ELSEVIER

International Journal of Pharmaceutics 181 (1999) 23–30

international journal of pharmaceutics

Design of controlled release inert matrices of naltrexone hydrochloride based on percolation concepts

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Received 25 September 1998; received in revised form 1 December 1998; accepted 7 December 1998

Abstract

The percolation theory is a statistical theory able to study chaotic or disordered systems that has been applied in the pharmaceutical field since 1987. Through the application of this theory, the design of controlled release inert matrices has been improved. The aim of the present paper is to estimate the percolation thresholds, the most important concept of the percolation theory, which characterise the release behaviour of controlled release inert matrices of naltrexone hydrochloride. Matrix tablets were prepared using naltrexone hydrochloride as a potent narcotic antagonist and Eudragit® RS-PM as matrix forming material in different ratios, keeping constant the drug and excipient particle sizes. In vitro release assays were carried out exposing only one side of the tablets to the dissolution medium. The drug percolation threshold was estimated using different methods. The method of Leuenberger and Bonny gives $31.11 \pm 7.95\%$ v/v as the critical porosity, which corresponds to a percolation range from 12 to 20% (w/w) of drug content. The release profiles and the release kinetics are in agreement with this result. A change in the exponent k (from 0.29 to 0.57) has been found in this region. Using scanning electron microscopy, the percolation threshold has been observed in a higher concentration range (20–35% w/w). This fact can be attributed to the low accuracy of the visual methods, mainly due to the extrapolation from 2D to 3D systems. If a percolating cluster is observed in two dimensions, the percolation threshold of the 3D system will be already clearly exceeded. The excipient percolation threshold is estimated between 25.4 and 31.1% (v/v) based on the release profiles and the analysis of the release kinetics.

Keywords: Naltrexone hydrochloride; Eudragit® RS-PM; Controlled release matrix; Percolation theory; Percolation threshold.

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0378-5173/99/$ - see front matter
PII: S0378-5173(98)00415-3

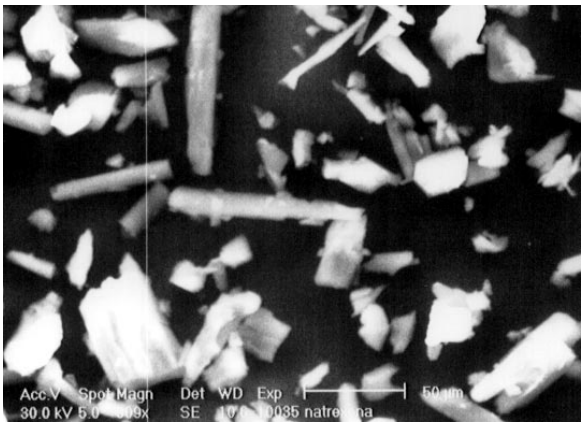

Fig. 1. SEM micrograph of naltrexone hydrochloride powder.

Naltrexone hydrochloride is a potent narcotic antagonist, approximately 30–40 times as active as nalorphine and two to three times as active as naloxone. Consequently, it is used as an adjunct to the maintenance of the opioid-free state in detoxified, formerly opioid-dependent, individuals (Blumberg and Dayton, 1974).

It is absorbed rapidly and almost completely following oral administration, but undergoes extensive first-pass metabolism in the liver. Only 5–20% of an orally administered dose reaches systemic circulation unchanged. However, its principal metabolite, 6β-naltrexol, is also a pure antagonist and may contribute to the opioid receptor blockade. Mean elimination half-lives for naltrexone and 6β-naltrexol are 3.9 and 12.9 h, respectively (Swinyard, 1990).

The design of a controlled release system for the administration of naltrexone hydrochloride is advisable, mainly to reduce the side-effects of this drug.

Several systems to subcutaneous implantation of naltrexone hydrochloride have been developed (Schwope et al., 1976; Sullivan and Kalkwarf, 1976; Thies, 1976; Chiang et al., 1984; Bennett et al., 1991; Yamaguchi and Anderson, 1992).

Nevertheless, this route of administration needs sophisticated technology, being more expensive than the oral administration. On the other hand, the oral administration implies a determined interval of dosage that is a positive psychological factor in the treatment of opioid-dependent individuals.

