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Study of morphine hydrochloride percolation threshold in Eudragit® RS–PM matrices

L.M. Melgoza, I. Caraballo *, J. Alvarez-Fuentes, M. Millán, A.M. Rabasco

Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Seville, Seville, Spain

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Abstract

Percolation theory has been applied in the pharmaceutical field since 1987. The knowledge of the percolation thresholds of a system results in a clear improvement of the design of controlled release dosage forms such as inert matrices. In the present paper, the percolation thresholds of morphine hydrochloride inert matrices have been estimated and the obtained results have been applied to the design of controlled release inert matrices of this drug.

The tablets were prepared by compression of binary mixtures of morphine hydrochloride, as a drug of clinical interest to cancer patients, and Eudragit® RS–PM, a hydrophobic acrylic polymer as matrix forming material. Drug loadings between 10% and 90% (w/w) were prepared, keeping constant the drug and excipient particle sizes. The dissolution assay was carried out exposing only one side of the tablets to the dissolution medium. The drug percolation threshold was estimated following the method of Leuenberger and Bonny as 0.506 ± 0.014 of total porosity, corresponding to ca. 40% (w/w) drug content. The scanning electron microscopy (SEM) micrographs corresponding to the tablet side facing the lower punch and to the cross-section of these matrices are in agreement with the estimated percolation range.On the other hand, according to the SEM study and to the tablet integrity after the release assays, the excipient percolation threshold is expected to range from 65 to 80% (w/w) of drug, i.e. from 29.5 to 17% (v/v) of excipient. The release profiles of the matrices situated above the percolation threshold of the swelling substances (more than 41% v/v of excipient) have shown practically linear release profiles, which appear to not be sensitive to the drug load.

Keywords: Morphine hydrochloride; Eudragit® RS–PM; Percolation threshold; Percolation theory; Inert matrix; Controlled release; Solid dosage forms

1. Introduction

The percolation theory has a wide application in many disciplines of science. It was introduced

* Corresponding author. Present address: Departamento de Farmacia y Tecnología Farmacéutica, Cátedra de Farmacia Galénica, Facultad de Farmacia, Universidad de Sevilla, C/ Profesor García González s/n, 41012 Sevilla, Spain.

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Table 1
Statistical parameters from the image analysis of the morphine hydrochloride powder by SEM

n	Shape factor	Aspect ratio	ECD (μm)	Maximum diameter (μm)	Minimum diameter (μm)	Mean diameter (μm)
58	0.63 ± 0.024	1.357 ± 0.126	30.13 ± 1.405	46.9 ± 2.51	27.5 ± 1.51	40.6 ± 2.227

n, numbers of cases; ECD, equivalent circle diameter.

by Leuenberger et al. in the pharmaceutical field in 1987 to explain the mechanical properties of compacts and the mechanisms of the formation of a tablet (Leuenberger et al., 1987; Holman and Leuenberger, 1988). The percolation theory is a statistical theory, which deals with the formation of clusters and the existence of site and bond percolation phenomena.

A cluster is defined as a group of neighbouring occupied sites in the lattice and the probability at which a cluster just percolates a system is termed percolation threshold (Stauffer and Aharony, 1991). In a suitable pharmaceutical dosage form consisting of a binary mixture of substances A and B, the lattice sites can be occupied by the component A or B (Domb, 1983). The percolation threshold of component A depends on the type of lattice formed and indicates at which concentration of A this substance dominates the system A/B, or vice versa.

Only a few attempts have been made to apply percolation theory to the diffusion of a drug from an inert matrix. Bonny and Leuenberger (1991) explained qualitatively and quantitatively the changes in dissolution kinetics as a function of the drug loading of a matrix tablet with the help of percolation theory. Recently, Caraballo et al. (1996) and Millán et al. (1998) found a linear relationship between drug percolation threshold and particle size in matrix tablets. These theoretical studies were carried out using model drugs such as KCl and caffeine.

