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# Release of mifepristone from biodegradable matrices: experimental and theoretical evaluations

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**Abstract**

Diffusion of mifepristone in poly [(D,L) lactide-co-glycolide)] films was studied by release experiments. Five 50/50 copolymers of increasing molecular weights were used. The degradation effects were shown by gel permeation chromatography (GPC). Release kinetics show the effect of copolymer molecular weights on diffusion and degradation properties of loaded films. A new theoretical model for drug release from a biodegradable matrix was proposed with two assumptions: correlation of the diffusion coefficient with the polymer molecular weight and existence of a first order degradation kinetic. Higuchi's equation is verified at early time and the diffusion coefficient in the non-degraded polymer can be measured. The degradation constant is determined at long time and is compared with the results of GPC. 

*Keywords:* Diffusion; Poly lactide–glycolide copolymer; Modelling; Controlled release

## 1. Introduction

The lactide–glycolide homo and copolymers are well known for their biodegradability and biocompatibility. Their use for sustained delivery systems has been investigated for a long time. Several parental formulations as microcapsules (Beck et al., 1983; Ogawa et al., 1988), or microspheres (Spenlehauer et al., 1988; Tsakala et al., 1988), have been studied. A wide variety of drugs including contraceptive steroids, cancer drugs or antimalarial agents, peptide hormones, etc. have been investigated using these formulations.

Polymer systems for sustained drug delivery may be based on principles of drug diffusion, polymer degradation or bioerosion, and many factors, including polymer molecular weight, copolymer composition (Pitt et al., 1979; Beck et al., 1983), polymer glass transition, or core loading have an effect on drug release. In pharmaceutical range, physico-chemical and pharmacological properties of steroid hormones often lead to the use of such devices for these molecules.

In the present work, an attempt has been made to particularly show the composition effect of poly [(D,L) lactide-co-glycolide] on diffusion and

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degradation properties of loaded films, which can be regarded as a model of matrix-delivery systems. More particularly, we aimed to evaluate the validity of diffusional laws (Higuchi, 1963) in order to release modelise kinetics of PLGA matrices and to propose improved modelisations to describe concomitant degradation properties. For this study, mifepristone has been chosen as steroid hormone model molecule in relation to further pharmaceutical developments.

## 2. Materials and methods

### 2.1. Materials

The 50/50 (D,L) lactide–glycolide copolymers were furnished by Boerhinger Ingelheim. Five samples of increasing molecular weights and named Resomer® RG503, 504, 505, 506, 508 were chosen. Inherent viscosities were, respectively, 0.4, 0.5, 0.7, 0.8, and 1.2 dl/g and average molecular weights determined by GPC for RG503 to RG506 were Mw = 30 000, 40 000, 60 000 and 70 000. Molecular weight polydispersity was kept in the range 1.7–2.3. For RG508, Mw was estimated to be equal to 120 000 by extrapolation from the RG506 molecular weight value, according to Mark–Houwink equation (Kenley et al., 1987):

$$(\eta)_{inh} = (1.07 \times 10^{-4}) M^{0.761}$$

where $(\eta)_{inh}$ is inherent viscosity (dl/g).

The drug was supplied by Roussel-Uclaf. It was an antiprogestative norsteroid named Mifepristone® (17β-hydroxyl-11β-(4-dimethyl-aminophenyl)-17-(1-propyn) estra-4,9-dien-3-one).

At room temperature, the drug solubility in dichloromethane was 250 mg/ml. At 37°C, it was 34 mg/1 in a 80/20 water/ethanol solution.

### 2.2. Film preparation

Films were prepared by dissolving 10 mg of drug in dichloromethane. Then 500 mg of polymer were added under magnetic stirring, the volume of dichloromethane was adjusted to keep a constant viscosity. The solution was cast on teflon and the solvent was evaporated at a temperature of 95°C and under atmospheric pressure. The films obtained were 80 μm thick.