Through the application of percolation concepts, the design of controlled release inert matrices has been improved (Leuenberger et al., 1987; Bonny and Leuenberger, 1991, Caraballo et al., 1993, 1994, 1996a). The percolation theory was introduced by Leuenberger et al. (1987) in the pharmaceutical field, getting interesting advances to explain the mechanism of tablet disintegration, the wet granulation process or the behaviour of controlled release systems.

The percolation theory is a statistical theory able to study chaotic or disordered systems. The number and properties of clusters on virtual lattices of different types are studied. A cluster is defined as a group of neighbour-occupied sites in the lattice (Stauffer and Aharony, 1991).

The percolation theory deals with finite and infinite clusters. A cluster is considered infinite (or percolating if limited systems are studied) when it extends from one side to the rest of the sides of the lattice. The percolation threshold indicates the concentration at which a component starts to dominate the system. At this point, there is a maximum probability that a percolating cluster of this substance appears for the first time, and some properties of the system change suddenly.

Table 1
Statistical parameters from the image analysis of the naltrexone hydrochloride powder by SEM[a]

n	Shape factor	Aspect ratio	ECD (μm)	Maximum diameter (μm)	Minimum diameter (μm)	Mean diameter (μm)
101	0.57 ± 0.02	1.57 ± 0.14	41.47 ± 1.75	82.40 ± 4.49	40.77 ± 2.70	72.72 ± 4.16

[a] *n*, number of cases; ECD, equivalent circle diameter.

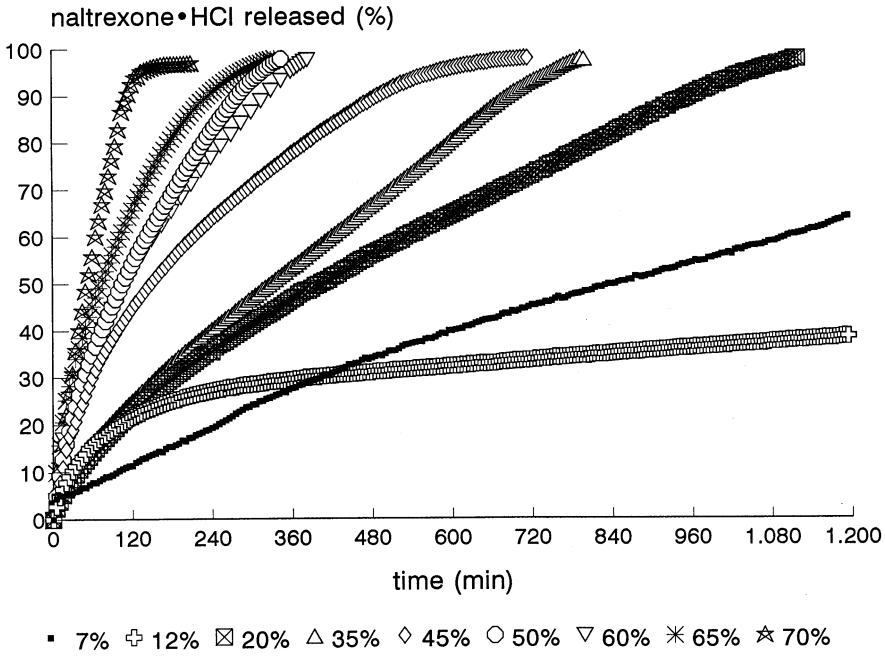

Fig. 2. Percentage of drug released vs time for tablets prepared with different loadings of naltrexone hydrochloride.

The objective of the present work is to estimate the different percolation thresholds that characterise the release behaviour of controlled release inert matrices of naltrexone hydrochloride in order to rationalise the design of these systems.

2. Materials and methods

Naltrexone hydrochloride (Laboratorios Zambón, Barcelona, Spain) was used as the drug and Eudragit® RS-PM (Hüls Española, Barcelona, Spain) as the matrix-forming material.

The drug was not sieved; nevertheless, its mean particle size was measured using an image analysis system linked to a scanning electron microscope (SEM) (Philips type XL 30) as 72 μm. The polymer was sieved (Retsch type Vibro) and the 100–150 μm granulometric fraction was selected. The mean diameter of the particles of this fraction was measured using a He–Ne laser diffraction system as 125 μm (Malvern Instruments, type Mastersizer x, 1.2b), with water/propylene glycol 40:60 v/v as solvent.

