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Research paper

Estimation of the percolation thresholds in acyclovir hydrophilic matrix tablets

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Abstract

The principles of percolation theory were applied to design controlled release matrix tablets containing acyclovir. This statistical theory studies disordered or chaotic systems where the components are randomly distributed in a lattice. The application of this theory to study the release and hydration rate of hydrophilic matrices allows to explain the changes in release and hydration kinetics of swellable matrix type controlled delivery systems. The objective of the present paper is to estimate the percolation threshold of HPMC K4M in matrices of acyclovir and to apply the obtained result to the design of hydrophilic matrices for the controlled delivery of this drug.

Matrix tablets have been prepared using acyclovir as drug and HPMC K4M as matrix forming material, employing five different excipient/drug percentages. Dissolution studies were carried out using the paddle method. Water uptake measurements were performed using a modified Enslin apparatus. In order to estimate the percolation threshold, the behaviour of the kinetic parameters with respect to the excipient volumetric fraction at time zero plus initial porosity was studied. According to percolation theory, the critical points observed in dissolution and water uptake studies can be attributed to the excipient percolation threshold. This threshold was situated between between 20.76% and 26.41% v/v of excipient plus initial porosity.

The knowledge of the percolation threshold of the components of the matrix formulations contributes to improve their design. First, reducing the time to market and second, increasing their robustness when they are prepared at Industrial scale, avoiding the formulation in the nearby of the percolation threshold.

Keywords: Percolation theory; Acyclovir; HPMC; Swelling matrix; Excipient percolation threshold; Controlled release

1. Introduction

Cellulose derivatives have been widely used in the formulation of hydrogel matrices for controlled drug delivery. Among them hydroxylpropylmethylcellulose (HPMC) is the most extensively employed, because of its ease of use, availability and very low toxicity [1].

Drug release from these systems is controlled by the hydration of HPMC, which forms a gelatinous layer at the surface of the matrix, through which the included drug diffuses [2].

Drug release from swellable matrix tablets is based on the glassy–rubbery transition of the polymer which occurs as a result of water penetration into the matrix. Therefore, the gel layer is physically delimited by the erosion (swollen matrix–solvent boundary) and swelling (glassy–rubbery polymer boundary) fronts [3].

Water-soluble drugs are released primarily by diffusion of dissolved drug molecules across the gel layer, whilst poorly water-soluble drugs are released predominantly by erosion mechanisms [4].

The factors influencing the release of drugs from hydrophilic matrices include, viscosity of the polymer, ratio of the polymer to drug, mixtures of polymers, compression pressure, thickness of the tablet, particle size, pH of the matrix, entrapped air in the tablet, solubility of the drug, the presence of excipients or

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additives and the mode of the incorporation of these substances [5–7].

Acyclovir is a potent inhibitory of viruses of the herpes group, particularly herpes simplex virus (HSV I and II) and herpes zoster varicellaous virus. Unfortunately, acyclovir has a short half-life (2–3 h), and the oral dosage form must be taken five times daily, which is very inconvenient for patients [8,9]. Consequently, the aim of this study was to develop a controlled release formulation of acyclovir that could be taken twice daily.

The principles of the percolation theory were applied to design controlled release matrix tablets containing acyclovir. This statistical theory studies disordered or chaotic systems where the components are randomly distributed in a lattice. It has wide application in many scientific disciplines and was introduced in the pharmaceutical field by Leuenberger and co-workers in 1987 to improve the characterization of solid dosage forms [10–13].

A cluster is defined as a group of neighbour-occupied sites in a lattice [14]. When this cluster extends from one side to the rest of the sides of the lattice – percolates the whole lattice – it is considered as infinite or percolating cluster. Applied to a pharmaceutical tablet, it is obtained as a sample-spanning cluster, formed by particles of the same component that contact each other from one side to the other sides of the tablet, generating a continuous phase through the matrix. The concentration of a component at which there is a maximum probability of appearance of a sample-spanning cluster of this component is named percolation threshold [15].

