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In-vitro release of fluoropyrimidines from PLGA film implants

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Abstract

The release of two low-molecular weight water-soluble fluoropyrimidines, 5-fluorouracil and 5-fluorouridine, from implants of PLGA films was modulated by varying the area (diameter) and number of layers of film per implant. The aim was to achieve continuous release without burst effect for at least a month. The film implants were prepared by the solvent evaporation technique. Except with 5-fluorouracil films, the in-vitro release profiles were in all cases triphasic, indicating that release proceeds by a combination of diffusion and polymer erosion. The experimental data fit the equation resulting from the sum of two exponentials, one direct and the other inverse. 5-fluorouridine release from simple films presented a relatively minor burst effect (24–28%). In contrast, the delivery of both compounds from sandwich-type implants occurred continuously without a burst effect, and lasted for 17–20 days. During the first phase, both 3- and 5-mm sandwiches released 55% of the dose of 5-fluorouridine, at rate constants of $0.037 \pm 0.021\ h^{-1}$ (n = 3) and $0.009 \pm 0.003\ h^{-1}$ (n = 3), respectively. In the second phase, release was gradual from both simple films (k_2 = 0.011–0.015 h^{-1}) and sandwiches (k_2 = 0.018–0.058 h^{-1}). According to the analysis-of-variance results, neither the area nor type of implant influenced the rate constants significantly. The release profiles of 5-fluorouracil from simple films showed a severe burst effect (64–71%). Release of 5-fluorouracil was gradual only from sandwiches, 5 mm in diameter, showing a lag time unobserved in the 3-mm sandwiches. In the second phase, release was gradual ($k_2 = 0.014 \pm 0.003\ h^{-1}$) from 3-mm implants. However, the high variability in results for 5-mm implants prevents conclusions being drawn about the model parameters. Therefore, the sandwich-type film implants showed their utility for releasing water-soluble drugs for a prolonged time, without burst effect.

Introduction

Implantable drug delivery systems (IDDS) have meant significant progress in developing new therapeutic systems. Their advantages include targeted local delivery of drugs at a constant rate, decreased overall dose and administration frequency, reduction of possible side effects and enhanced treatment efficiency. IDDS can be classified into two main categories: biodegradable or non-biodegradable implants and implantable pump systems. In general, two types or subclasses of biodegradable and non-biodegradable implants are recognised: reservoir devices and monolithic or matrix devices. The biodegradable systems have an important advantage over non-biodegradable devices in that no second surgical procedure is required for their removal (Dash & Cudworth 1998).

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A biodegradable monolithic device consists of a drug dispersed homogeneously throughout a biodegradable polymer matrix. Release occurs by a combination of diffusion and erosion, and can be modulated either by formulation changes or modification of the biodegradable polymers (Breitenbach et al 2000). Therefore, drug release depends on multiple factors such as the physicochemical properties of drug and polymer, implant geometry, preparation method and the use of different additives that enhance or reduce the permeation rate through the polymers (Bodmeier & Chen 1989; Sung et al 1998). For this reason, it is difficult to obtain drug release profiles with the required release rate and duration for each particular therapy. For hydrophilic drugs this difficulty is especially notable and in-vitro release from different biodegradable polyester implants has presented discontinuous (polyphasic) drug release profiles, often with a large initial burst and incomplete release (Benoit et al 1997; Kader & Jalil 1998; Breitenbach et al 2000). Hydrophilicity and drug loading seem to predominate in determining the release mechanism (Bodmeier & Chen 1989; Sung et al 1998; Yuan et al 1999).

The aim of this work was to study the possibility of controlling the release of low-molecular-weight hydrophilic drugs from biodegradable film implants, varying the area (film discs with 3 and 5 mm diameter) and the number of layers per implant (simple and sandwiched film discs). The techniques used for preparing the implants were solvent casting/compression and solvent casting only. The polymer chosen was poly(lactide-co-glycolide) (PLGA) as this type of copolymer is frequently employed to adjust the biodegradation rate, because of its excellent biocompatibility, biodegradability, and mechanical strength (Jain et al 1998). As model substances, two hydrophilic drugs with different solubility were used: 5-fluorouracil and 5-fluorouridine.