In the present study the percolation theory is applied to drug delivery systems of clinical interest. For this purpose, the percolation of morphine hydrochloride in matrix tablets has been studied using different methods. The method proposed by Bonny and Leuenberger (1991) is based on the calculation of the property β, derived from the release profiles and the total porosity of the matrices.

The equations proposed by Leuenberger and Bonny can be written as:

$$\beta = c(\epsilon - \epsilon_c) = -c\epsilon_c + c\epsilon$$

where β is a property of the tablet, c represents a constant, ϵ is the matrix porosity after leaching, due to the initial tablet porosity and to the drug content, and ϵ_c denotes the drug percolation threshold expressed as critical porosity. The property β is defined as:

$$\beta = \frac{b}{\sqrt{2 \cdot A - \epsilon \cdot C_s}}$$

where b is the slope of the Higuchi plot, A the concentration of the dispersed drug in the tablet and C_s the solubility of the drug in the permeating fluid. Plotting β versus ϵ, the drug percolation threshold (ϵ_c) can be readily calculated as the point of intersection with the abscissa.

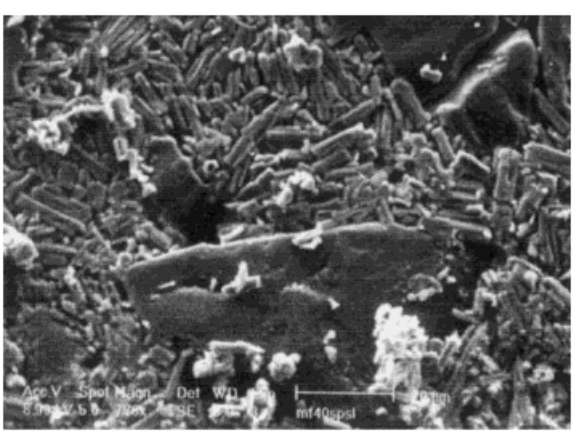

Fig. 1. SEM micrograph corresponding to the bottom side of the tablet containing 40% w/w of drug.

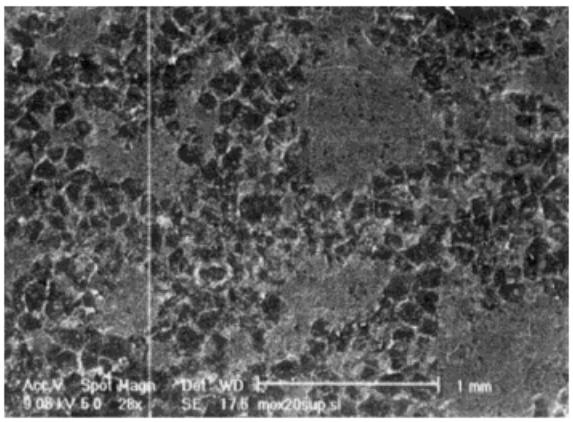

Fig. 2. SEM micrograph corresponding to the bottom side of a matrix containing 20% w/w of drug that shows groups of morphine hydrochloride (light grey particles) embedded by the excipient (dark grey particles).

Morphine hydrochloride is especially interesting for the treatment of chronic pain in cancer patients (Meed et al., 1987; Ferrell et al., 1989; Ahmedzai and Brooks, 1997). This drug is readily, but incompletely, absorbed from the gastrointestinal tract. Its first-pass metabolism reduces its bioavailability. Nevertheless, the oral administration of morphine hydrochloride, especially by controlled delivery systems is suitable (Zahirul and Khan, 1995). Morphine has a half-life of approximately 2.3 h (Muhtadi, 1988).

The design of controlled release matrices for the oral administration of morphine hydrochloride (Savarese et al., 1986; Bloomfield et al., 1993) presents the advantages of less frequent dosing, avoiding administration during the night, and a more simple technology than other controlled release systems which results in a lower cost.