In a binary pharmaceutical tablet, two percolation thresholds are expected: the drug and the excipient percolation threshold. These percolation thresholds are critical concentrations where some tablet properties (percentage of drug released, release rate, mechanical properties, etc.) may undergo sudden changes [16].

The percolation theory has been applied to describe controlled release inert matrix systems [11–13,15,17–19]. Recently our research group is starting to apply the percolation theory to the study of hydrophilic matrix systems. Miranda et al. demonstrated experimentally the influence of the particle size of the components on the percolation threshold in hydrophilic matrices, as well as the importance of the initial porosity in the formation of the gel layer (sample-spanning cluster of excipient) [20,21].

The objective of the present work was to estimate the percolation threshold of the excipient in acyclovir matrix tablets, and to characterize the release behaviour of these hydrophilic matrices, in order to rationalize the design of these controlled release system.

2. Materials and methods

2.1. Materials

The materials used to prepare the tablets were acyclovir (Kern Pharma, Tarrasa, Barcelona) and hydroxylpropylmethylcellulose (Methocel® K4M) (Dow Chemical Company) a hydrophilic cellulose derivative as the matrix forming material.

A scanning electron microscope (SEM) (Philips type XL-30) with a backscattering electrons detectors (BSE) was employed in order to study the excipient and drug particles before compaction (Figs. 1 and 2).

2.2. Preparation of matrix tablets

The polymer was sieved (Retsch type Vibro) and the 150–200 μm granulometric fraction was employed. The mean drug particle size was measured by sieving (313.85 μm) and powder no sieved was employed.

The true density of acyclovir has been calculated using an air pycnometer (Quantachrome type Stereopynometer spy-3) as 1.810 g/cm^3. The true density of HPMC K4M 1.316 g/cm^3 was taken from the literature [22].

The acyclovir solubility is 2.5 mg/ml.

Binary mixtures were prepared with varying drug contents (60%, 70%, 80%, 90% and 95%) keeping constant the drug and excipient particle size. Table 1 shows the composition of the studied batches as well as the tablet thicknesses. The mixtures were compressed on an eccentric

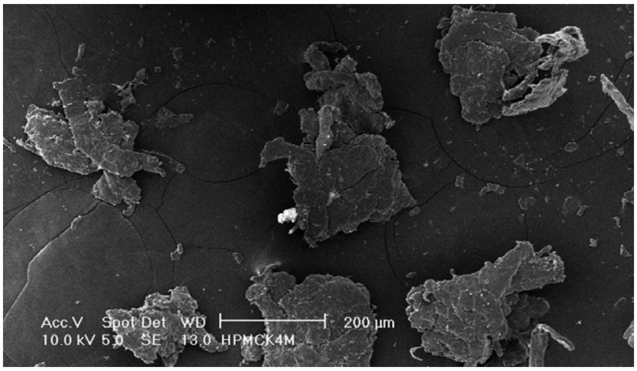

Fig. 1. SEM micrograph showing the HPMC K4M particles before compaction.

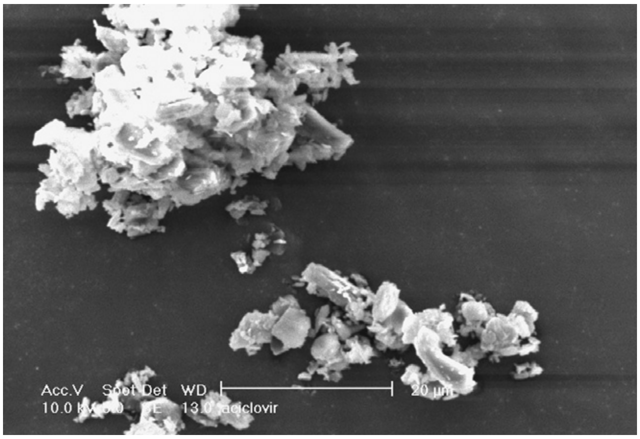

Fig. 2. SEM micrograph showing the acyclovir particles before compaction.