Materials and Methods

Synthesis of PLGA

The biodegradable PLGA was synthesised by ring-opening polymerisation of initial monomers D,L-lactide (Aldrich) and -glycolide (Boehringer Ingelheim) following the method described by Gilding & Reed (1979). D,L-lactide was recrystallised in ethyl acetate (Merck) at room temperature until the racemic mixture melting point was attained (124–126°C) and the glycolide was used directly (mp 88–90°C). Stannous octoate (0.1% w/w) and lauryl alcohol (0.01% w/w) (both Sigma) were used as catalyst and chain transfer agent, respectively. Thus, this mixture (45 g) of 75 mol% lactic acid and 25 mol% glycolic acid was loaded into three 30-mm (i.d.) glass ampoules. These ampoules were then immersed in an oil bath maintained at 140°C for 1 h, to obtain the solid copolymer, which was extracted by dissolution in chloroform (Merck) followed by precipitation with methanol (Merck). The polymerisation yield was 89%.

The average molecular weights of both copolymer and film discs were determined by gel-permeation chromatography (GPC) (Waters) relative to polystyrene standards (Tokyo Soda Ltd) with molecular weights 2800–700000. Filtered tetrahydrofuran (Merck) was used as the mobile phase at a flow rate of 0.9 mL min^{-1}.

The copolymer composition was determined by ^{1}H NMR with a Bruker model AMX-400 spectrometer using $CDCl_3$ as solvent. The relative proportions of lactic acid-glycolic acid (LA-GA) and glycolic acid-glycolic acid (GA-GA) units were assessed by ^{13}C NMR at 100.61 MHz using DMSO-d_6 as solvent (Dorta et al 1993).

Preparation of film implants

Two different types of biodegradable PLGA discs (weight-average molecular weight 47000 and 63/37 LA/GA) containing 10% w/w of drug (5-fluorouracil or 5-fluorouridine) were prepared by a solvent casting technique (Kwong et al 1986). The first of these was a simple (monolayer) monolithic device made up of a uniform drug–polymer mixture. The second type was a multilayer monolithic device consisting of an inner drug–polymer layer and two external polymer layers containing no drug. Briefly, the drug was first suspended in a 30% w/v PLGA–methylene dichloride solution. The films were prepared by casting of this suspension into petri dishes (4.7 cm diameter). The methylene dichloride was allowed to evaporate slowly at 2–8°C for 48 h and the films were vacuum-dried in a desiccator at room temperature for 12 h to remove the residual solvent.

Simple monolithic discs

The simple monolithic films were cut into small discs of 3 and 5 mm diameter and weighed individually. The thickness of the films thus obtained was 0.148 ± 0.028 mm (n = 10) for 5-fluorouridine discs and 0.158 ± 0.027 mm (n = 10) for 5-fluorouracil discs. The weights

of the four batches prepared were: 1.93±0.55 mg (3 mm; n = 10); 5.50±0.95 mg (5 mm, n = 10) for 5-fluorouracil discs and 1.79±0.38 (3 mm, n = 10) and 4.19±0.67 (5 mm, n = 10) for 5-fluorouridine discs.

Ten units with equal diameter and known weight were cut in a random manner from each film to determine the distribution of the two drugs within them. These samples were tested following the method described in the next section: Drug content determination and in-vitro release studies. The relative standard deviations were 6.23% for 5-fluorouracil discs (n = 10) and 5.32% for 5-fluorouridine discs (n = 10).

Multilayer monolithic discs (sandwiched film discs)

Each polymeric device was formed of three layers as previously described. The two external layers contained no drug and the third was a 30%-w/w drug-loaded inner layer. The multilayer device was prepared by compressing the layers at a pressure of 5×10^3 kgF applied for 3 min at room temperature using a hydraulic manual press (Perkin Elmer). The discs produced were cut into smaller discs of 3 and 5 mm diameter and weighed individually. The thickness of the films thus obtained was 0.571±0.062 mm (n = 10) for 5-fluorouridine and 0.487±0.070 (n = 10) for 5-fluorouracil discs. The weights of the four batches prepared were: 6.18±0.73 mg (3 mm; n = 10); 17.25±1.73 mg (5 mm, n = 10) for 5-fluorouracil discs and 6.53±0.66 mg (3 mm, n = 10) and 19.27±1.60 mg (5 mm, n = 10) for 5-fluorouridine discs.