The true density of naltrexone hydrochloride (1.401 g/ml, S.E. = 0.007) was determined using a Helium pycnometer (Quantachrome type Stereopycnometer spy-3). The true density of the Eudragit® RS-PM in the matrices was determined employing a mercury porosimeter (Fisons Instruments, type 4000) as 1.23 g/ml. (Millán et al., 1998). The aqueous solubility of naltrexone hydrochloride was measured in a previous paper (Alvarez-Fuentes et al., 1997) and was found to be 85.4 mg/ml (S.E. = 1.1).

Nine binary mixtures of naltrexone hydrochloride and Eudragit® RS-PM were prepared with drug contents of 7, 12, 20, 35, 45, 50, 60, 65 and 70% w/w. The mixtures were compressed without any further excipient on an eccentric machine (Bonals A-300). Flat, cylindrical tablets with a weight of 500 mg and a diameter of 12 mm were prepared. The applied compression force was the maximum accepted by the formulation.

The dissolution study was carried out in the USP 23 apparatus (Turu Grau, model D-6) using the rotating disk method and distilled water at 37 ± 0.5°C. The tablet was embedded in paraffin,

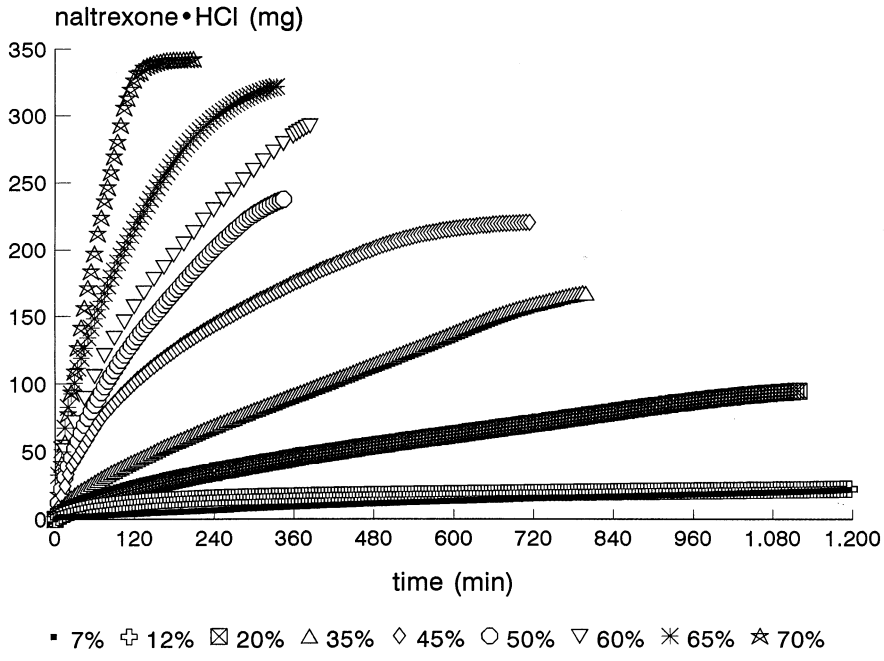

Fig. 3. Amounts of drug released vs time for tablets prepared with different drug loadings.

so that only the side facing to the lower punch was exposed to the dissolution medium. The rotational speed was kept constant at 50 rpm. The dissolution test was carried out under sink conditions during 20 h or until drug release reached completion.

The release of naltrexone 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. The system provides one conductivity datum per second. The conductometrical technique was evaluated by us (Caraballo et al., 1998), showing a good linearity from 50 to 1000 μg/ml. Precision (CV < 3%) and accuracy (− 5.45%) values were also adequate.

The regression analysis of the calibration curve ($y = (0.187 \pm 0.0008)x + (1.42 \pm 0.71)$) gave $r = 0.9999$ as the regression coefficient ($n = 6$) and $F = 48328.2$ as the Snedecor ratio ($P < 0.0001$).

A SEM (Philips, type XL 30) was used to examine the surface of the tablet with two different detectors (BSE and SE). A very thin coat of carbon was applied to each sample.

In a binary pharmaceutical tablet, two percolation thresholds are expected: the drug and the excipient percolation threshold.

The drug percolation threshold was calculated using the method of Leuenberger and Bonny. This method is based in the calculation of β, a property of the tablets derived from the diffusion coefficient, which is defined as:

$$\beta = \frac{b}{\sqrt{2A - \varepsilon C_s}} \quad (1)$$

where b is the slope of the Higuchi plot, A denotes the concentration of the drug dispersed in the tablet and C_s is the solubility of the drug in the permeating fluid. The determination of the percolation threshold, ε_c, is based on Eq. (2).

$$\beta = C\varepsilon - C\varepsilon_c \quad (2)$$

where C represents a constant, ε is the matrix porosity due to initial tablet porosity and to drug content after leaching, and ε_c denotes the critical porosity.

