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Research paper

Study of the critical points and the role of the pores and viscosity in carbamazepine hydrophilic matrix tablets

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ABSTRACT

Percolation theory has been applied to estimate the Hypromellose (HPMC) percolation thresholds and the influence of the polymer viscosity and the initial porosity on these thresholds in carbamazepine multicomponent matrix formulations.

Different batches containing two viscosity grades of HPMC as hydrophilic matrix forming polymer, MCC and lactose as fillers, and a lubricant mixture have been manufactured varying the compression pressure in order to obtain matrices with three levels of initial porosity. The results suggested the existence of an excipient percolation threshold between 13 and 15% v/v of HPMC for the different batches prepared. It has been found that the percolation threshold for this polymer is independent on the formulation factors studied in this paper: polymer viscosity and initial porosity of the matrices.

1. Introduction

Hydrophilic matrices are one of the most commonly employed extended release systems worldwide. These types of matrices have many favorable properties such as low cost and ease of manufacture, their proven record, and relative independent performance on the physico-chemical and physiological conditions of the gastro-intestinal tract [1]. These dosage forms are constituted by a dispersion of a drug in a hydrophilic polymer, which in contact with water, swells and forms a gel or a colloid of high viscosity gelatinous structure. Other excipients in the matrices are lubricant, glidant, water-soluble or water-insoluble fillers and pH modifiers if required [2,3].

Hydroxypropylmethyl cellulose (HPMC) is the most commonly used cellulose ether in the formulation of hydrophilic matrices for extended drug delivery [4]. This could be due to the wide approval as GRAS (Generally Regarded as Safe) by the regulatory bodies. Furthermore, it is compatible with numerous drugs, accommodates high levels of drug loading, and can be easily incorporated to form matrix tablets by direct blending or granulation [5].

The hydration of HPMC controls the drug release in swellable matrices, since it forms a barrier gel layer at the surface of the matrix, through which the drug is released by diffusion and/or erosion of the matrix [6]. Although the technology is well understood and utilized, there are a large number of research papers reporting about the complex mechanisms of drug release from these matrix systems [7–11].

Our research group has applied the concepts of the percolation theory to the study of extended release matrix systems including both hydrophilic and inert matrices [12–19]. This statistical theory was firstly applied to the field of pharmacy by Leuenberger and coworkers in the University of Basel [20–25]. This theory describes a cluster (called infinite, percolating or coherent), defined as a group of adjacent particles of the same component that extends from one side to the other sides of the system, acting as the outer phase of a disperse system. Otherwise, the cluster is called finite or isolated. The concentration of a component for which there is a maximum probability of appearance of an infinite cluster for the first time is called the percolation threshold of this component. This concentration is usually related to a critical point, because close to this point important changes in the properties of the system may be observed [26].

According to percolation theory, controlled release hydrophilic matrices must be formulated above the excipient percolation threshold. This fact assures that a coherent gel layer controlling the drug release rate is formed. The excipient percolation threshold is the limit between a fast release of the drug (below the excipient percolation threshold) and a drug release controlled by the formation of a coherent gel layer (above the excipient percolation threshold) [17,27,28].

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Table 1
Composition of the different formulations prepared.

	BATCH CX1		BATCH CX2		BATCH CX3		BATCH CX4		BATCH CX5	
	%	Tablet (mg)	%	Tablet (mg)	%	Tablet (mg)	%	Tablet (mg)	%	Tablet (mg)
Carbamazepine	30.0	180.0	30.0	180.0	30.0	180.0	30.0	180.0	30.0	180.0
HPMC	10.0	60.0	15.0	90.0	20.0	120.0	25.0	150.0	30.0	180.0
MCC	19.0	114.0	19.0	114.0	19.0	114.0	19.0	90.0	19.0	114.0
Lactose	40.0	240.0	35.0	210.0	30.0	180.0	25.0	150.0	20.0	120.0
SiO_2	0.5	3.0	0.5	3.0	0.5	3.0	0.5	3.0	0.5	3.0
Mg stearate	0.5	3.0	0.5	3.0	0.5	3.0	0.5	3.0	0.5	3.0
Total	100.0	600.0	100.0	600.0	100.0	600.0	100.0	600.0	100.0	600.0

In previous papers, the influence of several formulation factors on the excipient critical points has been studied. For example, Gonçalves-Araújo et al. [27] studied the existence of critical points in controlled release hydrophilic matrices containing verapamil·HCl and four different viscosity grades of HPMC. According to their results, the HPMC percolation thresholds would be situated between 10 and 20% v/v of HPMC for the four viscosity grades.

On the other hand, the role of the initial porosity of the matrix on its percolation thresholds has been extensively studied in inert matrices [13,21,22]. In inert matrices, the pores facilitate the water uptake and the drug release. Therefore, it is clear now that the initial porosity has to be added to the porosity due to the dissolution of the soluble substances of the matrix. This sum is the total porosity of the matrix [13,21]. The drug percolation threshold in inert matrices is expressed as total porosity. Therefore, the initial porosity here is undoubtedly influencing the drug percolation threshold [29].

Nevertheless, the situation is much more complex in hydrophilic matrices. Although a hypothesis has been proposed [17,30], the influence of the initial porosity on the percolation thresholds has not yet been experimentally studied in hydrophilic matrices. Miranda et al. [30] proposed the hypothesis that the pores would facilitate the establishment of the gel layer responsible for controlling the drug release. This hypothesis is based on the behavior of the critical points as a function of the particle size of the matrix component, making the assumption that the hydrophilic matrices would undergo exactly the same influence than the inert matrices obeying the same regression line. Nevertheless, this hypothesis has not yet been experimentally validated. Furthermore, a more recent paper [27] reported some critical points in verapamil·HCl hydrophilic matrices, which failed to fit the previously mentioned regression line.