Drug content determination and in-vitro release studies

The drug content was determined by dissolving each disc in methylene chloride and the drugs, which were both insoluble, were then extracted from the polymer solution with distilled water (yielding: 96±5%; n = 10). The aqueous phase was analysed by reverse-phase high-performance liquid chromatography (RP-HPLC). This apparatus (Water Corp., USA) was equipped with a UV-Vis detector (model 490E, Programmable Multiwavelength). The samples were analysed at 268 nm in a mixture (96:4) of 50 mM ammonium dihydrogen phosphate (adjusted to pH 3.5 with phosphoric acid) and acetonitrile using a reverse-phase C-18 column (Resolve 8×100 mm) at a flow rate of 1.7 mL min^{-1}.

The in-vitro release kinetics were determined by placing the pre-weighed drug-loaded discs in individual vials that contained 3 mL of 0.066 M isotonic (μ = 0.332 M) phosphate-buffered saline at pH 7.4 in a heater kept at 37°C. The release medium was periodically removed and replaced by equal volumes of fresh buffer taken into account in the calculations of the cumulative amount of released drug, which was analysed by HPLC as described above. The experiment was performed in triplicate.

Data analysis

The release profiles obtained from film discs presented three phases; therefore the drug-release parameters were calculated using the following equation:

$$x = x_{01}(1-e^{-k_1 t})+\frac{x_{02}}{1+e^{-k_2(t-t_0)}} \quad (1)$$

Accordingly, drug release occurs in two stages governed by two release rate constants (k_1 and k_2). The second stage is divided into two phases by the inflexion point (t_0). Here, x is the cumulative amount of drug released from the implant at time t, and x_{01} and x_{02} are the amounts of drug released during the first and second stages of release.

The model parameters were obtained by fitting nonlinear least-square regression of the above equation using Microsoft Excel Solver function (Billo 1997). The statistical analysis of the results was performed by two-factor analysis of variance (n = 3; level of significance < 0.05), the factors being type of implant (film and sandwich) and diameter (3 mm and 5 mm).

Results

Characterisation of PLGA

The number-average molecular weight (Mn), weight-average molecular weight (Mw), and polydispersivety (pd) of the PLGA were found to be 40000, 57000 and 1.42, respectively. The ratio LA/GA was 63:37 and LA-GA/GA-GA was 1:3.

In-vitro degradation of film discs

The in-vitro degradation of 5-mm PLGA film discs showed a continuous decrease in the average molecular weights from the onset of the assay. Thus, initially (t = 0) Mn, Mw and pd were found to be 31000, 47000 and

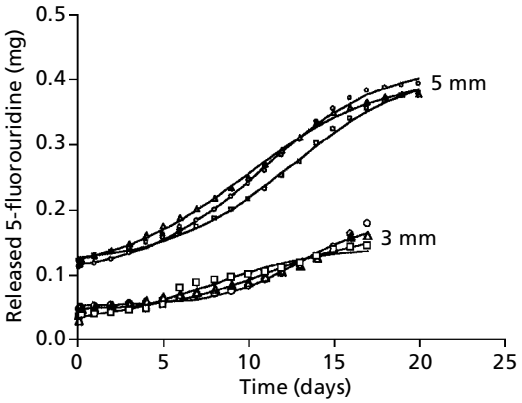

Figure 1 Release of 5-fluorouridine from 3- and 5-mm PLGA films in phosphate-buffered saline at 37°C. Dots are experimental data and solid lines are predictions from equation 2.

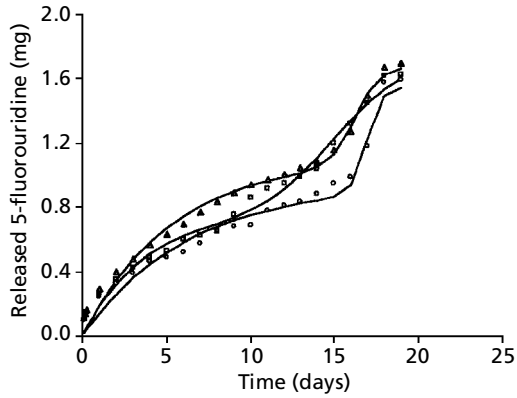

Figure 2 Release of 5-fluorouridine from 5-mm PLGA sandwiches in phosphate-buffered saline at 37°C. Dots are experimental data and solid lines are predictions from equation 1.

1.51, respectively and, after 21 days were found to be 6600, 9900 and 1.50.