This method has been modified by us, so that the percolation threshold, ε_c, is determined by

Table 2
Parameters for the study of the release kinetics[a]

Drug (% w/w)	n	Higuchi model		$Q(t)=a'+b't^k$	
		$b \pm$ S.E.	r^2	k	r^2
7	240	$0.84\times10^{-4}\pm1.0\times10^{-6}$	0.985	0.74659	0.999
12	241	$0.79\times10^{-4}\pm1.0\times10^{-6}$	0.970	0.29704	0.999
20	220	$0.345\times10^{-3}\pm2.0\times10^{-6}$	0.997	0.57522	0.999
35	234	$0.68\times10^{-3}\pm8.0\times10^{-6}$	0.987	0.72562	0.999
45	239	$1.129\times10^{-3}\pm7.0\times10^{-6}$	0.998	0.50484	0.999
50	118	$1.593\times10^{-3}\pm2.3\times10^{-5}$	0.993	0.61567	0.999
60	85	$1.784\times10^{-3}\pm2.7\times10^{-5}$	0.997	0.55897	0.999
65	63	$2.334\times10^{-3}\pm1.7\times10^{-5}$	0.999	0.53875	0.999
70	41	$3.51\times10^{-3}\pm1.9\times10^{-4}$	0.958	0.82362	0.999

[a] b, slope ($g\times s^{-0.5}\times cm^{-2}$); r^2, squared correlation coefficient; k, dimensionless exponent; n, number of cases.

linear regression of ε vs β instead of β vs ε. In this manner, the confidence intervals of the percolation thresholds can be easily calculated.

Therefore, we estimate the drug percolation threshold as a percolation range for a determined confidence level. The obtention of each percolation range makes possible the comparison between different percolation thresholds, which was difficult using just one numerical value.

3. Results and discussion

3.1. Characterisation of the naltrexone hydrochloride particles by image analysis

Naltrexone hydrochloride shows a heterogeneous particle size (see Fig. 1). Table 1 shows the statistical parameters obtained from the image analysis of the SEM micrographs of naltrexone hydrochloride powder. Due to the acicular form of the particles, the shape factor and aspect ratio were significantly different to 1.

3.2. Estimation of the drug percolation threshold, p_{c1}

3.2.1. Release profiles and release kinetics

The results of the tablet release profiles expressed as percentages and absolute released amount of drug versus time are plotted in Figs. 2 and 3. In order to apply the Higuchi equation, only values of Q corresponding to a release of up to 70% of the drug amount initially present in the matrices were considered. The fit of the data to the equation ($Q(t)=a'+b't^k$) by non-linear regression was also investigated. The results are showed in Table 2, together with the obtained for the Higuchi model. Concerning the release profiles, Fig. 2 shows that after 20 h of release assay, the matrices with a drug content of at least 20% (w/w) released the total amount of drug.

In Table 2, a high unexpected value of the exponent k for matrices with 7% w/w of drug can be appreciated. This behaviour has been confirmed by additional replicates. A possible explanation for this phenomenon could be a swelling process similar to that previously found in inert matrices prepared with morphine hydrochloride and Eudragit® RS-PM (Melgoza et al., 1998). Nevertheless, the intensity of this phenomenon should be much lower in the naltrexone matrices and should only affect the matrices with 7% w/w of drug.

On the other hand, as can be appreciated in Table 2, a change in the release kinetics can be found between tablets containing 12 and 20% (w/w) of drug. This change concerns an increase in the squared correlation coefficients for the Higuchi equation and a change in the exponent k, which approaches the diffusion kinetics ($k=0.5$).