### 2.3. In vitro release studies

A 80/20 water/ethanol solution allowing drug solubilization and sink conditions was used as release medium. The film was set between the two compartments of diffusion cell. Each compartment contained 60 ml of the release medium. For each system, experiments were realised with three identical cells, which were immersed in a water bath thermostated at 37°C. Aliquots of 3 ml were taken from the receptor medium at different times, and amounts of released drug were assayed by UV spectrophotometry at 311.8 nm. For each experiment, calculations of released drug were made from measurements carried out in the compartment in contact with the evaporation side of the film. The receptor volume was kept constant by adding fresh solution after each sampling.

### 2.4. Characterisation of polymers and films

Copolymer molecular weights were determined by GPC using a Waters 510 pump, a set of two Ultrastyragel® columns with nominal pore size of $10^4$ and 500 Å, and a Waters 410 differential refractometer (Waters, division of Millipore, St Quentin en Yvelines, France). The flow rate of tetrahydrofuran (THF) mobile phase was 1 ml/mn and calibration was made with polystyrene standards. Polymer powders and films after release studies were dissolved in THF to obtain solutions of 0.25 and 0.5% (w/v) concentration depending on the ability of the polymer to dissolve.

## 3. Results and discussion

We propose a strict modelisation, by searching an expression of instantaneous flux, which depends only on the value of the diffusion coefficient at this moment. The integration of the flux will lead to the expression of the release kinetic we are looking for.

The different steps to establish this modelisation may be presented as following. In the case of a planar matrix system which is oversaturated ($C_0 > C_s$), the drug concentration profile in the matrix at time $t$ can be represented following the mechanism where a sharp front is formed between the partly leached part of the matrix and the untouched portion (Fig. 1) ($h$ is the distance between the front and the surface).

At a given time $t$, the diffusion field is limited at the outer part of the matrix system ($h$ thickness), where the drug is solubilized by extraction. The drug is still crystallised in the inner part of the system and no transport process has to be considered. In the diffusion field, we assume that a linear concentration gradient exists (pseudo-steady state condition).

At the solubility interface, the amount of solubilized drug versus the front solubility recession can be evaluated with a good approximation. This amount is equal to the amount of drug released in the assumption of steady state.

$$\mathrm{d}Q = C_0 S\ \mathrm{d}h \tag{1}$$

where $\mathrm{d}Q$ is the amount of drug released, $S$ is the exposed area, and $\mathrm{d}h$ is the recession of the front of solubility during the period $\mathrm{d}t$.

If we assume a homogeneous matrix erosion process and that the chain cleavage follows a law of first order, we obtain the expression of the polymer molecular weight function of time:

$$\frac{\mathrm{d}M}{\mathrm{d}t} = -kM \Leftrightarrow M = M_0 \mathrm{e}^{-kt} \tag{2}$$

where $M$ is the polymer molecular weight at time $t$, $M_0$ is the initial polymer molecular weight, and $k$ is the constant of degradation rate.

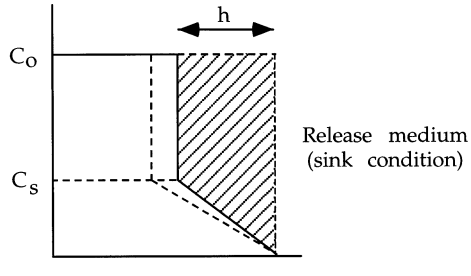


Fig. 1. Schematic diagram of drug concentration at time $t$ ($h$ is the distance between the front and the surface).

If we postulate that the diffusion coefficient $D$ depends on the polymer molecular weight $M$, and varies in inverse ratio to it, we can express the variation of $D$ with time by:

$$\frac{D}{D_0} = \frac{M_0}{M} \Rightarrow D = D_0 \mathrm{e}^{+kt} \tag{3}$$

Considering the mechanism of Fig. 1, the flux is given by Fick's first law used in the domain of linear gradient of concentration:

$$\frac{1}{S}\frac{\mathrm{d}Q}{\mathrm{d}t} = \frac{DC_s}{h} \tag{4}$$

and

$$\mathrm{d}Q = S\frac{DC_s}{h}\ \mathrm{d}t \tag{5}$$

where $C_s$ is the drug solubility in the matrix.

