Kinetics and Mechanism of Release from Glyceryl Monostearate-Based Implants: Evaluation of Release in a Gel Simulating in Vivo Implantation

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Abstract ☐ The overall objective of the study was to design an implantable delivery system based on glyceryl monostearate (GMS) for the site-specific delivery of antibiotics for the prevention of surgical wound infection. To design the implant, a release method had to be developed that simulate the in vivo implantation conditions to be able to predict the release characteristics from the implants when they are actually used in vivo. Also, identifying the release kinetics and mechanism and evaluating the factors that influence the release of drugs from the GMS-based matrix were necessary to allow further design of implants that could yield a desired release rate. The release of cefazolin was monitored from GMS matrixes implanted into agar gel, simulating subcutaneous tissues with respect to viscosity and water content. The gel method resulted in observation of spatial and temporal concentration profiles in the immediate vicinity of the implants, indicating the benefits of local drug delivery; however, there was no significant difference between the cumulative release profiles by the gel method or the vial release method. The release of cefazolin from the GMS-based matrix with the vial method followed Higuchi's square root of time kinetics. The release rate ($Q/\sqrt{t}$) was found to be directly proportional to cefazolin load (A) and the surface area (SA) of the matrix as expressed by the following equation: $Q/\sqrt{t} = 0.24ASA$. On the basis of this equation, one can design a variety of GMS matrixes that would result in a desired release rate or release duration. This also indicated that cefazolin release followed the release kinetics of a freely soluble drug from an insoluble matrix and hence it is a diffusion-controlled process. The effect of drug solubility on the release kinetics was determined by comparing the release kinetics of the poorly water soluble ciprofloxacin (0.16 mg/mL) to that of the highly water soluble cefazolin (325 mg/mL). The release duration of ciprofloxacin (80 h) was longer than that of cefazolin (25 h) from identical GMS matrixes. Although ciprofloxacin release was initially controlled by the matrix, agitation accelerated disintegration of the matrix and release due to its poor solubility, and ciprofloxacin release appeared to be a dissolution-controlled process following zero-order release kinetics.

Introduction

In vitro drug release from implantable drug delivery systems has been evaluated by various release methods such as the vial method, the continuous flow method, the constant rotation method, and the USP dissolution method.[1−6] These methods were designed to control the influence of variables such as sink condition, temperature, reproducibility of sampling, and the thickness of the diffusion layer on the results of the release studies. All of the above listed in vitro release methods involve placing the implant in direct contact with an aqueous solution. However, implants are designed to be placed in the body where they are surrounded by tissues and extracellular fluids. Under implantation conditions, the drug is released from the implants into the surrounding tissues and then cleared by hemoperfusion. Therefore, to closely simulate in vivo release under implantation situation, the implants need to be in contact with release media that simulate the tissues. The intracellular matrix of the subcutaneous tissues is mainly composed of collagen, mycopolysaccharides, and water. Protein (collagen) and polysaccharide (agar) gels could be used to simulate the subcutaneous tissues due to their resemblance to subcutaneous tissues in composition, rheologic nature, and water content. Thus, in vitro release from implants in an agar or collagen gel can be expected to closely simulate in vivo drug release of these implants at subcutaneous sites.

In this study, the use of agar gel was evaluated for studying the release of cefazolin from glyceryl monostearate (GMS)-based implants designed for the prevention of postsurgical wound infection. The gel release method was compared to the vial method in order to determine a suitable release method for studying and characterizing the release kinetics of cefazolin from the GMS-based matrixes. Since GMS is insoluble in water, erosion enhancers were used to accelerate its bioerosion by disintegration. However, the GMS-based matrixes were expected to behave as an insoluble matrix type system because of the insolubility of GMS in water. Drug release from such an insoluble matrix is generally achieved by the penetration of the release medium into the matrix and dissolution of the drug, followed by the diffusion of the drug solution through the channels and pores of the matrix.[7] In preliminary studies, the release of cefazolin from the optimized GMS-based matrix was found to be proportional to the square root of time as long as the matrix was intact (maintained a constant surface area), and the total amount released was less than 70% of the drug load.[8] Several equations have been derived to describe the release of water soluble drugs from an insoluble matrix.[9−11] In these equations, the amount of drug released per square root of time (release rate) is directly proportional to either the drug load or the square root of the drug load, depending on the extent of the solubility of the drug in the release medium; thus, drug solubility plays a significant role in its release duration and kinetics. An antibiotic with poor aqueous solubility, such as ciprofloxacin (0.16 mg/mL at pH 7.4, 37 °C), was expected to have a longer release duration from the GMS-based matrixes compared to that of cefazolin with high solubility (325 mg/mL).[12,13] Therefore, the specific aims of

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this study were (1) to evaluate the gel release method for implants and compare it to the vial method, (2) to characterize the release kinetics of cefazolin from the GMS-based matrix, and (3) to determine the effect of drug solubility on the release kinetics and duration from the GMS matrix.

Experimental Section

Materials—Cefazolin sodium USP was obtained from Lyphomed. Ciprofloxacin was a gift from Cipla Pharmaceutical Co. Glyceryl monostearate (GMS) was a gift from Eastman Chemicals. Sodium EDTA was purchased from Fisher Scientific. Monobasic sodium phosphate, dibasic sodium phosphate, HPLC grade acetonitrile, phosphoric acid, and triethylamine were purchased from Curtin Matheson Scientific Inc. Granulated agar was obtained from Becton Dickinson.

HPLC Assay For Cefazolin—Cefazolin was analyzed by reversed phase HPLC using a 3.9 mm × 30 cm Waters Microbondapak C18 column, an adaptation of the USP HPLC assay for cefazolin.[14] The mobile phase was composed of 90% pH 3.6 phosphate/citrate buffer and 10% acetonitrile. The mobile phase was pumped at a flow rate of 2.5 mL/min. The cefazolin peak was detected at 273 nm by UV.