Table 1
Composition for the hydrophilic matrices prepared with acyclovir/HPMC K4M (150–200 μm) and % v/v HPMC plus initial porosity

Batch	% w/w acyclovir	% w/w HPMC K4M	% v/v HPMC + initial porosity	Tablet thicknesses (mm)
A	95	5	20.76	3.01 ± 0.056
B	90	10	26.41	3.25 ± 0.052
C	80	20	37.60	3.84 ± 0.051
D	70	30	45.11	4.68 ± 0.063
E	60	40	55.82	5.81 ± 0.056

machine (Bonals A-300) without any further excipient. Cylindrical tablets with a mean dosage of 500 mg and a diameter of 12 mm were prepared at the maximum compression force accepted by the formulations.

2.3. *In vitro drug release studies*

The release profiles were measured with the USP 25th ⟨7 1 1⟩ dissolution apparatus 2 (Turu Grau, model D-6) at 100 rpm in distilled water (900 ml) at 37 ± 0.5 °C during 12 h. Filtered samples, taken at different times, were determined for their acyclovir content through ultraviolet absorption at $\lambda_{\max}$ (242 nm). Three replicates were performed for each determination and the mean values were employed to obtain the release profiles. The technique has been validated previously. The validation method was carried out by analyzing solution containing several concentrations of acyclovir in five replicate. Furthermore, these solutions were analyzed by triplicate on five different days ($n = 15$). The results show a good linearity ($r^2 = 0.9940$), with adequate precision (CV < 3%) and accuracy values ($\geqslant$97.98%).

Drug release data were analyzed according the following equations:

- Zero-order equation:

$$Q = k_0 t. \tag{1}$$

- Higuchi equation [23]:

$$Q = k_{\mathrm{H}} t^{1/2}. \tag{2}$$

- Korsmeyer–Peppas equation [24]:

$$Q = kt_n. \tag{3}$$

- Peppas and Sahlin equation [25]:

$$Q = k_{\mathrm{d}}^{m} + k_{\mathrm{r}}^{2m}, \tag{4}$$

where Q is the amount of drug remaining at time t; k_0 is the zero-order release constant, k_{H} is the Higuchi rate constant; k is the Korsmeyer–Peppas kinetic constant; n is the exponent indicative of the release mechanism; for matrix tablets, an n value of 0.5 indicate diffusion control and an n value of 1.0 indicate erosion or relaxation control [26], intermediate values suggest that at least two processes contribute to the overall release mechanism; k_{d} is the diffusion rate constant, k_{r} is the relaxation rate constant and m is the purely Fickian diffusion exponent for a device of any geometrical shape which exhibits controlled release. In our case, the aspect ratios and exponent values (m) are shown in Table 2 [25].

2.4. *Water uptake studies*

The process of water penetration into the hydrophilic matrix tablets was studied using a modified Enslin apparatus. This apparatus contains a fritted and a system to regulate the water level. When the tablet is placed on the fritted, the water is absorbed from a reservoir which is placed on a precision balance (Scatlec SBC 31). The amount of water uptaken at each time point was read from the balance as weight loss in the reservoir. The balance is linked to a chart recorder and a personal computer. The rate of water penetration was expressed as the weight gain of the swelled matrix, in percent w/w of penetrant fluid with respect to dry polymer [27]. The kinetics of the water uptake into hydrophilic matrices was analyzed according to the following equation:

$$W = k_{\mathrm{s}} t^{n}, \tag{5}$$

where W is the weight gain of the swelled matrix; k_{s} is the kinetics constant of water penetration; t is the penetration time and n is the exponent which depends on the water uptake mechanism [27].

2.5. *Estimation of the percolation threshold*

In order to estimate the percolation threshold, the behaviour of the kinetic parameters (Higuchi's slope "k_{H}", normalised Higuchi's slope "k_{H}/% v/v of HPMC", and relaxational constant of Peppas–Sahlin "k_{r}") with respect to the sum of the excipient volumetric fraction plus initial porosity at time zero was studied [28].