The objectives of this work were as follows: (i) to estimate the excipient percolation thresholds in carbamazepine (poorly soluble model drug) multicomponent matrix formulations; (ii) to study the influence of the polymer viscosity on these thresholds, and, especially, (iii) to carry out the first experimental study of the influence of the initial porosity of the matrices on the excipient percolation threshold and to discuss the results in light of the existing theories. For this purpose, identical formulations have been prepared with three different levels of initial porosity. These formulations have been characterized and their percolation thresholds have been estimated.

2. Materials and methods

2.1. Materials

The following materials were used in the manufacture of the matrix tablets: carbamazepine (Recordatti, Milan, Italy), METHOCEL™ K100 LV and METHOCEL™ K4M (Colorcon Ltd., Dartford, UK), lactose monohydrate (Safic-Alcan, Barcelona, Spain), microcrystalline cellulose (Mingtai Chemical, Taichung, Taiwan), magnesium stearate (Acofarma, Barcelona, Spain), and colloidal silicon dioxide NF (Acofarma, Barcelone, Spain).

2.2. Preparation of the tablets

Twenty-six batches of carbamazepine (180 mg) matrix tablets were prepared employing five different percentages of HPMC (10, 15, 20, 25 and 30% w/w). Table 1 shows the composition of the studied formulations. The letter X in this table can be replaced by the two letters indicated in Table 2, in order to obtain the name of the batch prepared with each polymer and compression force level applied. All the materials were blended for 10 min in a Turbula mixer (Willy A. Bachofen, Basel Switzerland) with the exception of magnesium stearate and colloidal silicon dioxide that were added after the initial 10 min and blended for an additional period of 5 min. 600 mg tablets of each batch were produced using direct compression on a standard eccentric tableting machine (Bonals A-300, Barcelone, Spain) using a 12 mm diameter die and manual feeding. Three different compression forces have been employed in order to obtain three porosity levels (mean porosity values 7.9%, 16% and 27.3%). For this purpose, three different positions of the upper punch in the eccentric tableting machine were selected monitoring the tablet porosity. The lots containing 10% HPMC were prepared by employing only the higher compression force level, since the drug release is too fast at lower compression forces with such a low polymer content.

2.3. Tablet characterization

2.3.1. Weight, diameter and thickness

The weight of 10 tablets corresponding to each batch was determined using an electronic balance (Scaltec, type SBC31) to assure the weight uniformity.

Thickness and diameter of 10 tablets of each batch were measured to ±0.001 mm using a 25-mm digital micrometer (Comecta, SA).

2.3.2. Volume and initial porosity

The volume of 10 tablets of each batch was calculated according to the following equation:

$$V = \pi H (D/2)^2 \quad (1)$$

Table 2
Name of the batches prepared with each polymer and force levels.

	Maximum force (mean porosity 7.9%)	Medium force (mean porosity 16%)	Minimum force (mean porosity 27.3%)
METHOCEL K100 LV	CA	CB	CC
METHOCEL K 4M	CD	CE	CF

Table 3
Results for the batches containing METHOCEL K100LV.

CARBAMAZEPINE	Batch CA1	Batch CA2	Batch CA3	Batch CA4	Batch CA5	Batch CB2	Batch CB3	Batch CB4	Batch CB5	Batch CC2	Batch CC3	Batch CC4	Batch CC5
Weight (g)	0.601	0.601	0.600	0.603	0.602	0.602	0.599	0.600	0.600	0.601	0.602	0.599	0.597
Drug w/w	0.300	0.300	0.300	0.300	0.300	0.300	0.300	0.300	0.300	0.300	0.300	0.300	0.300
HPMC[a] w/w	0.100	0.150	0.200	0.250	0.300	0.150	0.200	0.250	0.300	0.150	0.200	0.250	0.300
Lactose w/w	0.400	0.350	0.300	0.250	0.200	0.350	0.300	0.250	0.200	0.350	0.300	0.250	0.200
MCC w/w	0.190	0.190	0.190	0.190	0.190	0.190	0.190	0.190	0.190	0.190	0.190	0.190	0.190
Mg stearate w/w	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
SiO2 w/w	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005	0.005
Diameter (cm)	1.217	1.216	1.216	1.210	1.210	1.217	1.216	1.215	1.214	1.218	1.217	1.216	1.216
Thickness (cm)	0.396	0.387	0.407	0.410	0.430	0.435	0.434	0.422	0.440	0.490	0.498	0.500	0.506
Volume (cm^3)	0.460	0.449	0.473	0.471	0.494	0.506	0.504	0.489	0.509	0.571	0.579	0.581	0.588
% Initial porosity	**9.698**	**6.806**	**10.836**	**9.459**	**13.145**	**17.088**	**16.522**	**13.190**	**15.958**	**26.637**	**27.006**	**26.975**	**27.524**
%v/v Carbamazepine	29.459	30.163	28.633	28.850	27.462	26.835	26.807	27.661	26.573	23.745	23.440	23.269	22.916
%v/v HPMC	9.849	15.127	19.146	24.114	27.545	13.458	17.925	23.120	26.653	11.908	15.674	19.449	22.985
%v/v Lactose	33.661	30.157	24.537	20.603	15.689	26.830	22.973	19.754	15.181	23.739	20.087	16.617	13.092
%v/v MCC	16.412	16.804	15.952	16.072	15.299	14.950	14.934	15.410	14.804	13.228	13.059	12.963	12.766
%v/v Mg stearate	0.598	0.612	0.581	0.586	0.557	0.545	0.544	0.561	0.539	0.482	0.476	0.472	0.465
%v/v SiO^2	0.323	0.331	0.314	0.317	0.301	0.294	0.294	0.304	0.292	0.261	0.257	0.255	0.251

Bold values highlight the importance of the initial porosity values of the matrices.
[a] METHOCEL K100LV.

where V is the tablet volume, H and D are tablet thickness and diameter, and π is a constant.

