RELEASE OF ANTITUBERCULAR DRUG FROM POLYURETHANE

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Abstract

The sustained release of antitubercular drug ethionamide from synthetic polymer polyurethane has been studied. The antituberculous effect of the obtained systems was tested against museum strain of *Mycobacterium tuberculosis*. The therapeutic action of polyurethanes containing ethionamide was studied in experiments on guinea pigs. Results demonstrated the possibility of application polyurethane for prolongation of action of antitubercular drug ethionamide.

Key words: sustained release, antitubercular drug, ethionamide, polyurethane.

Introduction

Polyurethanes are an important class of polymers that have found many applications as biomaterials due to their excellent physical properties and relatively good biocompatibility. Many biomedical devices are made from segmented polyurethanes such as catheters, blood pumps, prosthetic heart valves and insulation for pacemakers [1,2]. The use of soft polyurethane foams as carriers of antitubercular drugs is of considerable interest. In such systems pharmaceutical agents are dispersed or dissolved in the polyurethane carrier and the kinetics of drug release are generally controlled by diffusion phenomena through the polymer [3].

The main method of tuberculosis treatment is chemotherapy. Although current chemotherapeutic agents for tuberculosis treatment are therapeutically effective and well tolerated, a number of problems remain. The chemotherapy is burden some, extends over long periods and requires continuous and repeated administration of large drug doses. Thus, traditional drug chemotherapy has serious limitations because the increasing of microbial drug resistance and toxico-allergic side effects. These problems can be approached by the use long-acting Polymeric Drug Delivery Systems. The development of implantable systems containing the antituberculous drugs in combination with biocompatible polymers would make possible to achieve the significant progress in treatment of this global debilitating disease [4,5].

In the present study we report our investigations on the incorporation of the antitubercular drug ethionamide into segmented polyurethanes. The drug release characteristics of such systems and antitubercular effect of the drug loaded polymers will be discussed.

Material and methods

The polyurethanes used in this study was prepared using polypropylene glycol, toluene-2,4-diisocyanate and water by a two-step polymerization method. By varying the ratio of components polyurethane having different hard and soft segment contents was synthesised. Polypropylene oxide

with molecular weight M_{me}, = 2000, previously dried in a vacuum at 80°C for 3-4hr, was placed in a three-necked flask equipped with a stirrer, a thermometer and a tube for argon supply, then tolylene-2,4-diisocyanate was added. The molar ratio of polyol and diisocyanate was 1:2.5. The reaction proceeded at 110-115°C for 2 h in the argon flow. Briefly, the polyurethane was dissolved in an appropriated solvent and various amounts of antibiotics added to the solution. After careful evaporation of the solvent at 60° C in air, the drug containing films were furthermore evaporated for 24 h at reduced pressure to remove solvent completely. The polyurethane samples contained 100-300 mg of heterogeneously dispersed antitubercular drug. The release behaviour of ethionamide from polymeric samples was examined by means of immersing the disc-shaped samples of 0,3-0,5 mm thickness and 10,0 mm diameter in a Ringer-Lock solution at 37°C. The amount of drug released was determined by UV-spectrometry by measuring the absorption maximum. UV spectra were recorded on a Jasco UV/VIS-7850 (Japan) spectrophotometer.

Results and discussion

One of the main characteristics of drug delivery systems is the program of drug release to the organism. The release behavior of drugs from polyurethane materials was studied by immersing polymeric samples into model biological media at 37°C. All the release data show the typical pattern for a mtrix-controlled mechanism. The cumulative amount of drugs released from the polyurethane was linearly related to the square root of time and the release rate decreased with time. The process is controlled by the dissolution of the drug and by its diffusion through the polymer. The release is described by Fick's law and proceeds by first-order kinetics. The total amount of ethionamide is released in 3-4 days, the release time for 50% of drug is 28-30 h. Increasing the drug loading from 100 to 300 mg/g resulted in an increase in the drug release rate.

The antimicrobial activity of drugs released from the polyurethanes was determined by diffusion into dense Levenshtein-Iensen nutrient medium compared with a museum strain of Mycobacterium tuberculosis. It has been shown that drugs introduced into a polymeric matrix have tuberculostatic activity on the level of free drugs. Ethionamide formed a microorganism growth delay zone of 35 mm.

The efficiency of tuberculosis treatment by polyurethanes containing ethionamide was studied in experiments on guinea pigs. Several groups of animals, consisting of 20-25 guinea pigs, were infected with a 6-week culture of a laboratory strain of *Mycobacterium tuberculosis*. Treatment was started 2 weeks after infection. Animals were treated by weekly administration of polyurethane containing 5-day doses of the drugs (PU-Eth), or by daily administration of a day's dose of ethionamide (Eth). Animals of the control group were not treated (C). The weights of the guinea pigs and the dimensions of ulcers at the site of infection were periodically determined during the experiment. All untreated animals died 1.5-2 months after infection. The animals of the other

groups were killed with ether 2.5 months after the beginning of the treatment. Guinea pigs were dissected and damage to lungs, livers, spleens and lymphatic ganglions was determined.

The experimental observations show that the treatment of tuberculosis in the animals by the polymeric systems gave the same therapeutic effect as daily treatment with single doses of the drug. The animals of the PU-Eth and Eth groups had the dissemination nidi in their inner organs practically cured: guinea pigs lost weight slightly (4·6 % and 1·2 %, untreated 30 %) and had small ulcers in the place of infection (3,0 mm and 3,2 mm in diameter. The treatment of experimental tuberculosis by the polymeric systems was analogous to daily treatment with free drugs. The use of a polyurethane carrier provides a stable bacteriostatic concentration of chemotherapeutic agents for 5-7 days. Clinical observations have shown the efficiency of polyurethane drug delivery systems for treatment of tuberculosis-infected cavities (wounds, pleural empyema, bronchial fistula). The results obtained in the present work have shown the possibility of using polyurethane as a matrix for drug delivery systems for prolonging the action of ethionamide in tuberculosis treatment.

Conclusion

In this study the incorporation of antitubercular drug ethionamide into polyurethanes were described. The effect of drug loading, polymer macrodomain structure on the release characteristics was discussed. The antibiotics loaded polyurethane systems might be useful for prevent foreign body infection. Medical-biological tests show that polyurethane ensures sustained release of antituberculous drugs and maintains effective drug concentration for long time.

References

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