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APPLICATION OF CARBOXYMETHYLCELLULOSE IN CONTROLLED DRUG RELEASE

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ABSTRACT

Controlled drug release was investigated by using Carboxymethylcellulose as carrier and erythromycin as model drug. Carboxymethylcellulose was chosen because of its biologically inert characteristics. It was crosslinked by ferric salts to obtain biodegradable beads. Controlled release was improved by coating with gelatin/caboxymethylcellulose and by crosslinking with ferric salts/chromium sulfate

INTRODUCTION

In last decades medical research activities were focused on the discovery of new and more efficient drugs. Another important point in this area is the delivery of drugs to specific locations in the body, and controlled release in that location to obtain a required drug level in plasma. The main reason of increased interest on controlled drug release from polymeric systems is the difficulty of adjusting drug level between minimum effective and maximum safe levels [1]. Among the different types of polymeric drug delivery systems biodegradable systems have the distinct advantage of not having to remove the

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drug-depleted device. In addition a drug release mechanism controlled by the biodegradation of the polymeric carrier offers the advantages of simplicity and versatility [2]. The development of biodegradable polymers during the last two decades has increased exponentially going hand in hand with new applications for such materials [3 - 7].

Sodium carboxymethylcellulose (CMC) is physiologically inert and used in food, pharmaceuticals, detergents, textiles, paper, paints and drilling muds. CMC is the most easily dissolving cellulose derivative but salts of CMC with heavy metal ions do not dissolve in water [8].

Aim of this work is to progress in development of a new drug delivery/release system by using physiologically inert material CMC. Ferric chloride (FC), ferric sulfate (FS) and chromium III sulfate (CS) were used to crosslink CMC and erythromycin was used as model drug. Parameters such as concentration of crosslinking agents, coating and second crosslinking were investigated to develop a method for the usage of CMC as a drug delivery/release system.

MATERIALS

Carboxymethylcellulose was purchased from SIGMA chemical Co., USA.

Gelatine was obtained from Croda Gelatine Co., USA.

Erythromycin was obtained from FAKO Pharmaceutical Co., Turkey.

Other chemicals are analytical grade and obtained from Merck, Germany.

METHODS

Preparation of beads: Appropriate amounts of erythromycin and CMC were dissolved in distilled water to obtain a solution containing 100 mg CMC and 10 mg erythromycin in 1 cm^3. 1 cm^3 Samples taken from previously mentioned stock solution were dropped into crosslinker solutions through an injector with an orifice of 1 mm diameter. Beads are rested in crosslinker solution {(FC)/(FS)} for

2 minutes and removed by filtration. Beads of 3 mm in diameter were obtained by this procedure.

Coating: Prepared beads were dipped in CMC (10 %, w/v)/Gelatin {(G); %7.5,w/v} solutions rested for 2 minutes and removed by filtration.

Second crosslinking: Prepared beads were dipped in crosslinker solutions (FC/FS/CS), rested for 2/5 minutes (coated/non coated) and removed by filtration.

Determination of erythromycin: Quantity of erythromycin was determined by sulfuric acid method [9].

Release experiments were performed at pH 7.0, 37 °C. Beads prepared by 1 cm^3 solution were used to investigate release in a total volume of 50 cm^3 phosphate buffer 1.5 cm^3 samples were withdrawn for drug analysis, and replaced with 1.5 cm^3 of phosphate buffer.

RESULTS and DISCUSSION

Effect of crosslinker type and concentration was analyzed by using FC (0.06-0.14 $moldm^{-3}$) and FS (0.04 - 0.14 $moldm^{-3}$). Results are given in Figure 1. As seen from the figure drug release decreased by increasing crosslinker concentration as expected. For FC crosslinked samples release rate was very high above 65% (0.14 $moldm^{-3}$ FC) in first 15 minutes and above 85% in first hour. In case of FS crosslinked samples release rates are lower but still high in first 15 minutes (above 48% for 0.14 $moldm^{-3}$ FS). For all samples very low release rates were obtained in the period 60-210 minutes. Since none of the results were satisfactory crosslinker concentrations which gave fastest release (0.06 $moldm^{-3}$ FC) and slowest release (0.14 $moldm^{-3}$ FS) were chosen and method was modified to have a better release pattern.

