

Preparation and Characterization of Polyethylene Oxide Hydrogels with Cytisine

M. Dimitrov^{1*}, D. Dotcheva², N. Lambov¹

¹Department Pharmaceutical Technology, Faculty of Pharmacy, Medical University, 2 Dunav Str., 1000, Sofia, Bulgaria ²Institute of Polymers, Bulg. Acad. Sci., G. Bonchev 103A, Sofia 1113, Bulgaria

Abstract

This paper presents a study of the possibilities for preparation of hydrogel systems via UV initiated crosslinking of Polyoxyethylene oxide (Polyox). Cytisine was included as a model drug in the matrix. The investigations carried out in vitro have shown that the crosslinking of Polyox results in hydrogels, that swell within 120 ± 180 min and the loaded drug in them is with a retarded release. The Cytisine concentration in the matrix and the degree of crosslinking turned out to be the major factors determining the release rate.

Keywords: hydrogels; UV-irradiation; polyethylene oxide; cytisine

Introduction

The possibilities to control the drug release from hydrogel systems in a wide range have made these systems the subject of considerable pharmaceutical interest. Besides, the systems under question are the sole monolithic systems that under given conditions are able to release drugs at constant rate close to that of the reaction kinetics of zero order as a result from the Case II transport (Lindner *et al.*, 1996).

In the last decades, polyoxyethylene has been intensively studied as a carrier for the hydrogel systems.

The research interest in the latter systems is because of their unique properties, polyfunctionality and universal application, non-toxicity, and immunogenicity (Tsvetanov *et al.*, 1998).

Their advantages of technological point of view are in their good solubility both in water and many organic solvents, their ability to form PEO-salt complexes, their high mobility and their large exclusion volume in aqueous media (Tsvetanov *et al.*, 1998).

However, the matrix reveals a shortcoming when PEO based systems are prepared with retarded drug release, namely in the fact that the loaded drugs are released relatively rapid (more than 70% of the drug within 4-5). In our opinion, the crosslinking of PEO via UV or γ (⁶⁰Co) irradiation will give opportunities for retardation of the release process as it is reported by other authors (Minkova *et al.*, 1989; Belcheva *et al.*, 1996; Rosiak and Yoshii, 1999; Rosiak and Ulański, 1999).

It is known that with regard to the degree of addiction, Nicotine is the main mean in the process of giving up smoking (Benowitz, 1995). Our studies are carried out with Cytisine, an alkaloid comprising in the herb *Cytisus laburnum* L that belongs to the group of ganglion stimulating drugs. This substance manifests the same mechanism of action as Nicotine. After its resorption, Cytisine acts as Nicotine-replacing substance and thus shortens the time of interaction between Nicotine and the certain receptors in the organism (Schmidt, 1974; Petkov, 1982). Thus, the physical and psychological Nicotine addiction of the smokers can be gradually lessened and annulled.

* Corresponding author

The aim of the investigations is to study the possibilities for preparation and biopharmaceutical characterization of hydrogel systems with Cytisine based on UV-crosslinked polyoxyethylene.

Materials

Polyox-N 12 K of average molecular weight 1×10^6 was supplied by Sigma-Aldrich, Germany. Cytisine was purchased from Sopharma, AG, Bulgaria. Pentaerythritol triacrylate (PETA) was purchased from Aldrich. The materials were used as received.

Methods

The hydrogels containing Cytisine as a model drug were obtained by UV-irradiation of the films cast from methylene chloride solutions of Polyox in the presence of PETA as a crosslinking agent. The duration of the irradiation was 30 min. at 25° C (TQ 150 ORIGINAL HANAU high pressure 150 W mercury lamp). The UV-irradiation experiments were conducted in an inert atmosphere (Doytcheva et al., 2001).

Series of hydrogel matrices were prepared by variation in the amount of the components as follows:

Polyox	3,0 g;
Cytisine	0,03±0,25 g;
Weight ratio PETA/Polyox	0±10%

Disks with a diameter of 33 mm and ~200µm thick were cut from the prepared polymeric film and subjected to investigation.

