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Furazolidone Immobilized in a Hydrogel Based on Crosslinked Carboxymethyl Cellulose

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Abstract

The paper deals with the obtainment of a polymer-drug system with controlled release of the biological active principle, based on furazolidone included in a hydrogel obtained by crosslinking of carboxymethylcellulose with epichlorohydrine. The influence of temperature and duration of crosslinking reaction on the crosslinking degree of carboxymethylcellulose (indirectly appreciated by its swelling capacity in polar liquids as water and dimethylformamide/water mixtures) is studied. Kinetic data concerning the inclusion of furazolidone from solution, in the hydrogel of crosslinked carboxymethylcellulose, as well as the release of the drug from the obtained polymer-drug system, are performed. The obtained results evidence that the inclusion rate as well as the amount of furazolidone diffused into the support depend on the dymethylformamide/ water ratio utilized as solvent, and on the drug concentration in solution. The product obtained through the insertion of furazolidone from a DMF/water mixture = 5/1 (with a content of 8.9 mg drug/hydrogel) was studied as to the kinetics of the active principle's release, *in vitro*, by using as an eluent a buffer solution, which simulates the gastric fluid (pH = 2.4). The experimental results prove the obtention of a polymer-drug system with controlled release of the biologically active principle, conform to a *zero order* kinetic, in the time interval ranging between 3 – 12 hours.

Introduction

Most of the existing pharmaceutical agents are compounds with relatively low molecular weight, which penetrate rapidly cells of any type and are easily eliminated from the organism. That is why, in view of attaining the desired therapeutical effect, their administering in quite high doses, repeated at quite short time intervals, becomes a necessity, which might nevertheless induce some unfavorable secondary effects to the organism.

Drugs' association with macromolecular compounds modifies their release rate off the organism, making possible their releasing and, consequently, their prolonged action in time [1]. More than that, this occurrence reduces drug's processing by endocytes, and frequently orientates the drug towards a certain type of cells, *i.e.*, to a place where its action is required.

Obviously, the polymers selected as drug carriers should meet certain requirements, among which mention should be made of: simple synthesis ways, biocompatibility, lack of toxicity, biodegradability, easy elimination off the organism after accomplishing its function, high reactivity towards drug or special availability for its insertion [2].

Some of the most largely applied macromolecular supports, known as meeting all such requirements, are the natural polymer – based hydrogels [3-8]. They should have a high degree of swelling in water or in its mixtures with solvents of the active principle, as well as a high permeability to drugs, for facilitating their diffusion in and from the polymeric network.

The present paper analyzes the possible obtention of a polymer – drug system, the support of which is constituted crosslinked carboxymethyl cellulose and the active principle is N (5' nitro –2-furfuryliden)-3-amino-oxazolidine-2-one (furazolidone) [9]. The swelling properties of crosslinked carboxymethyl cellulose – based hydrogel in water/dimethylformamide (DMF) mixtures are studied, along with the kinetics of the processes of furazolidone's insertion and release

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from and, respectively, off the support with the highest swelling degree in water.

Experimental

Materials

Carboxymethyl cellulose (CMC) – Braila, (Romania), substitution degree, $\gamma_{DS} = 0.57$.

Furazolidone (F) – pharmaceutical product [10].

Epichlorohydrin (ECH) – "Victoria" Fagaras (Romania) 98% purity.

Method

Carboxymethyl cellulose crosslinking.

In a 50 mL Berzelius glass, 2 g CMC and 10 mL distilled water are introduced, and the mixture thus formed is vigorously stirred with a rod, up to the obtention of an uniform gel. 1 mL solution is then added, stirring being continued for 15 minutes, up to the gel's homogenization. Further on 0.8 mL epichlorohydrin are added, on stirring for other 15 minutes. The reaction mixture is then introduced into the oven, at the temperature and for the duration established in the experimental program.

After crosslinking, the reaction products are purified; this operation involves suspension in 1 L distilled water, under vigorous stirring for 5 hours, followed by supernatant's decantation.