The comparison between Eqs. (1) and (5) leads to:

$$C_0 h\ \mathrm{d}h = DC_s\ \mathrm{d}t$$

and after integration:

$$\frac{1}{2} C_0 h^2 = \int_0^t D_0 C_s \mathrm{e}^{kt}\ \mathrm{d}t = D_0 C_s \frac{\mathrm{e}^{kt} - 1}{k} \tag{6}$$

The kinetic of the recession of the solubility front can be given by the following expression:

$$h^2 = \frac{2D_0 C_s(\mathrm{e}^{kt} - 1)}{kC_0} \tag{7}$$

From Eq. (4), we obtain the flux:

$$\frac{1}{S}\frac{\mathrm{d}Q}{\mathrm{d}t} = \frac{DC_s}{h} = \sqrt{\frac{D^2 C_s^2 C_0 k}{2D_0 C_s(\mathrm{e}^{kt} - 1)}} = \sqrt{\frac{D_0 \mathrm{e}^{2kt} C_s C_0 k}{2(\mathrm{e}^{kt} - 1)}} \tag{8}$$

and after integration, this leads to the expression of the amount of drug released as a function of time:

$$Q = S\sqrt{\frac{2C_0 C_s D_0(\mathrm{e}^{kt} - 1)}{k}} \tag{9}$$

This last equation appears easier to use than the expression of the flux, and will represent the reference of the new modelization that we have to estimate.

It is more feasible in practice to transform this expression into:

Table 1
Parameters of the diffusion–degradation model for different copolymers

| | $A$ (mg per $\sqrt{k}$) | $k$ ($h^{-1}$) | $R$ (S.E.M.) (%) |
|---|---|---|---|
| RG503 | $8.3\times10^{-3}$ | $16.6\times10^{-3}$ | 0.97 |
| RG504 | $7.0\times10^{-3}$ | $11.9\times10^{-3}$ | 0.40 |
| RG505 | $6.6\times10^{-3}$ | $9.8\times10^{-3}$ | 0.39 |
| RG506 | $6.1\times10^{-3}$ | $11.2\times10^{-3}$ | 0.32 |
| RG508 | $5.9\times10^{-3}$ | $4.6\times10^{-3}$ | 0.38 |

$$Q = A\sqrt{\frac{e^{kt}-1}{k}} \quad \text{with} \quad A = S\sqrt{2C_0C_sD_0}$$

At early times ($t$ near 0), $e^{kt} \approx 1 + kt$, and:

$$Q = A\sqrt{t} \quad \text{or} \quad Q = S\sqrt{2C_0C_sD_0t}$$

This last expression which is Higuchi's one where $C_0 \gg C_s$, shows the existence of diffusion process in this new model.

So, the slope at initial time of the graph $Q = f(\sqrt{t})$ allows the determination of coefficient $A$ and then, the product of the initial diffusion coefficient with the drug solubility in the matrix, $D_0C_s$.

At longer times, the exponential law function of time

$$Q = A\sqrt{\frac{e^{kt}-1}{k}}$$

allows to know the degradation constant rate $k$, by iterative numerical optimisation made on the last points of the kinetic.

From this value and by computerised optimisation, a better assessment of $A$ and $k$ can be achieved by directly comparing the experimental and theoretical drug amounts released according to the least squares. The adjustment parameter taken into account for the optimisation is:

$$R\ \text{(S.E.M.)} = \sqrt{\frac{E\,(Q_{exp}-Q_{theo})^2}{N-1}}$$

The results are given in Table 1.

The correlations between the model and experiments with different copolymers are shown in Fig. 2.

We can see that this model is a good representation of the complete release kinetic from a degradable polymer matrix, while Higuchi's model is only a representative of the initial part of experiment.

