CONTROLLED RELEASE OF FLUOROURACIL FROM POLYMERIC FILMS

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Abstract

The immobilization of anticancer drug fluorouracil on polymeric films is carried out. Drug release from polymeric forms is investigated. Drug containing polymeric films shows a high initial release rate and the matrix-controlled release for more 7-9 h. The release data depends on drug loading and polymer structure. The possibility of application of polyvinyl alcohol for prolongation of fluorouracil action is show.

Key words: drug release, fluorouracil, polymeric films, polyvinyl alcohol.

Introduction

Development of film dosage forms received from biocompatible polymers is actual area in pharmaceutic technology. The medical films containing various drugs widely applied in dentistry and ophthalmology. The prolonged effect in such films is reached by the immobilization of drugs on various polymeric carriers. The main advantage of medicinal films is possibility of the programmed delivery of drug by regulation of the nature of polymeric matrix. Using various methods it is possible to change the physical and chemical properties of polymer matrix and respectively the release of drug [1].

The cancer chemotherapy demands application of high doses of the drugs, often bringing to the toxic phenomena. One of solutions of this task is application of essentially new drug forms based on synthetic polymers [2, 3]. The most effective drug for cancer treatment is fluorouracil. It is low-molecular substance and its pharmacological effect is kept quickly.

The purpose of present work is development of polymeric medicinal forms with the controlled action by immobilization of the anticancer drug fluorouracil on polymeric films. The drug release characteristics of such systems are discussed.

Material and methods

The anticancer drug fluorouracil was used pharmaceutical grade. Polyvinyl alcohol (PVA) with MM 70 000 was purchased from Sigma Chemicals, St. louis, USA.

Polymeric films are received from the corresponding solutions of polymer and drug by water evaporation. The amount of PVA is filled with distilled water and maintained on magnetic mixer at temperature 80-90°C before full dissolution. The calculated amount of substance fluorouracil it

added to cooling at room temperature homogeneous solution of PVA. After stirring the received solution poured out in glass established horizontally and dried in at room temperature up to constant weight. The received medicinal form had an appearance of thin elastic transparent film from which by means stamp cut out squares 0,2-0,5 mm thick. Calculation of dose of drug was carried out from criterion of the minimum dose.

The release behaviour of drug 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

The development of new highly effective medicinal films intended for delivery of drugs in organism through mucous surface or skin is now intensively researched. Polyvinyl alcohol is widely used as polymeric carriers in medicinal films. This polymer already found application in medicine as emulsifier, thickener and stabilizer of suspensions, filming agent for capsules and tablets, bases for ointments [4].

We developed medical films on the basis of PVA containing various doses anticancer drug fluorouracil. Release of drug in conditions *in vitro* is investigated by means of the UV-spectroscopy method. It is shown that the drug which has been evenly dispersed in polymer is released on model solution on the diffusion mechanism with rate reduction. Process of diffusion is described by Fick's law and occurs according to kinetics of the first order.

Data on drug release from polymeric films are presented in the table. It is established that release process of fluorouracil from films in environment consists of three main stages: 1) water sorption by polymeric film and its swelling; 2) diffusion of drug in film on phases polymeric system - environment; 3) diffusion of drug in solvent volume.

Table - Release parameters of fluorouracil from PVA-films

Loading, мg/g	Time of 50% release, h	Time of max release, h	$Dx10^{-7}$, cm^2/s
25	2,5	6,5	3,9
50	3,0	7,5	3,6
100	3,5	8,0	3,2

Dependence of fluorouracil release lat various drug loading is studied. It is shown that fluorouracil almost completely diffused from PVA-films within 7-8 hours, without undergoing any changes. With increase in thickness of film the process of diffusion of drug is slowed down. The increase in loading of drug leads to delay of fluorouracil diffusion rate from the film.

All the release data show the typical pattern for a matrix controlled mechanism [5]. The cumulative amount of drug released from films was linearly related to the square root of the time and the release rate decreased with time. The process is controlled by the dissolution of drug and diffusion through the polymer in accordance with Fick law.

Duration of drug release from monolithic therapeutic systems considerably depends on the swelling of polymeric matrix. Dependence swelling degree of PVA-films from thickness of samples shown that the most optimum properties films 0,4-0,6 mm thick possessed. Such materials swelled for 55-60% within initial 0,5 hours with the subsequent achievement of the maximum value of 80% in 2 hours, thicker films very slowly swelled for 45-50% within 1,5-2 hours that didn't conform to medical requirements. Release of drug is limited by the rate of swelling and thickness of polymeric matrix.

Conclusion

In this paper the immobilization of anticancer drug fluorouracil on polymeric films is carried out and drug release from polymeric forms is investigated. The obtained data testify to possibility of use of synthetic polymer polyvinyl alcohol for creation of film medicinal forms of fluorouracil. The determined consistent patterns allow to predict drug release and to create polymeric materials with necessary rate of delivery drug in organism.

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