The aim of the present work is to calculate the percolation threshold of morphine hydrochloride in matrix tablets and to apply the obtained result to design inert matrices for the controlled delivery of this drug.

2. Experimental

2.1. Materials and methods

The materials used to prepare the tablets were morphine hydrochloride (Lab. Alcaliber, Madrid) and Eudragit® RS–PM (Hüls Española, Barcelona) a hydrophobic, acrylic polymer as the matrix forming material.

The drug was not sieved and its particle size was measured using an image analysis system linked to a scanning electron microscope (SEM) (Philips type XL 30). On the other hand, the polymer was sieved (Retsch type Vibro) and the 100–150 μm granulometric fraction was employed. The mean particle size of this granulometric fraction was measured using a He–Ne laser diffraction system (Malvern Instruments, type Mastersizer x, 1.2b). The solvent mixture employed to disperse the particles was water/propylene glycol (40:60 v/v).

The true density of morphine hydrochloride has been calculated using an air pycnometer (Quantachrome type Stereopynometer spy-3) as 1.46 g/cm^3. The true density of Eudragit® RS–PM in the matrices has been calculated experimentally using a mercury porosimeter as 1.23 g/cm^3 (Fisons Instruments, type 4000) (Millán et al., 1998).

Matrix tablets were prepared with different drug contents (10, 20, 30, 40, 50, 55, 60, 65, 70, 80 and 90%) keeping constant the drug and excipient particle size. The mixtures were compressed on an eccentric machine (Bonals A-300) without any further excipient. Cylindrical tablets with a mean weight of 500 mg and a diameter of 12 mm were prepared at the maximum compression force accepted by the formulation.

The intrinsic dissolution assay was carried out at 37 ± 0.5°C in distilled water during 20 h, in the USP 23 apparatus (Turu Grau, model D-6) using the rotating disc method so that only the tablet side facing the lower punch (1.13 cm^2) was exposed to the dissolution medium. The rotation speed was kept constant at 50 rpm. Release of morphine hydrochloride was detected by the increase in conductance of the dissolution medium using a Crison micro CM-2201 digital conductivity meter linked to a chart recorder and a personal computer. This method has been previously validated (Caraballo et al., 1998), showing adequate accuracy (-6.63%) and precision (CV < 2%) values.

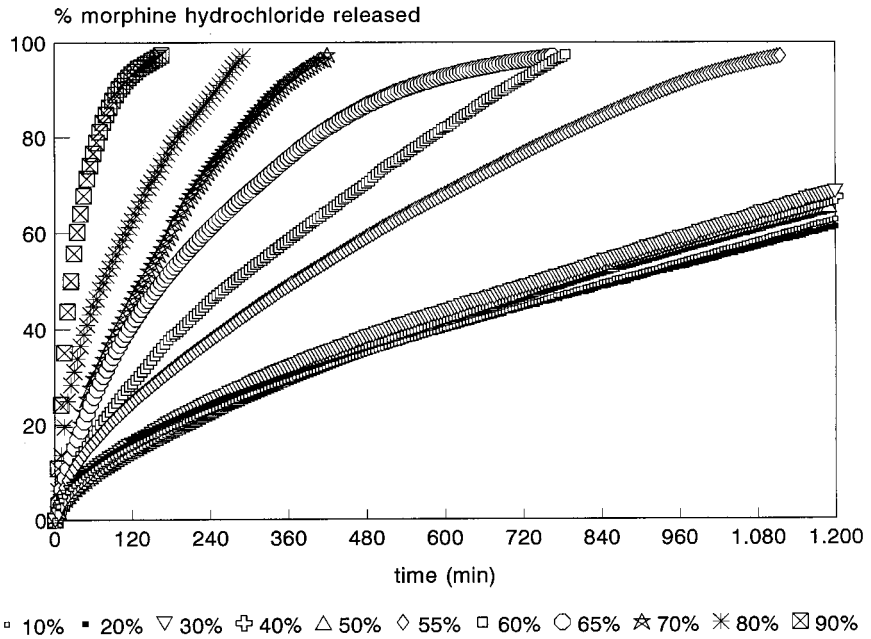

Fig. 3. Percentage of drug content released versus time for tablets prepared with different loadings of morphine hydrochloride.