In vitro release study of the matrices was carried out by using the Apparatus 5 – Paddle over disc method of USPXXIV (Erweka DT8, Germany), at a stirring rate of 50 rpm, 900 ml distilled water and a temperature of 37°C.

The amount of the released drug was determined spectrophotometrically (Hewlett Packard 8452 A diode array spectrophotometer) at $\lambda = 306$ nm

The degree of swelling of the matrix was determined by the dynamical weight method. For the purpose of the experiment, samples of the studied systems were put in 100 ml of distilled water and afterwards, at regular time intervals (0.5; 1; 2; 3; 4; 5; 6;h.), the sample mass was determined with an accuracy of 0.0001g.

The degree of swelling is calculated by the formula

$$H_t = M_t / M_c \times 100$$

where,

H_t -degree of swelling; (%)

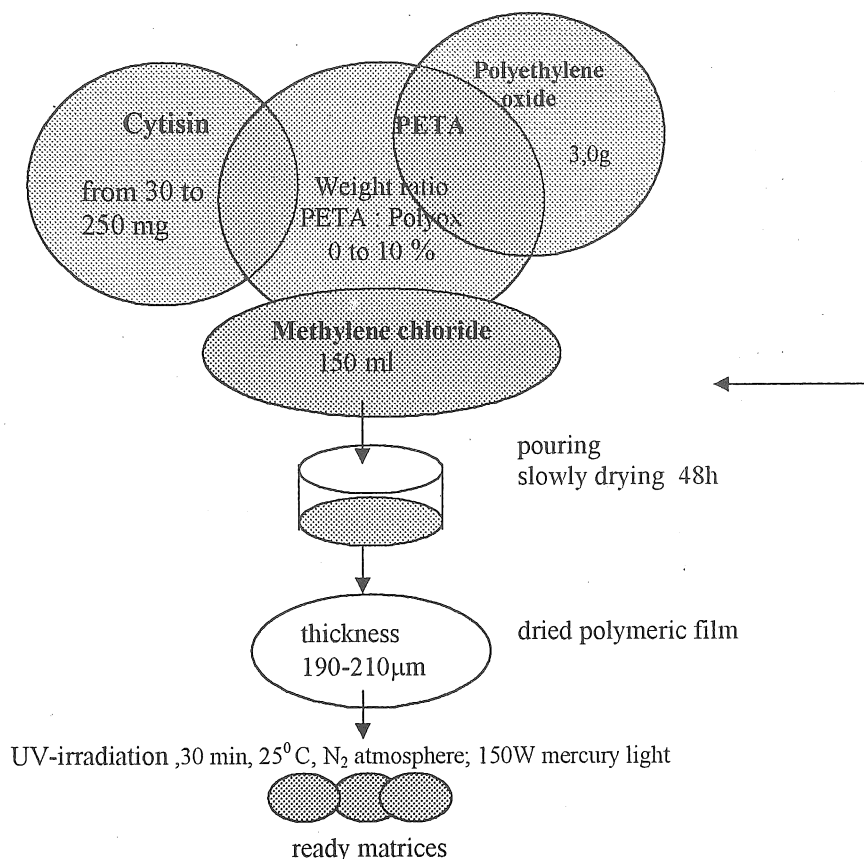
M_c - the weight of dry sample;

M_t - the weight of swollen sample at the moment (t);

Results and discussion

The optimum technological regime and the effect of its main factors that are shown in Scheme 1 were basely determined on a preliminary screening of the preparation of series of model Polyox based compositions.

Scheme 1. Preparation of Polyox matrices by UV irradiation



The prepared matrices are about $\sim 200\mu\text{m}$ thick and are able to swell in aqueous medium within $120\div 180$ min.

The evaluation of the possibilities to use UV-irradiated Polyox hydrogels as carrier systems with retarded drug release revealed the major factors that determine the release rate of the model drug.

