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Controlled release of drug encapsulated as a solid core: Theoretical model and sensitivity analysis

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ABSTRACT

The object of the present work is one of the new devices used to deliver the drug at a controlled release rate: microparticles made up of a solid drug core surrounded by a polymer coating.

A theoretical model has been developed to describe the release of the microencapsulated solid active principle: the diffusion process has been modelled in detail and the temporal evolution of the drug concentration profile has been evaluated in the polymer shell and in the encapsulated solution.

Then a sensitivity analysis has been carried out to investigate the influence of certain system characteristics and operating conditions on the lag time, on the core dissolution time and on the release curve.

Keywords: Drug-controlled release; Diffusion; Pharmaceuticals; Polymeric microcapsule; Mathematical modelling; Simulation

1. Introduction

Controlled release systems, that is systems that release the drug in a controlled fashion to maintain an appropriate concentration for a long period of time, are of great interest.

As a matter of fact they allow to achieve more effective therapies while eliminating the potential for both under- and overdosing and permit the maintenance of drug levels within a desired range, leading to a better use of the drug in question and to a reduction of the drug administrations required, thus improving patient's life.

Different devices may be used (micro or nanoparticles, plasters, osmotic pumps, ...), and different types of release may be requested (continuous, pulsatile), according to the medicine that has to be taken.

In polymeric microparticles the polymer must be both biodegradable and biocompatible while the drug may be encapsulated as a solid core, as a solution, or dispersed in the polymer matrix. In these systems several mechanisms may be responsible for the release of the therapeutic agent: erosion of the polymer coating, diffusion of the drug through the polymer layer, dissolution of the drug in the surrounding medium. The relative importance of each mechanism varies from system to system.

Many researches about controlled release systems have been carried out so far.

Many of them aim at optimising the preparation method in order to increase the encapsulation efficiency and to obtain a desired release profile. In order to do that, experimental investigations on different preparation methods, process conditions and materials are carried out, to identify the influence of the different parameters on drug loading, on microparticles morphology, on polymer structure and consequently on the resulting release curve, as reported in the works of Birnbaum et al. (2000), Jain et al. (2000), Ko et al. (2002) and Jeong et al. (2003).

Other studies, like those carried out by Benoit et al. (2000) and Cleland (1998), aim at tailoring the microparticle formulation process for specific applications such as delivery of drugs to the central nervous system, delivery of vaccines, etc.

Besides there are works, like the current research, where attention is focused on the mathematical modelling of the release process. Some of them have considered coated particles, with a matrix core in which the drug is dispersed, surrounded by a coating.

A detailed analytical model of the drug release was developed by Lu and Chen (1993), providing first a general analytical solution and then special solutions valid when

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Nomenclature

A	dimensionless group, def. in Eq. (11)
A_v	ratio of the volume of the external solution (relative to the microparticle) to the volume of the microparticle (dimensionless)
B	dimensionless group, def. in Eq. (11)
c_{le}	total concentration of external solution (mol m^{-3})
c_{li}	total concentration of internal solution (mol m^{-3})
c_{tot}	total concentration of polymeric coating (mol m^{-3})
D_{dp}	drug diffusivity within the polymer coating (m^2 s^{-1})
D_{dw}	drug diffusivity in water (m^2 s^{-1})
D_{wp}	water diffusivity within the polymer coating (m^2 s^{-1})
K_{dp}	drug partition coefficient on the polymer coating (dimensionless)
K_{wp}	water partition coefficient on the polymer coating (dimensionless)
M_d	drug molar mass (kg mol^{-1})
n_d	number of active principle moles (mol)
r	radius (m)
R%	percentage of drug released in the external solution (dimensionless)
R_e	microcapsule outer radius (total microcapsule radius) (m)
R_i	inner microcapsule radius (m)
t	time (s)
t_{dis}	solid core dissolution time (s)
t_{pen}	penetration time (s)
V_e	volume of the external solution relative to the single microparticle (m^3)
x_{de}	drug molar fraction in the external liquid solution (dimensionless)
x_{di}	drug molar fraction in the internal liquid solution (dimensionless)
x_{dp}	drug molar fraction in the polymer coating (dimensionless)
$x_{d,sat}$	active principle molar fraction at saturation point in water (dimensionless)
x_{we}	water molar fraction in the external liquid solution (dimensionless)
x_{wp}	water molar fraction in the polymer coating (dimensionless)