Some of the matrix surfaces were examined using a scanning electron microscope (Philips, type XL 30), with two different detectors (BSE and SE). In addition, some tablets were cut following a diameter and the cross-section was examined.

3. Results and discussion

3.1. Measurement of the particle size

The mean particle sizes of the components were measured and the obtained results were 125 μm for Eudragit® RS–PM and 40 μm for morphine hydrochloride (Table 1). Nevertheless, when the prepared matrices were examined using SEM, a much finer particle size (approximately 10 μm) has been observed for morphine hydrochloride (see Fig. 1). This fact indicates that an extended fragmentation process has occurred.

On the other hand, as Fig. 2 shows, these little drug particles are distributed as large/extended groups of morphine hydrochloride particles inside the tablet. Therefore, in these matrices the effective drug particle size, i.e. the size of the groups in which morphine hydrochloride is distributed and which will determine its effectiveness to percolate the system, may be bigger than the real drug particle size.

3.2. Estimation of the drug percolation threshold

Taking into account the percentage of drug released from the studied matrices, a very similar behaviour has been obtained for matrices containing up to 50% w/w of drug (see Fig. 3). This fact can be attributed to the increase that the tablet volume underwent during the release assay. After the 20-h release assay, the tablets showed a low but significant increase in volume (7% v/v approximately).

This increase in volume can be due to a little relaxation of the matrix structure that can result in the development of additional porosity and in the penetration by the dissolution medium. Therefore, water can percolate the region of the tablet near to the free surface. As a consequence, the

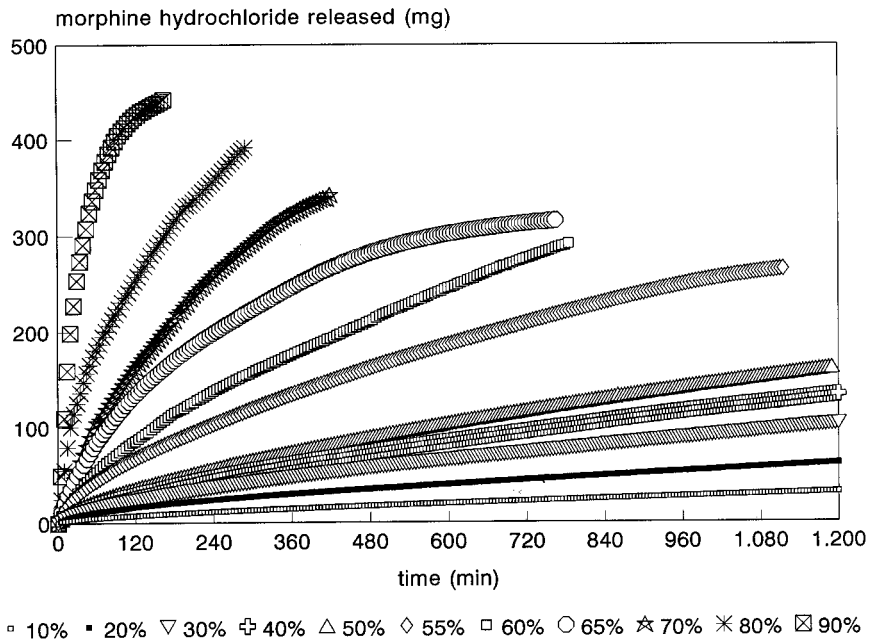

Fig. 4. Amounts of drug content released versus time for tablets prepared with different loadings of morphine hydrochloride.

entire drug included in this region will be released, even if a drug infinite cluster does not exist in this tablet. This process can mask the influence of the drug percolation threshold on the release profiles.