UV Assay For Cefazolin—In addition to the HPLC assay, a UV assay was used to quantitate cefazolin in the release studies when cefazolin degradation was not observed. The absorbance of cefazolin was measured at 272 nm using an HP diode array spectrophotometer (HP 8452A).

Cefazolin standards (2−80 μg/mL) were prepared in pH 7.4, 0.1 M phosphate buffer containing 2 mg/mL sodium EDTA since in a preliminary study EDTA protected cefazolin against degradation.[8]

HPLC Assay For Ciprofloxacin—The USP HPLC assay for ciprofloxacin was used to determine ciprofloxacin concentrations in the release study samples.[15] Ciprofloxacin was analyzed by reversed phase HPLC using a 3.9 mm × 30 cm Waters Microbondapak C18 column. The mobile phase was composed of 87% 0.025 M phosphoric acid adjusted to pH 3 by triethylamine and 13% acetonitrile. The mobile phase was pumped at a flow rate of 1.7 mL/min. The ciprofloxacin peak was detected at 278 nm.

Preparation of Cefazolin- and Ciprofloxacin-Loaded GMS-Based Matrixes—In preliminary studies, degradation of cefazolin was observed when the GMS matrixes were prepared by melt-casting. Therefore, GMS matrixes were prepared by dispersion of drug in GMS in a Micro-Mill as described below. GMS with erosion enhancers was heated to 5 °C above the melting point of GMS (69 °C) in a water bath, while being stirred with a glass rod. The molten blend was removed from the water bath and allowed to cool to room temperature, while being mixed until the molten mass solidified. The solidified blend was stored in the freezer for at least 24 h before any further processing. The frozen mass of the GMS-based blend was loaded into Micro-Mill grinder (Technilab Instruments) along with dry ice and milled for 30−60 s, resulting in a very fine powder. Dry ice was added to prevent overheating and consequent melting of the milled mass. Cefazolin sodium or ciprofloxacin was added to the powdered blend of GMS and mixed for 30 min in a 50 mL centrifuge tube attached to a V-mixer (Patterson Kelley Company, Twin Shell Dry Blender). Three random samples were obtained from the powder after mixing and assayed for cefazolin or ciprofloxacin concentration, to test for content uniformity. The results of the three samples were averaged, and the relative standard deviation (RSD) was determined. Batches with RSD > 10% were rejected, and the powder was remixed and assayed again for content uniformity. The drug-loaded blend from the previous step was compressed into tablet-shaped implants in a die of 9.53 mm diameter at a pressure of 1.2 metric ton using a Carver Laboratory Press, each implant weighing approximately 200 mg.

In Vitro Release Studies—*The Gel Method*—This in vitro release method was conducted by the implantation of the cefazolin devices into agar gel as described below. The agar crystals were dissolved in boiling pH 7.4, 0.1 M phosphate buffer to prepare 1.5% agar solution, 20 g of which was poured into a Petri dish and left to congeal. A hole, equivalent in size to one matrix, was made in the gel at the center of the agar plate with a cork borer and matrix (9.53 mm, 200 mg, 10% w/w cefazolin) was implanted in the hole. Another 20 g of the hot (50−60 °C) agar solution was poured on top of the first layer of gel containing the matrix and left to congeal. The plate was covered and placed in a 37 °C oven. Several agar plates implanted with cefazolin devices were prepared at the same time, and samples were collected at 6, 12, 24, 36, 44, 77, and 96 h. At each sampling time, one plate was removed from the oven. Using a guide template, the plate was divided into four sampling zones (Figure 1), and three samples (600 mg) were removed from each zone using a cork borer size 4 (8 mm in diameter).

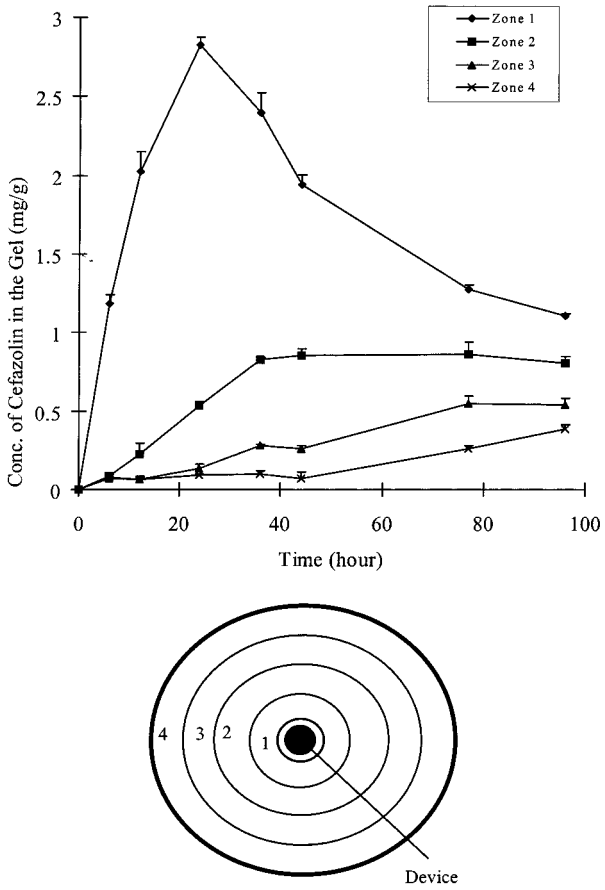

Figure 1—(top) Spatial release of cefazolin from the GMS-based matrix into the various zones of the agar gel plate after the implantation of cefazolin-loaded matrix in the center of the agar plate. (bottom) The guide template used to divide the agar plate into four sampling zones. The width of each zone is 9 mm, the device's zone is 11 mm (n = 3).