5-Fluorouridine implants

Figure 1 shows the 5-fluorouridine release profiles from films. After an initial burst effect (during the first 2 h), the release was gradual. The experimental data fit equation 2 (Table 1), which was simplified from equation 1 on considering $k_1 = 0$:

$$x = x_{01} + \frac{x_{02}}{1 + e^{-k_2(t-t_0)}} \quad (2)$$

The percentage of 5-fluorouridine initially released (dur-

Table 1 Model parameters for PLGA films or sandwiches incorporating 5-fluorouracil or 5-fluorouridine, obtained by fitting non-linear square regression.

Type of implant	Model parameters						SS_{res}
	Replicates	x_{01}(mg)	x_{02} (mg)	k_1 (h^{-1})	k_2 (h^{-1})	t_0 (h)	
5-Fluorouridine films 5 mm	1	0.102	0.322		0.012	259.7	6.0×10^{-4}
	2	0.100	0.306		0.011	236.9	4.0×10^{-4}
	3	0.119	0.300		0.012	301.3	3.0×10^{-4}
5-Fluorouridine films 3 mm	1	0.053	0.130		0.018	310.3	4.0×10^{-4}
	2	0.045	0.115		0.014	265.1	1.1×10^{-3}
	3	0.025	0.118		0.012	184.8	7.0×10^{-4}
5-Fluorouridine sandwich 5 mm	1	0.941	0.659	0.007	0.097	406.7	8.0×10^{-2}
	2	1.101	0.609	0.008	0.058	389.4	6.1×10^{-2}
	3	0.733	1.001	0.012	0.019	359.5	6.7×10^{-2}
5-Fluorouridine sandwich 3 mm	1	0.362	0.258	0.022	0.020	362.5	1.7×10^{-2}
	2	0.352	0.276	0.028	0.019	362.1	2.4×10^{-2}
	3	0.336	0.315	0.060	0.015	317.2	3.0×10^{-2}
5-Fluorouracil sandwich 5 mm	1		1.042		0.017	331.7	1.2×10^{-1}
	2		1.250		0.015	274.6	3.4×10^{-2}
	3		1.469		0.012	303.1	9.5×10^{-3}
5-Fluorouracil sandwich 3 mm	1	0.085	0.326	0.146	0.025	266.7	1.5×10^{-3}
	2	0.382	0.229	0.008	0.013	266.7	4.6×10^{-3}
	3	0.220	0.560	0.039	0.011	268.5	1.3×10^{-2}

SS_{res}, sum of square of residuals.

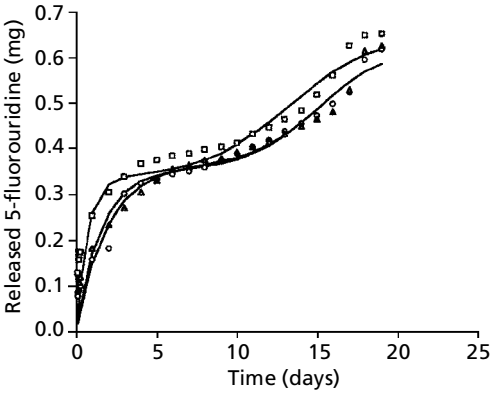

Figure 3 Release of 5-fluorouridine from 3-mm PLGA sandwiches in phosphate-buffered saline at 37°C. Dots are experimental data and solid lines are predictions from equation 1.

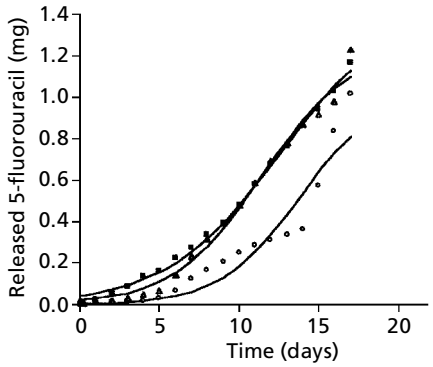

Figure 4 Release of 5-fluorouracil from 5-mm PLGA sandwiches in phosphate-buffered saline at 37°C. Dots are experimental data and solid lines are predictions from equation 3.

ing the first 2 h from the beginning of the assays) was 24% from 3-mm and 28% from 5-mm films. 5-Fluorouridine release then continued for 17 and 20 days respectively, the rate constants being $k_2 = 0.011 \pm 0.001\ h^{-1}$ (n = 3) for 5-mm implants and $k_2 = 0.015 \pm 0.003\ h^{-1}$ (n = 3) for 3 mm.

