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Hydrogels based on the chemically crosslinked polyacrylic acid: Biopharmaceutical characterization

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This study is an attempt at biopharmaceutical characterization of hydrogels based on crosslinked polyacrylic acid (PAA). Macrodiisocyanates (MDIC) or oligomethanediisocyanate (DO) were used as crosslinking agents. The drug release rate from such hydrogels is determined by a density of the net and is lowered by a decrease in the PAA : MDIC mass ratio. The increase of the drug concentration in the matrix improved the release process. The drug release from the hydrogels was found to be pH dependent.

Key words: hydrogels, polyacrylic acid network, crosslinking, macrodiisocyanates, drug release

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Hydrogels are well known as networks of hydrophilic polymers, which can absorb a significant amount of water (> 20% of their dry mass) without dissolving or losing their structural integrity (1, 2). The networks can be formed by various methods: γ-irradiation (^{60}Co) (3–7) or UV irradiation (8, 9) on different biomaterials. Chemically crosslinked hydrogels were developed in the last decades as carriers for drugs (10). The controlled drug delivery devices assure a sustained release and targeted effect (11). The great advantage of the drug-controlled release from the mentioned hydrogels is a possibility for improvement of patient compliance (12). In recent years, the polyacrylic acid (PAA) and its copolymers have been often used as carriers in drug release systems, because of their multifunctional nature, unique properties and good biocompatibility (13).

The aim of the present work is to investigate the possibility of applying PAA-based hydrogels crosslinked by macrodiisocyanates (MDIC) (14) for retarded drug release.

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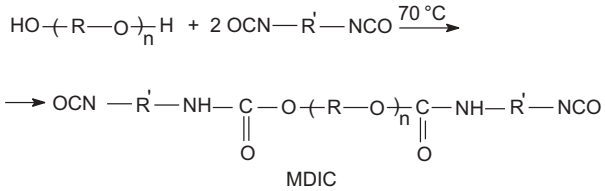
EXPERIMENTAL

Excipients

All studied drugs (nicotine, paracetamol, ethophylline, theophyline) were provided by Pharmachim (Bulgaria). Polyethylene glycols (PEG) with molecular masses 400, 600 and 1000, decamethylene diol (DMDO); polyoxytetramethylene glycol (PTMG) 1000 (also known as polytetrahydrofuran), were purchased from Sigma-Aldrich Chemie GmbH (Germany).

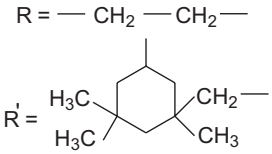
Methods

The synthesis and chemical characterization of chemically crosslinked PAA hydrogels were described in a previous paper (14). Macrodiisocyanates (MDICs) were obtained by reaction of dioles (PEG 400, 600, 1000, PTMG 1000) and isophorone diisocyanates in the molar ratio 1:2 according to the following scheme:

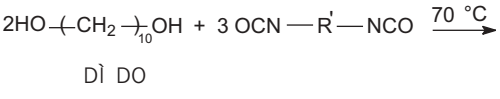


MDIC

where



The polymer net used in the current research was obtained on the basis of PAA crosslinked with oligomeric MDI. Oligourethanediisocyanate (DO) obtained through a chemical reaction of decamethylenediol (DMDO) and isophoronediisocyanates in molar ratio 2:3 was also applied as a crosslinking agent (15):



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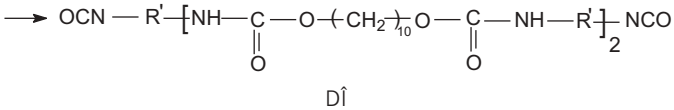

DÎ

The drug loaded polymer networks based on PAA were obtained by dissolving the drug in a mixture of MDI and PAA in various mass ratios in dimethylformamide (DMF) (70 °C for 24 hours, atmospheric pressure). The reaction was carried out until a constant mass of reaction mixture. The drug content in the obtained polymer network was 1, 5, 10 or 15% (*m*/*m*).

In the current research, the obtained polymeric material was divided into 6 symmetric, equal, separate pieces, each with a 35 mm diameter. Included drug was quantitatively determined in every piece. The total amount of the drug release from all six samples corresponded fully to the initial amount of the drug included in the polymeric system. The drugs were spectrometrically determined on a Hewlett-Packard 8452 A spectrophotometer (USA) (nicotine: λ_{max} = 260 nm, paracetamol: λ_{max} = 240 nm, ethophylline: λ_{max} = 276 nm, theophylline: λ_{max} = 270 nm).

The buffer solutions of pH 2, 5 and 7.4 were prepared by appropriate combinations of 0.2 mol L^{-1} solutions of hydrochloric acid, potassium biphthalate and potassium monobasic phosphate (16).