The samples were accurately weighed and dissolved in 15 g of boiling buffer to dissolve the gel, the solution was then cooled in an ice bath, and 5 g of NaCl was added to precipitate the agar. The resultant suspension was weighed, sonicated, and then centrifuged to obtain a clear supernatant containing cefazolin. The supernatant was analyzed by both HPLC and UV assay to determine the concentration of cefazolin. The concentration of cefazolin in each agar sample was converted into the total amount of cefazolin released into the various zones of each plate, on the basis of the weight of each zone. The total amount of cefazolin released from the implanted matrix was also calculated at each time point and the release profile was compared to that obtained by the vial method. The extraction method was validated for both the recovery and the stability of cefazolin during the extraction procedure. Three agar gels with different known concentrations of cefazolin (0.2, 1.3, and 2.1 mg/g) were prepared, and the cefazolin was extracted from each agar gel. The cefazolin concentration was determined by HPLC assay and the recovery was calculated. The chromatographs were examined for the presence or absence of degradation products' peaks.

Vial Method—The GMS-based implants were individually placed into 20 mL glass vials with 15 mL of 0.1 M, pH 7.4 phosphate buffer and agitated at 60 oscillations per min in a horizontal water bath shaker at 37 °C. The release medium was replaced with fresh solution each time a sample was withdrawn. The samples collected at different time intervals were filtered, appropriately

diluted to fit into the range of the calibration curve, and then assayed for cefazolin. The release profiles obtained by the vial method and the gel method were compared. The positive correlation allowed the vial method to be used exclusively to study the effect of the devices' surface area and drug load on the release kinetics.

USP Dissolution Method—Due to the lower solubility of ciprofloxacin, its release from GMS matrixes was studied in a USP dissolution apparatus II (paddle method) at 37 °C in 1 L of pH 7.4, 0.1 M phosphate buffer and compared to the release profile of cefazolin. Two agitation speeds, 50 and 100 rpm, were used to conduct the release studies.

Kinetics of Drug Release—*Effect of Cefazolin Load in the Matrix on Release Rate*—Matrixes with different cefazolin load were prepared in order to study the effect of drug load on the release rate. The matrixes had identical geometrical shape, size, weight (9.53 mm diameter, 200 mg), and formulation composition, with cefazolin loads of 5.34, 9.99, 15.90, and 21.08% w/w. The release studies were conducted in triplicate by the vial release method, and the release profiles were plotted versus the square root of time. The release rates determined from the slopes of the lines, using only the data points obtained while the matrixes were intact (constant surface area) and less than 70% of the loaded cefazolin released, were plotted versus the corresponding cefazolin load to determine the relationship.

Effect of Matrix Surface Area on Release Rate—Matrixes with identical geometric shape, formulation composition, cefazolin load (10% w/w), and weight (200 mg), but with differing surface areas, were prepared using different die sizes (7.0, 9.53, and 10.0 mm in diameter). This resulted in matrixes having the following surface areas: 1.63, 1.85, and 2 cm^2. The release rates determined from the slopes of the lines, using only the data points obtained while the matrixes were intact and less than 70% of the loaded cefazolin released, were plotted versus the corresponding surface area to determine the relationship.

Effect of Drug Solubility on Release Kinetics—Cefazolin is highly water soluble (325 mg/mL), while ciprofloxacin has poor aqueous solubility (0.16 mg/mL) at pH 7.4. Therefore, to study the effect of drug solubility on its release kinetics, ciprofloxacin devices identical to cefazolin devices (identical load, formulation, shape, size, and weight) were prepared and their release profiles compared. The 10% w/w ciprofloxacin and cefazolin devices weighing 200 mg were prepared by compression at a pressure of 1.2 metric tons in a 9.53 mm die.

Results

The Gel Release Method—The method for extraction of cefazolin from the agar gel was validated for recovery, stability, and reproducibility. The recovery samples showed no evidence of degradation during the extraction process with 97−106% of the spiked cefazolin recovered intact, and the RSD of all the recovery samples was less than 10%. Recovery of cefazolin from the agar gel was 97, 97, and 106% at concentrations of 0.2, 1.3, and 2.1 mg/g, respectively. Since the recovery process did not result in the degradation of cefazolin, the UV assay for cefazolin was used to determine the concentration of cefazolin in the agar gel samples of the release study.

Figure 1 shows the spatial release of cefazolin into the agar gel plate at different time intervals. As time progressed, the total amount of cefazolin released from the matrix increased, leading to the further diffusion and an increase of cefazolin concentration in the various zones. Initially, the concentration of cefazolin in zone 1 was the highest and concentrations in the gel decreased as the distance from the implant increased. After 24 h, the concentration of cefazolin in the first zone started to decrease, leading to an increase in cefazolin concentrations in the outer zones (zones 2−4). Eventually the concentration of cefazolin in the entire plate reached a constant value. Almost 100% of the loaded cefazolin was released within 24 h, and the implants turned into a pasty mass 24 h after implantation.

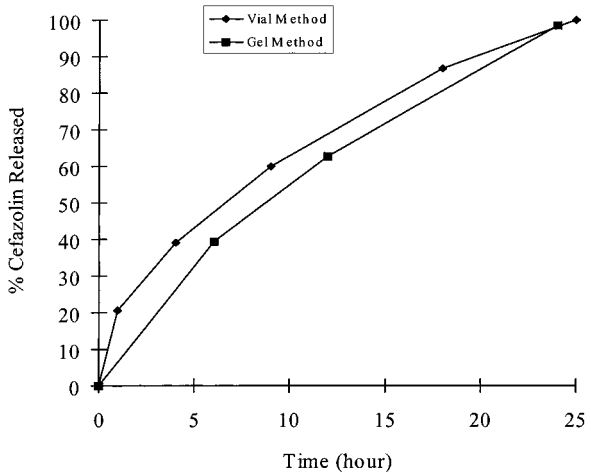

Figure 2—Release profiles of cefazolin from the optimized GMS matrix monitored by the vial and the gel methods ($n = 3$).