Therefore, the drug percolation threshold cannot be deduced from the release profiles that were very similar for tablets containing up to 50% (w/w), showing that the dissolution profiles were not sensitive to the drug load within this range. So, alternative methods have been employed to estimate the drug percolation threshold in the studied matrices.

3.2.1. Estimation of the drug percolation threshold based on SEM

When percolation theory is applied to binary systems, two percolation thresholds can be defined, the percolation threshold of the drug substance and the percolation threshold of the excipient. The percolation threshold of a substance is the probability or volume fraction at which this substance starts to percolate the sample.

Figs. 3 and 4 show the tablet release profiles expressed as the percentage and total amount of drug released as a function of time, respectively. After 20 h, the matrices containing up to 50% (w/w) of drug have released less than 70% of the drug loading. In the SEM micrograph corresponding to the bottom side of the tablets containing 20% (w/w) of drug (see Fig. 2), it can be observed that morphine hydrochloride is surrounded by the excipient particles (dark grey particles). Therefore, it can be deduced that part of the drug will be encapsulated by the excipient and the drug release will not reach completion.

Fig. 5a shows the SEM micrograph corresponding to the tablet side facing the lower punch for matrices containing 30% (w/w) of drug. In comparison with matrices containing 20% (w/w) of drug (Fig. 2), morphine hydrochloride (light grey particles) appears to be not so clearly surrounded by the excipient (dark grey particles).

Nevertheless, when the cross-section of these matrices (30% drug loading) is observed (see Fig. 5b), it is clear that the drug (light grey particles) is embedded by the excipient, which percolates the

system. Therefore, the drug infinite cluster does not yet exist, and the drug release does not reach completion. The release data showed that 26% of the drug was not released from these matrices during 20 h.

In addition, two SEM micrographs for the inert matrices containing 30 and 40% (w/w) have been taken at low magnification (29 ×) (see Fig. 6). When these micrographs are compared, a clear change in the distribution of the drug can be observed. In the matrix with 40% drug loading (Fig. 6b), the drug particles begin to form a connective network from the left to the right and from the top to the bottom side of the picture. This fact suggests the existence of a drug infinite cluster percolating the entire sample. Therefore,

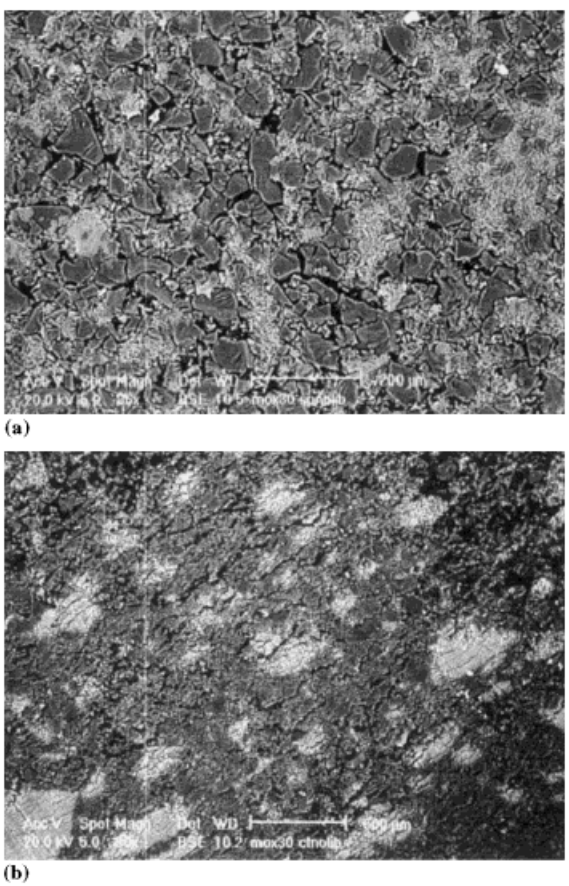

Fig. 5. SEM micrograph corresponding to the tablet with 30% of drug using the BSE detector. (a) Bottom side of the matrix. (b) Cross-section of the matrix.

according to the SEM study, the morphine hydrochloride percolation threshold is expected to be between 30 and 40% (w/w) of drug.

