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Study of the critical points of experimental HPMC–NaCMC hydrophilic matrices

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ABSTRACT

The purpose of the present work was to study the existence of critical points on the drug release and water uptake behaviour of ternary hydrophilic matrix tablets and to study the possibility of simplifying a ternary to a binary system. The ternary hydrophilic matrix tablets were prepared between 40 and 100% (w/w) of KCl, HPMC and NaCMC. Dissolution studies were carried out using the paddle method and the water uptake studies were measured using the modified Enslin apparatus and the behaviour of the kinetic parameters was studied. According to the percolation theory, both studies confirm the existence of critical points; those were related to the excipients percolation tresholds. The percolation thresholds for the binary hydrophilic matrix tablets were found between 28.7–40.7% (v/v) of HPMC and 38.6–53.9% (v/v) of NaCMC. For the ternary hydrophilic matrix tablets, the existence of a critical barrier between 54 and 61% (v/v) KCl (60–70%, w/w of KCl) was found. In the studied ternary systems HPMC and NaCMC showed that is not possible to simplify the system but they present a partial collaboration in order to establish the gel layer. The knowledge of this critical barrier will be useful in order to optimize the design of the ternary hydrophilic matrix systems.

1. Introduction

Mixtures of different non-ionic cellulose ethers like HPMC and NaCMC have been widely employed in the formulation of controlled release hydrophillic matrices. The use of mixtures of polymers represents a strategy to obtain the required release properties (Juárez et al., 2001). Their drug release kinetics will be determined by the hydrogel relaxation and erosion behaviour as well as by the processes of water and drug diffusion through the formed gel (Michailova et al., 2000). An extensively number of publications have studied the drug release from these systems, combining different kinds of excipients (Baveja et al., 1987; Kim and Fassihi, 1997) and different ratios of the excipients in order to find zero order drug release or better drug release properties (Walker, 1982; Dabbagh et al., 1999; Juárez et al., 2001). The degree of hydration and the viscosity of the gel layer formed by the mixture of these excipients have also been studied (Michailova et al., 2000; Conti et al., 2007).

The evolution of the pharmaceutical dosage form design has been important in the last decades. One of the new tools that have been incorporated to this field is the percolation theory. This statistical theory was first applied in 1987 to the pharmaceutical field by Leuenberger and co-workers.

The percolation theory studies the distribution of a high number or elements that randomly occupy a lattice, as well as their relationship with the behaviour of the macroscopic properties of the system. The percolation theory introduces the concept of percolation threshold, as the concentration where a component of the system just reaches a macroscopic connectivity through the system (Leuenberger et al., 1989; Sahimi, 1994). The percolation threshold determines the existence of "critical points", where important changes in the system's properties occur. This theory has been proved useful, especially for the characterization and design of binary dosage forms (Bonny and Leuenberger, 1991, 1993; Leuenberger and Leu, 1992; Sahimi, 1994).

In the case of solid dosage forms, the changes on the dissolution kinetics and water uptake of a matrix system can be explained using this theory.

In previous works, this theory has been applied to design inert matrix systems (Caraballo et al., 1993, 1996; Millán et al., 1998; Melgoza et al., 2001). More recently, the percolation theory is being applied to explain the behaviour of binary hydrophilic matrix systems (Miranda et al., 2006; Fuertes et al., 2006).

As it was previously mentioned, percolation theory has been developed for binary systems, whereas most pharmaceutical formulations include more than two components. In previous

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works (Caraballo et al., 1994) dealing with carteolol hydrochloride inert matrices, multicomponent systems were simplifyed to binary systems. On the other hand, Caraballo et al. (1996) found the existence of a "combined percolation threshold" on inert ternary matrix systems.

In ternary systems A,B,C, several percolation thresholds can be expected: the percolation thresholds of each substance and those that has referred to as "combined percolation threshold". Caraballo et al. (1996) have defined the "combined percolation threshold" of several components, two components in ternary systems, as the volume fraction at which these components, jointly considered, start to percolate the sample. So, in ternary systems, the "combined percolation threshold" of the components B and C, is related to the second percolation threshold of the component A.

