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Note

The effect of gamma-irradiation on drug release from bioerodible microparticles: a quantitative treatment

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Abstract

The two major objectives of this study were: (i) to monitor the effect of different gamma-irradiation doses (4–33 kGy) on the release kinetics from 5-fluorouracil (5-FU)-loaded poly(D,L-lactide–co–glycolide) (PLGA)-based microparticles, and (ii) to analyze the obtained experimental data with a new mathematical model giving insight into the occurring mass transport phenomena. Drug release was found to depend significantly on the applied gamma-irradiation dose. Interestingly, the obtained release profiles were all biphasic: a rapid initial drug release phase (''burst'') was followed by a slower, approximately constant drug release phase. Surprisingly, only the initial rapid drug release was accelerated by gamma-irradiation; the subsequent zero-order phase was almost unaffected. Importantly, the new mathematical model which is based on Fick's second law of diffusion and which considers polymer degradation was applicable to all the investigated systems. In addition, the gamma-irradiation dose could be quantitatively related to the resulting drug release rate. In conclusion, diffusion seems to be the dominating release rate controlling mechanism in all cases, with a significant contribution of the polymer degradation process.

Keywords: Biodegradable polymers; Mathematical model; Poly(D,L-lactide–co–glycolide); Anticancer agents; Controlled release

Poly(D,L-lactide–co–glycolide) (PLGA)-based microparticles offer various advantages compared to conventional dosage forms, such as the possibility to control the resulting drug release rate accurately over prolonged periods of time, easiness of administration, good biocompatibility and complete bioerosion. Consequently, the practical importance of these advanced drug delivery systems is remarkably increasing. When administered parenterally, gamma-irradiation is often used to sterilize this type of delivery system. It is well known that PLGA undergoes radiolytic degradation during this treatment (Hausberger et al., 1995; Montanari et al., 1998; Bittner et al., 1999), and that the resulting drug release rate increases

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upon gamma-irradiation (Shameem et al., 1999). But, yet up to now, only little knowledge is available concerning the underlying drug release mechanisms and the effect of this sterilization method on the occurring mass transport phenomena.

5-Fluorouracil (5-FU)-loaded PLGA (Resomer® 506; PLGA 50:50; containing 25% D-lactic units, 25% L-lactic units and 50% glycolic units; with a high molecular weight, obtained from Boehringer Ingelheim, Paris, France) microparticles were prepared using an O/W solvent extraction technique in a 5 g scale (drug loading: approximately 20% w/w). The polymer and drug were dissolved and dispersed in dichloromethane, respectively. This organic phase was then emulsified into an aqueous polyvinyl alcohol solution. Upon solvent evaporation, the microparticles were separated by filtration, freeze-dried and sieved. Gamma-irradiation was performed using a ^{60}Co source (Ionosos, Dagneux, France). Drug release studies were conducted by placing microparticles within dialysis bags (molecular weight cut-off 6–8 kDa; Bioblock, Illkirch, France) at the bottom of USP XXIV paddle apparatus glass vessels (Sotax AT7; Sotax, Basel, Switzerland). Phosphate buffer pH 7.4 was chosen as the release medium, kept constant at 37 °C and stirred at 100 rpm. The apparatus was protected from light. At pre-determined time intervals, samples were withdrawn and analyzed UV-spectrophotometrically (Uvikon 922; Kontron, St Quentin en Yvelines, France). Each experiment was conducted in triplicate.

The mathematical analysis of the physical mass transport phenomena is based on Fick's second law of diffusion (Crank, 1975):

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial c}{\partial t}\right) + \frac{\partial}{\partial y}\left(D\frac{\partial c}{\partial y}\right) + \frac{\partial}{\partial z}\left(D\frac{\partial c}{\partial z}\right).$$

Here, c and D are the concentration and the diffusion coefficient of the diffusing species, respectively; t represents time, and x, y and z the three spatial coordinates. The spherical geometry of the microparticles is considered as well as the contribution of polymer degradation. Upon contact with the release medium, water imbibes into the system, leading to hydrolytic polymer chain cleavage. The resulting decrease in the macromolecular weight leads to an increase of the polymer chain mobilities and, thus, to non-constant drug diffusion coefficients. The respective partial differential equations were solved numerically, using the programming language C++ (Borland C++ V.5.0 Developer).

