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Theoretical approach to the destruction or sterilization of drugs in aqueous solution

Catherine Slegers*, Bernard Tilquin

Université Catholique de Louvain, Unité d'Analyse Chimique et Physico-chimique des Médicaments, CHAM 7230, Avenue E. Mounier, 72, B-1200 Bruxelles, Belgium

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Abstract

Two novel applications in the radiation processing of aqueous solutions of drugs are the sterilization of injectable drugs and the decontamination of hospital wastewaters by ionizing radiation. The parameters influencing the destruction of the drug in aqueous solutions are studied with a computer simulation program. This theoretical approach has revealed that the dose rate is the most important parameter that can be easily varied in order to optimize the destruction or the protection of the drug.

Keywords: Radiation processing; Radiosterilization; Decontamination; Drugs; Wastewater; Computer simulation

1. Introduction

Radiation processing techniques have evolved so that radiosterilization has become the first choice for thermosensitive solid state drugs as described in the EMEA decision trees for the selection of sterilization methods (EMEA, 2000). However, the use of ionizing radiation for drugs in aqueous solution is not even considered. There is a consensus that radiosterilization should not be applied to drugs in aqueous solution because of the greater degradation of the drug compared to the solid state (Boess and Bögl, 1996; IAEA, 1995; Nordhauser and Olson, 1998). The destruction of the drug in aqueous solution by ionizing radiation is very useful for the decontamination of hospital wastewater, a novel application in radiation processing. While the radiolysis of water is extensively documented (Ferradini and Pucheault, 1983; Spinks and Woods, 1990), there is a lack of knowledge concerning the fundamental mechanisms of the destruction of drugs in aqueous solution.

The degradation of a drug solute in aqueous solution is brought about by the attack of free radicals generated by the water radiolysis and depends on several parameters such as the absorbed dose, the dose rate, the temperature and the drug concentration. In this preliminary work, these parameters are studied with the use of a computer simulation program at room temperature. The computer simulation program will play a vital part in determining how each parameter influences the degradation of the drug and thus in optimizing the sterilization of drugs in aqueous solution and decontamination of hospital wastewater.

2. Experimental: computer simulation

Chemsimul® is used to simulate the radiolysis of drugs in aqueous solution. Chemsimul® is a simulator

*Corresponding author. Tel.: +32 2 764 72 31; fax: +32+2 764 72 96.
E-mail address: catherine.slegers@cham.ucl.ac.be (C. Slegers).

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for complex chemical kinetics and solves the non-linear differential equations of the reaction rates of all the species in the irradiated solution. The simulation program is suitable to the radiolysis of aqueous solutions as it allows the input of the radiation chemical yields, the absorbed dose and the dose rate of the ionizing radiation. The 30 or more reactions of the water radiolysis used in the computer simulation program are well documented in other publications (Bjergbakke et al., 1984).

In this study the hydroxyl radical is chosen as the free radical responsible for the degradation of drugs in aqueous solutions as it readily reacts with many organic compounds (Ferradini and Pucheault, 1983; Spinks and Woods, 1990). Rate constants of 10^8 and $10^{10}\,M^{-1}\,s^{-1}$ (Buxton et al., 1988) are incorporated into the simulation to study the effect of the hydroxyl radical reactivity towards the drug solute.

To study the influence of the conditions of irradiation, the absorbed dose and the dose rate are purposely varied. The absorbed doses used in the simulation program range from 0 to 5 kGy, consistent with the values that are easily achieved in industrial irradiators. Dose rates of 1 kGy/10 s and 1 kGy/10 ms are used to represent traditional irradiators and a high dose rate of 1 kGy/10 ns to represent the upper limit of new electron beam accelerators.

To study the influence of the drug formulation, different solute concentrations ranging from 10^{-5} to 10^{-3} M are used to represent trace amounts found in hospital wastewaters and higher concentrations found in injectable drugs.

3. Results and discussion

The first simulation (Fig. 1) shows the destruction of a drug (10^{-3} M) with a rate constant of $10^8\,M^{-1}\,s^{-1}$ with the hydroxyl radical, as a function of the irradiation dose. This simulation studies the influence of the irradiation dose rate on the loss of potency of the drug. For very high dose rates (1 kGy/10 ns) the destruction of the drug at 5 kGy is negligible and comparable to that of other sterilization methods of the European Pharmacopoeia (EP, 2001). However, at traditional (1 kGy/10 ms) and lower (1 kGy/10 s) dose rates, the destruction of the drug is fast and complete after a few kGys. This protective effect of the dose rate could be due to the high radical–radical recombination in the ionization spurs before radicals have time to diffuse and react with drug solute molecules. A promising research would be the use of extremely high-dose rates for sterilization of drugs in aqueous solutions. Gamma irradiators (1 kGy/h) are therefore not suited for radiosterilization of aqueous solutions but could be useful for the destruction of drugs in hospital wastewaters.