Figures 2 and 3 show the 5-fluorouridine release profiles from both 5- and 3-mm sandwiches, respectively. The release was triphasic, governed by two constants, with the experimental data fitting equation 1 (Table 1). During the first stage, 55% of the 5-fluorouridine was released from both 3- and 5-mm discs. The rate constant during this first stage for 3-mm implants was found to be 4 times higher for 3 mm ($k_1 = 0.037 \pm 0.021\ h^{-1}$, n = 3) than that for 5-mm implants ($k_1 = 0.009 \pm 0.003\ h^{-1}$, n = 3). The rate constants during the second stage of release were $k_2 = 0.058 \pm 0.038\ h^{-1}$ (n = 3) and $k_2 = 0.018 \pm 0.002\ h^{-1}$ (n = 3) for the 3- and 5-mm implants, respectively. The release period lasted 19 days for both.

According to the analysis of variance results the difference in k_2 values (films and sandwiches) was not statistically significant ($P = 0.142$; $\propto = 0.05$). The t_0 value increased on changing from 3- to 5-mm implants (12.5 h for films and 38 h for sandwiches). However, this was not significant either ($P = 0.305$; $\propto = 0.05$). The release from both films and sandwiches was complete, as confirmed by RP-HPLC.

5-Fluorouracil implants

5-Fluorouracil release from both 3- and 5-mm films showed a pronounced burst effect (64–71%) during the first 2 h under assay. Release then levelled off, increasing only 5% during the following 118 h. Residual 5-fluorouracil content in films was analysed by RP-HPLC.

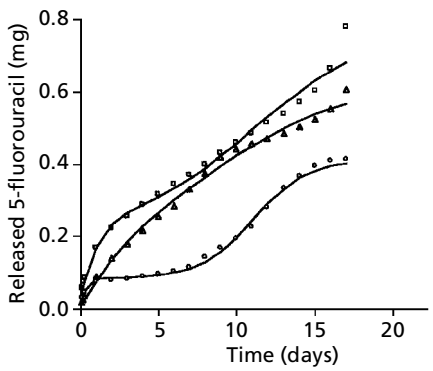

Figure 5 Release of 5-fluorouracil from 3-mm PLGA sandwiches in phosphate-buffered saline at 37°C. Dots are experimental data and solid lines are predictions from equation 1.

Figures 4 and 5 show 5-fluorouracil release profiles from sandwiches. Release from 5-mm sandwiches (Figure 4) showed a lag time, with the experimental data fitting equation 3, which was simplified from equation 1 on considering both x_{01} and k_1 equal to 0. From then on, release was gradual with a rate constant (k_2) of $0.014 \pm 0.003\ h^{-1}$ (n = 3) and a t_0 of 303.1 ± 28.54 h (n = 3).

$$x = \frac{x_{02}}{1 + e^{-k_2(t - t_0)}} \quad (3)$$

Release from the 3-mm diameter implants (Figure 5) was triphasic, governed by two constants, so the experimental data again fitted the complete equation 1.

The parameters of the model (Table 1) present a high degree of variability. The percentage of 5-fluorouracil released during the first stage varied between 21 and 62% and the rate constant k_1 between 0.008 and 0.146 h^{-1}.

During the second phase, the quantities released ranged from 38 to 79% and the k_2 values from 0.011 to 0.025 h^{-1}. In contrast, t_0 (267.28 $\pm$ 1.045 h, n = 3) presented low variability. Drug release lasted 17 days from both 3- and 5-mm implants.

Discussion

Due to numerous factors it is difficult to control the release of water-soluble drugs from biodegradable polymeric matrixes (Breitenbach et al 2000). In this study we have attempted to modulate the release of two low-molecular-weight water-soluble compounds (5-fluorouracil and 5-fluorouridine) from PLGA film implants, to achieve continuous release for at least one month without any burst effect. The release mechanism involves the diffusion of the drug out of the matrix as a consequence of polymer degradation in the release medium (Jain et al 1998). The release rate is influenced by the physicochemical properties of both polymer and drug: average molecular weight, lactide/glycolide percentage in copolymers, drug load, drug solubility in release medium and preparation method (Bodmeier & Chen 1989; Kader & Jalil 1998; Sung et al 1998). In our case, all these variables were kept constant except the drug incorporated. The selected variables in each case were: area of the system (diameter) and number of layers per implant. The film implants were prepared by the solvent evaporation technique as it allows release to be modulated by simply varying the formulation parameters.

