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Determination of percolation thresholds in matrix-type controlled release systems: application of a resistance analysis technique

M.J. Fernández-Hervás [a,*], M.T. Vela [a], M.A. Holgado [a], J. del Cerro [b], A.M. Rabasco [a]

[a] *Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, 41012 Sevilla, Spain*

[b] *Departamento de Física de la Materia Condensada, Facultad de Física, Universidad de Sevilla, 41012 Sevilla, Spain*

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Abstract

In this work, matrix tablets have been prepared with binary mixtures of the inert polymer Eudragit® RS 100 and a soluble, power-conductor model substance, sodium chloride. The sodium chloride content comprised between 20 and 80% w/w. A technique based on the measurement of the resistance of the matrix tablets has been used to achieve easy estimation of the values of the percolation thresholds, as a function of the sodium chloride loadings. The results obtained have been expressed in terms of resistivity and evaluated on the basis of percolation theory. The tablet resistivity has been considered as a critical property of the system. A change in this property and the presence of the percolation threshold were observed to appear simultaneously. From the data obtained, we have determined a first percolation threshold comprising between 30 and 40% (w/w) sodium chloride loading. The tablets made with a sodium chloride charge higher than 70% (w/w) undergo a disintegration process. The results obtained have been corroborated by scanning electron microscopy.

Keywords: Percolation theory; Controlled release; Resistance; Percolation threshold; Inert matrix

1. Introduction

The application of percolation theory to pharmaceutical technology, proposed by Leuenberger et al. (1987, 1989) and Blattner et al. (1990), has enabled new insights about the design and characterization of dosage forms and drug release properties of matrix systems to be obtained.

Percolation theory deals with the formation of clusters and the existence of site or bond percolation phenomena. In site percolation, a cluster is defined as a group of neighboring occupied sites in a lattice. A cluster in bond percolation is defined as a group of neighbors connected by bonds. When clusters are isolated, they are termed finite. On the other hand, when a cluster percolates a lattice is considered infinite. The probability at which a cluster just percolates a system (a tablet in this case) is termed the percolation threshold.

* Corresponding author.

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The study of percolation thresholds seems to be a promising new research area in pharmaceutics. It may provide an interesting and new tool for a more rational solid dosage form design, including fast and slow release dosage forms.

For a matrix tablet formulated with two different materials, site percolation constitutes an interesting model which permits one to explain phenomena associated with this dosage form. In this three-dimensional system a lower and upper percolation threshold can be defined. Between both of them, the two components span the length, breadth and height of the matrix tablet, i.e., they form two infinite clusters. Below or above the designated percolation thresholds the two materials form finite clusters. Thus, in a binary system the percolation thresholds correspond to a critical concentration ratio of the two components. Close to the percolation threshold a significant change in the properties of a compact may occur suddenly and this effect is known as a critical phenomenon.

In this sense, Bonny and Leuenberger (1991) have studied the release profiles of matrix-type solid dosage forms and have explained the changes in dissolution kinetics over the whole range of drug loadings, proposing a model for the ready estimation of the values of the percolation thresholds for diffusion behavior.

More recently, the application of this theory to matrix systems formulated with sodium chloride and Eudragit® RS 100 (Rabasco et al., 1992) or potassium chloride and Eudragit® RS PM (Caraballo et al., 1993), both with different particle size, demonstrates the great interest in this theory for the study of the release behavior of controlled release matrices.

In this work, an easy and fast technique is proposed to show the presence of the percolation threshold. The resistance of tablets prepared with a complete range of sodium chloride loadings has been measured. This model drug is a power-conductor substance.

From these resistance values, the resistivity has been calculated, a parameter which is independent of tablet size, and it has been considered as a critical property of the system. A sudden change in this property suggests the presence of the percolation threshold. A large difference can be detected between the resistivity values if a finite sodium chloride cluster is formed inside the tablet, or an infinite sodium chloride network spans the whole tablet, in all three dimensions.

Then, the presence of infinite or finite clusters has been confirmed by scanning electron microscope.