Greek symbols

α	ratio between microcapsule internal and external radius (dimensionless)
γ	ratio between water molar fraction in saturated solution and the one in external solution (supposed constant and equal to the initial value) (dimensionless)
Γ	dimensionless drug concentration
Γ_{wp}	dimensionless water concentration
ϑ	dimensionless time defined for drug diffusion
ϑ_{dis}	dimensionless dissolution time
ϑ_{pen}	dimensionless penetration time
ϑ_{wp}	dimensionless time defined for water penetration
ξ	dimensionless radius (ratio between radius and microcapsule external radius)
ρ_d	drug density (kg m^{-3})

certain assumptions hold; Lu and Chen (1995) also examined the effects exerted on the release by different initial drug concentration profiles in the coating (lag time, burst effect, pseudo-stationarity). In both works the particles were considered spherical and non-deformable; the effect of a possible deformation of the coating and of the matrix on the local drug release and on the average release rate was investigated by Lee and Liao (1995) and Liao and Lee (1997).

The case of a polymeric matrix in which the drug is dispersed has also been considered. A mathematical model has been proposed by Faisant and his group (2003) to describe the release curve variation with the irradiation intensity to which the polymer coating (PLGA) is subjected; Narasimhan and Langer (1997) elucidated the burst effect in an essentially zero-order-controlled release coated hemispherical polymeric device containing a single small orifice in its centre face, to examine how it changes with parameters like drug solubility and diffusion and so how it can be manipulated to advantage. Planar matrices were the object investigated by Frenning (2003) whose purpose was to examine the effect of the finite dissolution rate on the drug release profile from a matrix assumed initially fully wetted by the solvent and containing finely dispersed solid drug. Multi-laminate structures were modelled by Charalambopoulou et al. (2001), who investigated the effect of the incorporation of supersaturated matrices in the formation of multi-laminate devices, with spatial variation of drug loading.

Bioerodible-controlled drug delivery systems were modelled by Siepmann and Göpferich (2001), who focused their attention on erosion-controlled release, much less investigated so far than diffusion-controlled or swelling-controlled release. The phenomenon of polymer erosion was also modeled by Kiil and Dam-Johansen (2003), who mathematically described swelling, diffusion, and erosion front movements in a high-viscosity HPMC matrix.

Aqueous–organic partition-based system (in which drug molecules are initially present in solution or dispersed in a reservoir bounded by a microporous membrane whose pores are filled with a liquid immiscible with the reservoir phase liquid) were instead the object of many researches by Farrell and Sirkar (1999, 2001), who modelled the diffusion of a drug initially present in the reservoir as a solution and then as a solid dispersed phase, above saturation concentration, so describing also the process of drug dissolution.

Coated pellets with granular core, in which the solid drug is dispersed, surrounded by a coating, were modelled by Borgquist et al. (2002) and Frenning et al. (2003). Borgquist et al. (2002) considered a pellet with a core made up of remoxipride (80%) and microcrystalline cellulose (MCC) and formulated a mathematical model with the assumption of instantaneous water penetration and perfectly mixed solutions (internal and external); Frenning et al. (2003) investigated the effect on the release curve of parameters related to the porosity of the pellet core and the solubility of the drug in the dissolution medium for a pellet made up of MCC containing 10 wt% dispersed salicylic acid (SA) in the initial state, coated by a thin layer of ethyl cellulose.

A different system in which the drug was not dispersed, but effectively bound to the polymer, was investigated by Abdekhodaie and Wu (2008); in this case drug ions are bound to the polymeric matrix and are exchanged with counterions coming from the external solution and not only diffusion but also ion-exchange must be described. The assumption of diffusion-controlled process was made and a local equilibrium was assumed between free and bound solute (Langmuir isotherm). The effects exerted on the release rate by the salt concentration in the external solution, by the valence of cations and by Langmuir constant were investigated.

In capsules the active principle is usually present as a solid drug core surrounded by a coating. Also works on the release of substances other than drugs can be of interest. Lu and Lee (1992) studied the controlled release from an urea ball (15 mm) with a latex coating. Their mathematical model described the dissolution of the solid encapsulated, the diffusion and exhaustion of the internal solution. The process of water penetration was not described and the diffusion in the coating was modelled with the assumption of pseudo-stationarity.

The same assumption was also made by Koizumi et al. (2001), who described the release of a drug from a chitosan-coated tablet; in this case however the coating was considered dissolving with time.