According to the fundamental equation of percolation theory, Eq. (5), if these parameters behave as critical properties, we can expect that

$$X \propto S \cdot (\phi - \phi_c)^{q}, \tag{6}$$

where X is the studied property; S is a constant; p is the volumetric fraction of the component, p_{c} is the percolation threshold, $(\phi - \phi_c)$ is the distance to the percolation threshold and q is a critical exponent.

Table 2
Aspect ratios and exponent values (m) for the hydrophilic matrices studied

Batch	Aspect ratio	Exponent (m)
A	3.80	0.45
B	3.59	0.44
C	3.03	0.43
D	2.65	0.42
E	2.16	0.43

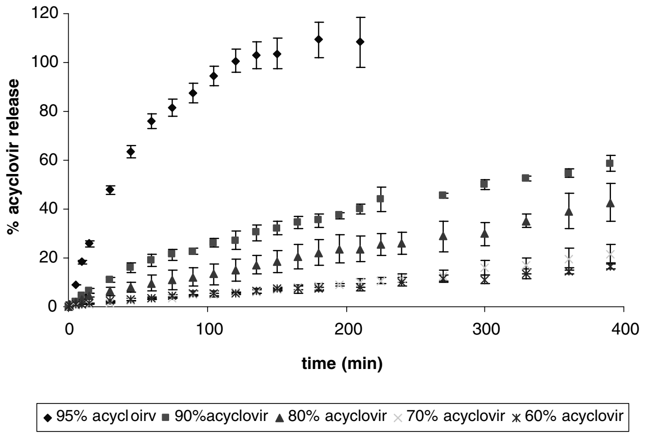

Fig. 3. Acyclovir release from matrix tablet with a total drug content of 95%, 90%, 80%, 70% and 60% prepared with acyclovir/HPMC K4M (150–200 μm) (mean values ± SD, $n = 3$).

The kinetic parameters studied show a nonlinear behaviour as a function of the volumetric fraction of the excipient plus initial porosity. Two linear regressions have been performed as an approximation for estimating the trend of the parameter, one regression line below and the other above the percolation threshold. The point of intersection between both regression lines has been taken as an estimation of the percolation threshold [20,21].

The initial porosity was calculated using the following equation:

$$\varepsilon = V_{\mathrm{T}} - \left(\frac{w \cdot \%\mathrm{drug}}{\rho_{\mathrm{d}}}\right) - \left(\frac{w \cdot \%\mathrm{excipient}}{\rho_{\mathrm{e}}}\right), \qquad (7)$$

where ε is the initial porosity; V_{T} is the total volumen; w is the tablet weight; ρ_{d} is the drug density and ρ_{e} is the excipient density.

3. Results and discussion

In order to estimate the percolation threshold of the excipient (HPMC K4M), the matrices were studied from different points of view.

3.1. Release profiles and release kinetics

Fig. 3 shows the release profiles obtained from hydrophilic matrices formulated with acyclovir and HPMC K4M 150–200 μm.

In order to study the release mechanism of acyclovir from the tablets the fitting of the data to Eqs. (1)–(4) has been studied. The results obtained are shown in Table 3.

The analysis of the release profiles and the kinetic data indicate two different behaviours and a sudden change between them. In the first behaviour which corresponds to the matrices that release the drug at slow rates, the release was controlled by the fully hydrated gel layer. For these matrices, the erosion of the hydrophilic gel structure has shown an important influence on the drug release. This is indicated by the better fit of the drug release kinetics to the zero-order equation, the n value of Korsmeyer–Peppas equation near to 1 and the higher value of the relaxation constant, k_{r}, in comparison with the diffusion constant, k_{d} in the Peppas–Sahlin equation. Taking into account the drug solubility (2.5 mg/ml), the prevalence of the erosion versus swelling mechanism can be expected.