2. Materials and methods

Powder sodium chloride (Acofarma, Tarrasa, Barcelona, Spain) was used as a power-conductor and water-soluble model active substance. Eudragit® RS 100 (Industrias Sintéticas Curtex, Barcelona, Spain) was chosen as a matrix forming material. Both materials were adequately crushed and sieved (Retsch, type Vibro) to obtain a granulometric fraction comprising between 50 and 100 μm.

Seven binary mixtures of sodium chloride and Eudragit® RS 100 were prepared in a V blender for 10 min. The sodium chloride contents were varied between 20 and 80% (w/w) in 10% intervals.

The different mixtures were compressed in an eccentric machine (Bonals A-300), without any further excipients, using 6 mm flat cylindrical punches. Tablets weighing 150 mg each were prepared at the maximum compression force accepted by our formulations. Tablets of pure sodium chloride were also prepared under the same conditions.

To determine the resistivity change as a function of the concentration, the resistance of each matrix tablet was measured at ambient temperature, by using a cell specially made for this purpose and an electrometer (Takeda Riken model TR-8651). In order to ensure electrical contact on both sides of each tablet, two electrodes covered with silver paint were used. The resistance between the electrodes of the cell was at least double that of the tablets. The assay was carried out in triplicate.

The resistance data obtained were converted to resistivity data according to Eq. 1, which en-

ables one to consider the dimensions of the tablets:

$$R = \rho(h/s) \quad (1)$$

where:
R is the resistance, ρ denotes resistivity, h is the tablet thickness and s the tablet section.

Dissolution studies of formulations were performed using the USP XXII paddle method (Turu Grau, model D-6). 700 ml of purified water at 37 ± 0.5°C was employed as dissolution medium. The rotation speed of the paddle was 50 rpm. Release of sodium chloride was detected by the increase in conductance of the dissolution medium, using a digital conductivity meter (Crison, model micro CM-2201) linked to a chart recorder and an IBM-compatible personal computer which permits recording of one conductivity datum per s. For each mixing ratio, the drug release from three tablets was measured until complete release under sink conditions.

Finally, the prepared tablets were examined under a scanning electron microscope (Philips model XL30). By means of an image analysis technique, the disposition of the particles in the tablet was observed and the formation of finite or infinite clusters was evaluated.

A microanalysis technique was carried out for the identification of the components of the sample. An energy dispersion analyzer (Philips model XL30) was used. Therefore, in relation to the atomic weight and nature of the mixture components, it was possible to evaluate the elemental composition of the product under study.

3. Results and discussion

3.1. Resistance analysis

The resistance to the flow of electric current through the solid particles of a power-conductor substance, sodium chloride, enabled us to design the investigation reported in this paper. A study of this property vs the sodium chloride concentration allowed detection of the formation of finite or infinite clusters inside the tablet. The resistance values are higher if no infinite network of neighbor occupied sites are present; i.e., for sodium chloride concentrations lower than the percolation threshold. When this ratio is larger than the percolation threshold, practically all the sodium chloride particles have clustered together to form an infinite network and the resistance values decrease appreciably.

Table 1
Resistance and resistivity data obtained as a function of sodium chloride tablet loading

NaCl (%)	Resistance (Ω)	Resistivity (Ω mm)
100	1.91×10^{9}	3.0008×10^{10}
80	1.91×10^{9}	3.0008×10^{10}
70	1.92×10^{9}	3.0163×10^{10}
60	1.91×10^{9}	3.0008×10^{10}
50	1.92×10^{9}	3.0163×10^{10}
40	1.93×10^{9}	3.0320×10^{10}
30	4.50×10^{11}	2.5360×10^{12}
20	4.50×10^{11}	2.5360×10^{12}

Table 1 lists the obtained results corresponding to the resistance and the resistivity studies, according to Eq. 1.

It can be observed that the tablets prepared with percentages of sodium chloride equal to or less than 30% (w/w) show greater resistance values than the rest of the prepared matrix tablets. It can be also observed that all the lots of tablets prepared with sodium chloride percentages higher than 30% (w/w), with smaller resistance values, show virtually the same value.

