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Modelling of release kinetics of drugs from irradiated NaCMC matrix

P. Sébert [a,*], E. Bourny [a], A. Benghalem [b], J.M. Vergnaud [b], M. Rollet [a]

[a] *Laboratoire de Pharmacie Galénique Industrielle et Biogalénique, Faculté de Pharmacie, I.S.P.B., Domaine Rockefeller, 69373 Lyon Cedex 08, France*

[b] *Laboratoire de Chimie des Matériaux et Chimie Industrielle, Faculté des Sciences et Techniques, 23 rue du Docteur Paul Michelin, 42023 Saint Etienne Cedex 2, France*

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Abstract

The purpose of this work was to study the release kinetics of an active substance from a solid structure after irradiation, in order to examine the possible modifications induced in drug delivery. This method of sterilization seems to be convenient for obtaining sterile parenteral or ophthalmic dosage forms. The problem of controlled release of drug from a polymeric matrix is very complex. In this case, the phenomena take place under transient diffusion and the transfer of matter is controlled by diffusion. The modelling of the process has been successfully tested, by comparing experimental and calculated values. The diffusivity of the liquid through the various dosage forms increases significantly with irradiation.

Key words: Sodium carboxymethylcellulose; Gamma irradiation; Matrix; Release kinetics

1. Introduction

The first object of this work was to prepare sustained release parenteral or ophthalmic solid dosage forms, sterilized by gamma irradiation, which could be 'inserts' of different shapes: flat or long cylinders or spherical microparticles which include only an hydrophilic polymer and an active substance. It appears to be essential to demonstrate that the method of sterilization, selected on account of its efficiency and of the possibility of sterilizing these dosage forms into their final packaging (Sébert et al., 1988), does not modify the release kinetics of the active substance (diffusion). Thereby, a cylinder of defined shape and size (flat tablet) only composed of the hydrophilic polymer (NaCMC) and of the tracer (sodium salicylate) was used. The release kinetics before and after irradiation at different doses were studied. A study on the evolution of the physicochemical and technological properties of this polymer has recently been published (Sébert et al., 1994).

The second purpose in this study was to develop and test a model able to describe the process of drug delivery. With a constant diffusivity,

* Corresponding author.

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an analytical solution for the problem exists, which is equal to the product of the solutions obtained for plane sheet with one directional diffusion and for radial diffusion through a cyclinder of infinite length (Vergnaud, 1991). Moreover, as the tangent of the kinetic curves is not vertical at the beginning of the process, the coefficient of matter transfer in the liquid next to the surface of the dosage form is finite (Vergnaud, 1992).

2. Materials and methods

2.1. Raw materials

NaCMC is a cellulose carboyxmethyl ether sodium salt. The material used was a Blanose® cellulose gum (Aqualon, 1990). The type selected was Blanose® 7 HCF which presents a substitution degree near 0.7 and a polymerization degree close to 2000. In aqueous solution (1%) at 25°C, the viscosity value is intermediate between 1500 and 2500 mPa s. The active substance used as a tracer was sodium salicylate.

2.2. Irradiation

Dry powders of NaCMC were irradiated with gamma rays emitted by a radioactive isotope (^{60}Co). The radiation energies were 1.17 and 1.33 MeV. The power of the source and the dose rate were 2.0×10^5 GBq and 1.2 kGy/h, respectively. The samples of NaCMC received three irradiation doses: 5, 15 and 25 kGy. One non-irradiated sample was kept as a reference.

2.3. Tablet formulation

The tablet formulation engaged could be applied to implants, inserts or spherical microparticles. It was a simple blend of NaCMC (85%) and sodium salicylate (15%).

2.4. Preparation of tablets

After blending the two components with a Turbula mixer (5 min), wetting was performed by spraying water until suitable consistency was attained (60 ml of water per 100 g of the powder mixture). The wet granulation was forced, by hand, through a 2 mm screen. The granulate was then dried into a tray dryer (60°C, 4 h). After drying, dry grinding was carried out on a Frewitt GLA-ORV oscillating mill with a 1 mm opening sieve. Sifting was performed on an Erweka VT vibrating sieve and particles included between 315 and 750 μm were kept. An alternative Frogerais press (Esstic 55) with flat punches (11 mm diameter) was used for compression. No modification of the initial setting, carried out on the non-irradiated reference batch, was effected for the other batches (1–25 kGy). The tablets were prepared individually; the mass was precisely weighed to 500 mg and the hardness adjusted from 60 to 70 N. With this fine adjustment, the tablets were 4.3 mm thick.

2.5. Drug release

The release of sodium salicylate was examined on the apparatus described in P.F.X. This study was carried out in 500 ml of physiological aqueous solution (NaCl 9‰) in order to reflect the ionic strength of the body fluids. The temperature was adjusted to 37 ± 1°C and regular sampling was effected during 12 h. The released sodium salicylate was then determined by UV spectrophotometry at 300 nm.

2.6. Diffusion study: Theoretical aspects

2.6.1. Assumptions

Some assumptions were made in order to clarify the problem:

(i) The dosage forms have the shape of a solid cylinder with finite length.