3.2.2. Estimation of the drug percolation threshold using the method of Leuenberger and Bonny

In order to estimate the drug percolation threshold of the studied controlled release devices, the method proposed by Bonny and Leuenberger (1991) was used.

For the estimation of the drug percolation threshold, ϵ_c, the above mentioned equations were used considering only the release data up to 70% of drug released to allow the application of the Higuchi's equation. The results obtained for the β property and the related parameters are shown in Table 2. As Fig. 7 shows, the drug percolation threshold or critical porosity is estimated from the regression of the β values corresponding to bicoherent systems which exhibited a linear behaviour versus ϵ (solid circles in Fig. 7).

The obtained value for the critical porosity, the intercept with the abscissa, was 0.51 ± 0.014, which corresponds to a morphine hydrochloride content of ca. 40% (w/w).

Therefore, the result of the method of Leuenberger and Bonny is in agreement with the SEM observations. According to these two methods, the drug percolation threshold for the studied inert matrices is situated between 30% and 40% (w/w) of morphine hydrochloride (0.426 and 0.512 of total porosity, respectively).

3.3. Study of the swelling process from the point of view of percolation theory

As has been indicated in the previous section, the estimation of the drug percolation threshold by the method of Leuenberger and Bonny results in values which soundly correspond to those of the SEM micrographs. Nevertheless, experimental release data do not confirm this estimation. As Fig. 3 shows, release profiles of tablets containing up to 50% (w/w) of drug are very similar whereas higher drug contents result in significantly different profiles. This fact is due to the swelling of the matrix, which seems to be optimal in the range 10–50% (w/w) drug load.

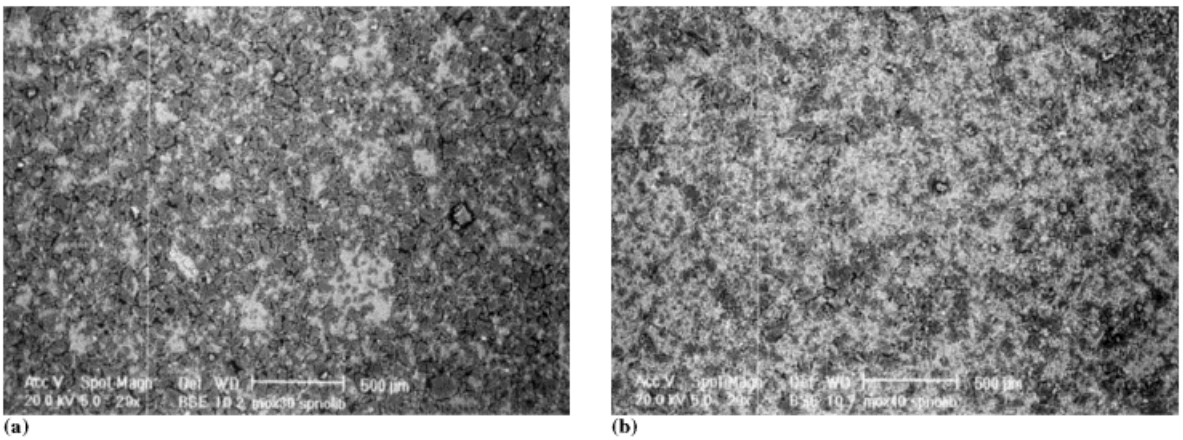

Fig. 6. SEM micrograph corresponding to the bottom side of the tablets at low magnification (29 ×) using the BSE detector. (a) Matrices containing 30% of drug. (b) Matrices containing 40% of drug.

It must be emphasised that different percolation thresholds exist for different properties: it seems to be evident that there is a percolation threshold between 50 and 55% (w/w) drug load, concerning the swelling property. This range corresponds to 38–41% (v/v) of excipient.