In the prepared binary mixtures, the acrylic resin Eudragit® RS 100, used as an inert matrix forming excipient, is not a power-conductor material. In contrast, the solid powder sodium chloride conducts electricity. The effect of increasing the initial sodium chloride loading in the tablets will be reflected in the formation of a more extensive power-conductor material cluster and in a less extensive excipient network. This situation can explain the obtained resistivity data.

When an appropriate drug-polymer ratio is used, an infinite cluster of sodium chloride is formed. The sodium chloride particles form a connected network which spans the tablet in all three dimensions. In this case, when the tablet is placed inside an electric circuit, a flow of electricity can be detected. Then, the electrometer

records a low resistance value, about 10^9 Ω. In comparison, the tablets which contain finite clusters of sodium chloride do not show any connection between the particles. They cannot conduct electricity and the resistance values obtained are higher, about 10^{11} Ω. When the resistivity parameter is considered, similar results are obtained.

It is not possible to establish the appearance of a continuity between the particles of sodium chloride in the tablets prepared with a percentage of 20 and 30% (w/w) of the salt. When the percentage of active substance increases, the number of particles is greater and the probability that these particles are arranged neighboring and joined is also increased. In Fig. 1, a sudden change in the studied property when the sodium chloride concentration is higher than 30% (w/w) is clearly observed. This is indicative of the presence of an infinite cluster of the power-conductor model substance which readily allowed the conduction of the electric current in the matrix tablet.

From the results obtained, the first percolation threshold was determined as between 30 and 40% (w/w) of sodium chloride loading.

In this sense, the proposed technique provides a rapid, uncomplicated and repetitive way to assess percolation thresholds. Such information will enable one to explain the observed changes in the dissolution process of prepared matrix tablets. It may provide a valuable tool for a more rational solid dosage form design.

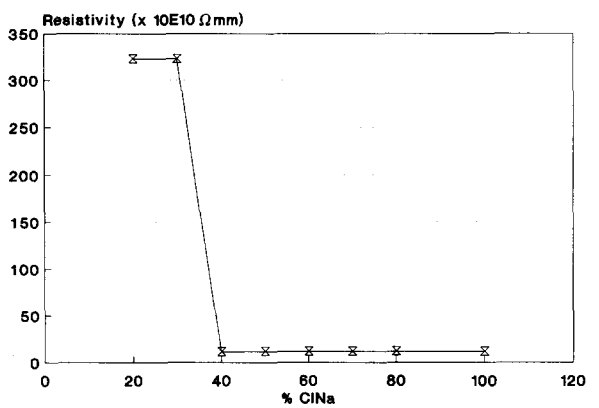

Fig. 1. Resistivity data as a function of sodium chloride tablet loading.

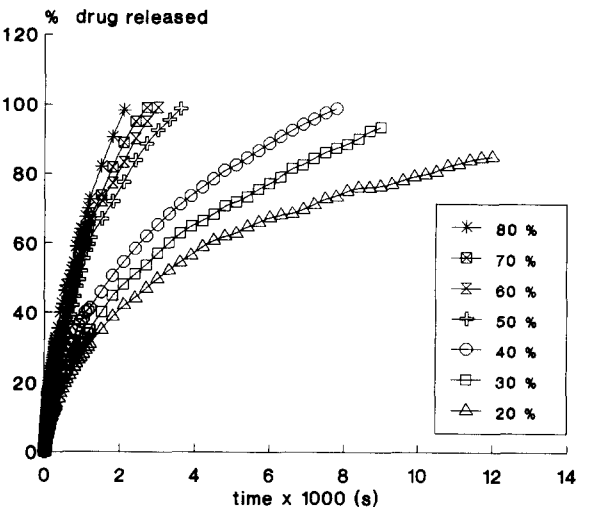

Fig. 2. Cumulative amounts (%) of sodium chloride released vs time for tablets containing sodium chloride and Eudragit® RS 100, with sodium chloride contents from 20 to 80% (w/w).

