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DEVELOPMENT OF AN IMPLANTABLE, BIODEGRADABLE, CONTROLLED DRUG DELIVERY SYSTEM FOR LOCAL ANTIBIOTIC THERAPY

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ABSTRACT

A novel drug delivery system was developed using a monoglyceride (Glycerol Monostearate) and a water-soluble release rate modifier as the matrix. Cefuroxime sodium (Zinacef®) was chosen as a model drug in this study. Formulations (cylindrical implants 6 x 6 mm) were prepared by a melt-dispersion method. Dissolution studies were performed using USP paddle method. The effect of glycerol, PEG 400 and their combination on drug release profiles was studied. Two assay methods (UV and HPLC) for cefuroxime analysis were compared. Percent recovery from four formulations (A-D) was higher with UV than HPLC assay. While both UV and HPLC assay methods were developed for cefuroxime, only HPLC assay is stability indicating. Glycerol showed higher accelerating effect than PEG 400 on the drug release. All formulations exhibited extended release of cefuroxime. Degradation of cefuroxime occurred mainly during dissolution suggesting drug stability in the formulations.

INTRODUCTION

The site-specific delivery of antibacterial agents in conjunction with systemic therapy and rigorous surgical debridement can be effective in the treatment of bone infections. Antibiotic-impregnated polymethacrylate beads, although not approved in the U.S., have been used clinically for the treatment of infected joint replacements and osteomyelitis in Europe for several years[1-3]. Numerous studies have been reported on the development of polymer-based carrier systems for the sustained release of antibiotic[4-7]. These systems are designed to deliver antibiotics for relatively long periods of time ranging up to six weeks.

By comparison, the goal of prophylactic antibiotic therapy is the prevention of postoperative infections. Repeated doses of antibiotic, particularly cephalosporins, administered parenterally over the course of several days have been effective in cases of contaminated and clean-contaminated surgery[8]. Advantages of a biodegradable controlled release delivery system include: achievement of high local antibiotic tissue levels, while minimizing prolonged elevated serum levels; bacterial spread and cross-contamination from irrigation/drainage devices are avoided; complete release of drug and complete degradation and absorption of the matrix; reduced patient care costs as a result of earlier patient mobilization and reduced hospital stay; elimination of daily drug administration.

We report here on the development of a drug delivery system composed of a biodegradable, hydrophobic, monoglyceride and a water-soluble release rate modifier. In vitro as well as In vivo, the modifier dissolves out of the matrix, creating pores from which the drug is released

from the monoglyceride component of the matrix. Thus, drug release rate can be controlled by varying the amount of modifier. The hydrophobic monoglyceride retards the release of drug. Eventually, the monoglyceride will be hydrolyzed to soluble components and absorbed from the implant site. This system is being developed as an implant for the short term delivery of drugs, particularly antibiotics, as well as peptides and proteins.

Cefuroxime sodium (Zinacef®) is a semisynthetic, broad spectrum cephalosporin antibiotic for parentral use which is stable to most of the ß-lactamases. It is widely used for prophylaxis in primary and revision total hip and knee replacement surgery[9]. A comparison of systemic cefuroxime and cefuroxime loaded bone cement in the prevention of early infection after total joint replacement indicated no significant difference between the two modes of administration[10]. The study showed a low incidence of early infection with both parentral and cefuroxime loaded acrylic cement[10].

The objective of the present study was to evaluate the feasibility of incorporating and prolonging the release of cefuroxime from this delivery system. The overall objective was to evaluate the monoglyceride as biodegradable, implantable drug delivery system.

EXPERIMENTAL METHODS

Materials

Cefuroxime Sodium (Zinacef®, Glaxo Inc.) Glyceryl Monostearate, GMS (Eastman Fine Chemicals) were used as received. Glycerol, polyethylene glycol (PEG) 400, sodium acetate, acetic acid and acetonitrile (Sigma) were used as received.