The total amount of cefazolin released in the agar gel was calculated by cumulating the amounts found in the four zones and the amount of cefazolin in the gel portion (300 mg) that immediately surrounded the implanted device. All (98%) of the loaded cefazolin was released with in 24 h in the gel method, which is comparable to the release by the vial method (Figure 2). Since no cefazolin degradation was detected in the first 24 h, there was no interference by the degradation products with the UV assay of cefazolin released from the matrix. Degradation products were detected by HPLC assay only after 36 h of the beginning of the release study. This degradation of cefazolin at 36 h was a result of the extended exposure of the released cefazolin to 37 °C, since in the gel method, unlike in the vial method, the released cefazolin remained in the gel for the entire duration of the release study. However, the degradation beyond 36 h did not influence the release profile, since all cefazolin was released into the gel after 24 h.

Kinetics of Cefazolin Release—*Effect of Cefazolin Load on the Release Rate*—As seen in Figure 3a, release of cefazolin from matrixes with the different loads of cefazolin (5.34, 9.99, 15.90, and 21.08% w/w) was proportional to the square root of time, and the release rates of these different matrixes were found to be directly proportional to the drug load of the matrix (Figure 3b). The relationship between the release rate ($Q/\sqrt{t}$) and cefazolin load (A) can be described by the following equation ($r^2 = 0.98$)

$$Q/\sqrt{t} = 0.44A \quad (1)$$

where $Q/\sqrt{t}$ is the release rate in $mg/h^{1/2}$ and A is the load in % w/w. Equation 1 is written as follows when the load (A) is described in mg/cm^3:

$$Q/\sqrt{t} = 0.038A \quad (2)$$

Equation 1 or 2 can be used to predict the release rate of cefazolin based on the cefazolin load in the optimized GMS matrix with a surface area of 1.85 cm^2.

Effect of Surface Area of the Matrix on Cefazolin Release Rate—As seen from Figure 4a, release of cefazolin from matrixes with different surface areas (1.63, 1.85, and 2.00 cm^2) was also proportional to the square root of time. These release rates of cefazolin were found to be directly proportional to the surface area of the matrix. The relationship between the release rate ($Q/\sqrt{t}$) and the surface area of the matrix (SA) can be described by the

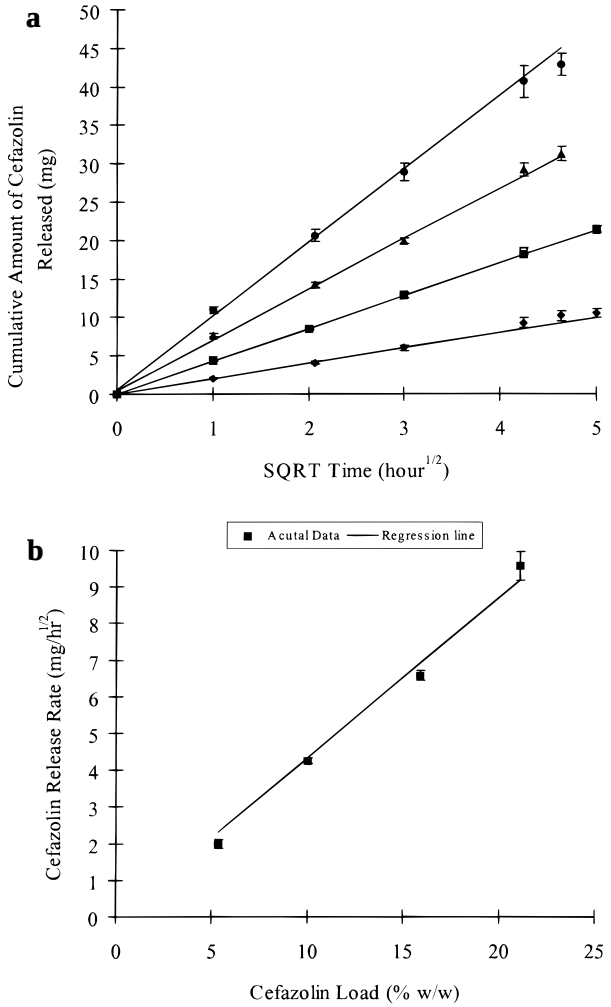

Figure 3—(a) Release profiles of the matrixes with cefazolin loads of 5.34% (◆), 9.99% (■), 15.90% (▲) and 21.08% (●) ($n = 3$). The solid lines are the regression lines, used for the calculation of the release rates ($Q/\sqrt{t}$) which were then (b) correlated with cefazolin load (A) following a linear relationship described by $Q/\sqrt{t} = 0.44A$ ($r^2 = 0.98$, $n = 3$).

following equation ($r^2 = 0.91$):

$$Q/\sqrt{t} = 2.4SA \qquad (3)$$

Equation 3 can be used to predict the release rate of cefazolin based on the surface area of the optimized GMS matrix, when the cefazolin load is 10% w/w (11.6 mg/cm^3).