The operation is repeated 4 times, after which the product is five times washed on a filter with portions of 200 mL distilled water heated at 50°C, up to complete removal of the natrium hydroxide. Washing on the filter with three portions of 30 mL ethylic alcohol is finally applied, followed by extraction on a Soxhlet apparatus, with ethylic alcohol, for 24 hours, for the complete removal of the epichlorohydrin traces.

The product is vacuum dried (at 50°C) and then jarred.

Study of the process of swelling in water

The synthesized products are studied from the viewpoint of the kinetics of swelling in water; to this end, precisely – weighed amounts of hydrogel (m_o, between 0.15 and 2 g) are introduced in closed small propylenic bags, which are weighed (m_1) and immersed periodically into a constant volume of distilled water, exact weighing being performed after each immersion (m_2).

The mass of water inserted into the hydrogel is given by the difference between the initial weight of the polymer – containing little bag and its weight after swelling.

The swelling degree at different times is calculated with the following relation:

$$\alpha_t\ (\%) = (m_2 - m_1/m_0) \times 100 \qquad (1)$$

Starting from the values obtained, the kinetic curves of swelling may be drawn, from which the constant of the swelling rate, K (min^{-1}), may be above calculated:

$$d\alpha_t/dt = K\times(\ \alpha_{max} - \alpha_t) \qquad (2)$$

By integration, the following relation is obtained:

$$-\ \ln(\alpha_{max} - \alpha_t) = Kt + const \qquad (3)$$

From the limit conditions ($t = 0$; $\alpha_t = 0$), there may be determined the value of constant, $const = -\ln\alpha_{max}$.

Substituting in relation (3) and processing the obtained equation, one may obtain:

$$\ln[\alpha_{max}/(\alpha_{max} - \alpha_t)] = Kt \qquad (4)$$

which may be represented, in coordinates: $\ln\alpha_{max}/\ln(\alpha_{max} - \alpha_t) - t$, as a straight line the slope of which constitutes the constant of the swelling rate, K.

Furazolidone insertion into the hydrogel

Study of drug's insertion into crosslinked CMC started with the selection of a hydrogel, synthesized through crosslinking for 9 hours, at a temperature of 60°C, and characterized by a maximum swelling degree, $\alpha_{max} = 669\%$ and $K = 5{,}632\times10^{-2}\ min^{-1}$.

Furazolidone's diffusion into the hydrogel was studied by utilizing a solution of furazolidone in DMF/water mixtures, at different values of the mixing ratio (DMF/water = 10/1, respectively, 5/1, in volumes). 0.2 g furazolidone is dissolved in a 30 mL mixture of solvents, followed by suspension of 0.2 g crosslinked polymer, under slight stirring. Periodically, for 24 hours, 0.2 mL supernatant subsequently brought to 100 mL with distilled water is collected; in the thus resulted solution, the amount of existent furazolidone is dosed photocolorimetrically.

Prior to this, the standard curve was plotted on the 0–2 mg/mL domain of concentrations, by photocolorimetring furazolidone solutions in DMF/water mixtures with concentration values within the

mentioned domain, at a 367 nm wavelength (UV – VIS Spektrophotometer, Spekord 71, Germany).

The standard curve is plotted in Fig. 1.

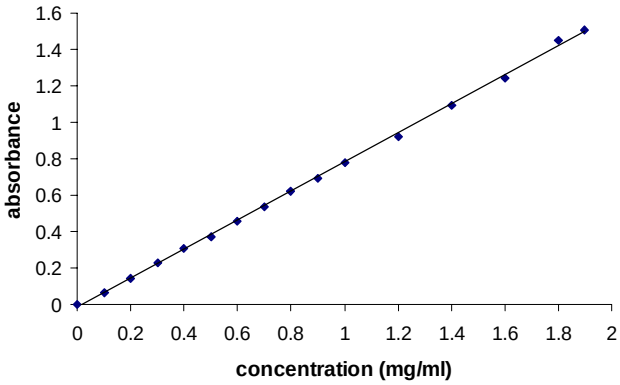


Fig. 1. Calibration curve for furazolidone solutions in DMF/water mixture (10/1 volumic ratio).