Obviously, these percentages correspond to the tablet before the release assay. It is clear that, when an additional volume is created, these volume fractions will be changed. Nevertheless, it is not possible to know the fraction of the new volume that corresponds to the excipient, due to the fact that additional porosity can be developed. This porosity is different to the initial porosity, ϵ_c, and to the porosity due to the dissolution of the drug.

3.4. Estimation of the excipient percolation threshold

The excipient percolation threshold is the concentration at which this substance ceases to form an infinite cluster. Therefore, tablets containing higher drug concentrations will no longer have a coherent insoluble structure and will disintegrate during the release process.

The SEM micrographs corresponding to the cross-section of the matrices containing 70 and 80% (w/w) of drug (see Fig. 8) show a change in the distribution of the excipient. In the matrix with 80% drug loading (Fig. 8b) the Eudragit® RS–PM particles (dark grey particles in the picture), start to become isolated between the morphine hydrochloride particles. In this region, no more coherent matrix appears to be present and the tablet will disintegrate during the dissolution process.

It must be borne in mind that the estimation of the percolation threshold by visual means is not very accurate, mainly due to the extrapolation from 2D to 3D systems.

In order to confirm the previous result, the tablet integrity after the 20-h release assay was studied. Formulations containing more than 65% (w/w) were unable to keep the tablet integrity.

These results suggest that the percolation threshold of the excipient (Eudragit® RS–PM) in the assayed tablets can be situated between 65 and 80% (w/w) of drug, which corresponds to an excipient concentration ranging between 29.5 and 17% (v/v).

Although further studies concerning drug release through the whole surface and pH gradient are necessary, very attractive release behaviour has been found for matrices formulated below the swelling percolation threshold.

In fact, as Fig. 3 shows, drug loads up to 50% (w/w) yield practically linear profiles, as desired for a controlled release system. Furthermore, drug loadings between 10 and 50% (w/w), correspond-

Table 2
Calculation of the tablet property β and related parameters[a] in matrices containing 125 μm Eudragit® RS–PM particles

Drug (%)	ϵ	$b \pm$ S.E	R	n	F	Prob.	A	$\beta \times 10^3$
10	0.238	$1.09 \times 10^{-4} \pm 5.6 \times 10^{-7}$	0.997	241	36917.9	9.9×10^{-16}	0.105	0.244
20	0.306	$2.07 \times 10^{-4} \pm 8.1 \times 10^{-7}$	0.998	241	64735.7	9.9×10^{-16}	0.214	0.321
30	0.426	$3.88 \times 10^{-4} \pm 2.0 \times 10^{-6}$	0.997	220	35638.8	9.9×10^{-16}	0.304	0.506
40	0.512	$5.03 \times 10^{-4} \pm 2.0 \times 10^{-6}$	0.997	234	42059.5	9.9×10^{-16}	0.402	0.569
50	0.589	$5.89 \times 10^{-4} \pm 3.0 \times 10^{-6}$	0.997	239	35110.9	9.9×10^{-16}	0.507	0.592
55	0.613	$9.67 \times 10^{-4} \pm 7.0 \times 10^{-6}$	0.997	118	18259.7	9.9×10^{-16}	0.585	0.905
60	0.658	$1.293 \times 10^{-3} \pm 1.0 \times 10^{-5}$	0.998	85	16553.8	9.9×10^{-16}	0.633	1.163
65	0.705	$1.634 \times 10^{-3} \pm 1.3 \times 10^{-5}$	0.998	63	16494.9	9.9×10^{-16}	0.677	1.42
70	0.747	$2.240 \times 10^{-3} \pm 4.0 \times 10^{-5}$	0.994	41	3086.97	9.9×10^{-16}	0.729	1.876
80	0.83	$2.832 \times 10^{-3} \pm 4.3 \times 10^{-5}$	0.997	28	4416.16	9.9×10^{-16}	0.838	2.212
90	0.914	$6.116 \times 10^{-3} \pm 4.1 \times 10^{-4}$	0.985	9	220.875	1×10^{-6}	0.955	4.47