Effect of Drug Solubility on Release Kinetics. Comparison of the Release Kinetics of Cefazolin and Ciprofloxacin—The duration of ciprofloxacin release was longer than that of cefazolin from identical matrix formulation (Figure 5). All of loaded cefazolin was released in 25 h, and the release followed square root of time kinetics. In contrast, ciprofloxacin release duration was 80 h and followed zero-order release kinetics for the first 28 h. After 32 h, an increase of the release rate was noticed, due to an increase in the surface area of the dissolving surface after the matrix disintegrated into smaller matrixes. To further evaluate the effect of drug solubility on release kinetics by influencing the hydrodynamic diffusion boundary layer resistance, the effect of agitation on ciprofloxacin release kinetics was studied.

Effect of Agitation on Ciprofloxacin Release Kinetics—During the first 16 h, the ciprofloxacin matrixes were intact under the two agitation rates and the amount of ciprofloxacin released at 50 rpm was identical to that at 100 rpm

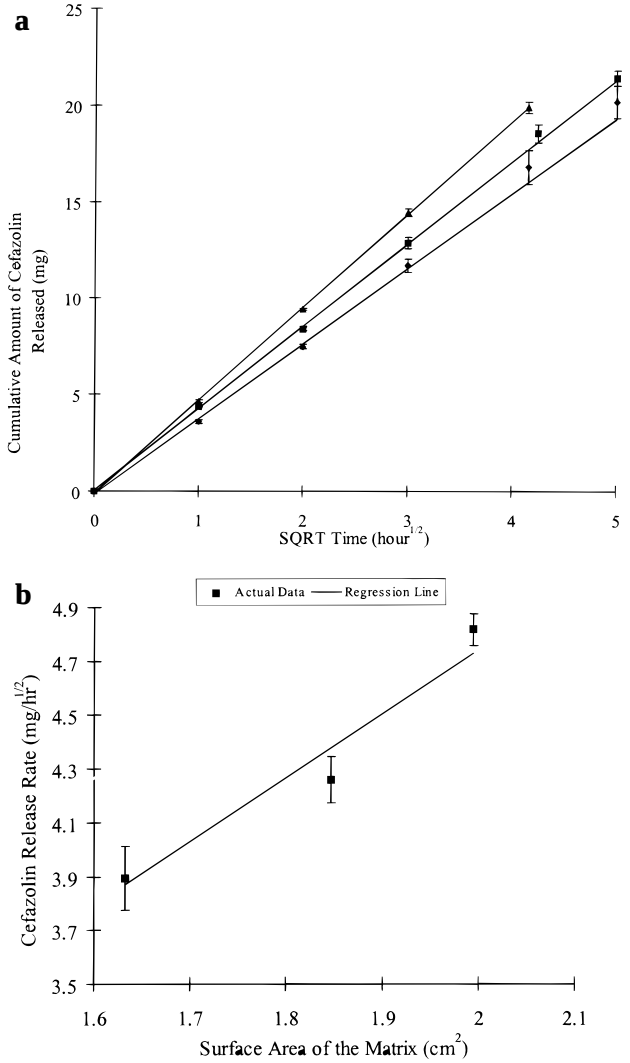

Figure 4—(a) Release profiles of the matrixes with surface areas of 1.63 cm^2 (◆), 1.85 cm^2 (■) and 2.00 cm^2 (▲) ($n = 3$). The solid lines are the regression lines, used for the calculation of the release rates ($Q/\sqrt{t}$) which were then (b) correlated with the matrix surface area (SA) following a linear relationship described by $Q/\sqrt{t} = 2.4SA$ ($r^2 = 0.91$, $n = 3$).

(Figure 6). However, the onset of the disintegration of the ciprofloxacin devices was affected by the agitation rate, begining at 18 and 28 h for 100 and 50 rpm, respectively. Under these two agitation rates, the disintegration of the devices led to an increase in the release rate of ciprofloxacin due to an increase in the overall surface area of the dissolving surface. The disintegration of the matrixes and the increase of the surface area was faster at 100 rpm than at 50 rpm, and consequently, the release of ciprofloxacin was faster at 100 rpm.

Discussion

Comparison of Release by the Vial and the Gel Methods—Agar gel plates seeded with microorganisms were used to study the efficacy and the release of antibiotics from bone cement in order to mimic the in vivo implantation situation.[16] Similarly, in this study, the release of cefazolin from GMS matrixes in the gel method was conducted in order to simulate the in vivo implantation conditions, under which the implanted matrixes are surrounded by tissues rather than aqueous solution. The gel in this case represented the tissues at the implantation site

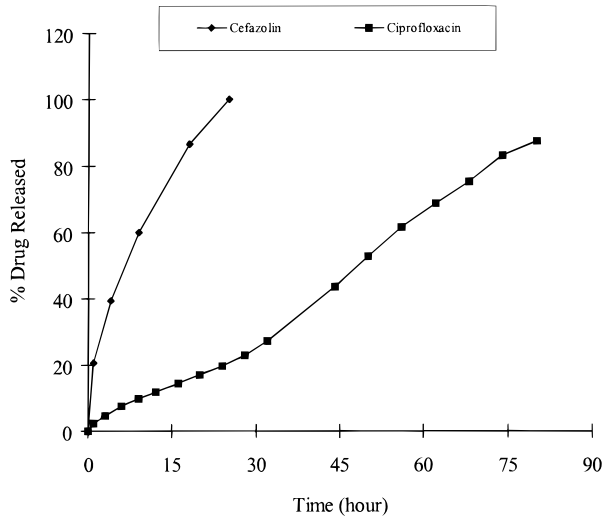

Figure 5—Release profiles of cefazolin (vial method) and ciprofloxacin (USP method) from identical GMS matrixes, demonstrating the effect of the aqueous solubility of the antibiotic on the release kinetics ($n = 3$).