To decrease the fast release seen in first 60 minutes second crosslinking was adopted to the method by using 0.16 $moldm^{-3}$ FC, 0.14 $moldm^{-3}$ FS and 0.1 $moldm^{-3}$ CS as second crosslinkers. Results are given in Figure 2. As

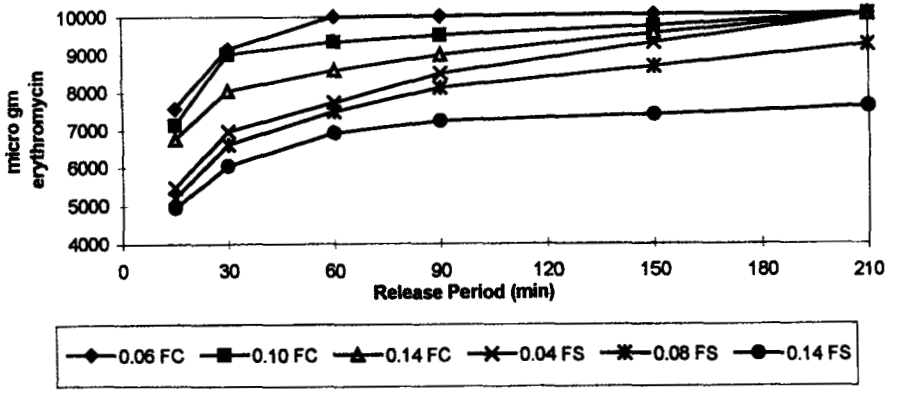

Figure 1. Effect of Crosslinker Type and Concentration (mol dm^{-3}) on Release

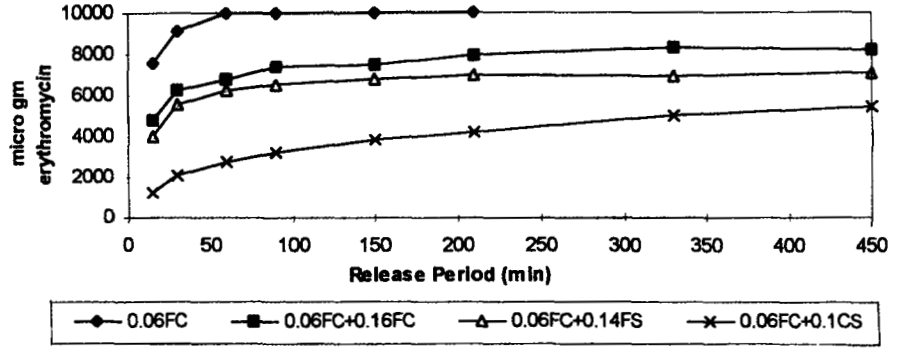

Figure 2. Effect of Second Crosslinking on 0.06mol dm^{-3} FC Crosslinked core

seen from the results second crosslinking caused a considerable decrease in release specially when 0.1moldm^{-3} CS was used as second crosslinker. Release in first 15 minutes decreased from 504 μg/min to 83 μg/min and release period extended to 450 minutes (55% release), and a relatively constant release rate was obtained between 60-450 minutes. Other crosslinkers used for second crosslinking were also caused a decrease in release in first hour but still high rates in first 15 minutes

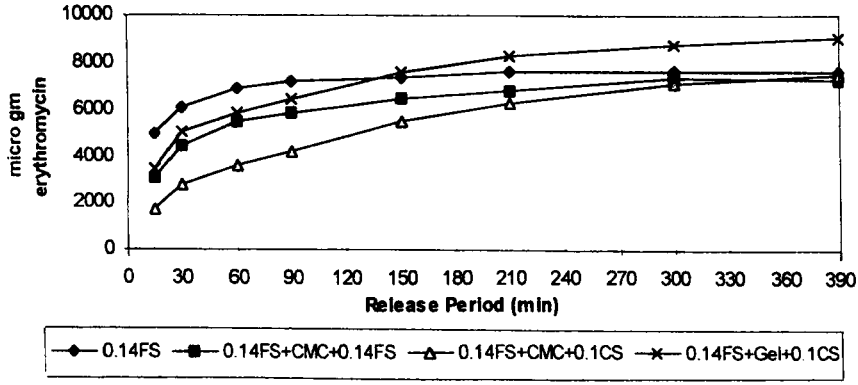

Figure 3 Effect of Coating and Second Crosslinking on 014mol dm^{-3} FS Crosslinked Core

(between 222 and 270 μg/ min) and were not satisfactory in the rest of the test period.