Table 3
Kinetics constant k_0, k_{H}, k, n, k_{d} and k_{r} values based on Eq. (1)–(4), calculated in the range of 5–70% acyclovir release for all the batches studied[a]

Batch % w/w acyclovir		A 95	B 90	C 80	D 70	E 60
Zero-order equation	k_0	1.222	0.122	0.096	0.057	0.042
	r^2	0.984	0.974	0.994	0.995	0.987
	Sum of squares total	3545.9	10352.6	6531.4	5149.2	1268.0
	Sum of squares residual	53.7	278.3	51.8	24.8	16.4
Higuchi equation	k_{H}	12.440	3.4167	2.8518	1.7683	1.4694
	r^2	0.998	0.993	0.956	0.932	0.959
	Sum of squares total	3545.9	10352.6	12367.8	5149.2	1268.0
	Sum of squares residual	7.0	66.9	483.6	362.4	54.6
Korsmeyer–Peppas equation	k_{H}	3.167	0.290	0.254	0.027	0.041
	n	0.782	0.843	0.856	1.114	1.008
	r^2	0.999	0.994	0.998	0.998	0.997
	Sum of squares total	13220.9	26297.6	33309.1	13879.4	5673.5
	Sum of squares residual	16.7	159.5	65.5	10.1	15.2
Peppas and Sahlin equation	k_{d}	2.239	2.056	0.357	−0.81	−0.38
	k_{r}	1.615	0.161	0.205	0.202	0.127
	r^2	0.998	0.999	0.994	0.997	0.997
	Sum of squares total	49567.0	13220.9	28716.1	13879.4	5673.5
	Sum of squares residual	42.9	23.3	165.0	43.7	15.2

[a] k_0 (% min^{-1}) zero-order constant, k_{H} (% min$^{-1/2}$), Higuchi's slope; k (% min^{-n}), kinetics constant of the Korsmeyer model; n, diffusional exponent; k_{d} (% min^{-m}), diffusional constant of Peppas and Sahlin model; k_{r} (% min^{-2m}), relaxational constant of Peppas and Sahlin model; m is the diffusional exponent that depends on geometric shape of the releasing device through its aspect ratio.

After the transition point, the tablets allow the free dissolution of the drug when they are exposed to the dissolution medium due to the fact that the gel layer is not established since the first moment and, in these conditions, this structure cannot control the drug release. The Korsmeyers release rate increases from 0.290 to 3.167% $\text{min}^{-1/2}$. For these matrices, according to Higuchi ($r^2 = 0.998$), Korsmeyers ($n = 0.782$) and Peppas–Sahlin ($K_r < K_d$) equations, drug release is governed by the diffusion process.

Therefore, the results obtained from the kinetics analysis are in agreement with the release profiles, indicating a clear change in the release rate and mechanism between matrices containing 90% and 95% w/w of drug (5–10% w/w of excipient). The existence of a critical point can be attributed to the excipient percolation threshold.

From the point of view of percolation theory, this means that above 10% w/w of HPMC K4M, the existence of a network of HPMC (able to form a hydrated layer from the first moment) controls the drug release.

3.2. Water uptake assays

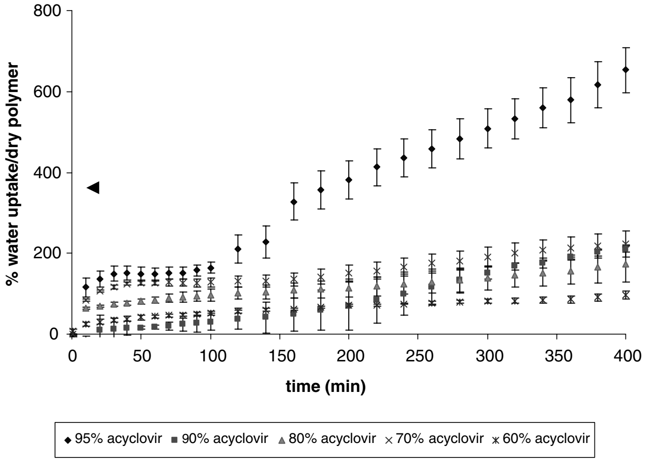

Fig. 4. Weight gain of the systems as a function of swelling time for matrix tablet with a total drug content of 95%, 90%, 80%, 70% and 60% prepared with acyclovir/HPMC K4M (150–200 μm) (mean values ± SE, $n = 3$).