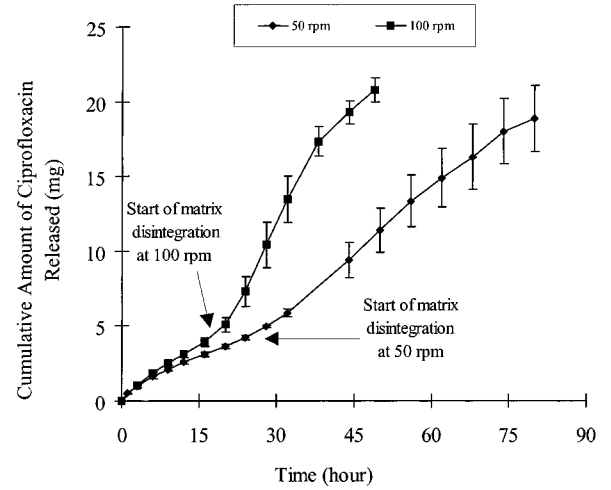

Figure 6—Effect of agitation rate (50 and 100 rpm) on the release of ciprofloxacin from identical GMS matrixes ($n = 3$).

primarily with respect to composition, viscosity, and water content. The release characteristics of cefazolin from the matrixes implanted in the gel were expected to be closer to the in vivo release than in the vial method. The gel method was intended to be an intermediate step between the in vitro (vial method) and the in vivo evaluation of the cefazolin release from the GMS matrixes.

There was no significant difference between the release by the two methods when comparing the release profile obtained by the gel and the vial methods. This similarity in the release profiles is due to the high aqueous solubility of cefazolin and the fact that 98.5% of the gel is composed of water despite its high viscosity. The release medium in the vial method was under constant agitation, which led to homogeneous cefazolin concentration in the entire release medium. In contrast, the release medium (gel) in the agar gel method could not be agitated and the released cefazolin had to diffuse through the gel, driven only by its concentration gradient. This demonstrated the concept of how high local concentrations are achieved in the immediate vicinity of the implant for prolonged periods of time for the objective of site-specific drug delivery (Figure 1). In the gel method, multiple samples to represent the entire area of the gel were required since cefazolin concentration was not homogeneous through out the entire gel medium. Therefore, samples were withdrawn from various zones of the agar plate, where each sample covered the entire width of the corresponding zone. The gel portion (<300 mg) that immediately surrounded the implanted device was not assayed for its content of cefazolin due to the difficulty in separating this gel portion intact from the implanted device. Thus, for the calculation of the total amount of cefazolin released, the concentration in that gel portion was assumed to be equal to that in the first zone, even though it should have been much higher at the earlier stages of the release study. On the basis of this fact, it is expected that the release by the gel method is even closer to the release by the vial method than seen in Figure 2.

Although the gel method demonstrated the concept of achieving high local concentrations in the immediate vicinity of the implant for prolonged periods of time for the objective of site-specific drug delivery, the method is cumbersome, invasive, and not feasible to perform routinely. Sampling in the gel method was an invasive process, and extraction from the gel samples was a tedious process. Furthermore, the released cefazolin accumulated in the gel and therefore it was liable to degradation as seen in samples collected after 36 h. On the basis of the similarity of the release profiles between the two release methods, it is expected that the in vivo release of cefazolin will not be much different from the release in the vial method. Therefore, the vial method was used to study the release of cefazolin from the GMS-based matrixes, as the vial method showed comparable results to those obtained by the gel method without the disadvantages that are associated with the gel method.

Kinetics of Drug Release—Drug release from an insoluble matrix is generally achieved by penetration of the release medium into the matrix and dissolution of the drug, followed by the diffusion of the drug solution through the channels and pores of the matrix. For a highly soluble drug, when its solubility in the release medium (C_s) is much greater than the drug load (concentration) in the matrix (A), i.e., $C_s \gg A$, the release medium penetrates the matrix and instantaneously dissolves all the drug in the part of the matrix that is penetrated. Drug release from the matrix follows the release kinetics of a solution entrapped in an insoluble matrix (Fick's law, diffusional release).[7,9,11] The release of such a drug from an insoluble matrix can be described rather well by the following equation:

$$Q = 2A\mathrm{SA}\sqrt{Dt/\pi\tau} \qquad (4)$$

Where Q is the amount of drug released after time t, SA is surface area of the matrix, A is the initial concentration of the drug in the matrix (drug load), D is the diffusion coefficient of the drug in the release medium, and τ is the tortuosity of the matrix.

In contrast, when the drug solubility in the release medium is less than two times the drug load in the matrix, i.e., $2A > C_s$, the release is controlled by both the dissolution rate of the drug and the diffusion rate of the drug solution out of the matrix, and the release of the drug is characterized as diffusion from a moving dissolution front.[9–11] As time progresses, the depletion zone grows and the dissolution front recedes from the part of the matrix in which the drug has been depleted from. The release of such a drug is described by Higuchi's equation (diffusional release with a moving dissolution front) as shown below[9,10]

$$Q = \mathrm{SA}\sqrt{(\mathrm{D}\epsilon C_s/\tau)(2A - \epsilon C_s)t} \qquad (5)$$

Where Q, SA, D, A, τ, and t are as defined above, ϵ is the porosity of the matrix, and C_s is the solubility of the drug in the release medium.

