ELSEVIER

International Journal of Pharmaceutics 112 (1994) 47–54

international journal of pharmaceutics

Mathematical analysis of drug delivery from swellable systems with partial physical restrictions or impermeable coatings

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Received 14 March 1994; accepted 3 May 1994

Abstract

Mathematical analysis is presented of the water transport and drug release from hydrophilic tablets coated with impermeable coatings. Numerical solutions are provided for a number of cases of partial coating. It is shown that depending on the restriction provided to the tablets by the coating, Fickian or non-Fickian transport can be observed.

Keywords: Keywords: Swellable system; Swelling; Partial coating; Physical restriction

1. Introduction

In recent years, we have seen an explosion in the preparation and utilization of swellable controlled release systems from simple nasal, buccal and rectal administration applications (Lee, 1988) to more complex bioadhesive uses (Lejoyeux et al., 1989). Whether in the form of microspheres, discs or the more conventional tablets, such systems have now found applications in various fields.

Swellable tablets and related systems continue being of commercial interest. Several recent studies have been reported where the releasing area of these systems has been modified in order to achieve a desirable release rate. In fact, the patent and public literature contains ample information on a new type of tablets, known as Geomatrix®, which are coated either on one or both of their surfaces or laterally to achieve desirable rates (Colombo et al., 1988, 1989, 1990).

Prediction of release rates from such systems requires expressions of the Fickian or non-Fickian penetrant transport by an appropriate equation, and similar expression of the drug diffusion. In both cases, the problem must be solved in a three-dimensional form with appropriate initial and boundary conditions. This requires extensive numerical solutions as shown, for example, by Ritger and Peppas (1987) or Lustig and Peppas (1989).

We consider five cases of swelling/ release of coated tablets. The so-called Case 0 is the trivial situation of a three-dimensional tablet prepared

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SSDI 0378-5173(94)00157-Z

from a hydrophilic polymer and a hydrophilic drug and able to swell in all directions. Case 1 is the situation where one of the circular surfaces has been covered with an impermeable, hydrophobic polymer layer. Coverage of both circular surfaces defines Case 2. In Case 3, the lateral area is covered by an impermeable coating, whereas Case 4 describes tablets with only one surface being available for swelling and release.

In previous work (Colombo et al., 1990, 1992) we discussed the physical behavior of such systems. In this work we present an exact mathematical analysis of the polymer swelling and drug delivery from a number of these systems, and comment on the advantages of each type of coating and release device prepared.

2. Model

A new model was developed to describe water and drug transport in partially coated tablets. Water and drug transport in crosslinked hydrophilic polymer networks were described by Fick's second law in cylindrical coordinates:

$$\frac{\partial v_i}{\partial t} = \frac{D_i}{r}\frac{\partial}{\partial r}\left(\frac{1}{r}\frac{\partial c_i}{\partial r}\right) + D_i\frac{\partial^2 c_i}{\partial z^2} \qquad (1)$$

where c_i is the concentration of the diffusing species (1, water or 2, drug), D_i denotes the diffusion coefficient of the diffusing species, r is the radial coordinate, and z represents the axial coordinate.

In Case 0 the tablet was not coated with any impermeable coating on any surface and hence diffusion was permitted through all the available exposed area of the tablet, as shown in Fig. 1. The tablet was allowed to swell in both the radial and the axial directions. The swelling was assumed to be ideal. Hence, the total volume of the tablet at any instant is given by the sum of the volumes of the polymer and water.

Initially, the tablet was assumed to be dry and hence, the water concentration at any position inside the tablet was zero. The drug concentration inside the tablet was uniform and was equal

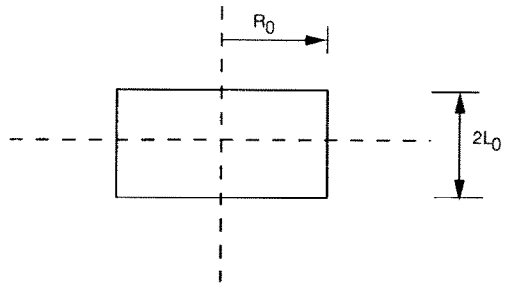

Fig. 1. Case 0 tablet.

to the loading concentration. This may be written for water as:

$$t=0 \quad 0<r<R_0 \quad -L_0<z<L_0 \quad c_1=0 \qquad (2)$$

and for drug as:

$$t=0 \quad 0<r<R_0 \quad -L_0<z<L_0 \quad c_1=c_{2,1} \qquad (3)$$

where R_0 is the initial radius of the tablet and $2L_0$ denotes the thickness of the tablet.