Release of furazolidone off the hydrogel

0.2 g furazolidone's insertion products are transformed, under the above mentioned conditions (*i.e.*, separated from the reaction mixture, dried and jarred), through pressing into tablet and introduced in the installation studying the kinetics of controlled release of the drugs immobilized on polymeric supports, represented in Fig. 2.

Through the installation there circulates an eluent, in our case, a buffer solution, which simulates the gastric juice (pH = 2.4), with a flow constantly regulated at a value of 0.0166 mL/s, which takes over the furazolidone released from the polymer – drug system, and is continuously concentrated (at a temperature of 37°C). Periodically (at time intervals between 0.5 – 2 hours), for 16 hours, from the installation there are collected 0.2 mL solution, each time, which are subsequently replaced with the same volume of fresh eluent.

The collected samples are diluted at 100 mL (with a DMF/water mixture, volumic ratio 10/1), then photocolorimetered at 367 nm wavelength.

Calculation of the furazolidone mass released in time is based on relations:

$$m_t = c_p V_l + \sum V_i C_i \ \ (g) \qquad (5)$$

$$V_i = (1/m) \times (\Delta m_t/\Delta t) \times (mg/g \times h) \qquad (6)$$

where:

- m_t – amount of furazolidone released at moment *t* (mg);
- c_p – furazolidone's concentration in the tablet;
- V_l – initial volume of eluent (40 mL);
- C_i – concentration of furazolidone released with the previous sample;
- V_i – volume of solution collected (0.2 mL);
- m – sample's weight in the form of tablet, taken into study;
- Δm – mass variation of the released furazolidone (mg);
- Δt – time interval between two collected successive samples (h).

Based on the data thus obtained, the kinetic curve of drug's release may be plotted, followed by plotting of the curve expressing the release rate's variation in time.

Results and discussion

CMC crosslinking with basically – catalyzed ECH, leads to the following structure:

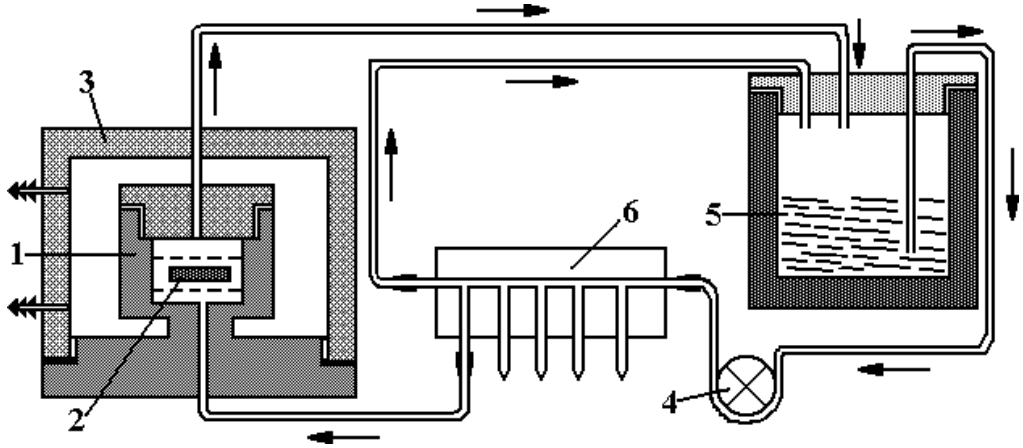
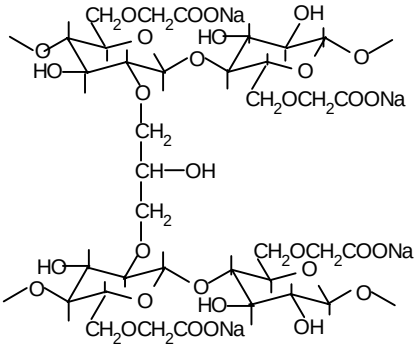


Fig. 2. Installation for the study of the release kinetics of drugs immobilized on polymeric supports. 1 – sample cell; 2 – tablet made of the product under study; 3 – thermostated cell; 4 – peristaltic pump; 5 –eluent reservoir; 6 – flow regulator.



Furazolidone's insertion involved selection of a hydrogel synthesized through reticulation at a temperature of 60°C, for 9 hours, the maximum swelling degree of which is practically attained after 60 minutes, at a value α_{max} = 669% (Fig. 3).