Table 2
Comparison of $DC_s$ values obtained from Higuchi model and diffusion–degradation model

| | $DC_s$ Higuchi ($\times10^{15}$ g/cm s) | $D_0C_s$ model ($\times10^{15}$ g/cm s) |
|---|---|---|
| RG503 | 13.6 | 4.2 |
| RG504 | 6.0 | 3.0 |
| RG505 | 2.5 | 2.6 |
| RG506 | 2.8 | 2.2 |
| RG508 | 3.2 | 2.1 |

Similarly, a comparison between $DC_s$ values calculated by this model and those obtained by experiment are given in Table 2.

We can see that for RG503 and RG504 copolymers, this model leads to $DC_s$ coefficient values which are twice lower than those obtained by release experiments. This can be explained by the fact that calculation of diffusion coefficient by Higuchi model is made from the slope of $Q = f(\sqrt{t})$ during 100 h. This time is long enough to allow degradation, which facilitates the diffusion process.

On the contrary, $DC_s$ determination by the slope at initial time only concerns the diffusion phenomena in the non-degraded polymer, and the correlation model experiment is the best when the slope is considered on a very short time.

Our model completes the informations on the mechanism of drug transport. It shows that for both copolymers RG503 and RG504, the degradation would modify the diffusion process earlier than we supposed, and may be before physicochemical characterisation could show a notable

Table 3
Comparison of degradation constant $k$ obtained from GPC and diffusion–degradation model

| | $k_{GPC}$ ($\times10^3$) ($h^{-1}$) | $k_{model}$ ($\times10^3$) ($h^{-1}$) |
|---|---|---|
| RG503 | 8.2 | 16.6 |
| RG504 | 8.1 | 11.9 |
| RG505 | 9.5 | 9.8 |
| RG506 | 11.0 | 11.2 |
| RG508 | – | 4.6 |