The initial porosity (ε_0) was determined using the known values of the volume and weight according to the following equation:

$$\varepsilon_0 = (V_{real} - V_{theoretical})/V_{real} \quad (2)$$

where V_{real} is the volume of the tablet and $V_{theoretical}$ is the theoretical volume of the tablet, calculated as the sum of the volumes obtained dividing the mass of each component by their real density.

2.3.3. Study of the drug release

Tablets were subjected to a modified dissolution testing, in an attempt to achieve the critical points of the system faster. More vigorous hydrodynamic conditions were employed during the dissolution assay. The dissolution studies were carried out using the paddle method in a USP Apparatus II Sotax AT7 smart (Allschwil, Switzerland). Tablets were fixed to the paddle using string, and 900 ml of distilled water at 37 ± 0.5 °C has been used as dissolution media. The stirring speed was fixed at 150 rpm. 5 ml samples were withdrawn at 0.25, 0.5, 1, 1.5, 2 and 3 h. The percentage of drug released was measured in a UV spectrophotometer (Hitachi U-2000) at 284 nm. The assay was performed in triplicates.

Drug release data were analyzed according to the zero-order model (Eq. (3)), Higuchi [31] (Eq. (4)), Korsmeyer [32] (Eq. (5)), and Peppas and Sahlin [33] (Eq. (6)) equations. Linear and non-linear least squares fitting methods were carried out with SPSS version 14.0 to determine the optimum values of the parameters corresponding to each equation.

$$Q = k_0 t \quad (3)$$

$$Q = b\sqrt{t} \quad (4)$$

$$Q = k_k t^n \quad (5)$$

$$Q = k_d t^m + k_r t^{2m} \quad (6)$$

where Q is the amount of drug released at time t, k_0 is the zero order release rate constant in Eq. (3), b is the Higuchi's release rate constant in Eq. (4), and k_k is the Korsmeyer's kinetic constant in Eq. (5). t is the release time, n is the diffusional exponent that depends on the release mechanism and on the shape of the swelling device tested [34], k_d is the diffusional constant, k_r the relaxational rate constant, and m is the purely Fickian diffusion exponent that depends on the geometrical shape of the releasing device through its aspect ratio.

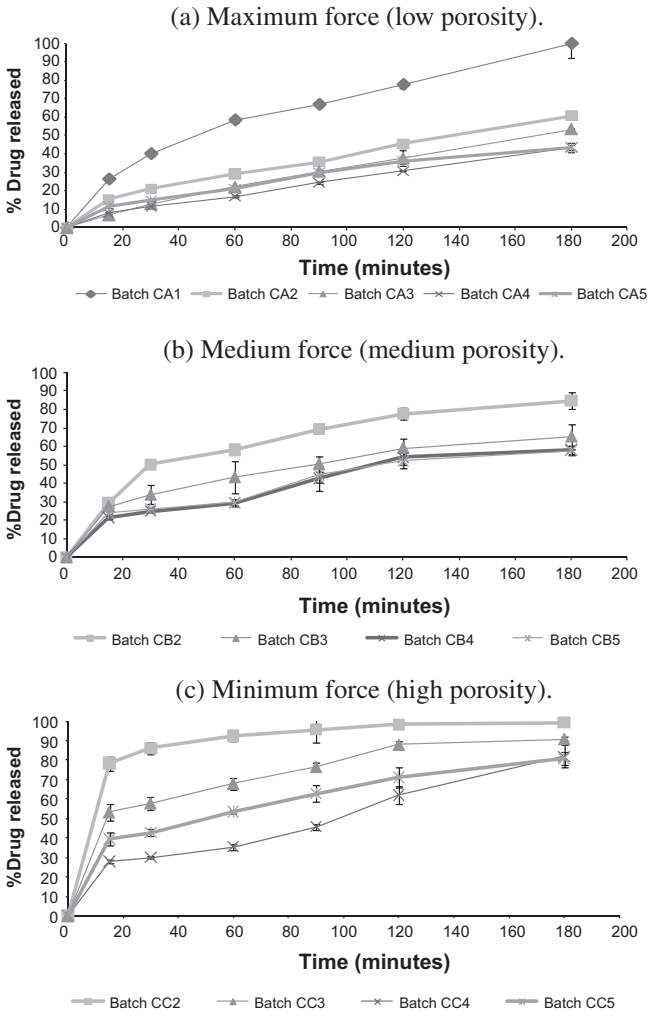

Fig. 1. Dissolution profiles for batches containing HPMC K100 LV. Numbers 1–5 in the name of the batches indicate the percentage of polymer (w/w), being 1 = 10%; 2 = 15%; 3 = 20%; 4 = 25%; and 5 = 30%.

Table 4
Initial porosity values and volume fractions of HPMC for the batches containing METHOCEL K100 LV.