The drug release rate was determined by the paddle over disk method according to USP (16) using the Erweka DT8 (Germany) assembly. Dissolution medium was: 900 mL distilled water, gastric fluid without enzymes, or intestinal fluid at a stirring rate of 50 rpm.

RESULTS AND DISCUSSION

In a previous study (14), the authors described in detail the methods for the synthesis and studied the structure and characteristics of the polymer nets based on PAA and MDI containing polyethylene glycol chains. This paper aims to study the possibility of incorporating different drugs in a polymer net and investigating the influence of both the drugs and the polymer network on the drug release rate.

Drugs of various chemical structures and dissolution in water (paracetamol, ethophylline, nicotine and theophylline) were used as model drugs. The results obtained for

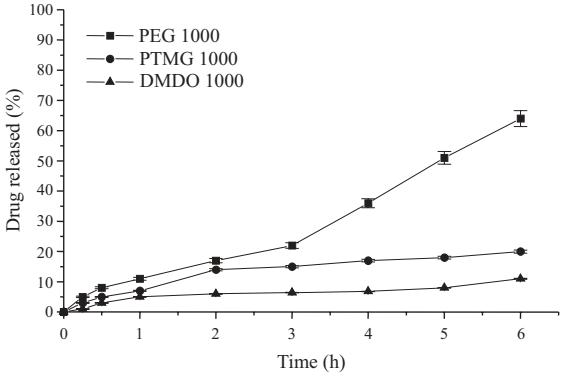

Fig. 1. Influence of the type of the crosslinking agent on the release rate of paracetamol. PAA : MDI = 1:1; 5% paracetamol of total network mass; each point represents the mean ± SD, n = 12.

the studied drugs allow us to assume that the chemical structure and dissolution in water do not have a significant influence on the drug release rate from the polymeric network. The main factors that determine the drug release from hydrogel systems are the network density and the amount of the loaded drug (17).

The results presented in Fig. 1 explain the effect of the crosslinking agent type: increase of the hydrophobicity of the crosslinking agent slowed down the release of the drug. For example, with a crosslinking agent prepared from polyethylene glycol (PEG) 1000 the highest amount of paracetamol was released (67% after six hours), wheras with a crosslinking agent prepared from DMDO 1000 the lowest amount of paracetamol was released (10.5% after six hours).

With the increase of the molecular mass of the crosslinking agent, the released amount of nicotine increased (Fig. 2): almost direct proportionality was followed. With MDI prepared form PEG 400 the released nicotine amounted to 42% after six hours, and from PEG 1000 it amounted to 66%.

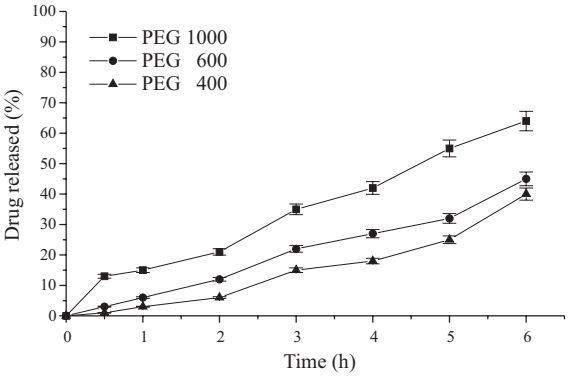

Fig. 2. Influence of molecular mass of the crosslinking agent on the release rate of nicotine. PAA : MDI = 1:1, drug amount 5% of total network mass; each point represents the mean ± SD, n = 12.

In the process of obtaining MDI diols of different chemical composition (PEG, PTMG) and DO, all of equal molecular mass about 1000 were used their chemical nature determined the different hydrophobicity of the chains. From Fig. 1 it is obvious that the chemical structure of the diol used to obtain MDI influenced the drug release, which decreased in the following sequence: PEG 1000 > PTMG 1000 > DMDO 1000.

The MDICs of different lengths chain determined by the different molecular mass of PEG (400, 600, 1000) were used as crosslinking agents. Fig. 2 shows that the drug release rate depends on the molecular mass of the crosslinking agent. With an increase of the chain length, the net density decreases, swelling increases, and the rate and the degree of the drug release also increase.

As it can be seen from Fig. 3, the amount of drug released increases with the increase of the mass ratio PAA : MDI. As expected, the increase in the amount of MDI crosslinking agent led to an decrease of the drug release rate.

The increase of the amount of the drug loaded enhanced the release process (Fig. 4).