Fig. 1 shows the significant effect of the applied gamma-irradiation dose on the resulting drug re-

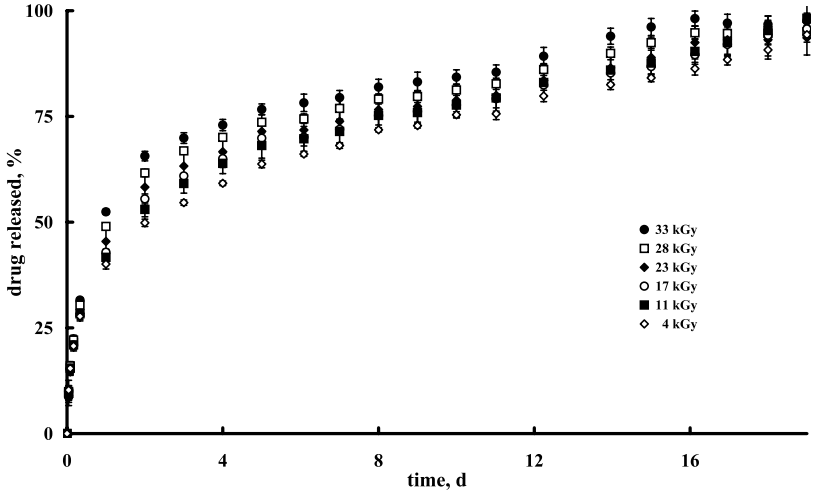

Fig. 1. Effect of the gamma-irradiation dose on the resulting, experimentally measured release kinetics of 5-FU from PLGA-based microparticles (the applied gamma-irradiation dose is given in the figure).

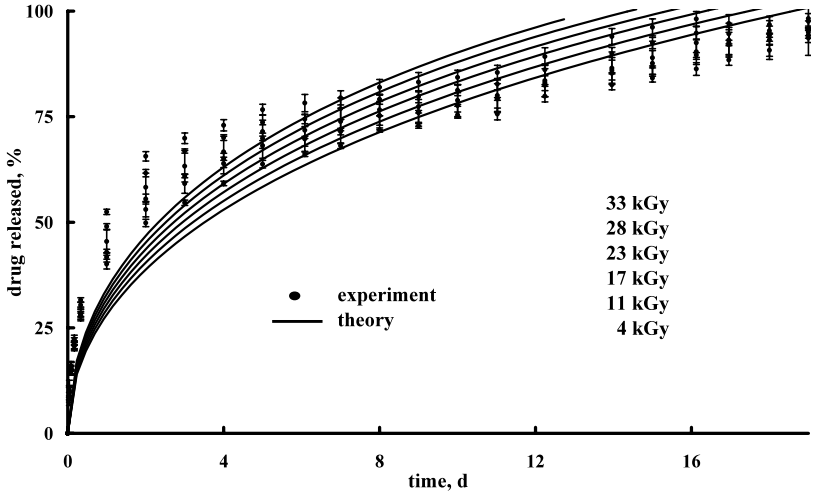

Fig. 2. Comparison of the mathematical model and the experimentally measured release data of 5-FU from PLGA-based microparticles.

lease kinetics. Interestingly, the obtained release profiles were all biphasic: a rapid initial drug release phase ("burst") was followed by a slower, approximately constant drug release phase (zero-order kinetics). As expected, the release rate increased with increasing gamma-irradiation dose. This can be explained with the free volume theory of diffusion: During exposure to the gamma-irradiation source, random polymer chain scission occurs (Mohr et al., 1999), and the average macromolecular weight decreases. This leads to a decrease of the extent of polymer chain entanglement and to an increased mobility of the macromolecules. Consequently, the free volume available for diffusion and, thus, the probability that a drug molecule can jump from one cavity into another increase. Hence, the resulting drug release rate increases. With increasing gamma-irradiation dose this effect becomes more pronounced. Importantly, only the initial rapid drug release phase was affected, not the subsequent constant drug release phase (Fig. 1).

As can be seen in Fig. 2, rather good agreement between theory and experiment was obtained when fitting the mathematical model to the experimentally determined drug release data. This was the case independent of the applied gamma-irradiation dose. Thus, the underlying chemical reactions and physical mass transport phenomena controlling the release rate of the drug out of this type of controlled drug delivery system do not seem to be altered by the gamma-irradiation process. Diffusion is likely to be the dominating mechanism in all cases, with a significant contribution of the polymer degradation process. However, it has to be pointed out that there are systematic deviations between the theoretical and experimental values (underestimation of drug release at early time points and overestimation at late time points), indicating that the mathematical model does not take into account all the important physicochemical processes occurring during drug release.

The practical benefit of this model is the possibility to predict the effect of a new, different gamma-irradiation dose on the resulting drug release rate.

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