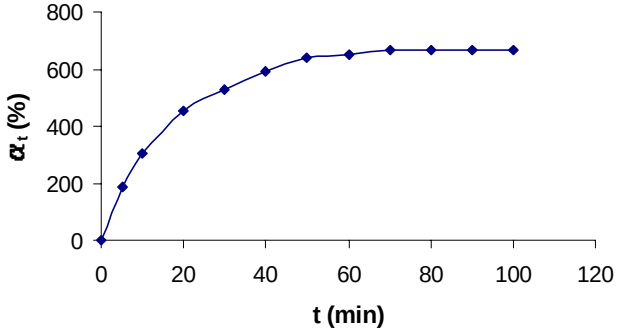


Fig. 3. Time variation of the swelling degree of a CMC – based hydrogel crosslinked with epichlorohydrin, obtained at a temperature of 60°C, for 9 hours.

Furazolidone was inserted into this support by the application of the previously – mentioned method, from solutions in DMF/water mixture, corresponding to two different volumetric ratios: 10/1 and respectively, 5/1.

Based on the standard curve for furazolidone (Fig. 1), the amount of drug diffused into the hydrogel – expressed in mg furazolidone/g support – was calculated. Its variation in time is presented, for the two DMF/water ratios, in Fig. 4.

A continuous increase, in time, of the amount of furazolidone inserted into the polymeric network is observed, at lower values for the DMF/water = 5/1 mixture (curve 2). A possible explanation might be the presence of a higher amount of water mixed with DMF, which results in hydrogel's stronger swelling, *i.e.*, a higher accessibility of the drug inside the three-dimensional network.

Starting from the results plotted in Fig. 4, furazolidone's diffusion rate through the hydrogel has been presented in Fig. 5.

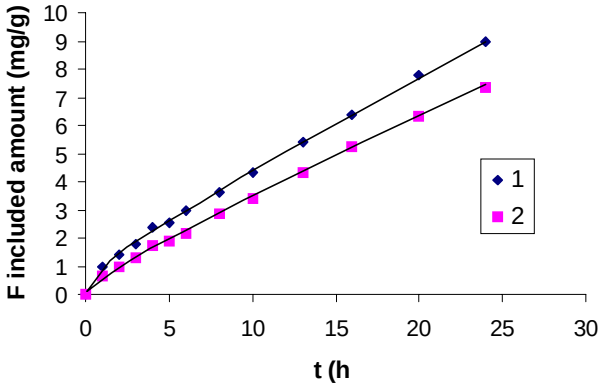


Fig. 4. Time variation of the amount of furazolidone inserted into the hydrogel (1 g) obtained through crosslinking at 60°C, for 9 hours, from 0.66 g F/100 mL concentrated solution. 1 – DMF/water = 10/1; 2 – DMF/ water = 5/1.

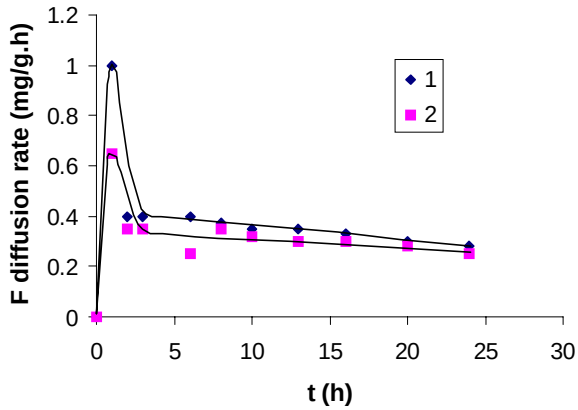


Fig. 5. Time variation of furazolidone's diffusion rate into a hydrogel (1 g) obtained through crosslinking at 60°C, for 9 hours, from 0.66 g F/100 mL concentrated solution. 1 – DMF/water = 10/1; 2 – DMF/ water = 5/1.