(ii) The process of delivery of the drug is controlled by transient diffusion. Only the drug transfer is considered, in spite of the fact that the whole process is far more complex: diffusion of liquid into the dosage form enabling the drug to leave the dosage form through the liquid located in it (Armand et al., 1987; Liu et al., 1988).

(iii) As the tangent at the origin is not vertical to the kinetic curves of drug delivery, a coeffi-

cient of matter transfer of finite value at the surface of the dosage form is evaluated.

(iv) An attempt is made to attain constant diffusivity of the drug, and the equation of diffusion has thus an analytical solution.

(v) The initial concentration distribution of the drug is uniform throughout the dosage form.

(vi) The volume of the surrounding liquid is so large that the whole amount of drug initially in the dosage form is delivered after infinite time. Moreover, the concentration of drug in the liquid is very low and negligible.

2.6.2. Mathematical treatment

The equation of transient diffusion through the cylinder of finite length with constant diffusivity is:

$$\frac{\partial C}{\partial t} = D\left[\frac{\partial^2 C}{\partial z^2} + \frac{\partial^2 C}{\partial r^2} + \frac{1}{r}\cdot\frac{\partial C}{\partial r}\right] \quad (1)$$

where the contributions of longitudinal and radial diffusion are represented by the term on the right.

The initial condition is as follows:

$$t = 0 \quad -L < x < L \quad C = C_{in} \quad (2)$$

and

$$0 < r < R$$

and the boundary conditions:

$$t > 0 \quad x = \pm L \quad -D\left[\frac{\partial C}{\partial x}\right]_L = h(C_L - C_{eq}) \quad (3)$$

or

$$r = R \quad -D\left[\frac{\partial C}{\partial r}\right]_R = h(C_R - C_{eq}) \quad (4)$$

express the fact that the rate of drug delivery is constantly equal to the rate at which the drug is brought to the surface by internal diffusion.

In the above, h is the coefficient of matter transfer on the surface (cm/s). $(\partial C/\partial x)_L$ and $(\partial C/\partial r)_R$ are the gradients of concentration of the drug next to the plane surface and the cylindrical surface, respectively.

C_L and C_R are the actual concentration of drug on the plane and cylindrical surfaces, respectively, and C_{eq} denotes the concentration of drug on the surface required to maintain equilibrium with the surrounding liquid.

The analytical solution for diffusion through the solid cylinder of finite length is the product of the two solutions obtained with either longitudinal or radial diffusion (Vergnaud, 1991, 1993):

$$\frac{M_\infty - M_t}{M_\infty} = \sum_{n=1}^{\infty} \frac{4S^2}{\beta_n^2(\beta_n^2 + S^2)} \exp\left(-\frac{\beta_n^2}{R^2} Dt\right) \cdot \sum_{m=1}^{\infty} \frac{2T^2}{\lambda_m^2(\lambda_m^2 + T^2 + T)} \exp\left(-\frac{\lambda_m^2}{L^2} Dt\right) \quad (5)$$

where the β_ns are the roots of:

$$\beta \cdot J_1(\beta) = S \cdot J_0(\beta) \quad (6)$$

J_0 and J_1 being the Bessel functions of the first kind of order, 0 and 1, respectively, and S is the dimensionless number:

$$S = h \cdot R / D \quad (7)$$

and where the λ_ns are the roots of:

$$\lambda \cdot \tan \lambda = T \quad (8)$$

with the dimensionless number T:

$$T = h \cdot L / D \quad (9)$$

L being half the length of the cylinder.

The values of the β_ns and λ_ns are available in various books (Vergnaud, 1991, 1992) for different values of the parameters S and T.

3. Results and discussion

The release of sodium salicylate is reported in Fig. 1. We can note that the release is not complete after 12 h with the non-irradiated sample; on the other hand, almost all of the tracer is liberated after 10 h with the 5 and 15 kGy doses and after 8 h with the highest dose (25 kGy). We observed a difference of 25% appearing between 0 and 25 kGy after 8 h and of 15–17% between 0 and 5–15 kGy after 10 h. We can relate this fact more closely to the viscosity decrease observed after irradiation on the NaCMC fluid gels (Sébert

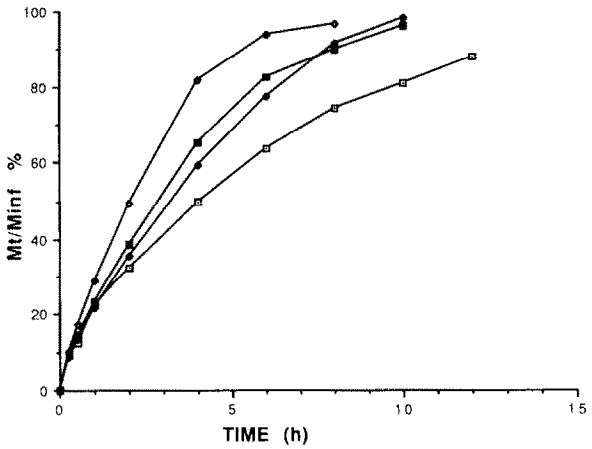

Fig. 1. Tracer liberation: (□) 0 Gy; (♦) 5 Gy; (■) 15 Gy; (◇) 25 Gy.

