some of the carboxylic groups are esterified with methyl groups. Pectic acid is a low-methoxycal pectin in which only a few alacturonic acid units are esterified. In our investigation pectin and pectic acid were used as carriers of tuberculous drug - isoniazid.

The aldehydederivatives of polysaccharides were synthesized by interaction with periodic acid. The content of aldehydegroups were 10-12%. The interaction of isoniazid

with aldehydepectins was carried out in water during 1h. It was shown that the degree of binding is 90-95% at polymer/drug ratio 2/1. The presence at the structure of pectins carboxylic groups permit to bind drug by electrostatic forces. The interaction of isoniazid with polyelectrolytes was carried out at 80-95% yield during 20-24h. In the obtained polymeric systems antituberculous drug was attached to the pectin derivatives through labile covalent or ionic bond.

One of the main characteristics of drug delivery systems is the program of drug release to the body. In this connection, the release behavior of isoniazid from pectin derivatives was studied by immersing polymeric samples into modelling biological media at 37^{0}C. It was shown that dosed drug release occurs in accordance with first order equation. The isoniazid release takes place with 80-95% yield during 2-4 days and depends on the nature of chemical bonds and biodestruction of the polymer matrix. The typical example of release profile are presented in fig.1.

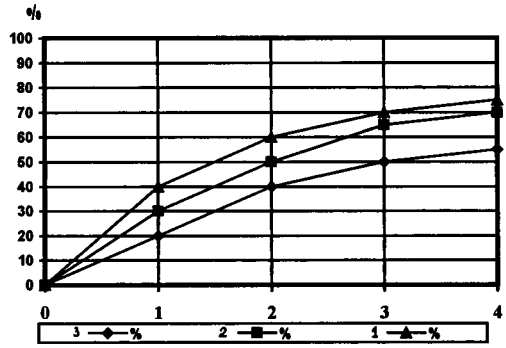

Fig.1. The Release of Isoniazid from Pectin Derivatives (Days) into Phosphate Buffer pH 7.4 at 37^{0}C.
1-aldehydepectin; 2-aldehydepectic acid;
3-pectic acid.

Medical-biological tests for the polymeric drugs on the pectin base were carried out. It was shown that isoniazid complex with pectin derivatives is 1.5-2 times less toxic in comparison with the low molecular drug. The investigation of tuberculostatic activity of obtained polymeric drugs show there action concerning Mycobacterium tuberculosis is on

the level of free drug. Minimal toxic action of polymeric device on the native organism tissue was established hystologically.

The polyvinyl alcohol (PVA) is the only polymer which has the carbon-carbon backbone chain degradable by bacterial enzymes. Besides, one and its fragments do not possess toxic effect and are easily taken out from the body. That way, PVA is a excellence carrier for drug delivery, because one is used in our research.

PVA, purchased from Serva, Switzerland were used without further purification. The aquatic solution of PVA was obtained with the addition of PVA's portion in the water. The solution receipt was carried out with the mixing, until being completely dissolved, at 80^{0}C. After cooled to the room temperature, the weighed portion of isoniazid was introduced in the PVA's solution. The solution having been obtained was put on the Petri dish and was being dried to a constant weight. The device has been a thin transparent film. The drug release from the film in the constant volume of a modelled biological media in presence or without mixing at 35^{0}C was carried out. A release kinetics of drug was determined with UV-spectroscope on the fixing length of wave at 262 nm. The results have been shown on the fig.2.

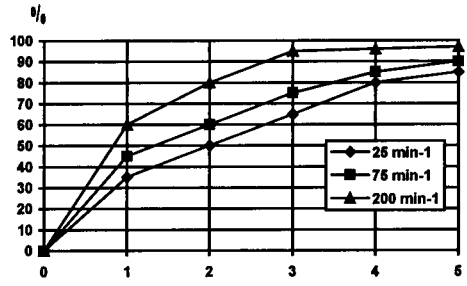

Fig.2. The Release of Isoniazid from PVA's Film (Days) into the Ringer-Lock Solution at 37^{0}C with Various Mixing.

The use of segmented polyurethanes as biodegradable carriers in drug delivery systems is of considerable interest. Such systems are being used for sustained and controlled delivery of various pharmaceutical agents [8]. In our investigation we

used segmented polyurethanes as carriers of isoniazid and ethionamide. Polyurethane films were synthesized by a two stage process from polyoxypropylen glycol (molecular weight 2000), toluene-2-4-diisocianate. Incorporation of the antituberculous drugs into polymeric films was carried out on the stage of film preparing. In synthesized samples pharmaceutical agents were dissolved in a solid polymeric matrix. The biodestruction of films containing drugshas been studied. The samples were held into modeling biological media (physiological and Ringer-Lock solutions) and in definite periods of time the films were taken out, washed and dried. Some physical-mechanical properties such as the breaking strength, relative elongation were determined for the initial films and those taken from the model media. It has been shown the hydrolysis is most rapid in the polyurethane films containing isoniazid, while samples with ethionamide is more stable. For the release studies the polymeric films were immersed into modeling biological solution at 37^{0}C. It was shown the release rate is generally controlled by the diffusion phenomena through the polyurethane matrix. The dosed release of isoniasid takes place during 2-3 days, and ethionamide releases from films during 3-4 days (fig.3). The release rate depends of a drug loading. The increasing of initial drug concentration in film from 50 to 200 mg/g resulted in an increase in the drug release rate.

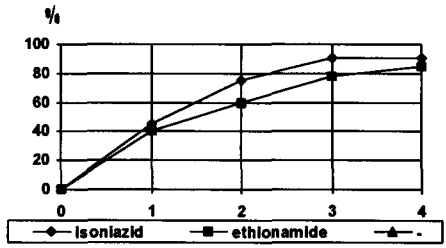

Fig.3. The Release of Isoniazid and Ethionamide from Segmented Polyurethane (days) into the Phosphate Buffer Solution pH 7.4 at 37^{0}C.

The tuberculostatic activity of isoniazid and ethionamide released from the polyurethane films was determined. It was shown drugs introduced into polyurethane films have antimicrobial activity identical of low molecular drugs. The efficiency of the

tuberculous treatment by polyurethane drug delivery systems was shown in experiments on animals. The use of polyurethane carrier provides a stable bacteriostatic concentration of the chemotherapeutical agents for 5-7 days.

The results obtained in the present work have shown the possibility of using some natural and synthetic polymers as carriers of antituberculous drugs for the delivery systems for prolonging the action of chemotherapeutical agents in tuberculous treatment.

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