The effect of particle size distribution on the release rate was investigated by Sirotti et al. (2002), who developed a mathematical model for the release of a drug from a polydisperse population of spherical microcapsules. In the model the assumption of perfectly mixed solutions (internal and external) and of a linear drug concentration in the coating were made.

In the model proposed by Manca and Rovaglio (2003) the diffusion process was not modelled in detail and the drug diffusion fluxes were evaluated using the global mass transfer coefficients instead of following the temporal evolution of the drug concentration profile in the coating.

In the present model drug concentration profiles have been modelled with great detail, without making the simplifying assumption of pseudo-steady state, for both polymer coating and internal solution, and their temporal evolution was followed. The external solution was not considered a perfect sink, as in previous works, and the accumulation of the drug released was considered.

Besides, in the present work, the process of water penetration was not assumed instantaneous, but was modelled considering a finite rate and the evaluation of the penetration time (that may represent an important contribution to the lag time) was given. The same was done for the dissolution of the solid drug, leading to the estimation of the solid dissolution time.

The choice to model in detail every step of the process, without making simplifying assumptions based on possible differences in the rates of these steps and so without identifying a controlling step and assuming instantaneous the others, was done in order to build a mathematical framework capable to describe the largest possible number of systems.

Eventually a sensitivity analysis of the system with the equations written in dimensionless form, to be as general as possible, has been carried out with the aim to investigate the influence exerted by different parameters on the release process.

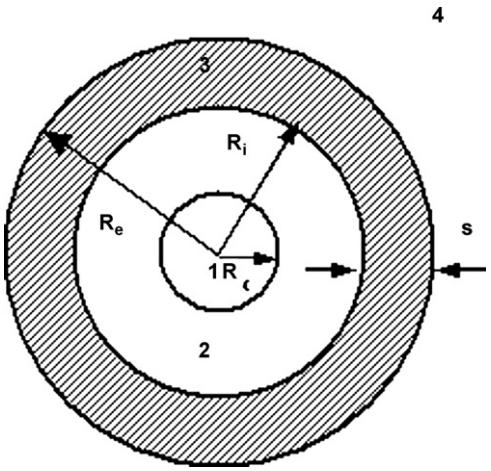

Fig. 1 – Schematic of the considered microparticle: 1, solid drug core; 2, internal aqueous solution; 3, polymeric coating; 4, external solution. Initially the solid core fills completely the interior of the microparticle and zone 2 is not present (i.e. $R_c = R_i$).

2. Drug release model

In the studied configuration a solid active principle encapsulated by a polymer layer is immersed in an aqueous solution as shown in Fig. 1. A single spherical particle and the relative surrounding solution, assumed perfectly mixed, are considered in the model but the results obtained can be also applied to systems with a population of particles, all with the same features.

The additional hypotheses were made:

- The geometric and the physical–chemical characteristics of the polymer do not change during the release process (i.e. negligible swelling and degradation).
- No drug is initially trapped in the coating.
- The system is dilute, thus diffusion-induced convection is neglected.

The release process may be divided into three consecutive steps.

In the first phase water, from the external solution, seeps into the polymer coating, its concentration increases in the polymer layer until the liquid state is reached on contact with the encapsulated solid core; at this point the dissolution of the drug particle can start (second step), and it goes on till the whole solid has disappeared.

Finally there is the exhaustion of the active principle in the internal solution (third and last phase of the release process).

2.1. *Water penetration*

Water seeps into the polymeric coating from the external solution and diffuses through the polymer, up to the internal surface of the layer.

Here, at the beginning, it is in vapour state, owing to its low concentration; therefore its flux, through the internal surface, is so small that can be neglected. Consequently water accumulates at the internal surface of the covering, until it reaches the saturation pressure. At this point liquid water can flow out of the layer, reach the solid core and start its dissolution.

Water diffusion through the polymer takes place throughout the release process (i.e. in the three aforementioned steps), but it limits the overall process rate in the first step only. In

fact, in the second and third step the process is limited by the transfer of the active principle which is normally characterised by molecules much bigger than those of water and hence by a much smaller diffusion in the coating. Therefore we examine the water diffusion step in order only to estimate the penetration time and see when the solid core dissolution begins.