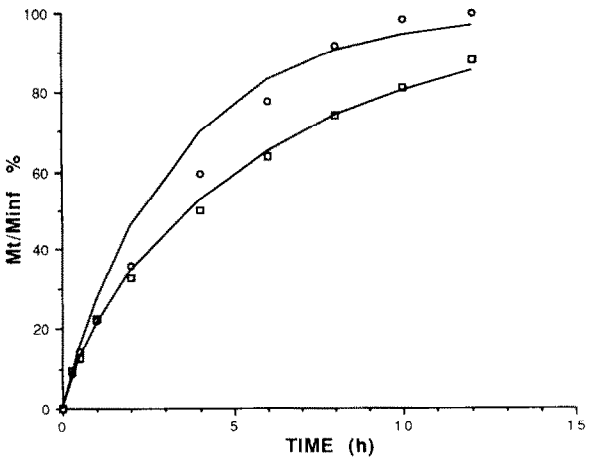

Fig. 2. Release of the drug: dosage form treated at 0 and 5 kGy: (continuous line) theoretical; (□) experimental, 0 Gy; (○) experimental, 5 Gy.

et al., 1994). The study of diffusion parameters therefore holds considerable interest.

The kinetics of drug delivery determined either by experiments or via calculation using the analytical solution and the values of the parameters shown in Table 1 are depicted in Fig. 2 (0 and 5 kGy) and Fig. 3 (15 and 25 kGy). The following conclusions are worth noting: (i) rather good agreement is obtained between the experimental and calculated kinetics, except perhaps sometimes at the end of the process; (ii) the process is described by transient diffusion with a constant diffusivity; (iii) moreover, the coefficient of matter transfer at the liquid-solid interface is not infinite, and the dimensionless numbers S and T are not very high. Of course, the coefficient of matter transfer is the same in the four cases, as it depends only on the operational conditions of the test: especially the nature and rate of stirring of the liquid, and to a lesser extent the dimensions and shape of the dosage form; (iv) the value of the diffusivity increases with the intensity of treatment of the dosage form.

For the various specimens, the values of S and T are between 0.1 and 18, meaning that the process is controlled by internal diffusion through the dosage form and by the matter transfer on the surface. The following statement is of interest: when the values of the dimensionless numbers are greater than 50, the coefficient of matter transfer on the surface is so high with respect to

Table 1
Parameters for matter transfer

Dose (kGy)	D ($\times 10^6$) (cm^2/s)	h ($\times 10^5$) (cm/s)
0	0.8	1.3
5	4	1.3
15	4	1.3
25	30	1.3

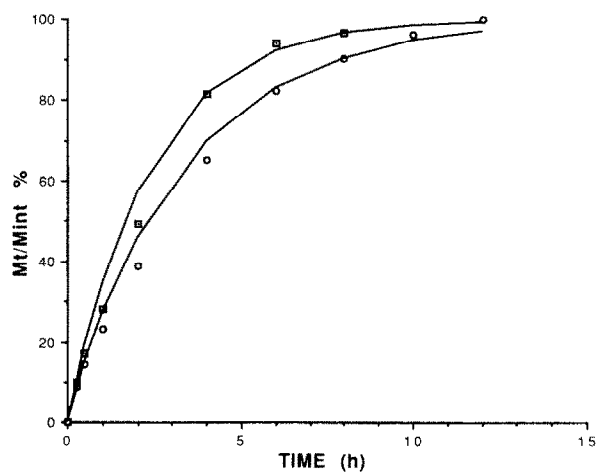

Fig. 3. Release of the drug: dosage form treated at 15 and 25 kGy: (continuous line) theoretical; (○) experimental, 15 Gy; (□) experimental, 25 Gy.

the diffusivity that it can be considered as infinite, signifying that the process is controlled only by diffusion. When the dimensionless numbers S and T range from 0.1 to 18, the process is controlled by the diffusion of the substance through the solid and also by diffusion of the substance in the surrounding liquid next to the surface of the dosage form, so that stirring at a higher rate can improve the rate of delivery.

4. Conclusions

We have observed that irradiation increases the rate of delivery of a drug included into a sustained release dosage form of the NaCMC matrix type. This observation has been confirmed by determining the kinetics of drug delivery. Therefore, it should be interesting to initiate an in vivo study in order to examine the modifications induced in this parameter by irradiation.

These changes in diffusion involved the selection of the only necessary and sufficient irradiation dose to sterilize the pharmaceutical dosage form, in accordance with the initial level of microbiological contamination of the preparation.

This kinetics of release were found to be controlled by transient diffusion through the dosage form with a finite coefficient of matter transfer through the solid-liquid interface. The coefficient of matter transfer on the surface was about the same for all dosage forms, meaning that experiments were performed under identical conditions, in particular, at the same rate of stirring. These results of main interest are concerned with the diffusivity that increases with the irradiation dose.

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