The second simulation (Fig. 2) studies the influence of the drug solute concentration on the destruction of the drug as a function of the absorbed dose. The reaction rate constant with the hydroxyl radical is $10^8\,M^{-1}\,s^{-1}$ and a traditional electron-beam dose rate of 1 kGy/10 ms is used. For trace amounts (10^{-5} M or less), such as can be found in hospital wastewaters, a low-irradiation dose of 2 kGy is enough to completely destroy the drug solute. In injectable drugs, the concentration of the drug solute ranges from 10^{-4} to 10^{-3} M, and depends on the drug formulation. The lower the drug solute concentration, the quicker its degradation because as the absorbed dose is increased the amount of reactive hydroxyl radicals formed in solution is increased. The decontamination of hospital wastewaters by low irradiation doses is very feasible, while the sterilization of drugs in aqueous solution depends on the formulation.

The third simulation (Fig. 3) uses an average drug solute concentration of 10^{-3} M with a traditional dose

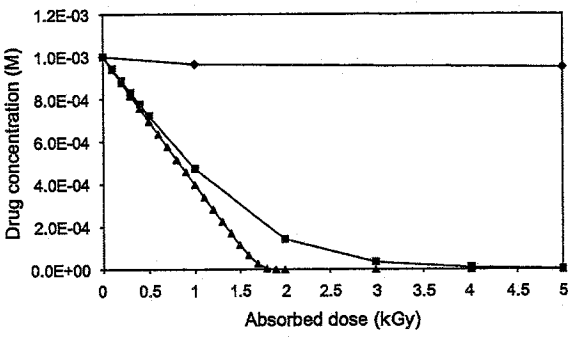

Fig. 1. Drug solute concentration (M) as a function of the absorbed dose (kGy) for an irradiation dose rate of 1 kGy/10 ns (♦), 1 kGy/10 ms (■), and 1 kGy/10 s (▲). Drug solute concentration of 10^{-3} M and reaction rate constant of $10^8\,M^{-1}\,s^{-1}$ with the hydroxyl radical.

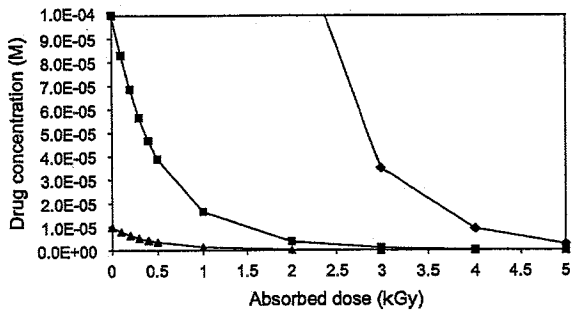

Fig. 2. Drug solute concentration (M) as a function of the absorbed dose (kGy) for a drug solute concentration of 10^{-3} M (♦), 10^{-4} M (■), and 10^{-5} M (▲). Dose rate of 1 kGy/10 ms and reaction rate constant of $10^8\,M^{-1}\,s^{-1}$ with the hydroxyl radical.

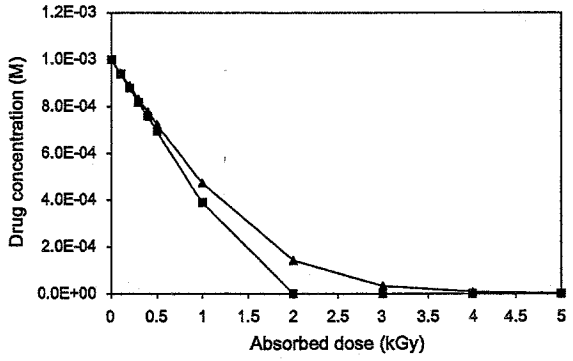

Fig. 3. Drug solute concentration (M) as a function of the absorbed dose (kGy) for a reaction rate constant of $10^8\,M^{-1}\,s^{-1}$ (▲) and $10^{10}\,M^{-1}\,s^{-1}$ (■) with the hydroxyl radical. Drug solute concentration of 10^{-3} M and irradiation dose rate of 1 kGy/10 ms.

rate of 1 kGy/10 ms to study the effect of the reactivity of the drug towards the hydroxyl radical. A difference of 100 in the reaction rate constant with the hydroxyl radical reduces by a factor of 2, the absorbed dose of destruction.

This theoretical work will be validated by the analysis of the final products of radiolysis of drugs in aqueous solution.

4. Conclusion

The most important parameter that can be controlled with modern electron-beam accelerators and that influences the degradation of the drug in aqueous solutions is the dose rate of irradiation. If the destruction of the drug solute is sought after for the decontamination of hospital wastewaters, medium or low-dose rates are to be used. Only very high-dose rates (1 kGy/ns) are promising for the radiosterilization of drugs in aqueous solution.

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