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CYTOSINE ARABINOSIDE RELEASE FROM POLYMERIC MATRICES

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ABSTRACT

Cytosine arabinoside (Ara-C) has been used in the treatment of acute myeloid leukemia. However, rapid deamination reduces its effectiveness. Polymeric matrices containing ara-C were prepared in polyether polyurethane copolymer to form a protective supply of ara-C. Release studies from these devices showed linear relationships between Q, the amount release per unit area, versus the square root of time. Burst effects were predominant at higher loading doses. The diffusivity values indicated that enough drug could pass through the polymer for the combination to have potential application as implants in cancer therapy.

INTRODUCTION

Cancer is probably one of the most widely researched areas since it has become the second leading cause of death since the 1960's (1). Although all this attention has brought significant progress in this field, many problems still remain to be overcome. The limiting factor in the effectiveness of cancer chemotherapy is the fact that most agents fail to differentiate between normal and tumor cells. The goal of effective anticancer treatment is not only to achieve total erradication of neoplastic tissue, but also reduce toxicity to normal tissues. Many strategies have been attempted, however, most of them are hindered by the lack of qualitative biochemical differences between tumor and normal cells (2).

Coupled with this problem is the lack of proper modes of drug administration for these chronic cases. In addition, many potent antineoplastic agents have been found to be unstable. These problems could be alleviated if a dosage form were prepared that would contain a protected supply of the drug which would be released at a controlled rate. Polymeric devices present an alternative method of administration of antineoplastic agents that allows for continuous targeted release. Drugs released continually at or near tumor sites may result in greater effectiveness

and less toxicity. The use of polymers as drug carriers in cancer therapy has been shown to be effective in many cases (3,4,5).

Cytosine arabinoside (Ara-C) has been reported to be very active in the remission, induction, and maintenance therapy of acute myeloid leukemia in adults and similarly in the blast phase of myeloid leukemia (6). Its effectiveness has been found to improve clinically in combination with other cytotoxic agents (7). However, instability of Ara-C decreases the effectiveness of the drug. The drug undergoes rapid deamination in the body (8) and has been reported to have short half lives (9).

In order to optimize the usefulness of Ara-C as an antineoplastic agent, polymeric matrices with the drug were developed. Polyether polyurethane copolymer was used for this purpose as it has been shown to be biocompatible and therefore suitable for implantation studies (10,11). In addition, the hydrophobic-hydrophilic character of the polymer makes it suitable for for drugs with varying solubilities (12,13). The purpose of this investigation was to fabricate suitable monolithic polymeric devices for Ara-C, which would provide a more effective mode of administration for prolonged periods, as implants.

EXPERIMENTAL

Materials

Cytosine arabinoside (Ara-C) was obtained as the free base from Sigma Chemical Company and used without further purification. Segmented polyether polyurethane (Biomer) was supplied in N,N-dimethylacetamide as a 30% solution (Ethicon, Inc.). All other chemicals used were USP, NF or ASC grade.

Methods

PREPARATION OF POLYMERIC MATRICES

The polymeric matrices, in planar monolithic form, of variant concentration of cytosine arabinoside were fabricated by a solvent casting process (5). Ara-C was accurately weighed out and mixed to the copolymer in solution. After reaching the proper consistency, the drug-copolymer mixture was poured onto a clean glass plate. The solvent was evaporated by placing the plate in a vacuum oven set at 30 psi and 50° C for a period of 48 hours. These matrices were prepared containing three different loading doses of Ara-C (4.90, 9.28, 17.27% w/w). The loading dose was calculated on the basis of weight-ratio of the drug and the polymer used.

Dissolution studies of the matrices were

performed using the Rotating Basket Method, USP. Each of the polymers, of variant concentration of Ara-C, were cut into pieces (2cm x 2cm) and placed into a Vander Kamp Dissolution Machine (Van Kel Industries, NJ) to determine the release characteristics of the drug. The dissolution apparatus was connected to a water bath and maintained at a temp of 37 ± 1°C. The basket was rotated at a speed of 75 r.p.m. in a dissolution medium containing 500ml of pH 7.4 phosphate buffer. At each sampling interval, a 5ml aliquot of the dissolution buffer solution was drawn off and assayed by HPLC analysis. The volume of solution was kept constant by replacing the volume of samples withdrawn with an equal amount of the dissolution medium. Each polymeric matrice, of different concentration, was done in triplicate.

SOLUBILITIES IN THE POLYMERIC MATRIX

Plain polymer sheets, devoid of drug, were used to determine the solubilities. Sheets of known sizes were submerged in vials containing different concentrations of Ara-C. The vials were placed in an agitating water bath (Versa Bath, Fischer Sci. Co.) maintained at 37°C for a period of 4 days to obtain equilibrium. The concentration of the drug in solution, before and after incorporation of the

polymer, was determined using HPLC analysis. The content of the drug in polymer was then determined in units of mg/ml. All studies were done in triplicate.