Doubtless, the concentration of the model drug in the matrix is one of the important factors determining its release rate. Our investigations were carried out with hydrogel matrix crosslinked with 5% of the crosslinking agent PETA and comprising various amounts of Cytisine: 3; 10; 15; 30 mg (matrix weight 0,20 g). Similar dependencies have been observed for the rest matrices, obtained with different weight ratio PETA: Polyox.

The achieved results are presented in Figure 1. As it can be seen, the high drug concentration in the matrix (30 mg Cytisine) at constant values of the rest characteristics provides a more rapid drug release. The dissolution efficiency (DE) in this case is 85,6%. Meanwhile significant differences in the amounts of the released drug have not been found when the drug concentration is varied in the matrix in the range $3\div 15$ mg, and DE in these cases varies in the range $62,9\div 66,8\%$.

The major factors related to the matrix are the degrees of the crosslinking in the matrix and of swelling (Lambov *et al.*, 1997).

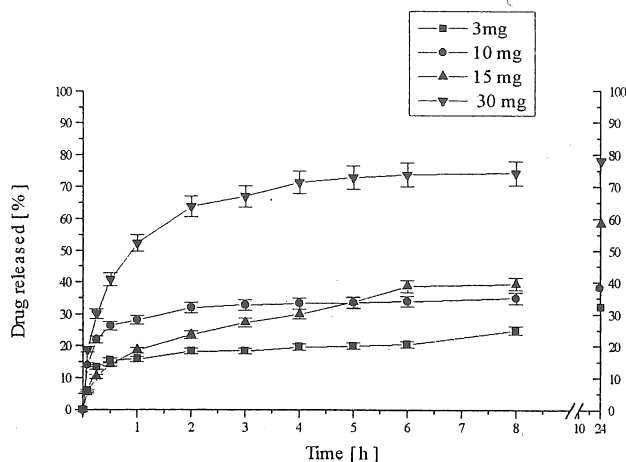


Fig.1 Influence of Cytisine amount on the drug release (weight ratio PETA: Polyox 5%)

The degree of crosslinking depends on the weight ratio PETA: Polyox. The effect of this factor was studied for hydrogel matrices comprising 15 mg Cytisine and with the variation of the amounts of the crosslinking agent PETA as follows: 0; 1; 3; 5; 10%. Figure 2 summarizes the obtained data. The variations in the Cytisine amounts within the investigated limits do not lead to changes in the determined dependencies.

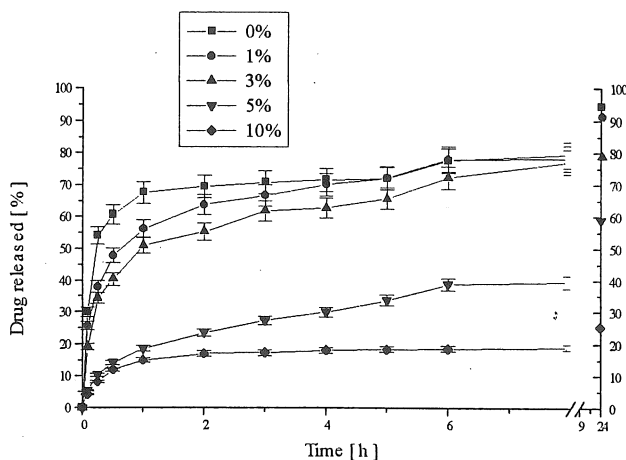


Fig.2 Influence of weight ratio PETA/Polyox (0,1,3,5,10 %) on the drug release (Cytisine amount in the matrix 15 mg)

It shows that with the increase of the amount of the crosslinking agent over 3% probably leads to a more dense polymeric network which ensures a greater retarding effect upon the drug release – DE in this case varies in the range 64,9 ÷ 67,36%, while its range at lower concentrations of the crosslinking agent (0÷3%) is in the range 85,1÷87,6%.

The augmentation of the amount of the crosslinking agent at a constant value of the rest characteristics provides more retarded drug release.