The best fit to the Higuchi equation was found between 20 and 65% (w/w) of naltrexone hydrochloride, with correlation coefficients higher

Table 3
Calculation of the tablet property β and related parameters[a] in matrices with different drug loading

Drug (% w/w)	ε_0	ε	*n*	*F*	Probability	*A*	$\beta \times 10^3$
7	0.185	0.236	240	15 318.5	9.9×10^{-16}	0.071	0.241
12	0.224	0.307	241	64 735.7	9.9×10^{-16}	0.117	0.174
20	0.233	0.371	220	35 638.8	9.9×10^{-16}	0.194	0.577
35	0.208	0.463	234	42 059.5	9.9×10^{-16}	0.357	0.828
45	0.207	0.539	239	35 110.9	9.9×10^{-16}	0.465	1.200
50	0.133	0.539	118	18 259.7	9.9×10^{-16}	0.569	1.524
60	0.191	0.652	85	16 553.8	1.2×10^{-15}	0.645	1.606
65	0.181	0.689	63	16 494.9	9.9×10^{-16}	0.712	1.998
70	0.224	0.746	41	3086.9	9.8×10^{-12}	0.732	2.967

[a] ε, total porosity; ε_o, initial porosity; *n*, number of cases; *F*, Snedecor ratio; *A*, concentration of drug dispersed in the tablet ($g \times cm^{-3}$); β, tablet property ($g^{0.5} \times cm^{-0.5} \times s^{-0.5}$). The data of Higuchi constant (*b*) have been given in Table 2.

than 0.99. The only exceptions are the matrices containing 35% w/w of drug, whose release kinetics is affected by an extended zero-order release period. As has been reported in previous papers (Gurny et al., 1982; Caraballo et al., 1993, 1996b), these periods are attributed to the saturation of drug into the water-filled pores of the matrix.

Therefore, on the basis of the release profiles and the release kinetics, the drug percolation threshold can be estimated between 12 and 20% (w/w) of drug, i.e. between 30.7 and 37.1% v/v of total porosity.

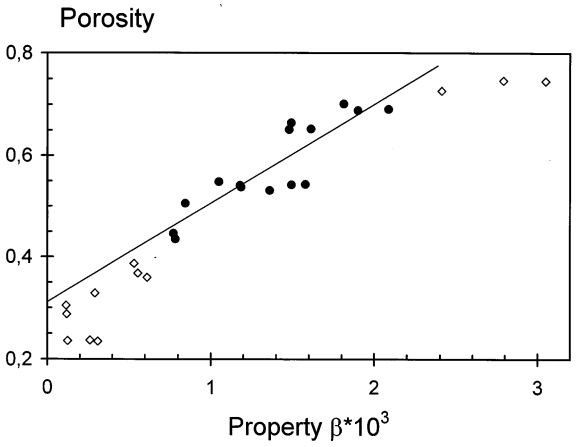

Fig. 4. Determination of the drug percolation threshold of the matrices using the method of Leuenberger and Bonny modified by us.

3.3. Method of Leuenberger and Bonny

The method proposed by Bonny and Leuenberger (1991) was also used for the estimation of the lower percolation threshold, p_{c1}. For this purpose, Eq. (1) was used and the results obtained are showed in Table 3.

Using Eq. (2), the value of the 95% confidence interval of the critical porosity, ε_c, was estimated by linear regression of ε vs β as $31.11 \pm 7.95\%$ v/v. This range corresponds to a naltrexone hydrochloride content between 12 and 20% (w/w) (see Fig. 4).

Following the method of Leuenberger and Bonny, only the ε and β values corresponding to the matrices containing from 35 to 65% (w/w) of drug have been used in this regression, due to its good agreement with the normal diffusion law (filled circles in Fig. 4).

3.4. Scanning electron microscopy.

The different matrices have been observed by SEM in order to investigate the distribution of the particles of drug and excipient. Fig. 5 show the SEM micrographs corresponding to the tablet side facing the lower punch for matrices containing 20 and 35% (w/w) of drug, respectively. As these figures show, a change in the distribution of naltrexone hydrochloride can be appreciated between them. The drug (light-grey particles) seems to form isolated groups in the matrix containing