At the surface of the tablet, the concentration of water was assumed to be at its equilibrium value, $c_{1,eq}$, at all times. It was also assumed that the equilibrium was attained instantaneously.

The boundary conditions were written for water as:

$$t>0 \quad r=R_t \quad -L_t<z<L_t \quad c_1=c_{1,eq} \qquad (4)$$

and

$$t>0 \quad z=\pm L_t \quad 0<r<R_t \quad c_1=c_{1,eq} \qquad (5)$$

where R_t and L_t are the radius and semi-thickness of the tablet at any time t, respectively. The drug concentration at the surface of the tablet, $c_{2,ext}$ was assumed to be constant during the diffusion process and was equal to the value far away from the tablet, thereby assuming negligible mass transfer resistance for the drug from the surface to the surrounding fluid. These conditions for the drug were written as:

$$t>0 \quad r=R_t \quad -L_t<z<L_t \quad c_2=c_{2,ext} \qquad (6)$$

and

$$t>0 \quad z=L_t \quad 0<r<R_t \quad c_2=c_{2,ext} \qquad (7)$$

Drug transport from the tablet to the surrounding medium is slightly more complicated

than water transport into the tablet. This arises due to the very high loading of the drug in the tablet. At such high drug concentrations, the drug remains in the dispersed state. As the water diffuses into the tablet, the drug dissolves and a front develops in the tablet separating the dispersed from the dissolved drug. This front moves towards the center of the tablet as described in Fig. 2.

The position of the moving front is determined from the drug flux at the front. When the total amount of drug released from the front exceeds the loading over and above the solubility limit, the front advances. However, since the drug front moves in both radial and axial directions, it was very difficult to describe it in mathematical terms. This was dealt with in a special case described at the end of this section when swelling of the tablet was restricted to one direction only. For the first three cases, Cases 0–2, the drug concentration in the swollen polymer was assumed to be equal to its solubility in the polymer.

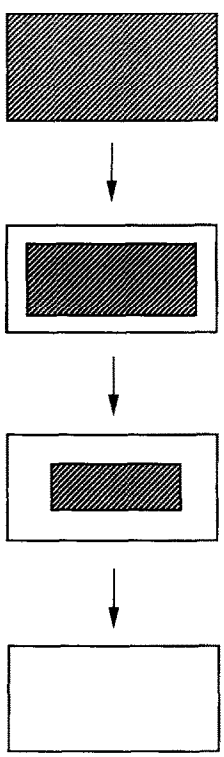

Fig. 2. Movement of the dispersed/dissolved drug front during swelling of a Case 0 tablet.

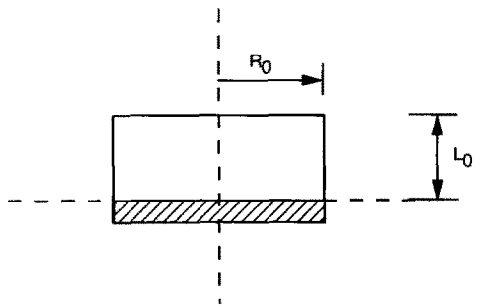

Fig. 3. Case 1 tablet.

In Case 1 the tablet was coated with an impermeable coating on one of its circular faces as shown in Fig. 3. Since the water and drug flux at the coated surface was zero, it was advantageous to fix the coordinate system on this face. The swelling of the polymer in this case was very different. The tablet evolved from a cylindrical shape to a conical shape and finally to a paraboloid. The polymer was assumed to be dry initially and the drug concentration was assumed to be uniform and equal to the loading concentration, $c_{2,1}$. These conditions were written for water as:

$$t > 0 \quad 0 < r < R_t(z) \quad 0 < z < L_t \quad c_1 = 0 \qquad (8)$$

and for drug as:

$$t > 0 \quad 0 < r < R_t(z) \quad 0 < z < L_t \quad c_2 = c_{2,1} \qquad (9)$$

At the lateral surface of the tablet, it was assumed that the concentration of water was equal to its equilibrium value and the concentration of the drug was equal to the value at a point far way from the tablet. Both the water and drug fluxes were equal to zero at the coated surface due to the impermeable nature of the coating. These conditions were written for water as:

$$t > 0 \quad r = R_t(z) \quad 0 < z < L_t \quad c_1 = c_{1,\mathrm{eq}} \qquad (10)$$

$$t > 0 \quad z = L_t \quad 0 < r < R_t \quad \partial c_1/\partial z = 0 \qquad (11)$$

and for drug as:

$$t > 0 \quad r = R_t(z) \quad 0 < z < L_t \quad c_2 = c_{2,\mathrm{ext}} \qquad (12)$$

$$t > 0 \quad z = L_t \quad 0 < r < R_t \quad \partial c_2/\partial z = 0 \qquad (13)$$

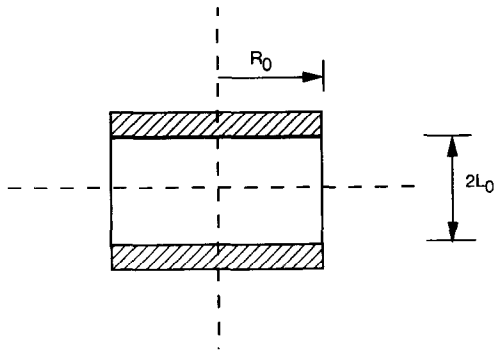

Fig. 4. Case 2 tablet.

The radius at each cross-section of the tablet, $R_t(z)$, was determined during the simulation process by integrating the total amount of water in that section.

In Case 2 the tablets are coated with an impermeable coating on both circular surfaces as shown in Fig. 4. The initial conditions remained the same as in Cases 0 and 1, namely the polymer was dry and the drug loading was uniform in the tablet. It was assumed that at the impermeable coating the flux of water into the tablet and the flux of drug out of the tablet were zero. Swelling of the polymer was allowed in both the radial and axial directions. The concentration of water on the lateral surface was at equilibrium at all times. Since the coating was impermeable to water, the water fluxes at both surfaces were zero. The initial condition was written for water as

$$t > 0 \quad 0 < r < R_t \quad -L_t < z < L_t \quad c_1 = 0 \tag{14}$$

and for drug as:

$$t > 0 \quad 0 < r < R_t \quad -L_t < z < L_t \quad c_2 = c_{2,1} \tag{15}$$

The boundary conditions were written for water as:

$$t > 0 \quad r = R_t \quad -L_t < z < L_t \quad c_1 = c_{1,\mathrm{eq}} \tag{16}$$

$$t > 0 \quad z = \pm L_t \quad 0 < r < R_t \quad \partial c_1/\partial z = 0 \tag{17}$$

and for drug as:

$$t > 0 \quad r = R_t \quad -L_t < z < L_t \quad c_2 = c_{2,\mathrm{ext}} \tag{18}$$

$$t > 0 \quad z = \pm L_t \quad 0 < r < R_t \quad \partial c_2/\partial z = 0 \tag{19}$$

The solution of the model was obtained by numerically solving the set of differential equations using finite difference techniques. Since it was convenient to solve dimensionless equations, the following dimensionless variables were defined which on substitution in the original equations lead to dimensionless equations.

The dimensionless concentrations of water and drug were defined as:

$$\Psi_1 = c_1/c_{1,\mathrm{eq}} \tag{20}$$

and

$$\Psi_2 = c_2/c_{2,\mathrm{sol}} \tag{21}$$

Here, $c_{2,\mathrm{sol}}$ is the solubility of the drug in the wet tablet.

The dimensionless time was defined as:

$$\tau = D_2 t/L_0^2 \tag{22}$$

For numerical simulations, the tablet was divided into concentric circles in the radial direction and thin slabs in the axial direction. The differential equation was converted to a difference equation using forward time-center space approximation. The number of grids was kept the same during the swelling process. The size of the grids was adjusted in each time step to account for the swelling of the polymer samples.