Obviously, the alternation of the amount of the crosslinking agent is a reliable way to conduct Cytisine release from the hydrogel matrices in desired ranges.

It is known that the swelling degree is a significant factor that determines the release rates of drug from hydrogel matrices. Preliminary investigations have shown that the swelling of our model matrices takes about 120÷180 min (Fig.3) .

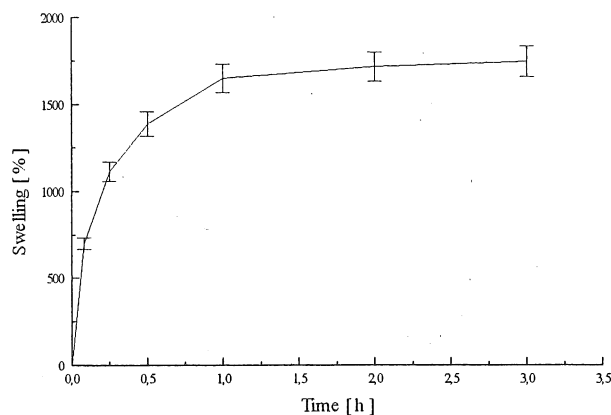


Fig.3 Swelling of Polyox matrices in distilled water weight ratio PETA:Polyox 5%;Cytisine amount in the matrix 15 mg)

The relatively short swelling period is an indication for the slight effect of this factor upon the drug release, which might be important only at the beginning of the release process.

Conclusions

The carried out experiments allow the conclusion that the main factors determining the drug release rate are the degree of swelling, the degree of crosslinking in the matrix and the amount of comprised drug. The swelling degree of the matrix affects the release process only at the beginning.

The Polyox based hydrogel matrices are suitable for the preparation of therapeutic systems with retarded drug release for prophylactic treatment of chronic nicotine addiction.

References:

- Belcheva, N., Stamenova, R., Tsvetanov, Ch., Lambov, N., Tsankov, St. and Smid, J.(1996). Crosslinked poly (ethylene oxide) for drug release systems. *Macromol. Symp.* 103: 193.
- Benowitz, N. L.(1995). Clinical pharmacology of transdermal nicotine. *Eur. J. Pharm. Biopharm.* 41: 168-174.
- Doytcheva, M., Dotcheva, D., Stamenova, R. and Tsvetanov, Ch. (2001). UV- initiated crosslinking of poly(ethylene oxide) with pentaerythritol triacrylate in solid state. *Macromol. Mater. Eng.* 286:30-33.
- Lambov, N., Dimitrov, M. and Tsankov, S. (1997). Biopharmaceutical study of cross-linked polyethylene oxide hydrogels. *Pharmazie* 52: 790-794.
- Lindner, W. D., Möckel, J. E. And Lippold, B.C. (1996). Controlled release of drugs from hydrocolloid embeddings *Pharmazie* 51: 263-272.
- Minkova, L., Stamenova, R., Tsvetanov, C. and Nedkov, E. (1989). Structural study of radiation-crosslinked poly(ethylene oxide). *J. Polym. Sci., Polym. Phys.* 27: 621-642
- Petkov, V.(1982). Contemporary Phytotherapy, Medicina and Fiskultura, Sofia, p.257.

- Rosiak, J. M. and Ulański P.(1999). Synthesis of hydrogels by irradiation of polymers in aqueous solution. *Radiation Physics and Chemistry* 55:139-151.
- Rosiak, M. J. and Yoshii, F.(1999) Hydrogels and their medical applications. *Nuclear Instruments and Methods in Physics research B* 151:56-64.
- Schmidt, F.(1974). Medicamentöse Unterstützung der Raucherentwöhnung. *Munch. med. Wschr.* 11:116.
- Tsvetanov, Ch., Stamenova R., Dotcheva D., Doytcheva M., Belcheva N., Smid J.(1998). Intelligent networks based on poly(oxyethylene). *Macromol. Symp.* 128:165-182.

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