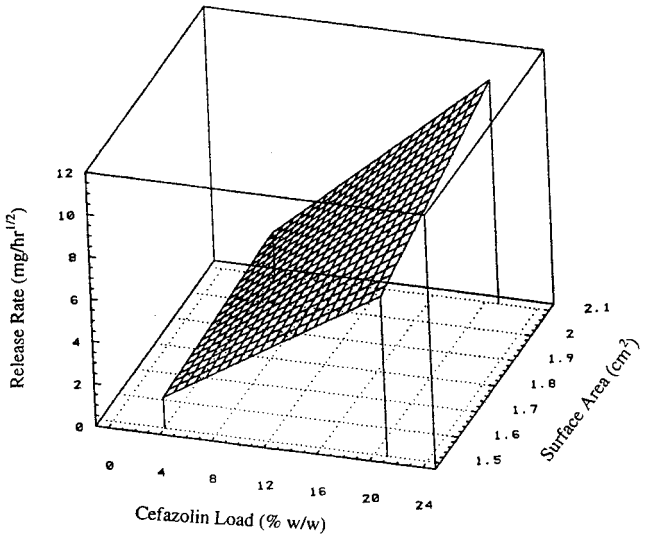

Figure 7—Surface response plot of cefazolin release rate versus cefazolin drug load and the surface area of the GMS matrix. On the basis of the plot, one can design a matrix with a desired release rate by selecting the appropriate drug load and matrix surface area.

Since cefazolin has a high dissolution rate (15 mg/cm^2/min) and a very high aqueous solubility (C_s = 325 mg/mL) that exceeds its load (A) in the GMS matrix, its release would be expected to follow eq 4 rather than eq 5. However, eq 4 implies that the release rate ($Q/\sqrt{t}$) is directly proportional to the load (A) while eq 5 suggests that the release rate ($Q/\sqrt{t}$) is proportional to the square root of the drug load (A). As expected, experimentally, the release rate ($Q/\sqrt{t}$) of cefazolin was found to be directly proportional to its load (eqs 1 and 2, Figure 3), proving that the release of cefazolin from the GMS-based matrix follows eq 4 for the release of a highly water soluble drug from an insoluble matrix. The release rate was also found to be directly proportional to the surface area of the matrix (eq 3).

On the basis of eqs 2 and 3, the value of $\sqrt{D/\pi\tau}$ in eq 4 was calculated to be 1.7×10^{-4} cm/s$^{1/2}$; therefore, eq 4 for the release of cefazolin from the GMS-based matrix can be written as follows

$$Q = (3.4 \times 10^{-4})ASA\sqrt{t} \quad (6)$$

Where Q is the amount of cefazolin released (mg) at time t (s), A is the drug load (mg/cm^3), and SA is the surface area (cm^2) of the matrix. When time is expressed in hours, and the drug load as % w/w, eq 6 can be rewritten as:

$$Q = 0.24ASA\sqrt{t} \quad (7)$$

For the calculation of the release rate, eq 7 can be rearranged as follows:

$$Q/\sqrt{t} = 0.24ASA \quad (8)$$

From eq 8, desired release rates of cefazolin can be obtained on the basis of the load and surface area of the optimized GMS-based matrix. Using eq 8, a surface response plot was generated (Figure 7) from which the desired release rate could be obtained by using different combinations of surface area and load values. Equations 6–8 can also be used to predict the release of drugs with comparable diffusion coefficients and solubility to that of cefazolin.

Effect of Drug Solubility on its Release Kinetics—When the drug is poorly soluble, dissolution is very slow and since only dissolved drug diffuses out of the matrix through the pores and channels, the rate-limiting step in this case is the dissolution of drug in the release medium. Therefore, the release rate of such a drug is nearly zero-order.[11] The solubility of cefazolin sodium and ciprofloxacin HCl at pH 7.4 are 325 and 0.16 mg/mL, respectively, and therefore, cefazolin release followed square root of time kinetics (diffusional release), obeying eq 3, while ciprofloxacin release was found to follow zero-order kinetics for the first 28 h (50 rpm). This suggests that the release of ciprofloxacin is a dissolution-controlled process, where the rate-limiting step is the slow dissolution of ciprofloxacin in the penetrating release medium. The release duration of ciprofloxacin (80 h at 50 rpm) was 3 times longer than the release duration of cefazolin (25 h), indicating the effect of drug solubility on the release kinetics from the GMS-based matrix. The release duration of 1–3 days from GMS implants is adequate for antibiotic prophylaxis in most surgical procedures; however, in surgeries such as prosthetic arthroplasty and orthopedic procedures, the release duration may have to be extended using other controlled-release technologies.

Effect of Agitation on Ciprofloxacin Release Kinetics—If the dissolution of a drug controls the rate of its release from the matrix, the release rate will be influenced by the factors that influence dissolution such as the thickness of the diffusion boundary layer. The aqueous diffusion boundary layer around the matrix offers significant resistance to the dissolution of poorly soluble drug. The agitation rate of the dissolution medium affects the thickness of the aqueous diffusion boundary layer: the higher the agitation rate, the thinner the aqueous diffusion boundary layer. If the release of ciprofloxacin is solely controlled by its dissolution in the release medium, then increasing the agitation rate should accelerate the release of ciprofloxacin. Thus, the release studies of ciprofloxacin-loaded matrixes were conducted at two agitation speeds, 50 and 100 rpm, to establish whether the release of ciprofloxacin is prolonged (extended) by the matrix (matrix-controlled release) or the release is simply prolonged because of the slow dissolution of ciprofloxacin. If the matrix is truly controlling the release, there should not be any effect of agitation on the release kinetics of ciprofloxacin.

Since there was no significant difference between the release of ciprofloxacin under the two agitation rates (50 and 100 rpm) for the first 16 h during which the matrixes were intact, the release was matrix controlled. However, increasing the agitation rate accelerated the onset of the matrixes' disintegration into smaller fragments (smaller matrixes). The matrixes started to disintegrate around 18 and 28 h at 100 and 50 rpm, respectively, which led to an increase in its surface area, resulting in an increase in the release rate of ciprofloxacin (Figure 6). Thus agitation affected release of ciprofloxacin only after disintegration of the matrix. The above observation indicated that the release of ciprofloxacin was independent of the agitation rate as long as the surface area of the matrix was kept constant. Thus, the matrix is truly controlling the release rate of ciprofloxacin rather than the poor solubility of ciprofloxacin. The GMS matrix used for ciprofloxacin delivery was designed for the delivery of cefazolin and was designed to erode 15–18 h after complete release. Therefore, a more suitable matrix formulation needs to be designed and optimized for the delivery of ciprofloxacin.