	Batch CA1	Batch CA2	Batch CA3	Batch CA4	Batch CA5
% Initial porosity	9.698	6.806	10.836	9.459	13.145
% v/v HPMC	9.849	15.127	19.146	24.114	27.545
		Batch CB2	Batch CB3	Batch CB4	Batch CB5
% Initial porosity		17.088	16.522	13.190	15.958
% v/v HPMC		13.458	17.925	23.120	26.653
		Batch CC2	Batch CC3	Batch CC4	Batch CC5
% Initial porosity		26.637	27.006	26.975	27.524
% v/v HPMC		11.908	15.674	19.449	22.985

The dissolution results were employed to estimate the excipient percolation threshold of each HPMC formulation. An abrupt change in the kinetic parameters indicates a change in the release behavior and could be indicative of a phase transition related to the presence of a percolation threshold of one component of the formulation [17,21].

3. Results and discussion

3.1. Tablet characterization

The results of tablets diameter and thickness as well as tablet weight and density of the different components were employed to calculate the volume and the initial porosity of the tablets manufactured, as well as the volume fractions corresponding to each component. As an example, Table 3 shows the results for the batches CA, CB and CC (batches containing METHOCEL K100LV at the three compression forces).

3.2. Study of the drug release profiles and release kinetics

As it has been stated in the previous section, a modified dissolution assay with stronger hydrodynamic conditions, such as higher stirring speed (150 rpm) and the tablet fixed to the paddle, was performed in order to determine the critical points of the formulations in a shorter period of time. The results for each batch are discussed in the following subsections.

3.2.1. Tablets containing METHOCEL K100LV

Batches containing 30% W/W of carbamazepine and varying amounts of METHOCEL K100LV were prepared at three compression forces leading to mean porosities of 7.9%, 16% and 27.3%, respectively.

Fig. 1 illustrates the release profiles of the different batches prepared at the three compression forces. Table 4 shows the initial porosity and the content of HPMC expressed in % v/v for the batches prepared, and Table 5 shows the kinetic parameters of the studied formulations.

Fig. 1a shows that for batches CA1 to CA5 (carbamazepine and 10%, 15%, 20%, 25% and 30% of HPMC K100LV at the maximum compression force) with a mean porosity of 7.9%, an important change in the release profiles appears between 10 and 15% (w/w) HPMC content; therefore, the critical point of the formulation is clearly between 9.8% and 15.1% v/v of HPMC K100LV (between batches CA1 and CA2). The observation of the critical point can be confirmed when we analyze the changes in kinetic parameters, according to the results presented in Table 5b (Higuchi equation), k_0 (zero order equation), k_k (Korsmeyer model), and k_d (Peppas and Sahlin model). Below the critical point of the excipient, the rate of drug release is clearly faster. However, above this point, the profiles were more constant, typical of controlled release systems. For batches CB2 to CB5 (carbamazepine and 15%, 20%, 25% and 30% of HPMC K100LV at the medium compression force) with a mean porosity of 16%, although a critical behavior is not clearly appreciated by direct observation of the release profiles (Fig. 1b), the results of the kinetic study showed (Table 5) that the critical range

Table 5
Kinetic parameters for the batches containing METHOCEL K100 LV.

	Higuchi equation		Zero-order equation		Korsmeyer equation			Peppas and Sahlin equation		
	b[a] ($t^{-0.5}$)	r^2[b]	k_0[c] (t^{-1})	r^2[b]	k_k[d] (t^{-n})	n[e]	r^2[b]	k_d[f] (t^{-m})	k_r[g] (t^{-2m})	r^2[b]
Batch CA1	**7.320**	0.988	**0.534**	0.952	**6.732**	0.515	0.997	**7.721**	0.298	0.997
Batch CA2	**4.670**	0.977	**0.272**	0.998	**2.482**	0.607	0.991	**3.084**	0.343	0.994
Batch CA3	4.794	0.989	0.277	0.996	0.713	0.829	0.999	0.266	0.580	0.999
Batch CA4	3.700	0.97	0.216	0.999	0.638	0.808	0.996	0.471	0.436	0.996
Batch CA5	3.517	0.987	0.202	0.979	2.045	0.591	0.994	2.370	0.248	0.996
Batch CB2	**6.613**	0.932	**0.478**	0.881	**12.965**	0.367	0.986	**11.719**	−0.272	0.988
Batch CB3	4.101	0.992	**0.231**	0.953	**9.518**	0.372	0.997	**8.460**	−0.154	0.997
Batch CB4	4.259	0.942	0.245	0.937	4.651	0.49	0.973	5.090	0.139	0.974
Batch CB5	3.939	0.936	0.227	0.936	5.929	0.439	0.968	5.916	0.034	0.969
Batch CC2	***[h]		****[h]		**61.547**	0.095	0.999	**27.534**	−1.875	0.976
Batch CC3	**3.835**	0.987	0.328	0.999	**26.108**	0.241	0.992	**16.862**	−0.783	0.984
Batch CC4	4.545	0.869	0.317	0.941	4.026	0.568	0.957	4.754	0.383	0.963
Batch CC5	4.260	0.974	0.320	0.996	14.604	0.326	0.993	11.465	−0.322	0.989

Bold values highlight an abrupt change in the kinetic paramenters, which indicates a change in the release behavior and could be indicative of the presence of a percolation threshold.

[a] Higuchi's slope.
[b] Determination coefficient.
[c] Zero order kinetic constant.
[d] Korsmeyer kinetic constant.
[e] Diffusional exponent.
[f] Diffusional constant of Peppas and Sahlin model.
[g] Relaxational constant of Peppas and Sahlin model; m is the diffusional exponent that depends on the geometric shape of the releasing device through its aspect ratio.
[h] Due to the fast release of batch CC2, the number of experimental data is not enough for the rational application of the kinetic model".