QUANTITATION OF ARA-C

Quantitation of Ara-C in all cases was done using high pressure liquid chromatography. The HPLC system was comprised of a Waters M-590 pump, a Model 710B sample handler, and a Model 490 programable U.V. detector monitored at 284nm. The analysis was performed using a mobile phase consisting of 3mM potassium dihydrogen phosphate (pH 3.2): methanol in a ratio of 92:8 pumped at 1 ml/min through a micro Bondapak C18 column.

RESULTS AND DISCUSSION

All data obtained from the release studies were analyzed according to the Higuchi equation (eq. 1) based on diffusion controlled transport in a polymeric matrix (14):

$$Q = \sqrt{[\, D\,(2A - Cs)\,Cs\,t\,]} \qquad (1)$$

where Q is the cumulative amount of the drug released per unit area of the device at time "t", D is the effective diffusivity of the drug in the polymeric matrix, A is the initial amount of the drug present per unit volume of matrix and Cs is the solubility of the drug in the matrix. The plot of Q, the cumulative

amount released per unit time, versus t, shown in Figure 1, indicates that the release is curvilinear. Release of other drugs from various polymers have shown similar results (15). However, when Q was

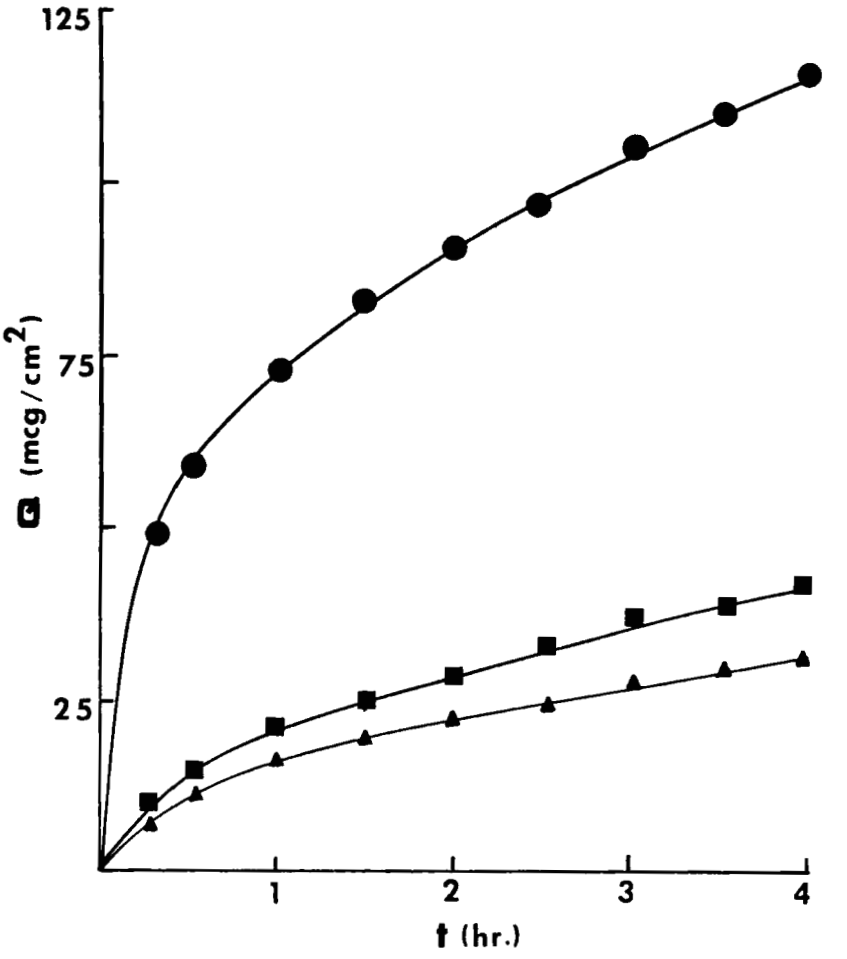

FIGURE 1

Release profiles of cytosine arabinoside from planar matrices. Key: (—▲—) 4.90% w/w; (—■—) 9.28% w/w; and (—●—) 17.29% w/w.

plotted against √t, linear relationships were obtained for all three concentrations tested as depicted in Figure 2. Plots for the lower loading doses (4.90, 9.28% w/w) were found to pass through the origin. On