Preparation of Formulations

The formulations were prepared by a melt dispersion method. Glyceryl Monostearate (GMS) was heated 5°C above its melting point (75°C) in a glass beaker. The modifier (glycerol or PEG 400) was heated to the same temperature and mixed with GMS with constant stirring. Cefuroxime powder was slowly added and dispersed in the mixture using a high speed homogenizer.

The molten mixture was drawn up into a 10 cc syringe and injected into a Teflon coated stainless steel mold containing 25 individual cylindrical cavities. The mold was allowed to cool at 4 °C for one hour. Each cylindrical device is 6 mm long, 6 mm in diameter and weighs 200 mg. The cylinders were stored in amber colored bottles at -15°C.

Cefuroxime HPLC Assay

HPLC Instrument: A high-pressure liquid chromatograph (Beckmann 110A pump, model 710 WISP injector, Waters, Milford, MA) was connected to a variable wavelength UV detector (Waters) and an integrator (Shimadzu, Kyoto, Japan).

Column: Microbondapak C18, 3.9 mm x 30 cm was used.

Chromatographic Conditions: The mobile phase consisted of acetate buffer (pH 3.4), 10 parts and acetonitrile, 1 part. The flow rate was 2.5 ml/min. The detector was set at 273 nm (the wavelength of maximum absorption) and the sensitivity was 0.02 AUFS. The temperature was ambient and the chart speed was 3 mm/min.

Preparation of Stock Solution: About 100 mg of carefully weighed cefuroxime was dissolved in 10 ml of 0.1 M phosphate buffer, pH 7.4 (USP) to obtain a stock solution of 10 mg/ml. One ml of the above solution was diluted to 100 ml in a volumetric flask to obtain 0.1 mg/ml cefuroxime

sodium. The standards for the calibration curve were prepared from 4-80 µg/ml from this 100 µg/ml solution after dilution with phosphate buffer. The standards were freshly prepared on each day of analysis. The mobile phase was delivered at a flow rate of 2.5 ml per minute and the effluent was monitored at 273 nm. The retention time of the cefuroxime peak was about 8.3 minutes.

Cefuroxime UV Assay

The absorbances of the standard solutions were measured at 274 nm using the HP diode array spectrophotometer HP 8452 A. The coefficient (K1) was 2.55 over a linear range of 4-40 µg/ml of cefuroxime.

Content Recovery Study of Cefuroxime

The formulation was melted in 0.1 M phosphate buffer (pH 7.4) at 70-75°C for 15 minutes with constant stirring. The suspension was then cooled, centrifuged and the clear supernatant was filtered. Analysis of the solution after extraction was conducted by both UV and HPLC assays.

Dissolution Studies

Dissolution experiments were carried out for all the formulations using a USP dissolution apparatus II (paddle method) at 37°C and 50 rpm. The dissolution medium was 500 ml 0.1 M phosphate buffer (pH 7.4). Samples (10 ml) were collected at specific time periods and replaced with equal volume of fresh buffer. Samples were filtered through 0.45 µm membrane and analyzed by both UV and HPLC assay for cefuroxime.

RESULTS AND DISCUSSION

Table 1 illustrates the compositions of the formulations evaluated in this study. Figure 1 shows typical chromatograms of cefuroxime. The

TABLE 1

FORMULATION	COMPOSITION and WEIGHT RATIOS
MPB1-73A	GMS:Cefuroxime 95:5
MPB1-73B	GMS:Glycerol:Cefuroxime 85:10:5
MPB1-73C	GMS:PEG 400:Cefuroxime 85:10:5
MPB1-73D	GMS:Glycerol:PEG 400:Cefuroxime 85:5:5:5

results of the content recovery study are shown in Figure 2. The percent recovery of intact drug was calculated based on a theoretical loading (5% w/w). The recovery of cefuroxime was almost hundred percent by UV assay and about eighty to ninety percent by HPLC assay. There appeared to be some degradation of cefuroxime either during the preparation of the formulations or during the recovery process which was detected only by HPLC, since HPLC separated intact drug from its degradation product(s).