The PLGAs are biodegradable polyesters that have been extensively used in the last two decades as matrixes for controlled delivery systems (Kader & Jalil 1998). They are easy to formulate into various devices for carrying a variety of drug classes, such as vaccines, proteins and low-molecular-weight compounds (Jain et al 1998). For this reason, the copolymer selected in this work for the preparation of the film implants was a PLGA. In an ideal situation, the biodegradation time may coincide with the release time. The biodegradation rates of PLGAs, for a given LA/GA proportion, are a function of molecular weight and can range from weeks to months. In this work, the PLGA used for preparing the film implants had an LA/GA ratio of 63:37 and Mw of 47000. The in-vitro degradation of these 5-mm PLGA film discs showed a continuous decrease in the average molecular weights from the onset of the assay. The degradation index (Glynn et al 1976) after 21 days was 4.7, corresponding to Mw of 6600 and Mn of 9900. Since the biodegradation time coincided approximately with the intended release time, this copolymer is especially suitable for our research.

Effect of size and type of implant

5-Fluorouridine implants

The percentage of 5-fluorouridine released during the first phase of release was not influenced by implant size (in films or sandwiches). However, 5-fluorouridine release from sandwiches occurred without the burst effect detectable with the films. This suggests that initial (first 2 h) release from films is due to the drug near the surface of the system dissolving into the release medium. This problem is frequent with this type of drugs, as they are highly soluble in this medium (Bodmeier & Chen 1989; Kunou et al 1995). To solve this problem, the sandwich discs are formed by adding two external polymeric films without drug content, which prevents the drug coming into immediate contact with the release medium. It thus has to be released by diffusion and erosion.

During the second stage, drug delivery proceeds via a mechanism of combined diffusion and erosion. However, though the rate constant during this second stage was slightly higher for sandwiches than films, the analysis of variance results revealed that neither the area (diameter) of the system ($P = 0.142$; $\propto = 0.05$) nor the type of implant ($P = 0.057$; $\propto = 0.05$) influence this significantly. On the other hand, changing the type of implant to a sandwich increased t_0 by an average of 107 h compared with the films ($P = 0.0017$; $\propto = 0.05$). Since this factor corresponds to the time taken for the release rate to increase to a certain level within the second release stage (inflexion point), this increase is in accordance with the greater quantity of polymer present in the sandwich. Although this last parameter increased by an average of 25 h on changing from 3- to 5-mm implants, it was not affected by the area of the system ($P = 0.305$; $\propto = 0.05$).

Release duration was approximately the same for films and sandwiches, being completed in 19 days. Continuous release, free of burst effect, was therefore achieved in the sandwiches although duration of one month was not reached. It is, however, possible to prolong drug delivery by simply adding successive layers of polymer to the sandwich, covering the loaded inner film.

5-Fluorouracil implants

The release profiles for 5-fluorouracil change completely according to the type of implant. In the sandwiches, besides eliminating the burst effect, drug release happens gradually. Size does not influence the release profiles of the films at all, although the initial release from 5-mm sandwiches presented a lag time, absent with those of 3 mm. The high variability in results prevents conclusions being drawn about the model parameters (x_0, k_1, x_{02}, k_2).

In this case the release from films did not fulfil the objective. On the other hand, release from sandwiches complied with the required profile, although as in the case of 5-fluorouridine, the release period was somewhat shorter than would be ideal.

Conclusion

In conclusion, the release profiles obtained from PLGA films differed substantially according to which drug was incorporated. Delivery of 5-fluorouridine was gradual, despite a relatively minor initial burst; it was practically the same as from the sandwiches. 5-Fluorouridine release showed a large burst effect. In contrast, 5-fluorouracil and 5-fluorouridine release from sandwich-type film implants was continuous and lasted nearly 3 weeks, without the burst effect typical of this type of drug from biodegradable polymeric matrixes. Drug delivery was triphasic and was governed by two rate constants (k_1 and k_2), except with 5-mm sandwiches that initially presented a lag time ($x_{01} = 0$ and $k_1 = 0$). This suggests a combined mechanism of both diffusion and polymer erosion.

Therefore, sandwich-type film implants allow release to be modulated by simply adding successive layers of polymer covering to both sizes of central-loaded film. In this way, the burst effect is eliminated in the majority of water-soluble drugs and continuous prolonged release is attained, easily controllable by altering the implant formulation.

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