The differential balance of water in the polymeric layer during the penetration phase reads as follows:

$$\frac{\partial x_{wp}}{\partial t} = \frac{D_{wp}}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial x_{wp}}{\partial r}\right) \tag{1}$$

$$\begin{aligned} &x_{wp} = 0 && R_i \le r < R_e && t = 0\\ &x_{wp} = K_{wp}x_{we} && r = R_e && t > 0\\ &\frac{\partial x_{wp}}{\partial r} = 0 && r = R_i && t > 0 \end{aligned}$$

At the beginning ($t=0$) there is no water in the polymeric layer. During water penetration a partition relationship establishes between water on the external surface of the microparticle and water in the external solution, whilst at the inner surface of the polymeric layer, before penetration time, water is in vapour state, so its diffusive flux through the internal surface is negligible.

Such conditions hold as long as water reaches the saturation condition at the internal surface of the covering and liquid water starts flowing in the internal core (penetration time).

According to the partition relationship between water on the inner surface of the polymeric coating and water in the first drop of internal solution, the penetration time (t_{pen}) is obtained by the following equation:

$$x_{wp}(R_i, t_{pen}) = K_{wp}(1 - x_{d,sat}) \tag{2}$$

By making Eq. (1) dimensionless through the following set of variables:

$$\xi = \frac{r}{R_e}, \quad \Gamma_{wp} = \frac{x_{wp}}{K_{wp}x_{we}}, \quad \vartheta_{wp} = \frac{tD_{wp}}{R_e^2} \tag{3}$$

one can easily argue that the solution results: $\Gamma_{wp} = \Gamma_{wp}(\xi, \vartheta_{wp}, (R_i/R_e))$.

The application of this result to Eq. (2) indicates that the dimensionless penetration time can be expressed as a function of two dimensionless parameters:

$$\vartheta_{pen} = \vartheta_{pen}\left(\frac{R_i}{R_e}, \frac{1 - x_{d,sat}}{x_{we}}\right) \tag{4}$$

2.2. Solid particle dissolution

After the penetration time water can flow out of the polymeric covering and come into contact with the solid particle, starting its dissolution. Therefore a liquid solution is formed inside the particle and coexists with the remaining solid core that starts shrinking with time. The active principle dissolves in the internal solution and diffuses through the covering, until it is released in the external solution.

The internal solution is considered perfectly mixed and with a concentration of dissolved active principle equal to its solubility until the whole solid has disappeared. The dissolution time is the time at which there is no more solid drug encapsulated, but only a saturated solution is left.

The differential balance for the drug in the polymeric covering during this step is:

$$\frac{\partial x_{dp}}{\partial t} = \frac{D_{dp}}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial x_{dp}}{\partial r}\right) \tag{5}$$

$$\begin{aligned} &x_{dp} = 0 && R_i \le r < R_e, && t = t_{pen}\\ &x_{dp} = K_{dp}x_{d,sat} && r = R_i && t > t_{pen}\\ &\frac{\partial x_{dp}}{\partial r} = -\frac{V_e c_{le}}{4\pi D_{dp}c_{tot}K_{dp}R_e^2}\frac{\partial x_{dp}}{\partial t} && r = R_e && t > t_{pen} \end{aligned}$$

The initial condition takes into account that at the beginning ($t = t_{pen}$) in all the points of the polymeric covering the drug molar fraction is equal to zero, whereas the first boundary condition relates the drug concentration on the inner surface of the covering, by a partition relationship, with the drug dissolved in the internal solution that stays at saturation point until the whole solid has disappeared.

The second boundary condition is obtained by rearranging the following drug balance for the external solution.

$$4\pi R_e^2\left(-D_{dp}c_{tot}\left.\frac{\partial x_{dp}}{\partial r}\right|_{R_e}\right) = V_e c_{le}\frac{dx_{de}}{dt} \tag{6}$$

where

$$x_{de} = \frac{x_{dp|R_e}}{K_{dp}} \tag{7}$$

The following balance leads to the calculation of dissolution time, at which the whole solid has disappeared and there is only a saturated solution left in the microcapsule:

$$\int_{t_{pen}}^{t_{dis}} 4\pi R_i^2\left(-D_{dp}c_{tot}\left.\frac{\partial x_{dp}}{\partial r}\right|_{R_i}\right)dt = n_d|_{t_{pen}} - n_d|_{t_{dis}} \tag{8}$$