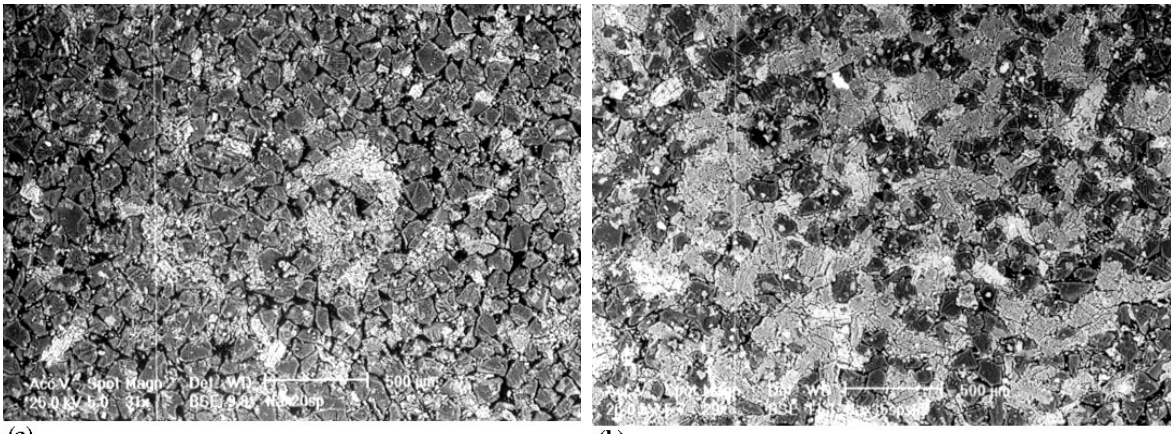

Fig. 5. SEM micrographs corresponding to the bottom side of the matrices using the BSE detector. The light-grey particles correspond to the naltrexone hydrochloride and the dark-grey particles to the Eudragit® RS-PM. (a) Matrices containing 20% w/w of drug showing groups of morphine hydrochloride embedded by the excipient. (b) Matrices containing 35% w/w of drug showing a continuos network of drug.

20% (w/w) of naltrexone hydrochloride (see Fig. 5a) and to form a continuous network in the tablet with 35% (w/w) drug load (see Fig. 5b). Therefore, using this method, the geometrical transition has been found between 20 and 35% (w/w) of drug. It must be noticed that a coherent structure is observed by 2D visual means, the percolation threshold will already be clearly exceeded. Therefore, according to the SEM study, the drug percolation threshold must be expected below 35% w/w of drug. It must be emphasised that the estimation of the percolation threshold by visual means (SEM) shows no strong evidence.

According to the previously employed methods, the drug percolation threshold is expected to range between 12 and 20% (w/w) drug load.

4. Estimation of the excipient percolation threshold, p_{c2}

In a 3D lattice, there are two percolation thresholds, the percolation threshold of the drug (mentioned above) and the percolation threshold of the excipient, p_{c2}. When the total porosity is higher than p_{c2}, no more coherent insoluble structure exits and the tablet will disintegrate during the dissolution process.

As can be observed in Table 2, a change from diffusion to zero-order kinetics (k approaches 1), can be observed between matrices containing 65 and 70% (w/w) of drug. At the same time, the squared correlation coefficient undergoes a clear decrease. According to these facts, the excipient percolation threshold, p_{c2}, can be situated in the range 25.4–31.1% v/v (see Table 3).

This represents a site percolation threshold for the excipient at a concentration between 25.4 and 31.1% v/v. In other words, above 31.1% v/v of excipient, the tablet contains an infinite cluster of excipient particles that are physically in contact and control the drug release.

However, when the tablet integrity after the 20-h release assay was studied, the tablets with a drug content of at least 50% w/w failed to keep the tablet integrity.

According to the site-bond percolation model, applied by Leuenberger and coworkers to the formation of a tablet (Leuenberger and Leu, 1992), the tablet integrity is due to the existence of an infinite cluster of bonds between the particles. In our case, these bonds must be formed between particles of the insoluble excipient (Eudragit® RS-PM). Therefore, the obtention of such bonds of an infinite cluster in the tablet, where only a part of the lattice sites are occupied by the excipient

particles, depends on both the excipient volume fraction, p_s, and the probability, p_b, of the formation of a bond between two neighbouring particles. In a tablet, p_b, depends on the compression force transmitted to the particles.

Obviously, this site-bond percolation threshold is higher than the excipient site percolation threshold. According to the obtained results, this threshold can be situated in our tablets near the 46% v/v of excipient (see Table 3), i.e., tablets with more than 46% v/v of excipient contain a percolating cluster of excipient particles that are bond with a cohesive force sufficient to keep them together when the drug particles are dissolved.

Between 31 and 46% v/v of excipient, the tablets contain an infinite cluster of excipient particles that controls the drug release. Nevertheless, there is not an infinite cluster of bonds between these particles. Therefore, in the last stages of the dissolution process, when the most of the drug particles have been dissolved, the tablet disintegrates.

Acknowledgements

The present paper is part of a research project developed in collaboration with Laboratorios Zambón. Naltrexone hydrochloride was a gift from Laboratorios Zambón.

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