Figures 3 and 4 show drug release profiles of cefuroxime from the formulations as estimated by UV and HPLC assays, respectively. All formulations exhibited a slow extended release for 98 hours when total cefuroxime was determined by UV assay. Cefuroxime was released from MPB1-73A at a slow, zero-order rate for 98 hours. Formulation B containing 10% glycerol, demonstrated a significant burst effect in the initial hours of release. Almost 50% of the total drug was released in the first 10 hours followed by slow release for the remaining 88 hours. By contrast, Formulation C containing 10% PEG 400 exhibited a smaller burst effect and a slower release rate. Formulation D containing a

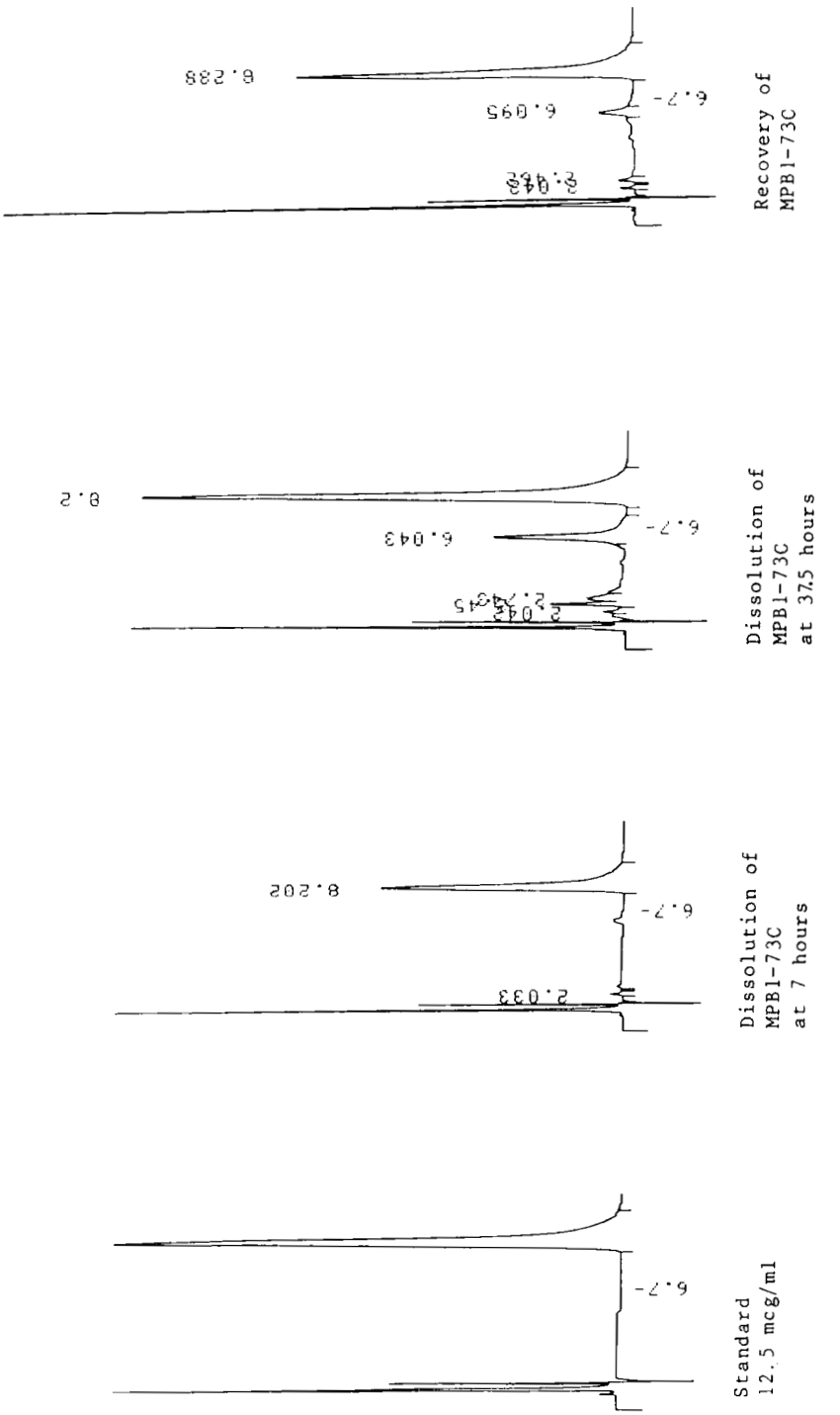

Figure 1.
Typical chromatogram of standard cefuroxime (R.T. 8.2 min) and dissolution and recovery samples