[a] ϵ, total porosity; b, Higuchi constant ($g/s^{1/2}$ per cm^2); R, linear correlation coefficient; n, number of cases; F, Snedecor ratio; A, concentration of drug dispersed in the tablet (g/cm^3); β, tablet property ($g^{1/2}/cm^{1/2}$ per $s^{1/2}$).

ing to 41–76% (v/v) of excipient, result in very similar release profiles, which suggest that the dissolution profiles are not sensitive to the drug load within this range.

Finally, it must be pointed out that obtaining such a high drug percolation threshold (0.506) can be attributed to the fact that morphine hydrochloride particles are grouped together. Therefore, the effective drug particle size is higher than the real particle size. As has been demonstrated in previous work (Caraballo et al., 1993, 1996; Millán et al., 1998), when a component of a mixture is grouped its percolation threshold increases.

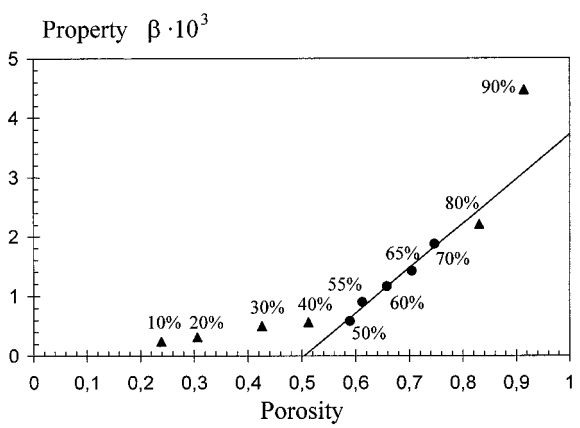

Fig. 7. Estimation of the drug percolation threshold of the matrices using the method of Bonny and Leuenberger, 1991.

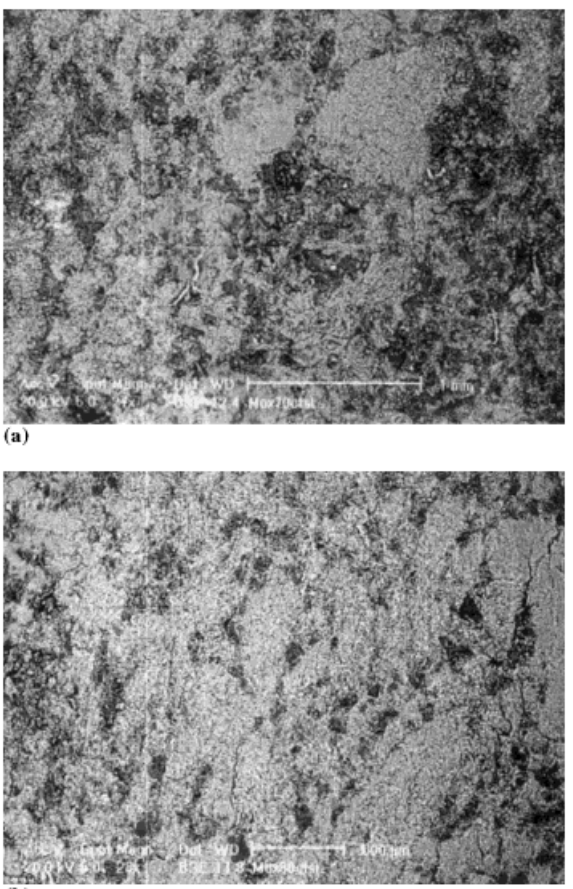

Fig. 8. SEM micrograph corresponding to the cross-section of the tablet using the BSE detector. (a) Matrices containing 70% of drug. (b) Matrices containing 80% of drug.

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