3.2. Effect of drug loading over release profiles

A study of the prepared matrix tablet release profiles led to corroboration of the results obtained. Fig. 2 shows the tablet release profiles expressed as percentual released amount of drug as a function of time. An inverse relationship between the percentage of polymer used and the release rate of active substance is evident.

It is observed that incomplete release occurs from compacts containing 20 and 30% (w/w) sodium chloride loading. This situation can be explained by the fact that the drug percolation threshold is not reached at this low drug concentration. The sodium chloride clusters do not span the whole tablet, remaining as isolated networks. Hence, part of the drug charge will be encapsulated by the plastic matrix and release will be incomplete.

On the other hand, it has been observed experimentally that the tablets prepared with a sodium chloride charge of 80% (w/w) undergo a disintegration process. In contrast, the rest of the lots maintain their structures until the end of the dissolution process. Therefore, the excipient percolation threshold is situated between 70 and 80% (w/w) of sodium chloride contents in this type of matrix system.

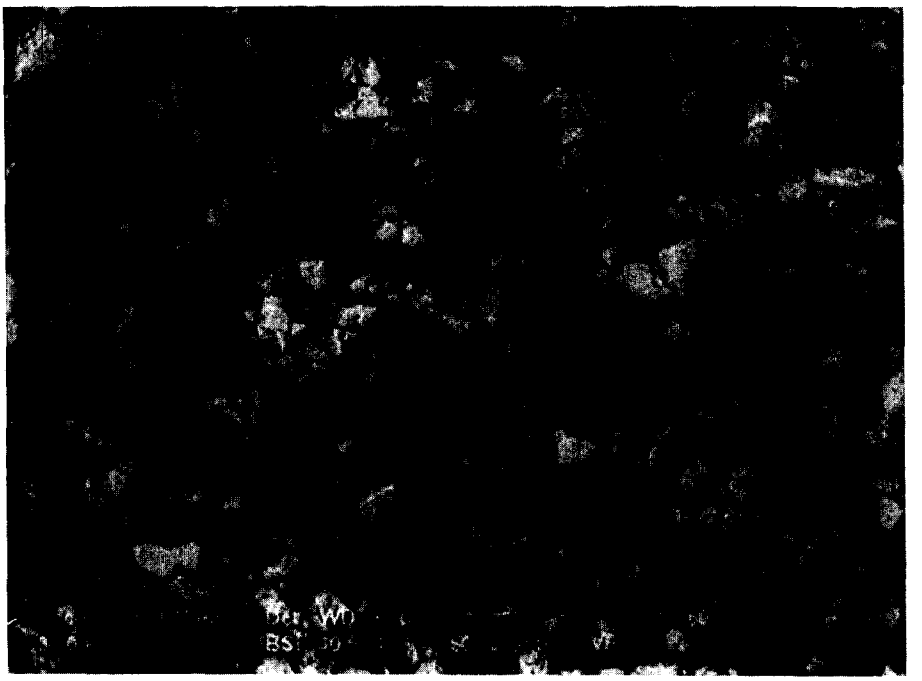

Fig. 3. SEM micrograph of matrix tablets with an initial sodium chloride content of 50% (w/w), before the dissolution process.

Considering excipient concentrations greater than its percolation threshold, an excipient infinite cluster will be formed. This condition prevents tablet disintegration although, between both percolation thresholds, the soluble drug is completely removed by dissolution.