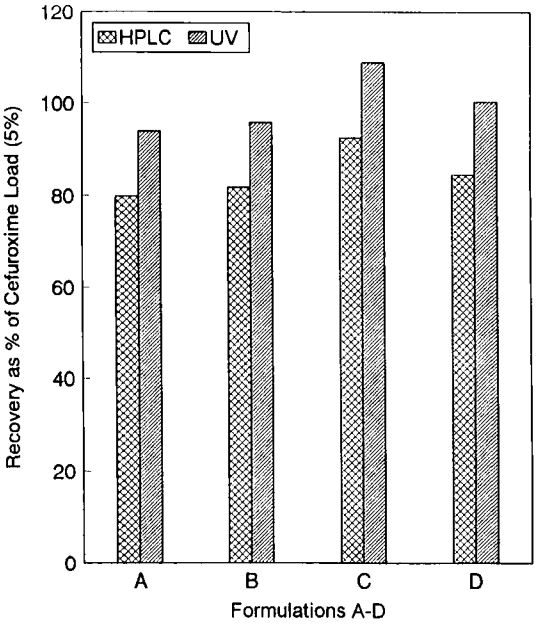

FIGURE 2

Recovery of Cefuroxime from MPB1-73 A-D

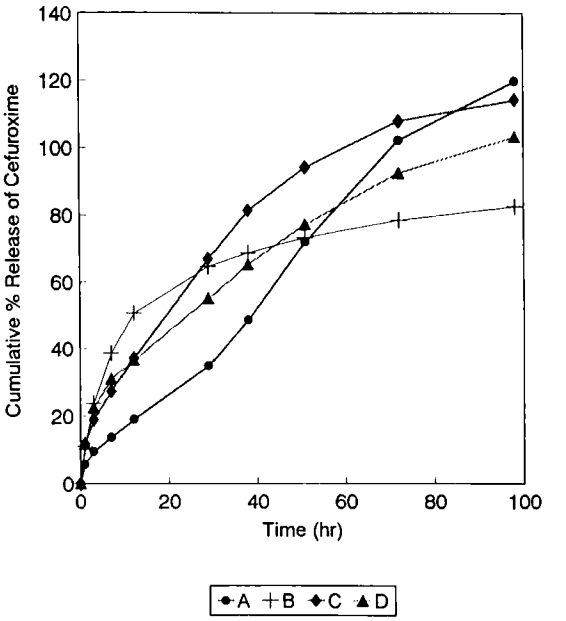

FIGURE 3

Dissolution of Cefuroxime from MPB1-73 A-D, UV Assay

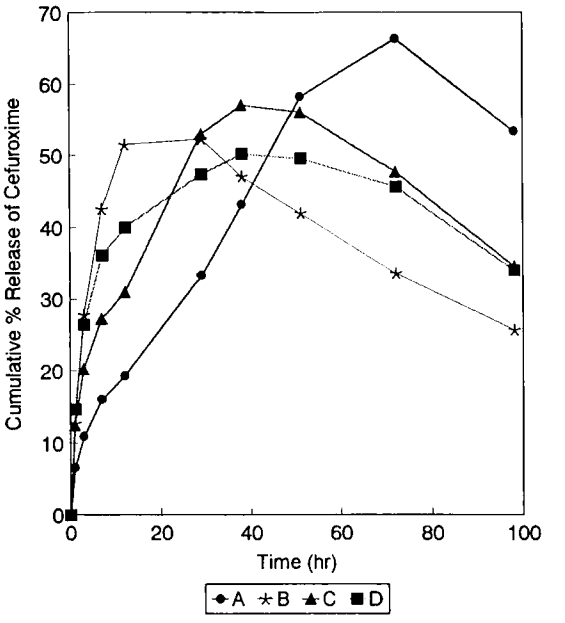

FIGURE 4

Dissolution of Cefuroxime from MPB1-73 A-D, HPLC Assay

combination of the two modifiers in equal proportions, yielded an intermediate release profile.

Analysis of drug release by HPLC revealed a degradation product with a retention time of approximately 6.2 minutes. Since the structure of the degradation product was unknown, it was not possible to quantitate the amount of degradation. However, the results (Figure 5) indicated the onset of degradation after a lag time of 15-20 hours and then a gradual increase in the amount of degradation product (expressed as peak area) as a function of dissolution time. Since there was very little degradation to begin with in the formulation, the degradation product in the dissolution was appearing from cefuroxime in solution. This was consistent with the

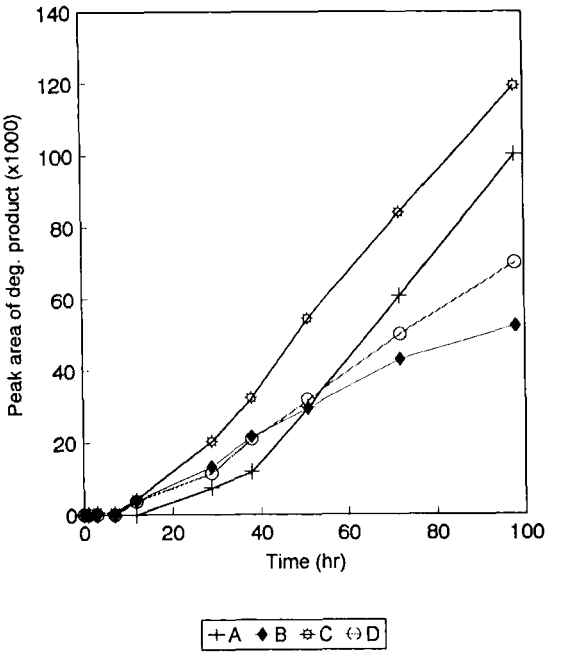

FIGURE 5

Degradation Product Profile from Dissolution

work by Das Gupta and Stewart[11], in which they found the stability of cefuroxime in aqueous buffered solutions decreased at elevated temperatures. Therefore, it was concluded that degradation of cefuroxime occured in the dissolution medium, since the recovery results clearly indicated that the formulations had only small amount of degradation product after preparation.

Preliminary subcutaneous implant studies in rats indicated the bioabsorption of monoglycerides as cylindrical devices was dependent on their carbon chain length. In general, an increase in carbon chain increased the absorption time (stearate > palmitate > laurate).

Formulations (A-D) in the present study appeared to change in their shape with slight swelling and surface erosion after one month in subcutaneous pockets of rats. This change was an indicator of matrix degradation and further studies are currently underway to evaluate complete absorption.

CONCLUSION

Incorporation of cefuroxime into GMS matrix was successful. All formulations exhibited extended release of the drug despite the occurence of degradation during the dissolution studies. If the drug was stable in aqueous solutions, release rate from the monoglyceride matrix will be slow and over a prolonged period of time (3-5 days). By selecting an appropriate release rate modifier, the rate can be modulated acccordingly.

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