Table 6
Initial porosity values and volume fractions of HPMC for the batches containing METHOCEL K4M.

	Batch CD1	Batch CD2	Batch CD3	Batch CD4	Batch CD5
% Initial porosity	6.701	6.544	5.496	6.294	6.214
% v/v HPMC	10.176	15.170	20.293	24.957	29.743
		Batch CE2	Batch CE3	Batch CE4	Batch CE5
% Initial porosity		16.070	16.492	14.006	17.913
% v/v HPMC		13.623	17.932	22.903	26.033
		Batch CF2	Batch CF3	Batch CF4	Batch CF5
% Initial porosity		27.499	26.441	27.143	26.308
% v/v HPMC		11.768	15.796	19.404	23.371

can be situated between 13.5% and 17.9% v/v HPMC K100 LV (i.e., between batches CB2 and CB3).

Fig. 1c shows the dissolution profiles for batches CC2 to CC5 (carbamazepine and 15%, 20%, 25% and 30% of HPMC K100LV at the minimum compression force) with a mean porosity of 26%. Taking into account the release profiles and the kinetic parameters for these batches showed in Table 5, the critical range can be situated between 11.9% and 15.7% v/v of HPMC K100LV. The behavior of batch CC3 indicates that this HPMC concentration is close to the percolation threshold.

Despite very different compression forces and porosities are involved, the critical range is very similar for all the HPMC K100LV matrices containing carbamazepine studied here. In other words, independent of the tablet porosity and the applied compression force, a critical volume fraction of approximately 14% v/v of HPMC K100 LV (or higher level to ensure robustness) must be reached to obtain a drug release controlled by the gel layer produced by the polymer.

3.2.2. Tablets containing METHOCEL K4M

Table 6 contains the initial porosity data and the content of HPMC expressed in% v/v for the matrices containing carbamazepine and concentrations of METHOCEL K4M between 10 and 30% (w/w).

Fig. 2a shows the release profiles of batches CD1 to CD5, manufactured with the maximum compression force and a mean porosity of 7.9%. Taking into account the fast release rate showed by batch CD1 in comparison with the other batches, the excipient percolation threshold could be situated between 10.2 and 15.2% v/v of HPMC K4M (between batches CD1 and CD2). This is supported by the change in the kinetic parameters that can be observed in Table 7. So, batch CD2 would be above the excipient percolation threshold, i.e., a percolating cluster of the excipient that controls the penetration of the liquid into the matrix and the release of the drug has been formed, leading to a slower drug release.

In relation with batches CE2 to CE5 (carbamazepine and 15%, 20%, 25% and 30% of HPMC K4M at the medium compression force), the release profiles illustrated in Fig. 2b show a critical behavior suggesting a critical point between 13.6 and 17.9% v/v of HPMC K4M. This critical range is also confirmed (Table 7) by the results obtained in the kinetic studies, showing an abrupt change in "b" slope of Higuchi, k_0 constant, Korsmeyer's constant, and diffusional constant in the Sahlin and Peppas' equation.

Fig. 2c shows the release profiles for batches CF2 to CF5 (carbamazepine and 15%, 20%, 25% and 30% of HPMC K4M at the minimum compression force). A faster release for batch CF2 is observed in comparison with batches CF3 to CF5. A significant change in the kinetic parameters studied can also be appreciated between batches CF2 and CF3, so it may be concluded that for these high porosity tablets, the critical point is situated between 11.8 and 15.8% v/v of HPMC K4M.

Therefore, also for the HPMC K4M matrices, the critical range seems to be similar (around 13% v/v) for the three compression force levels. However, it is also clear that the release rates are slower for higher compression forces.

3.3. The influence of the porosity and polymer viscosity on the critical ranges

As a general consideration, the release behavior of the assayed tablets containing carbamazepine, HPMC of different viscosities

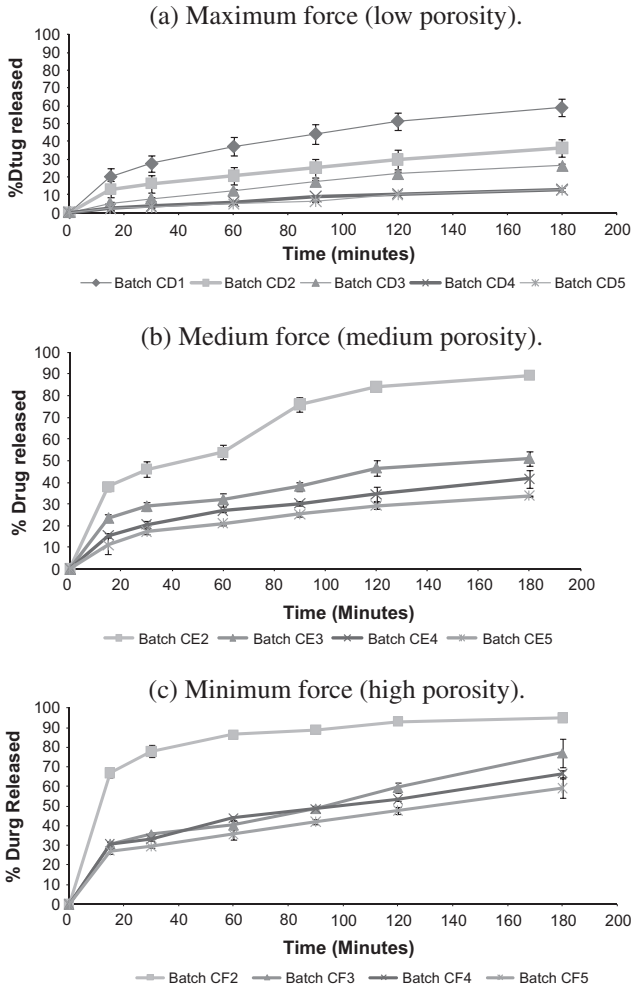

Fig. 2. Dissolution profiles for batches containing HPMC K4M. Numbers 1–5 in the name of the batches indicate the percentage of polymer (w/w), being 1 = 10%; 2 = 15%; 3 = 20%; 4 = 25%; and 5 = 30%.