Table 4
Kinetics parameters based on Eq. (5) for all the batches studied[a]

Batch	% w/w of acyclovir	k_s	n	r^2
Davidson and Peppas models				
A	95	1.865	0.989	0.995
B	90	0.287	1.083	0.991
C	80	15.663	0.393	0.994
D	70	28.313	0.337	0.995
E	60	8.138	0.403	0.999

[a] k_s (% min^{-n}) the kinetics constant of water penetration; n is the exponent which depends on the water uptake mechanism.

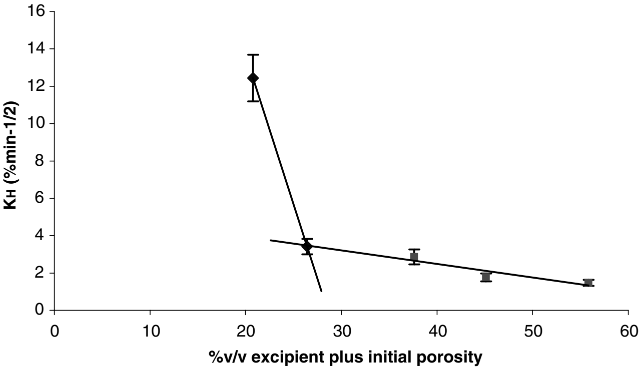

Fig. 5. Higuchi slope's (mean values ± SD, $n = 3$) versus percentage of the excipient volumetric fraction plus initial porosity for all the batches studied.

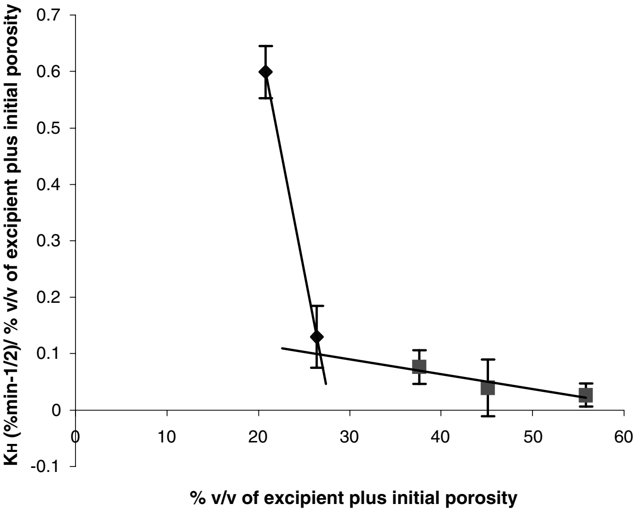

Fig. 6. Normalized Higuchi slope's (mean values ± SD, $n = 3$) versus percentage of the excipient volumetric fraction plus initial porosity for all the batches studied.

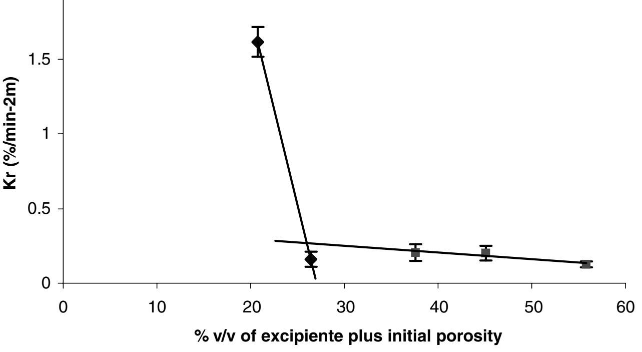

Fig. 7. Relaxational constant of Peppas–Sahlin (mean values ± SD, $n = 3$) versus percentage of the excipient volumetric fraction plus initial porosity for all the batches studied.