In order to better understand the dynamic swelling in coated tablets an additional case of tablet testing was simulated in which the swelling of the tablet was restricted to the radial direction by placing the tablet between two glass plates with the spacing between the plates held constant (e.g., using a spacer). The model developed to describe the diffusion consisted of a diffusion equation in cylindrical coordinates. The initial and boundary conditions were very similar to the Case 2 tablet except that diffusion was neglected in the axial direction and swelling was restricted to the radial direction. The dissolved/dispersed drug front was defined by the solubility of the drug in the swollen polymer. The motion of the front was calculated from the flux of the drug at the interface.

3. Numerical simulations and analysis

The new model was solved numerically for all the cases studied. The tablets were assumed to be

intact (non-disintegrating) during the swelling and release process and their initial diameter to thickness ratio was selected as $R_0/L_0 = 7/5$ or 2 to indicate special cases of interest.

The water diffusion coefficient in the tablet was assumed as 4.7×10^{-6} cm^2/s and the drug diffusion coefficient was 1.4×10^{-6} cm^2/s. Both values are typical of water soluble drugs in swelling-controlled release systems. The drug solubility in the tablet was assumed to be equal to the loading concentration.

The water concentration in the tablet at equilibrium was obtained from typical experimental studies using polyacrylate or cellulose-based tablets, although this value may be also calculated by assuming thermodynamic equilibrium and thus equating the chemical potential of water inside and outside the tablet (Hariharan and Peppas, 1993).

Typical solutions presented here show the water uptake in the tablet, M_t/M_∞, expressed as g of water per g of dry tablet, as a function of swelling time in h. Although the simulation has been carried out until equilibrium is attained, the graphs presented here show the initial portion of the uptake in order to compare the characteristics of water uptake. Fig. 5 presents the solutions of the new model for Cases 1 and 2 and their comparison with the standard Case 0. The simulation was carried out for tablets of $R_0/L_0 = 7/5$. The water uptake increased with time much faster

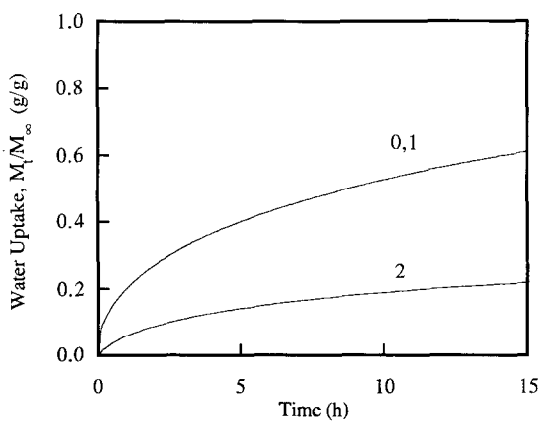

Fig. 5. Water uptake as a function of time in Case 0, 1 and 2 tablets with dimensions $R_0/L_0 = 7/5$.

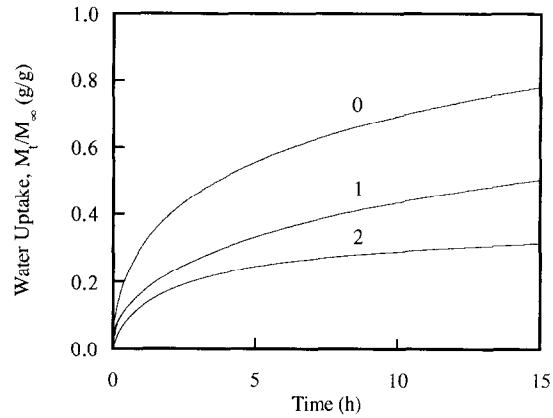

Fig. 6. Water uptake as a function of time in Case 0, 1 and 2 tablets with dimensions $R_0/L_0 = 2$.

for Case 1 than for Case 2. In fact, the results of Case 1 were almost superimposed on the results of Case 2, a distinct characteristic of the selected dimensions of the tablet. Indeed, simulations for $R_0/L_0 = 2$ indicated that the swelling behavior of Cases 0 and 1 was significantly different.

Probably the most interesting result of this simulation was that although the overall water uptake vs time behavior for Cases 0 and 1 could be fitted to the classical $t^{1/2}$ linear dependence (see Fig. 6) predicted by the approximate solution of Fick's equation (Ritger and Peppas, 1987), Case 2 could not be fitted to this dependence.