Table 7
Kinetic parameters for the batches containing METHOCEL K4M.

	Higuchi equation		Zero-order equation		Korsmeyer equation			Peppas and Sahlin equation		
	b^a ($t^{-0.5}$)	r^{2b}	$k_0{}^c$ (t^{-1})	r^{2b}	$k_k{}^d$ (t^{-n})	n^e	r^{2b}	$k_d{}^f$ (t^{-m})	$k_r{}^g$ (t^{-2m})	r^{2b}
Batch CD1	**4.132**	0.996	0.233	0.953	**6.377**	0.429	0.999	**6.413**	−0.010	0.999
Batch CD2	**2.436**	0.991	0.140	0.991	**3.448**	0.446	0.993	**3.464**	0.034	0.994
Batch CD3	2.294	0.991	0.131	0.977	0.733	0.692	0.996	0.872	0.214	0.995
Batch CD4	1.188	0.979	0.055	0.950	0.270	0.738	0.988	0.275	0.115	0.986
Batch CD5	1.510	0.947	0.065	0.924	0.097	0.931	0.987	−0.112	0.151	0.986
Batch CE2	**7.110**	0.944	**0.793**	0.724	**13.356**	0.371	0.955	**11.053**	−0.213	
Batch CE3	**3.632**	0.956	**0.234**	0.789	**9.776**	0.313	0.960	**6.418**	−0.159	0.983
Batch CE4	3.000	0.987	0.197	0.844	5.387	0.390	0.998	4.565	−0.062	0.998
Batch CE5	2.508	0.989	0.165	0.853	3.618	0.434	0.985	3.664	−0.037	0.996
Batch CF2	**17.298**	0.999	4.466	0.999	**47.323**	0.140	0.961	**21.690**	−1.268	0.986
Batch CF3	**4.946**	0.951	0.393	0.799	**10.848**	0.353	0.916	**6.287**	0.054	0.969
Batch CF4	4.679	0.946	0.362	0.755	12.341	0.312	0.963	7.815	−0.173	0.984
Batch CF5	4.048	0.964	0.265	0.822	10.729	0.312	0.944	6.377	−0.103	0.978

Bold values highlight an abrupt change in the kinetic paramenters, which indicates a change in the release behavior and could be indicative of the presence of a percolation threshold.

[a] Higuchi's slope.
[b] Determination coefficient.
[c] Zero order kinetic constant.
[d] Korsmeyer kinetic constant.
[e] Diffusional exponent.
[f] Diffusional constant of Peppas and Sahlin model.
[g] Relaxational constant of Peppas and Sahlin model; m is the diffusional exponent that depends on the geometric shape of the releasing device through its aspect ratio.

as matrix forming polymer, MCC and lactose as fillers, and a lubricant mixture, can be explained by a critical point around 13–15% v/v of HPMC.

This result is especially unexpected, considering that three levels of compression forces were employed, leading to three levels for the initial porosity of the tablets (Level A: 7.9%, Level B: 16%, and Level C: 27.3%).

In previous works [17,18,27,30,35], the low value obtained for the excipient percolation threshold in hydrophilic matrices was attributed to a contribution of the initial porosity of the tablets to the formation of the gel layer, which controls the drug release. All these matrices had porosities between 5% and 10%, corresponding to the lower porosity level of the present study. Although the results of the present work are not in disagreement with this hypothesis, they point out that in case that it would be a contribution of the initial porosity, it would be restricted to a relatively low range of tablet porosities. Therefore, when the tablet porosity is increased to values around 16% or 27% approximately, the critical points obtained remain almost unchanged, indicating that the additional porosity is not contributing to reach the excipient percolation threshold.

Even though showing a very similar critical point, the tablets prepared with higher initial porosities show faster release profiles. This behavior could be due to the role of the additional tablet porosity (allowing relaxation and dilution of the polymer in free space and helping the drug release).

Two different viscosity grades of HPMC have been employed, and no influence of this parameter in the percolation threshold of the studied systems has been found. Furthermore, according to the results of this study, the percolation threshold is independent on the tablet porosity (at least for medium and high porosity levels). These facts support the robustness of the percolation threshold parameter and its use in the characterization of the pharmaceutical formulations.

A Previous work by Gonçalves-Araújo et al. [27] pointed out the possibility that the microcrystalline cellulose employed as filler can help to establish the gel layer. The MCC is an insoluble excipient containing hydrophilic groups and, in theory, can absorb water and help to maintain the gel integrity (no dilution factor, such as the case is for a soluble filler like lactose) and to retard the release of the drug. In the present study, considerable concentrations of MCC have been employed (19%). A better knowledge of this contribution would help to interpret these results concerning responsibility of the tablet porosity and the MCC concentration on the low values obtained for the excipient percolation threshold in hydrophilic matrices, expressed as HPMC volume fraction.