where

$$n_d|_{t_{pen}} = \frac{4}{3}\pi R_i^3\frac{\rho_d}{M_d} \tag{9}$$

$$n_d|_{t_{dis}} = \frac{4}{3}\pi R_i^3 c_{li}x_{d,sat} \tag{10}$$

As before a dimensionless analysis shows that the dimensionless dissolution time is a function of a few dimensionless parameters. In fact, by making the equations for the dissolution phase dimensionless through the following set of parameters:

$$\xi = \frac{r}{R_e}, \quad \Gamma = \frac{x_{dp}}{K_{dp}x_{d,sat}}, \quad \vartheta = \frac{(t - t_{pen})D_{dp}}{R_e^2}, \quad \alpha = \frac{R_i}{R_e},$$

$$A_v = \frac{V_e}{(4/3)\pi R_e^3}, \quad A = A_v\frac{c_{le}}{3c_{tot}K_{dp}}, \quad B = \frac{(\rho_d/M_d) - c_{li}x_{d,sat}}{3c_{tot}K_{dp}x_{d,sat}} \tag{11}$$

it is possible to express the solution as $\Gamma = \Gamma(\xi, \vartheta, \alpha, A)$ and the dissolution time evaluated by Eq. (8) as $\vartheta_{dis} = \vartheta_{dis}(\alpha, A, B)$

2.3. Drug exhaustion in internal solution

This last phase starts after the solid core has disappeared completely. At the beginning the encapsulated solution is saturated, but the drug concentration decreases as the active principle enters the polymer coating, diffuses through it, and

reaches the external solution. A uniform concentration or a concentration gradient may be considered in the internal solution.

The assumption of perfectly mixed solution does not affect significantly the result, in fact a more complex model that considers the resistance to mass transfer in both polymeric coating and internal solution (with the evaluation of a concentration profile also for the internal solution) has been considered (and is omitted here for sake of brevity), but its results were similar to those obtained by assuming a perfectly mixed solution.

If the internal solution is supposed perfectly mixed, the drug concentration is uniform and the drug balance in the coating is:

$$\frac{\partial x_{dp}}{\partial t} = \frac{D_{dp}}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial x_{dp}}{\partial r}\right) \tag{12}$$

The initial drug concentration profile corresponds to the final one of the previous phase:

$$x_{dp} = x_{dp}|_{t_{dis}}, \quad R_i \le r < R_e$$

The boundary condition at the internal wall is now obtained by the drug balance in the internal solution:

$$4\pi R_i^2\left(-D_{dp}c_{tot}\left.\frac{\partial x_{dp}}{\partial r}\right|_{R_i}\right) + \frac{4}{3}\pi R_i^3 c_{li}\frac{\partial x_{di}}{\partial t} = 0 \tag{13}$$

where

$$x_{di} = \frac{x_{dp}|_{R_i}}{K_{dp}} \tag{14}$$

Thus the inner boundary condition is obtained:

$$\frac{\partial x_{dp}}{\partial t} = \frac{3D_{dp}c_{tot}K_{dp}}{R_i c_{li}}\frac{\partial x_{dp}}{\partial r}, \quad r = R_i$$

Then the balance of the active principle in the external solution is taken into consideration:

$$4\pi R_e^2\left(-D_{dp}c_{tot}\left.\frac{\partial x_{dp}}{\partial r}\right|_{R_e}\right) = V_e c_{le}\frac{\partial x_{de}}{\partial t} \tag{15}$$

where

$$x_{de} = \frac{x_{dp}|_{R_e}}{K_{dp}} \tag{16}$$

So the outer boundary condition is obtained:

$$\frac{\partial x_{dp}}{\partial t} = -\frac{4\pi D_{dp}c_{tot}K_{dp}R_e^2}{V_e c_{le}}\frac{\partial x_{dp}}{\partial r}, \quad r = R_e$$

3. Solution method

The numerical approach adopted in the simulations is the method of lines: every partial differential equation has been transformed into a system of ordinary differential equations in time by a second-order finite difference discretisation along the radial coordinate. Each ordinary differential equation is relative to one of the nodes in which the space, for the related region, has been discretised.

Equi-spaced nodes have been chosen: 30 nodes for the polymeric coating, 15 for the internal solution (when mass transfer resistance was considered and the concentration profile was evaluated).

In fact the increase of the number of nodes to 50 in the polymer coating and to 20 in the internal solution (in the case in which it was not considered perfectly mixed) did not lead to a significant improvement of the solution: the relative error on the drug release was of 0.0066% when the internal solution was assumed perfectly mixed, and 0.0076% in the other case.