Therefore, one concludes that a 'quasi-non-Fickian' behavior was observed in Case 2 tablets with dimensions of $R_0/L_0 = 7/5$. There are several possible explanations for the phenomenon, but probably the most appealing is that the restrictions applied by the coating on the swellable center core lead to an appreciable change in the relaxational behavior of the swelling system, which, in turn, leads to coupling of diffusion and relaxation so that non-Fickian behavior is observed (Peppas, 1987; Colombo, 1993). This mechanism has been expressed as a pure speculation for transport in Case 2 in a previous publication from our group (Colombo et al., 1990).

The drug release behavior from these tablets under the same conditions as in Fig. 5 is presented in Fig. 7. The fractional drug release, M_t/M_∞, is plotted as a function of the

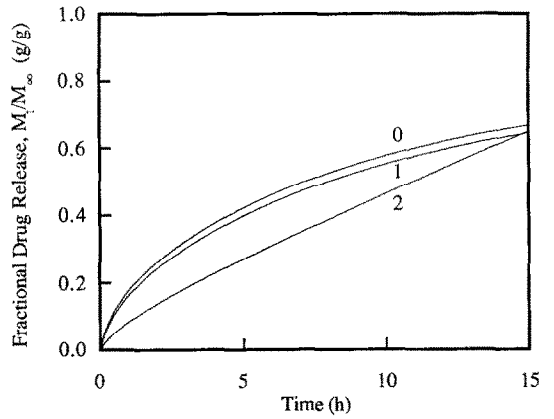

Fig. 7. Fractional drug release as a function of time in Case 0, 1 and 2 tablets with dimensions $R_0/L_0 = 7/5$.

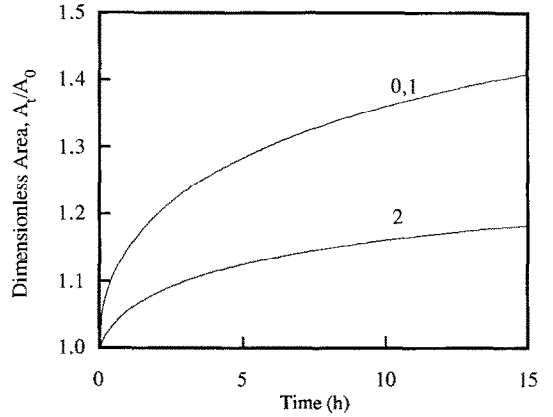

Fig. 9. Dimensionless release area as a function of time for Case 0, 1 and 2 tablets with dimensions $R_0/L_0 = 7/5$.

swelling/release time. Case 1 leads to a release behavior that was only slightly different than release from uncoated tablets. Case 2, however, was significantly different. Over a period of 15 h of release, the relationship between the drug released and time was almost linear, indicating that the drug could be released at an almost constant rate. Again, this behavior was observed for tablets with dimensions of $R_0/L_0 = 7/5$.

A significantly different behavior, however, was observed when simulations were carried out in tablets with $R_0/L_0 = 2$. As shown in Fig. 8, the restrictive characteristics of the coatings were such that Case 1 gave the quasi-non-Fickian release behavior with an almost zero-order release behavior.

The overall swelling and release behavior of the tablets is also associated with the available area for transport/release and its change as a function of time. This is clearly shown in the results of the solution of the model for dimensions of $R_0/L_0 = 7/5$ (Fig. 9) and $R_0/L_0 = 2$ (Fig. 10). The dimensionless area was the ratio of the area at any time, A_t, over the initial surface area, A_0, available for release. It is clear from both figures that tablets coated as in Case 2 showed the greatest restriction and therefore, the smallest increase of their surface area.

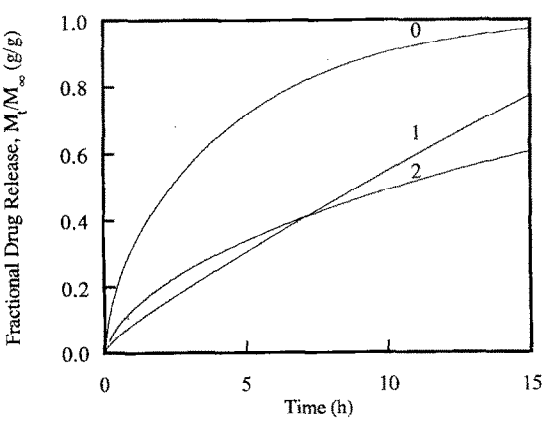

Fig. 8. Fractional drug release as a function of time in Case 0, 1 and 2 tablets with dimensions $R_0/L_0 = 2$.