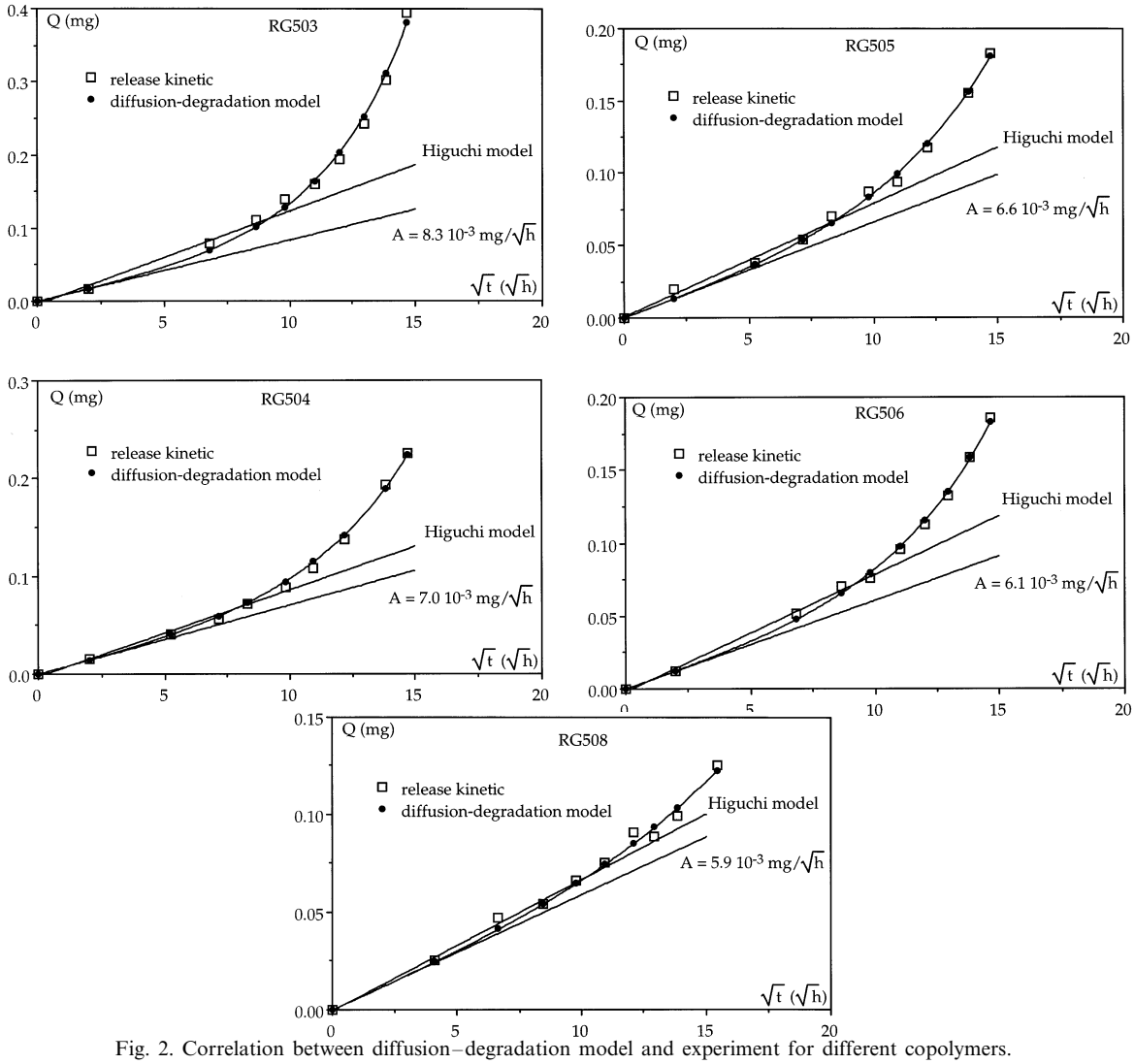


Fig. 2. Correlation between diffusion–degradation model and experiment for different copolymers.

polymer degradation. This is less evident for the other polymers having a higher initial molecular weight, for which degradation has less influence between 0 and 100 h.

If we consider now the degradation constant $k$, we can make a comparison between the values calculated by our model and those measured from the molecular weight determined by GPC after immersion during 4 and 9 days in a water/ethanol solution. If the polymer degradation kinetic follows a first order law as we suppose, the slope of the linear relationship $\ln(\mathrm{Mn}) = f(t)$ must give a constant $k$ value (Fig. 3). A comparison between $k$ values obtained by GPC and those calculated by our model is given in Table 3.

This table shows similar values between the two determinations, in agreement also with evaluations of Kenley et al. (1987) for 50/50 lactide–glycolide copolymers.

The discrepancy observed for RG503 copolymer can be explained by an underevaluation of $k$ by direct characterisation of degradation kinetics, which is not well adjusted by a first-order modelization (Fig. 3).

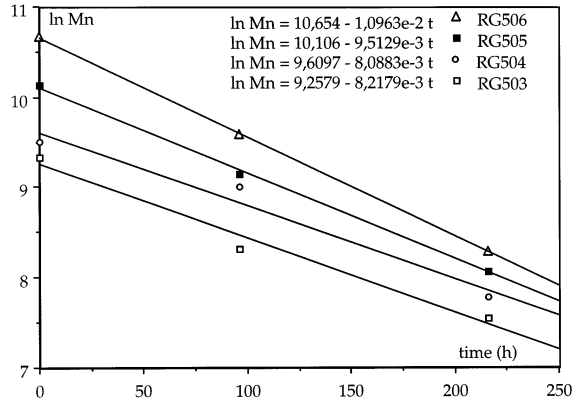


Fig. 3. Evaluation of degradation constant $k$ for different copolymers by the linear relationship $\ln(\mathrm{Mn}) = f(t)$.

## 4. Conclusion

By synthesising our diffusion and degradation studies, we have been able to propose a new theoretical model for drug release from a biodegradable matrix, taking strictly, for the first time, diffusion and degradation phenomena into consideration.

The hypothesis for this model is simple and realistic: correlation of the diffusion coefficient with the polymer molecular weight, existence of a first order degradation kinetic, and similarity of the drug transport conditions with the Higuchi's mechanism hypothesis.

At early time, our model is coherent with Higuchi's equation and we can measure the diffusion coefficient in the non-degraded polymer. At long time, the determination of the degradation constant is possible.

This model shows a good correlation with the experimental results, which could justify considering it for other biodegradable release systems.

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