The other modification applied to the method was first coating with CMC/G and then crosslinking with 0.061 $moldm^{-3}$ FC, 0.14 $moldm^{-3}$ FS and 0.1 $moldm^{-3}$ CS. Results are given in Figures 3 - 5. Figure 3 shows the effect of coating and second crosslinking on the core prepared by using 0.06 $moldm^{-3}$ FC. As seen from the figure best results were obtained by the method in which CMC coating and crosslinking with 0.1 $moldm^{-3}$ CS was used. Release rate in first 15 minutes dropped to 82 μg/min and a better release pattern was obtained in the second 15 minutes and first hour when compared to direct application of second crosslinking with 0.1 $moldm^{-3}$ CS. Figure 4 presents the effect of coating and second crosslinking on the core obtained by using crosslinker 0.14 $moldm^{-3}$ FS. Although release rates obtained with CMC coating and 0.1 $moldm^{-3}$ CS crosslinking were considerably low compared to core in first 15 minutes (329 μg/min - 116 μg/min), the effect of coating diminished after 4 hours. A better release pattern was also obtained for FS samples after this modification. Figure 5 shows the effect of coating materials (CMC/G) on release. Usage of G as coating material increased release considerably.

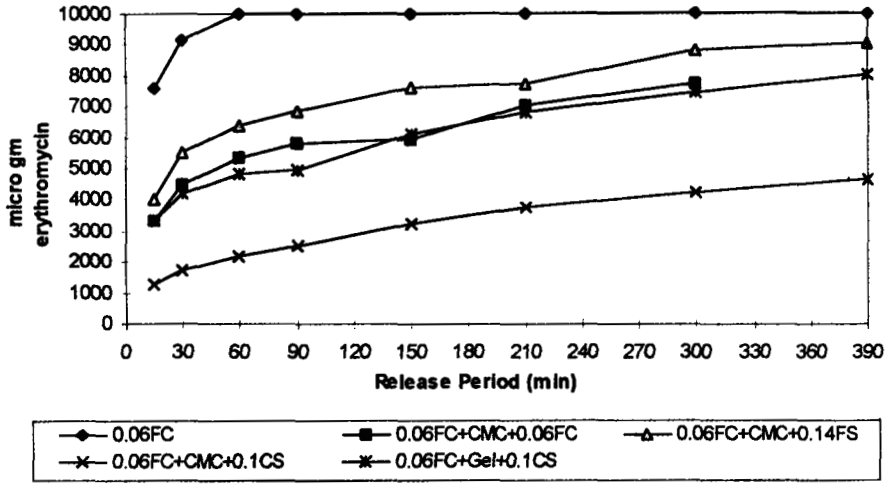

Figure 4 Effect of Coating and Second Crosslinking on 0.06mol dm^{-3} FC Crosslinked Core

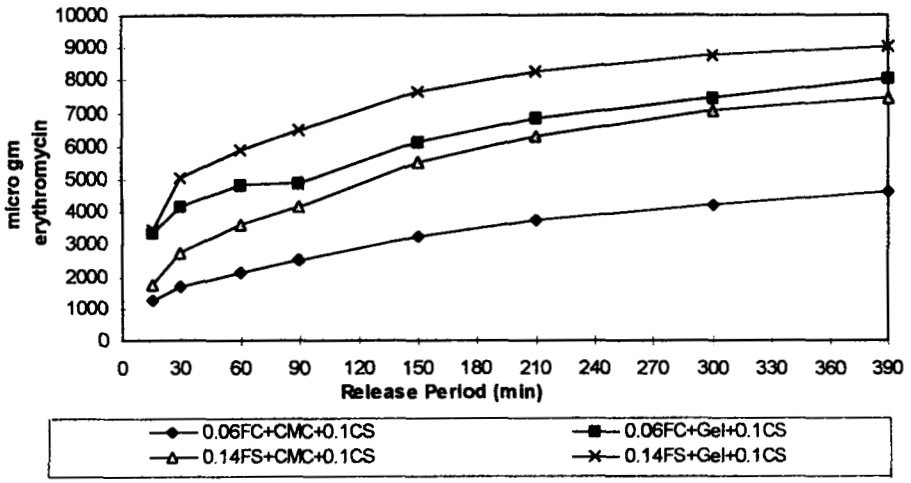

Figure 5 Effect of Coating Material (CMC/G) on release

In this work FC, FS crosslinked CMC was analyzed as a carrier system for drug release by using erythromycin as model drug. A method was developed and further modified by crosslinking and coating/crosslinking. A considerably good release pattern was obtained by applying a coating with CMC and crosslinking the coated core (CMC crosslinked with 0.06 moldm^{-3} FC) with 0. 1 moldm^{-3} CS. Gelatin (when used as coating material) increased the rate of drug release for both of the cores prepared.

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