Recently, the GMS-based implantable system that provided a prolonged delivery of cefazolin was found to be effective against *Staphylococcus aureus* infection in Sprague–Dawley rats and demonstrated suitable pharmacokinetics and biocompatibility with significant bioerosion.[17]

Also, there was an excellent correlation ($r^2 = 0.98$) between the in vivo and the in vitro release profiles of cefazolin from the GMS-based implants, suggesting suitability of the in vitro release methods used in this study.[17]

Conclusions

Although, the gel method resulted in observation of spatial and temporal concentration profiles in the immediate vicinity of the implants, indicating the benefits of local drug delivery, no significant difference was observed between the cumulative release profiles by the gel method and the vial release method. Cefazolin release follows the release kinetics of a freely soluble drug from an insoluble matrix and hence it is a diffusion-controlled process. The release rate ($Q/\sqrt{t}$) was found to be directly proportional to cefazolin load (A) and the surface area (SA) of the matrix as expressed by the following equation:

$$Q/\sqrt{t} = 0.24ASA$$

On the basis of this equation, one can design a variety of GMS matrixes that would result in a desired release rate or release duration. The release duration of ciprofloxacin (80 h), a moderately water soluble antibiotic, was significantly longer than that of cefazolin (25 h) from identical GMS matrixes. Although ciprofloxacin release was controlled by the matrix initially, agitation accelerated disintegration of the matrix and release due to its poor solubility, and ciprofloxacin release appeared to be a dissolution-controlled process following zero-order release kinetics.

References and Notes

1. Adams, K.; Couch, L., Cierny, G., Calhoun, J. H., Mader, J. T. In Vitro and In Vivo Evaluation of Antibiotic Diffusion from Antibiotic-Impregnated Poly(methyl methacrylate) Beads. *Clin. Orthopaed. Relat. Res.*, **1992**, *278*, 244−252.
2. Miclau, T.; Dahners, L. E., Lindsey, R. W. In Vitro Pharmacokinetics of Antibiotic Release from Locally Implantable Materials. *J. Orthopaed. Res.*, **1993**, *11* (5), 627−632.
3. Shah, S. S.; Cha, Y., Pitt, C. G. Poly (glycolic acid-*co*-DL-lactic acid): Diffusion or Degradation Controlled Drug Delivery? *J. Controlled Release* **1992**, *18*, 261−270.
4. Chien, Y. W. Methods to Achieve Sustained Drug Delivery *in Physical Approach: Implants, Sustained and Controlled Release Drug Delivery Systems*; Robinson, J. R., Ed.; Marcel Dekker Inc.: New York, 1978; pp 211−349.
5. Chien, Y. W.; Lambert, H. J., Grant, D. E. Controlled Drug Release from Polymeric Devices. I. Technique for Rapid In Vitro Release Studies. *J. Pharm. Sci.* **1974**, *63*, 365−369.
6. Kalkwarf, D. R.; Sikov, M. R.; Smith, L.; Gorden, R. Release of Progesterone from Polyethylene Devices In Vitro and in Experimental Animals. *Contraception* **1972**, *6*, 423−431.
7. Lordi, N. Sustained Release Dosage Forms In *The Theory and Practice of Industrial Pharmacy*; Lachman, L. H., Lieberman, A., Kanig, J. L., Eds., Lea and Febiger: Philadelphia, 1986; pp 430−456.
8. Allababidi, S.; Shah, J. Biodegradable site specific delivery of antibiotics for the prevention of postoperative wound infections. *Pharm. Res.* **1995**, *12* (9), 228S.
9. Higuchi, T. Mechanism of Sustained-action Medication: Theoretical Analysis of Rate of Release of Solid Drug Dispersed in Solid Matrixes. *J. Pharm. Sci.* **1963**, *52*, 1145−1150.
10. Higuchi, W. I. Diffusional Models Useful in Biopharmaceutics: Drug Release Rate Processes. *J. Pharm. Sci.* **1967**, *56* (3), 315−324.
11. Siegel, R. A. *Modeling of Drug Release from Porous Polymers in Controlled Release of Drugs: Polymers and Aggregate Systems*; Rosoff, M. Ed., VCH Publishers: New York, 1988; pp 1−51.
12. Yu, X.; Zipp, G. L., Davidson, G. W. R., III, The Effect of Temperature and pH on the Solubility of Quinolone Compounds: Estimation of Heat of Fusion. *J. Pharm. Res.* **1994**, *11* (4), 522−527.
13. Park, E. S. Investigation into the Mechanism of Drug Release from Biodegradable Polyanhydride Implantable Devices, Ph.D. Thesis, Department of Pharmaceutical Sciences, Medical University of South Carolina, 1995, pp 158−211.
14. Cefazolin official monograph. U.S. Pharmacopeia XXIII; Rand McNally: Taunton, MA, 1995; pp 289−290.
15. Ciprofloxacin official monograph. *U.S. Pharmacopeia XXIII*; Rand McNally: Taunton, MA, 1995; pp 375−377.
16. Welch, A. B. Antibiotics in Acrylic Bone Cement. In Vitro Studies. *J. Biomed. Mater. Res.*, **1978**, *12*, 679−700.
17. Allababidi, S.; Shah, J. Efficacy and Pharmacokientics of Site-Specific Cefazolin Delivery Using Biodegradable Implants in the Prevention of Post-operative Wound Infections. *Pharm. Res.*, **1998**, *15* (2), 329−337.

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