3.3. Image analysis

Examination of the tablets in a scanning electron microscope (SEM) made it possible to demonstrate visually the continuity or discontinuity between the particles of sodium chloride, and

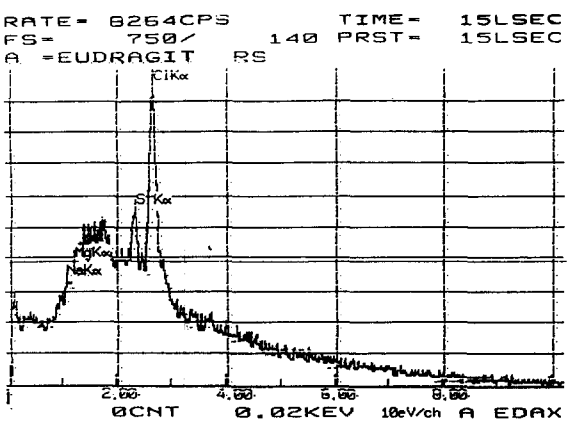

Fig. 4. Microanalysis chart corresponding to the matrix tablets prepared with an initial sodium chloride content of 50% (w/w), before the dissolution process.

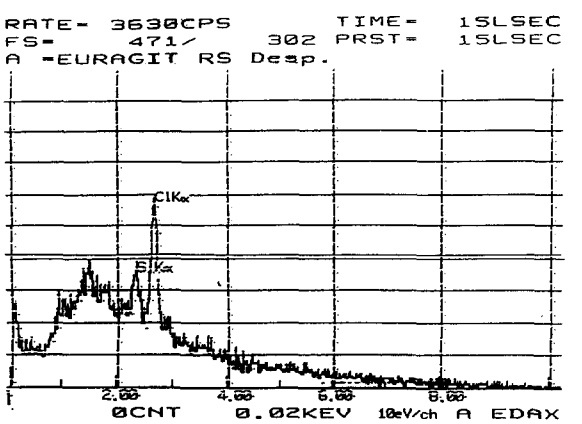

Fig. 5. Microanalysis chart corresponding to the matrix tablets prepared with an initial sodium chloride content of 50% (w/w), after the dissolution process.

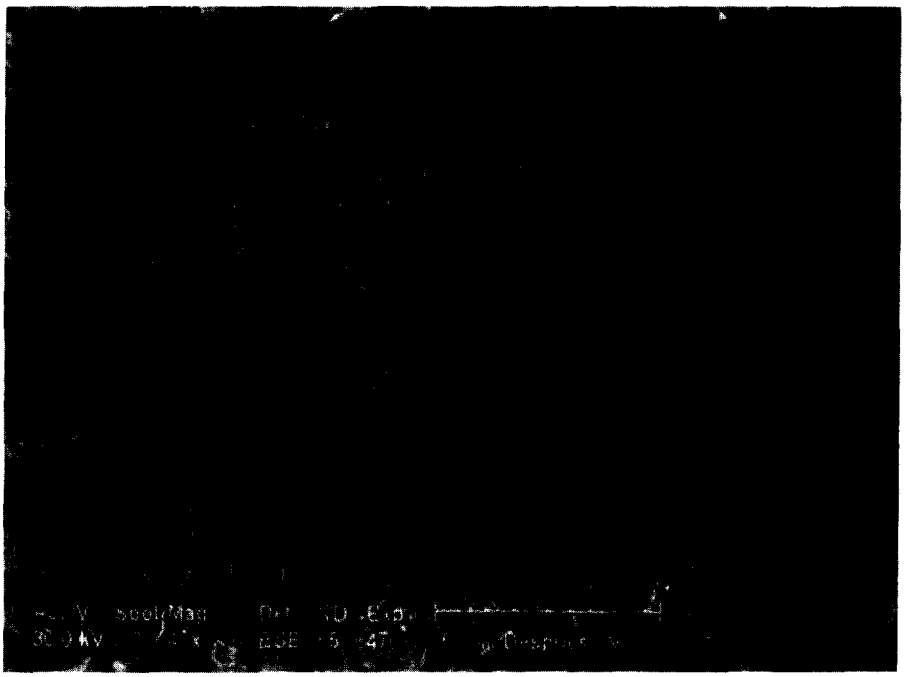

Fig. 6. SEM micrograph of matrix tablets with an initial sodium chloride content of 50% (w/w), after the dissolution process.