The temporal integration of the equations has been carried out by Matlab function ODE45, based on fourth–fifth-order Runge–Kutta method.

This function makes the integration by means of both fourth- and fifth-order approximations, it evaluates the error of the fourth-order method by comparing the two results obtained and adjust the time-step when the error is above a certain threshold.

The tolerances adopted are: 10^{-20} for the absolute error, 2.2×10^{-14} for the relative error.

4. Results and discussions

A sensitivity analysis on the variation of the release parameters, with some system characteristics and operating conditions is carried out and its results are presented by dimensionless groups.

Fig. 2 shows the influence of geometry and solubility on the dimensionless water penetration time (ϑ_{pen}) in terms of the variables $\alpha = (R_i/R_e)$ and $\gamma = (1 - x_{d,sat})/x_{we}$, according to Eq. (4).

In fact α is related to the microparticle geometry (it increases when the polymer layer becomes thinner), while the second parameter depends on the drug solubility (it decreases when the solubility becomes higher): this parameter is always very close to 1, yet its effect may be significant, as apparent from the figure, if the thickness of the coating is large in comparison with the particle diameter.

As it can be seen in Fig. 2 ϑ_{pen} decreases as a consequence of the increase of α and the reduction of γ.

The decrease is more considerable at low values of α and high values of γ.

Of course water takes more time to cross the polymer layer and reach the concentration necessary to transform from vapour into liquid state, on the inner polymer surface, when the coating gets thicker and the requested concentration for phase transition becomes higher; but it is interesting to see where the variation is more appreciable. That happens at higher values for the coating thickness and requested concentration.

Then the variation of the dissolution time ϑ_{dis} with α and A_v, and so with coating thickness and dilution, is shown in Fig. 3.

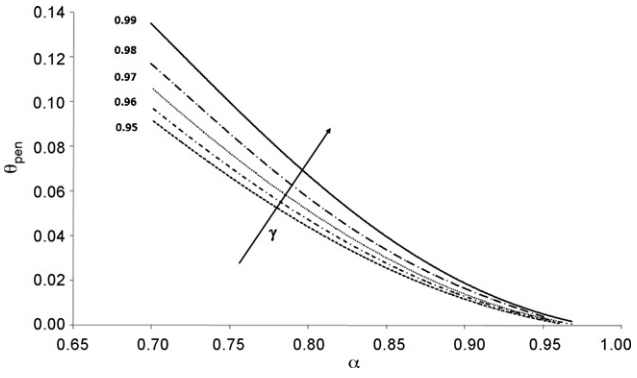

Fig. 2 – Dependence of ϑ_{pen} on the geometric characteristics of the microparticles and on the drug solubility.

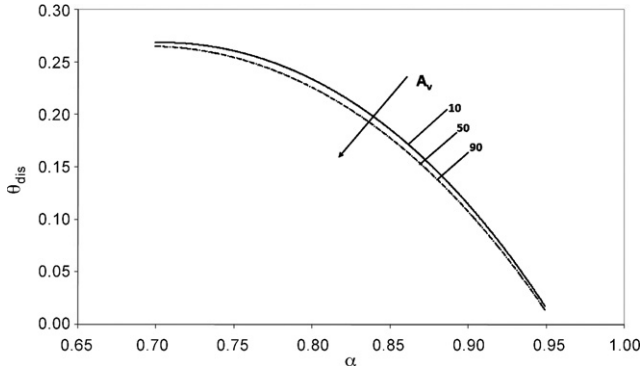

Fig. 3 – Dependence of ϑ_{dis} on geometric characteristics of the microparticles and on dilution of the external solution.

The dimensionless dissolution time is defined as:

$$\vartheta_{dis} = \frac{(t_{dis} - t_{pen})D_{dp}}{R_e^2} = \frac{\Delta t_{dis} D_{dp}}{R_e^2} \tag{17}$$

The following values are assumed for other groups of parameters:

$$\frac{c_{le}}{3c_{tot}K_{dp}} = \frac{5}{3}, \quad 3\frac{c_{tot}}{c_{li}}K_{dp} = \frac{3}{5}, \quad \frac{D_{dw}}{D_{dp}} = 10 \tag{18}$$

As previously said α is linked to the coating thickness, while A_v represents the ratio of the volume of the liquid surrounding the particle to the volume of the particle.