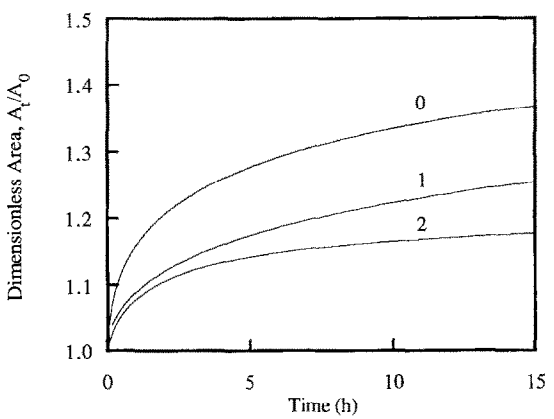

Fig. 10. Dimensionless release area as a function of time for Case 0, 1 and 2 tablets with dimensions $R_0/L_0 = 2$.

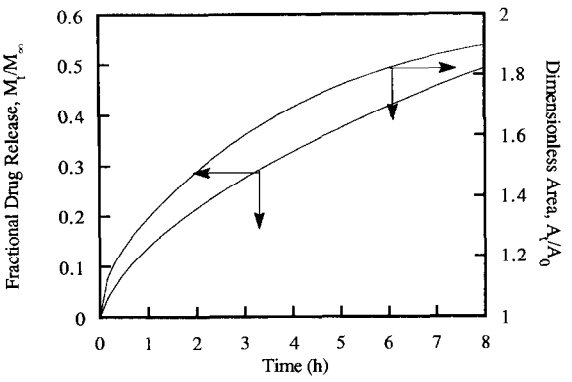

Fig. 11. Fractional drug release and dimensionless area as functions of time in a Case 2 tablet constrained to swell only in the radial direction.

These results are quite revealing because they indicate that the dynamic swelling behavior and the drug release behavior are dependent not only on the position of the impermeable coating (restriction) but also on the ratio of the diameter to the thickness (R_0/L_0). As this ratio increases the device becomes cylindrical, whereas for low values the geometry is that of a disc.

Of particular importance were the swelling and release predictions for tablets coated on both circular faces, as in Case 2, but allowed to swell by a process that was restricted to the radial direction. As indicated earlier, the complexity created by the dispersed drug in the tablet was accounted for in this case. Fig. 11 presents the fractional drug released and the dimensionless area as a function of time. The movement of the dissolved/dispersed drug front in the tablet, as well as changes in the tablet diameter are shown in Fig. 12.

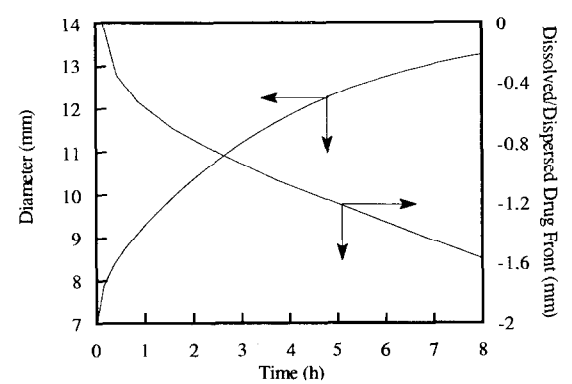

Fig. 12. Diameter and position of dissolved/dispersed drug front as functions of time in a Case 2 tablet constrained to swell only in the radial direction.

4. Conclusions

We have succeeded in developing a mathematical model that accurately describes the swelling and release of tablets coated in various ways and swollen as a function of time. It has been shown that the water uptake and the drug release can be calculated as a function of time and that the shape of the resulting curves, as well as the apparent Fickian or non-Fickian release are functions of the diameter to thickness ratio of the tablets, as well as the position of coating on the tablet.

Acknowledgements

This work was supported by grant no. GM 43337 (to NAP) from the National Institutes of Health, grant no. INT-90-19184 from the US-Italy Program of the National Science Foundation, and grant no. 93.02913.CT03 from the Consiglio Nazionale delle Ricerche (to P.C.).

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