The swelling of the matrix polymer matrix depends very strongly on the rate of penetration of fluid into the matrix. The results of the uptake water measurements are shown in Fig. 4.

An increase in the rate of water uptake can be observed when the HPMC concentration decreases. A critical point

Table 5
The values of the excipient percolation thresholds for the batches studied, according to the kinetic parameters used

Kinetic parameters	Equations	r^2	Point of the intersection
Higuchi's slope (% $\min^{-1/2}$)	$Y_1 = -1.5973x + 45.605$	0.9999	$X = 26.38$
	$Y_2 = -0.0726x + 5.3825$	0.8354	
Higuchi's slope (% $\min^{-1/2}$)/%v/v HPMC	$Y_1 = -0.0832x + 2.3258$	0.9999	$X = 26.77$
	$Y_2 = -0.0026x + 0.1678$	0.8682	
Relaxational constant kr (% $\min^{-2m}$)	$Y_1 = -0.2574x + 6.9591$	0.9999	$X = 25.99$
	$Y_2 = -0.0045x + 0.3843$	0.8565	

was found between 90% and 95% w/w of acyclovir. This range corresponds with the critical point which has been observed in the release profile studies.

The water uptake data were subjected to the Davidson and Peppas model to calculate the rate of water penetration. The results are shown in Table 4. According to the value of n, the matrices with low amount of drug follow a diffusion-controlled mechanism in which the rate of diffusion of the liquid is lower than the rate of relaxation of the polymer [29]. On the other hand, the change of the value of water uptake constant between the matrices containing 90–95% w/w of acyclovir, reflects the presence of the critical point previously observed.

3.3. Estimation of the excipient percolation threshold

When percolation theory is applied to binary pharmaceutical systems, two percolation thresholds are expected; the drug percolation threshold and the excipient percolation threshold. The percolation threshold of a substance is the probability or volume fraction at which this substance starts to percolate the sample. In hydrophilic matrices the drug threshold is less evident than the excipient threshold which is responsible for the release control [28].

In order to estimate the percolation threshold of HPMC K4M, different kinetic parameters were studied: Higuchi rate constant, normalized Higuchi rate constant and relaxation rate constant. The evolution of these release parameters has been studied as a function of the sum of the excipient volumetric percentage plus initial porosity. Recent studies of our research group have found that the existence of a sample-spanning cluster of excipient plus pores in the hydrophilic matrix before the matrix is placed in contact with the liquid, conditions for the release kinetics of the drug [20,28].

Fig. 5–7 show changes in the different kinetic parameters as the Higuchi rate constant, normalized Higuchi rate constant and relaxation rate constant. To estimate the excipient percolation threshold, these parameters were plotted versus the excipient volumetric fraction plus initial porosity.

As percolation theory predicts, the studied properties show a critical behaviour as a function of the volumetric fraction of the components. A critical point has been found between 21% and 26% v/v of excipient plus initial porosity (see Table 1). This critical point can be attributed to the excipient percolation threshold.

As it can be observed in Fig. 5–7, two linear regressions have been performed as an approximation for estimating the percolation threshold as the point of intersection between both regression lines. The values of the excipient percolation thresholds estimated for all the batches studied, based on the behaviour of the kinetic parameters, are shown in Table 5.

The knowledge of the percolation threshold of the components of the matrix formulations contributes to improve their design. First, in order to develop robust formulations, i.e., to reduce variability problems when they are prepared at Industrial scale, it is important to know the concentrations corresponding to the percolation thresholds. The percolation thresholds correspond to formulations showing a high variability in their properties as a function of the volume fraction of their components. Therefore, in order to increase the robustness of the formulation, the nearby of the percolation thresholds should be avoided.

Second, the excipient percolation threshold is the border between a fast release of the drug (below the threshold) and a drug release controlled by the formation of a coherent gel layer (above the excipient percolation threshold). Therefore the knowledge of this threshold will allow us to avoid the preparation of a number of unnecessary lots, during the development of a pharmaceutical formulation, resulting in a reduction of the time to market.

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