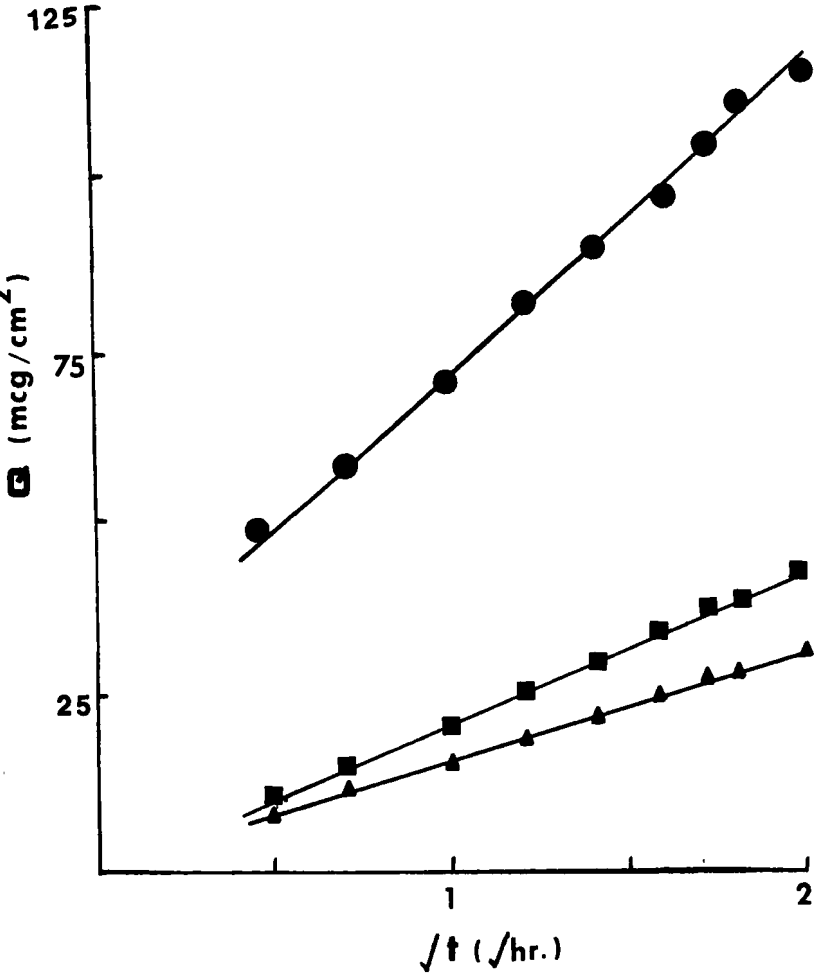

Figure 2

Plot of cumulative amount released, Q, versus the square root of time. Key: (—▲—) 4.90% w/w; (—■—) 9.28% w/w; and (—●—) 17.27% w/w.

the other hand, the line for the larger loading dose (17.27% w/w) had an intercept on the y-axis, indicating a "burst effect". Similar observations were also made for isopentenyl adenosine release from silicone matrices (16). The slopes of these lines are given by:

$$Q / \sqrt{t} = \sqrt{[D\ (2A - Cs)\ Cs]} \quad .. \ (2)$$

In cases where $2A >> Cs$, the above equation reduces to:

$$Q / \sqrt{t} = \sqrt{[2DCs]} . \sqrt{A} \quad .. \ (3).$$

The slopes of the $Q - \sqrt{t}$ plots are shown in Table 1. A linear relationship also existed between the slopes of the $Q - \sqrt{t}$ plots and $\sqrt{A}$. The slope of this line,

Table 1

Flux of ara-C obtained from Q versus $\sqrt{t}$ plots of the polymeric matrices

Drug conc. % w/w	Slope of Q vs $\sqrt{t}$ (± S.D.)	Regression Correlation Coefficient
4.90 (48 mg/ml)*	15.49 (0.88)	0.997
9.28 (71 mg/ml)	22.21 (0.95)	0.998
17.27 (158mg/ml)	46.55 (2.08)	0.997

* Concentration expressed as mg/ml.

$\sqrt{(2DCs)}$, according to Eq. 3 was 5.58 ug / sq.cm. $\sqrt{hr}$ (correlation = 0.998). Similar results were reported for the release of isopentenyl adenosine (17) and prostaglandin (18) from monolithic silicone devices.

The value for Cs, the solubility of the drug in polyether polyurethane was found to be 0.054 mg/ml. The diffusivity, D, was then obtained from eq.3 and the average value obtained for cytosine arabinoside, using the lower loading doses, was 1.105×10^{-4} hr^{-1}. On the other hand a much higher diffusivity value was obtained for the higher loading dose(2.54×10^{-4} hr^{-1}) As mentioned earlier, the higher loading dose showed a y-axis intercept. This indicated that drug particles dispersed at the surface did not have to "diffuse" out, thereby resulting in a high value for D. The lower value of D is thus a better representation of the actual diffusivity of cytosine arabinoside.

The results point to the fact that polyether polyurethane copolymer is sufficiently permeable to ara-C for use in controlled release drug delivery systems. The matrix system successfully released the drug at a constant rate. The rate can be changed as required by alteration of the loading dose. This drug-polymer combination holds promise for use as implants in the treatment of cancer.

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