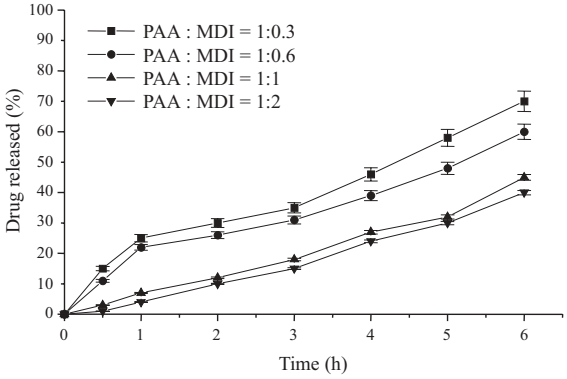

Fig. 3. Influence of mass ratio PAA : MDI of the crosslinking agent on the release rate of paracetamol, drug amount 5% of total network mass; each point represents the mean ± SD, n = 12.

This effect is not pronounced up to 5% of drug loading; the difference is negligible between 1% and 5%. The released amounts increased by almost two and three times with drug loading of 10 and 15%, respectively. The main reason for the observed effect might be the higher concentration gradient being responsible for a more efficient diffusion of the drug molecules through the hydrogel phase, while all other conditions were the same. Hence, changing the drug loading offers a real possibility of controlling the drug release.

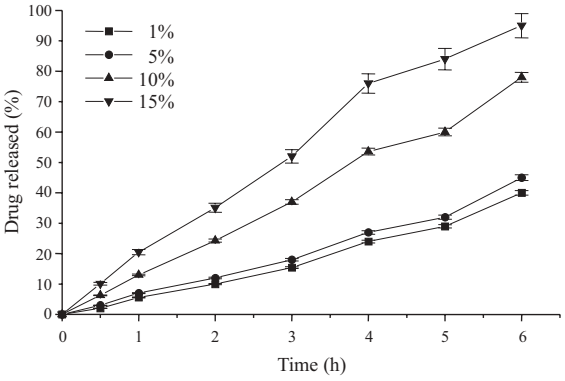

Fig. 4. Influence of the amount of paracetamol in the matrix on the release rate, PAA : MDI = 1:1; each point represents the mean ± SD, n = 12.

Fig. 5 demonstrates that the amounts of the drug released at pH 5 and pH 7.4 are different. This is explained by the fact that a hydrophobic complex between PAA and PEG units is formed at pH 5 (18). The existence of compact hydrophobic domains in the polymeric network hampers the drug release. However, at pH 7.4 a great part of PAA carboxylic groups are ionized. This leads to destruction of the complex and swelling of the network, resulting in full release of the drug. At pH 2 the complex is as stable as in the case of pH 5, but the amount of the drug released is bigger. The most probable rea-

son for this is the fact that in artificial stomach juice, namely at pH 2, the hydrolysis of the PAA network takes place at a higher rate and to a higher degree.

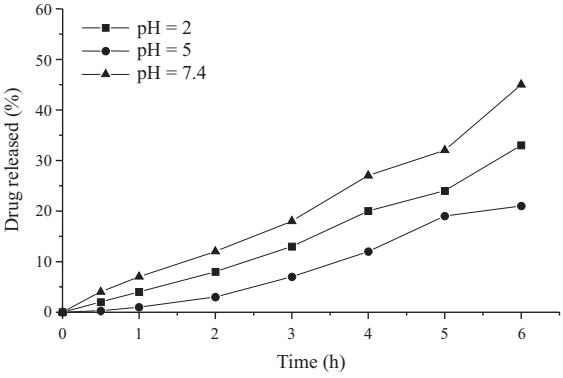

Fig. 5. Influence of pH on the release of paracetamol from the PAA hydrogel matrices, PAA : MDI = 1:1, drug amount 5% of total network mass; each point represents the mean ± SD, n = 12.

CONCLUSIONS

The chemically cross-linked hydrogels containing various drugs have been investigated. It can be summarized that the basic factors influencing the drug release are the type and the molecular mass of the crosslinking agents, the mass ratio PAA: MDI, drug concentration and the pH of the eluent. The studied systems provide retarded drug release and appear to be potential candidates for use in the pharmaceutical practice. Similar phenomena have been observed for all the drugs studied.

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S A Ž E T A K

Hidrogeli na bazi kemijski umrežene poliakrilne kiseline: Biofarmaceutska karakterizacija

MILEN DIMITROV, NIKOLAI LAMBOV, STOICHO SHENKOV, VENETA DOSSEVA i VLADIMIR Y. BARANOVSKI

U radu su biofarmaceutski karakterizirani hidrogelovi na bazi umrežene poliakrilne kiseline (PAA). Kao sredstva za umrežavanje upotrebljeni su makrodiizocijanati (MDIC) ili oligometandiizocijanati (DO). Oslobađanje ljekovite tvari iz takvih hidrogelova određeno je gustoćom umreženja i ovisi o pH medija. Oslobađanje se smanjuje sa smanjenjem omjera PAA i MDIC, a povećava s povećanjem koncentracije ljekovite tvari.

Ključne riječi: hidrogeli, poliakrilna kiselina, umreženje, makrodiizocijanati, oslobađanje lijeka

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