3.4. Influence of the porosity and polymer viscosity on the drug release rate

Although the polymer viscosity and the porosity of the matrices have not shown significant influence on the critical points, these parameters have a clear influence on the drug release rate. In the case of the matrices containing 15% W/W of HPMC, the majority of the batches are below the polymer percolation threshold, and in the case that a percolating cluster is formed, this is just an incipient cluster. By contrary, batches containing 30% W/W of HPMC have a percolating cluster of polymer much more consistent. For this reason, it is foreseeable that in batches with 15% W/W of HPMC, the polymer viscosity plays less influence on the release profiles than in the batches with 30% W/W of polymer.

This hypothesis is confirmed in the Figs. 3 and 4, where it can be appreciated that in batches with 15% W/W of HPMC (Fig. 3), the

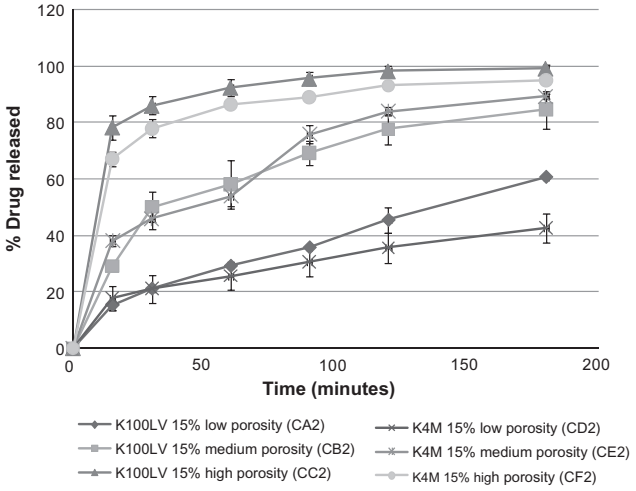

Fig. 3. Dissolution profiles for batches containing 15% w/w of HPMC.

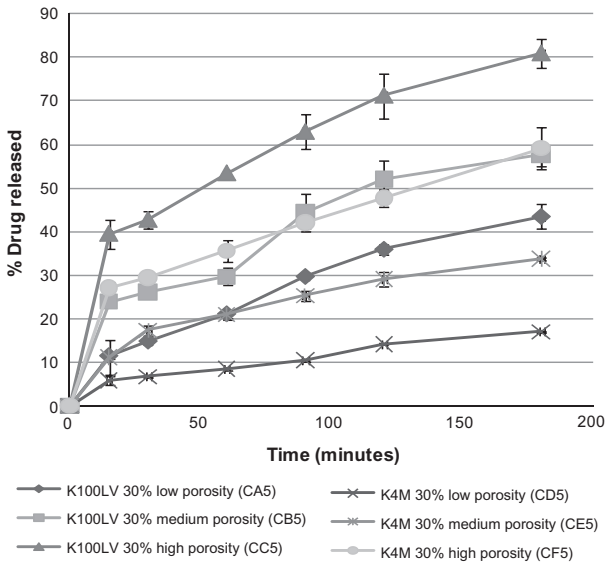

Fig. 4. Dissolution profiles for batches containing 30% w/w of HPMC.

polymer viscosity exerts much less influence than the porosity of the matrices on the drug release rate, while for batches containing a percolating cluster of polymer (30% HPMC) (Fig. 4), the influence of the polymer viscosity is much higher, exceeding in some cases the influence of the porosity of the matrices. For example, in Fig. 4, the release profile of batch CA5 (30% W/W of HPMC K100LV and low porosity) is above the release profile of batch CE5 (30% W/W of HPMC K4M and medium porosity). According to the previous hypothesis, this behavior is not observed in Fig. 3, where the main factor is the porosity level.

4. Conclusions

Based on the percolation theory, the ideal concentration for different types of HPMC to obtain extended release formulations is above 15% v/v of polymer. This concentration of polymer allows the formation of an infinite cluster of excipient that controls the hydration, the gel formation and the drug release.

In order to increase the robustness of the formulation, it is reasonable to avoid concentrations of HPMC in the neighborhood of its percolation threshold, which may be a point of high variability.

On the other hand, results here suggested that the HPMC percolation threshold is independent of the polymer viscosity and the initial porosity. However, further investigation in this area is required.