Obviously, higher values of the diffusion rate may be recorded if employing as a solvent a DMF/water mixture with the 5/1 component's ratio. The highest value of the process rate is recorded after 1 hour, which agrees with the variation of hydrogel's swelling degree, known as attaining its maximum value also one hour after the macromolecular support's immersion into the solvent mixture. Over this time interval, the simultaneous diffusion of both solvent and drug in the polymeric network occurs; in a subsequent stage, diffusion is controlled exclusively by the concentration gradient between the solution inserted into the polymer and the supernatant one, which explains rate's reduction and its situation at a practically constant value.

The aspect of the curves plotted in Fig. 4 suggests that the process of furazolidone's insertion may continue at longer durations, too, probably up to attaining an equilibrium concentration between the solution of the inserted drug and that of the supernatant. The product obtained through the insertion of furazolidone from a DMF/water mixture = 5/1 (with a content of 8.9 mg drug/hydrogel) was studied as to the kinetics of the active principle's release, according to the above discussed technique.

Figure 6 plots graphically the evolution of the amount of released drug (mg F/mg hydrogel), over a time interval up to 16 hours.

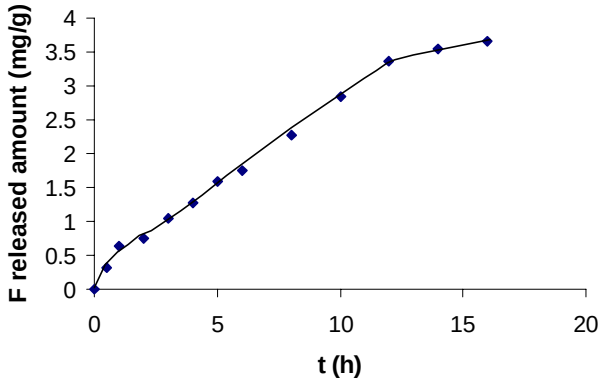


Fig. 6. Time variation of the amount of furazolidone diffused from the coupling product (1 g) through elution with a buffer solution simulating the gastric juice (flow regulated at a value of 0.0166 mL/s, temperature of 37°C).

From this curve, the time variation of drug's release rate was calculated and plotted graphically (Fig. 7).

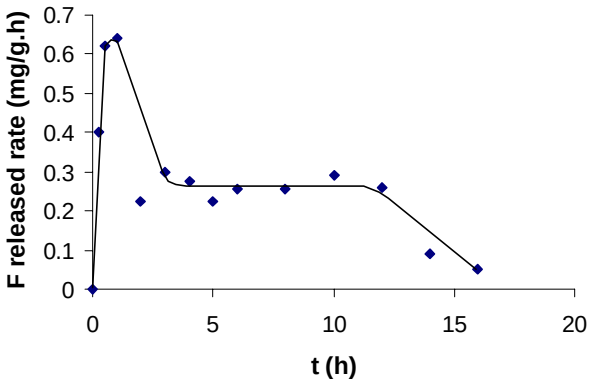


Fig. 7. Time variation of the release rate of furazolidone diffused from the coupling product (1 g) through elution with a buffer solution simulating the gastric juice (flow regulated at a value of 0.0166 mL/s, temperature of 37°C).

In this case, too, a maximum value of the release rate is to be noticed in the first 60 min of elution, corresponding to the attainment of hydrogel's maximum swelling degree, followed by its stabilization, practically over the 3–12 hour interval. Along this entire interval, the release is controlled, practically, only by the concentration gradient between hydrogel and eluent, which indicates the installation of zero order kinetics, characteristic to controlled release polymer – drug systems.

Conclusions

Carboxymethyl cellulose may be crosslinked with epichlorohydrin, in a strongly basic medium, the process being influenced by the reaction's duration and temperature.

Furazolidone may be inserted, through diffusion, in hydrogels of crosslinked carboxymethyl cellulose; the amount of inserted drug and the insertion rate depend on the DMF/water ratio in the mixture employed as a solvent.

Furazolidone is released through diffusion from hydrogel based on carboxymethyl cellulose crosslinked with epichlorohydrin, which suggests the reversibility of the insertion – release process.

Drug's release off hydrogels occurs according to a zero – order kinetics, which is indicative of the realization of furazolidone's controlled release from the crosslinked carboxymethyl cellulose, over a 3 – 12 hours interval.

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