The dependence is the same already evidenced for the penetration time: the dissolution time decreases if the coating becomes thinner and the external solution is more diluted, and so the overall driving force increases, but it is important to see where the variation is more significant. In this case the reduction is more appreciable at high values for α and low values for A_v, that is to say at low values of coating thickness and dilution.

Finally the effects of the changes of α and A_v on the release curve are examined and shown in Figs. 4 and 5. Here the results are expressed in terms of the following variables:

$$\vartheta = \frac{(t - t_{pen})D_{dp}}{R_e^2}, \quad R\% = \frac{V_e c_{le} x_{de}}{((4/3)\pi R_i^3(\rho_d/M_d))}100 \tag{19}$$

The first group is the dimensionless time, the second is the percentage of drug released in the external solution. Fig. 4 shows that the release of the drug is accelerated by a reduction of the polymer thickness in the initial and intermediate

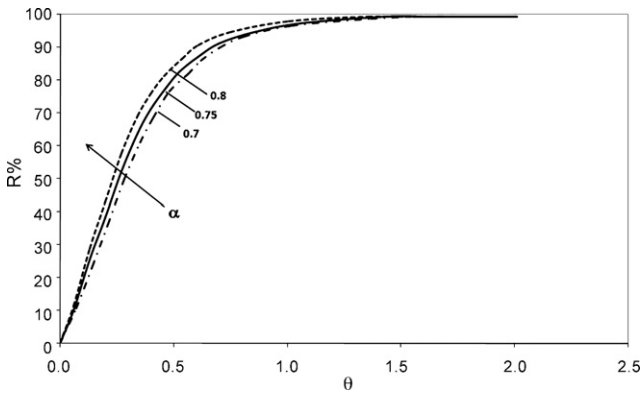

Fig. 4 – Dependence of the release curve on the geometric characteristics of the microparticles.

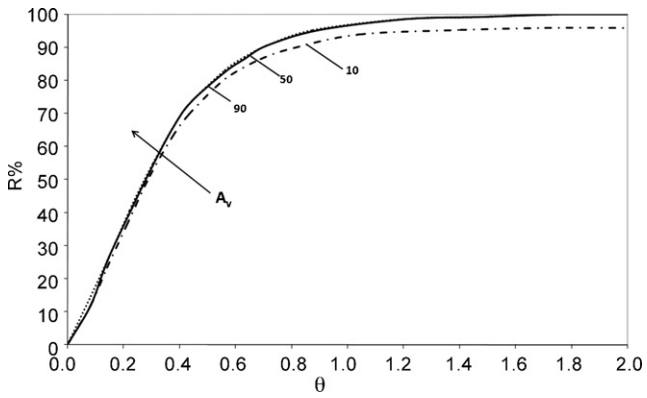

Fig. 5 – Dependence of the release curve on the dilution of the external solution.

phases of the process. After a long time the release rate slows down because the drug accumulates in the external solution, not modelled as a perfect sink, and consequently the driving force for the diffusion process decreases. Owing to that the dilution of the external solution gets greater importance at the end, when the drug has accumulated and has increased its concentration, as it can be seen in Fig. 5.

5. Conclusions

By carrying out the sensitivity analysis it was possible to see where variations of the release parameters with systems characteristics, whose trends could be reasonably predicted, are more appreciable.

The increase of the water penetration time, with the rise of the coating thickness and of the concentration that water must reach to transform from vapour into liquid, results more appreciable at higher coating thickness and lower drug solubility values (higher water concentration required for phase transition).

The water penetration time is very important in the release process since it gives the main contribution to the lag time; consequently it is important to know where its change is more significant and by which parameter it results more influenced.

Besides, the solid core dissolution time reduces with the decrease of the polymer thickness and the rise of dilution, and its decrease results more considerable at high values of α (lower thickness) and low values of A_v (lower dilution). Furthermore, by observing the behaviour of the release curves, it can be seen that if α increases (the polymer thickness decreases) the release is faster at the beginning and in the middle of the process, whereas it is slower at the end. That behaviour is due to a more rapid increase in the concentration of the external solution and to the consequent reduction of the overall driving force. Thus the increase of A_v (ratio of surrounding liquid volume to particle volume, thus dilution of particles suspension) influences the release curve more considerably at the end of the process, when the external solution is more concentrated and a higher dilution degree is needed to increase the driving force.

Finally it can be realized that the polymer thickness influences the release more significantly than the dilution of the particles suspension and thus it is the most important parameter that should be modified in order to obtain the desired release curve.

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