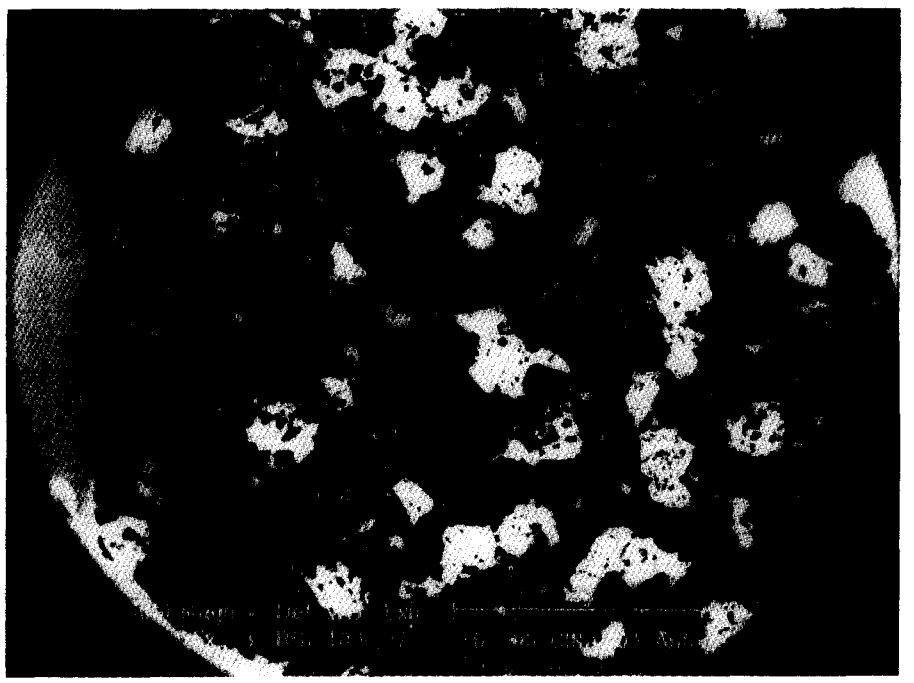

Fig. 7. SEM micrograph of matrix tablets with an initial sodium chloride content of 30% (w/w), after the dissolution process.

to corroborate the results obtained. The micrographs show the differences between the surface of the matrix tablets prepared with different sodium chloride loadings.

In Fig. 3, the image corresponding to a cross-section of a tablet containing 50% (w/w) of sodium chloride is presented. Both components, sodium chloride and Eudragit® RS 100, form infinite clusters and it is possible to appreciate, before the dissolution assay, the continuity between the particles of both products.

By means of a microanalysis technique, it was possible to identify the components of the clusters. In Fig. 4, the peak corresponding to the sodium chloride included in the sample can be observed. This peak does not appear in Fig. 5 as obtained from a microanalysis study performed on the same matrix tablet after testing in the dissolution assay. In this case, the sodium chloride was completely released and the continuity between the particles was replaced by a net of channels which spanned all the matrix tablet (Fig. 6).

Observations under the scanning electron microscope were also carried out on the matrix tablets prepared with percentages lower than 40% (w/w) of sodium chloride. As an example, in Fig. 7 the tablets containing 30% (w/w) of sodium chloride are shown. The micrographs clearly show that in these tablets the particles of Eudragit® form an infinite cluster while the salt, because of the lower concentration, remains as isolated networks (finite clusters), which explains the high resistance and the low conductivity values obtained. Fig. 7 enables us to confirm the established limit for the first percolation threshold.

As a final conclusion, the proposed technique allows determination via a fast, simple and repetitive procedure of the critical sodium chloride charge necessary to form infinite clusters of both components. We can verify a first percolation threshold comprising between 30 and 40% (w/w) of sodium chloride loading. Below this threshold, the release of drug is incomplete: the drug particles are connected to the surface of the tablet and those which are readily accessible to the dissolution medium. On other hand, an upper threshold was found, higher than 70% (w/w) sodium chloride loading. Between the two limits, the drug is completely released. A knowledge of the percolation thresholds is required for the appropriate design of matrix tablets, prepared with binary mixtures, to control drug release under determined conditions either in terms of the amount of released drug or release rate.

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