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References

[1] E. Costa, A. Arancibia, J.M. Aïache, Sistemas matriciales, Acta Farm. Bonaerense 23 (2004) 259–265.
[2] E. Castellanos-Gil, I. Caraballo, B. Bataille, Tablet design, in: S.C. Gad (Ed.), Pharmaceutical Manufacturing Handbook: Production and Processes, Wiley Interscience, New Jersey, United States, 2008, pp. 977–1052.
[3] H. Omidian, K. Park, Swelling agents and devices in oral drug delivery, J. Drug Deliv. Sci. Technol. 18 (2008) 83–93.
[4] C.L. Li, L.G. Martini, J.L. Ford, M. Roberts, The use of hypromellose in oral drug delivery, J. Pharm. Pharmacol. 57 (2005) 533–546.
[5] M. Ghimire, L.A. Hodges, J. Band, B. O'Mahony, F.J. McInnes, A.B. Mullen, H.N.E. Stevens, In-vitro and in-vivo erosion profiles of hydroxypropylmethylcellulose (HPMC) matrix tablets, J. Control. Release 147 (2010) 70–75.
[6] M.V. Velasco, J.L. Ford, P. Rowe, A.R. Rajabi-Siahboomi, Influence of drug:hydroxypropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets, J. Control. Release 57 (1999) 75–85.
[7] A.T. Pham, P.I. Lee, Probing the mechanisms of drug release from HPMC matrices, Pharm. Res. 11 (1994) 1379–1384.
[8] P. Colombo, R. Bettini, G. Massimo, P.L. Catellani, P. Santi, N.A. Peppas, Drug diffusion front movement is important in drug release control from swellable matrix tablets, J. Pham. Sci. 84 (1995) 991–997.
[9] J. Siepmann, N.A. Peppas, Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC), Adv. Drug Deliv. Rev. 48 (2001) 139–157.
[10] X.C. Fu, G.P. Wang, W.Q. Liang, M.S.S. Chow, Prediction of drug release from HPMC matrices: effect of physicochemical properties of drug and polymer concentration, J. Control. Release 95 (2004) 209–216.
[11] C. Ferrero, D. Massuelle, E. Doelker, Towards elucidation of the drug release mechanism from compressed hydrophilic matrices made of cellulose ethers. II. Evaluation of a possible swelling-controlled drug release mechanism using dimensionless analysis, J. Control. Release 141 (2010) 223–233.
[12] I. Caraballo, M. Fernández-Arévalo, M. Millán, A.M. Rabasco, H. Leuenberger, Study of percolation thresholds in ternary tablets, Int. J. Pharm. 139 (1996) 177–186.
[13] I. Caraballo, M. Fernández-Arévalo, M.A. Holgado, A.M. Rabasco, Percolation theory: application to the study of the release behaviour from inert matrix systems, Int. J. Pharm. 96 (1993) 175–181.
[14] I. Caraballo, M. Millan, A.M. Rabasco, H. Leuenberger, Zero-order released periods in inert matrices. Influence of the distance to the percolation threshold, Pharm. Acta Helv. 71 (1996) 335–339.
[15] M. Millán, I. Caraballo, A.M. Rabasco, The role of the drug/excipient particle size ratio in the percolation model for tablets, Pharm. Res. 15 (1998) 216–220.
[16] L.M. Melgoza, A.M. Rabasco, H. Sandoval, I. Caraballo, Estimation of the percolation thresholds in dextromethorphan hydrobromide matrices, Eur. J. Pharm. Sci. 12 (2001) 453–459.
[17] I. Fuertes, A. Miranda, M. Millán, I. Caraballo, Estimation of the percolation thresholds in acyclovir hydrophilic matrix tablets, Eur. J. Pharm. Biopharm. 64 (2006) 336–342.
[18] A. Miranda, M. Millán, I. Caraballo, Study of the critical points of HPMC hydrophilic matrices for controlled drug delivery, Int. J. Pharm. 311 (2006) 75–81.
[19] I. Fuertes, I. Caraballo, A. Miranda, M. Millán, Study of critical points of drugs with different solubilities in hydrophilic matrices, Int. J. Pharm. 383 (2010) 138–146.
[20] D. Blattner, M. Kolb, H. Leuenberger, Percolation theory and compactability of binary powder systems, Pharm. Res. 7 (1990) 113–117.
[21] J.D. Bonny, H. Leuenberger, Matrix type controlled release systems: I. Effect of percolation on drug dissolution kinetics, Pharm. Acta Helv. 66 (1991) 160–164.
[22] J.D. Bonny, H. Leuenberger, Matrix type controlled release systems II. Percolation effects in non-swellable matrices, Pharm. Acta Helv. 68 (1993) 25–33.
[23] L.E. Holman, H. Leuenberger, The relationship between solid fraction and mechanical properties of compacts – the percolation theory model approach, Int. J. Pharm. 46 (1988) 35–44.
[24] H. Leuenberger, R. Leu, Formation of a tablet: a site and bond percolation phenomenon, J. Pharm. Sci. 81 (1992) 976–982.
[25] H. Leuenberger, B.D. Rohera, C. Haas, Percolation theory – a novel approach to solid dosage form design, Int. J. Pharm. 38 (1987) 109–115.
[26] D. Stauffer, A. Aharony, Introduction to Percolation Theory, Taylor & Francis, London, 1992.
[27] T. Gonçalves-Araújo, A.R. Rajabi-Siahboomi, I. Caraballo, Application of percolation theory in the study of an extended release Verapamil hydrochloride formulation, Int. J. Pharm. 361 (2008) 112–117.
[28] I. Caraballo, Factors affecting drug release from hydroxypropyl methyl cellulose matrix systems in the light of classical and percolation theories, Expert Opin. Drug Deliv. 7 (2010) 1291–1301.
[29] I. Caraballo, M. Millán, A.M. Rabasco, Relationship between drug percolation threshold and particle size in matrix tablets, Pharm. Res. 13 (1996) 387–390.
[30] A. Miranda, M. Millán, I. Caraballo, Investigation of the influence of particle size on the excipient percolation thresholds of HPMC hydrophilic matrix tablets, J. Pharm. Sci. 96 (2007) 2746–2756.
[31] T. Higuchi, Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, J. Pharm. Sci. 52 (1963) 1145–1149.
[32] R.W. Korsmeyer, R. Gurny, E. Doelker, P. Buri, N.A. Peppas, Mechanisms of solute release from porous hydrophilic polymers, Int. J. Pharm. 15 (1983) 25–35.
[33] N.A. Peppas, J.J. Sahlin, A simple equation for the description of solute release. III. Coupling of diffusion and relaxation, Int. J. Pharm. 57 (1989) 169–172.
[34] P.L. Ritger, N.A. Peppas, A simple equation for description of solute release I. Fickian and non-fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs, J. Control. Release 5 (1987) 23–36.
[35] A. Miranda, M. Millán, I. Caraballo, Study of the critical points in lobenzarit disodium hydrophilic matrices for controlled drug delivery, Chem. Pharm. Bull. 54 (2006) 598–602.