It has already mentioned that multicomponent system can be reduced to a binary system on the basis of a common property, for example the hydrophilicity of the substances. The hydrophilic substances are in concentrations which could allow or not to percolate the system. The degree in which can be appreciated the "combined percolation threshold" will depend on the influence that the discriminating property exerts on the property of the system selected to calculate the threshold.

In the present work, the percolation theory is applied for the first time to ternary hydrophilic matrix tablets in order to obtain a better knowledge of the processes taking place during the water uptake and the drug release of ternary hydrophilic matrix tablets. Furthermore, the existence of critical points in these systems is investigated. Another objective of this work is to study the possibility to reduce from ternary to binary systems using a discriminating property. On the other hand, the existence of a "combined percolation threshold" in hydrophilic matrix tablets is investigated for the first time.

2. Materials and methods

2.1. Materials

Potassium chloride (KCl) (Acofarma, Barcelona, Spain) was employed as a model drug, hydroxypropylmethylcellulose (HPMC K4 M, Colorcon, S.A., Spain), and sodium carboxymethylcellulose (NaCMC Akucell AF 3185 Safic-Alcan, Spain), as matrix former excipients.

2.2. Preparation of the hydrophilic matrix tablets

The drug and the polymers were first sieved (Retsch type Vibro) and the 50–100 μm for the drug granulometric fraction and 150–200 μm for the excipients granulometric fraction were employed.

The true density was determined using an air pycnometer (Quantachrome mod. Stereopycnometer spy-3), of potassium chloride, HPMC K4M and NaCMC Akucell 3185, as 1.98, 1.285 and 1.376 g/cm^3, respectively.

The components were mixed using a Turbula mixer (Basel, Switzerland). The mixing time (3 min) was validated. Then binary and ternary hydrophilic matrix systems were prepared varying the percentages of the components (see Fig. 1). For example, batch 1 contains 40% (w/w) KCl, 30% (w/w) HPMC and 30% NaCMC.

Tablets with a total weight of 600 mg and a diameter of 12 mm were obtained using an eccentric machine Bonals A-300 (Barcelona, Spain) by direct compression, applying the maximum compression force accepted by the formulation.

The tablets were weighed using a precision balance (Scaltec, mod. SBC 31). The diameter and height were measured with an electronic digital micrometer with a sensibility of 0.01 mm.

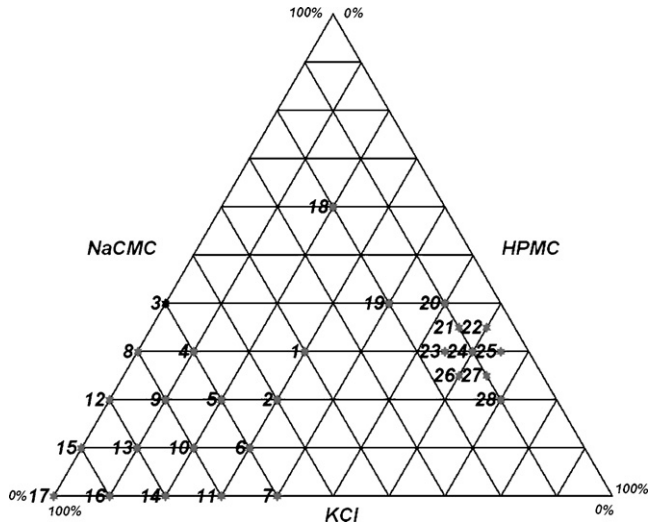

Fig. 1. ⋆ Composition % (w/w) of the studied batches containing KCl as model drug and different amounts of NaCMC and HPMC.

2.3. Dissolution studies

The *in vitro* KCl release was measured in 900 ml of deionizated water, using the apparatus II proposed by USP 26 (Turu Grau, type D-6) at 37 °C ± 0.5 °C and 100 rpm. This test was performed in triplicate. The KCl released was detected by conductometry using a Crison micro CM-2201 digital conductivity-meter linked to a chart recorder and a personal computer.

2.4. Kinetic analysis of drug release data

In order to find a possible change on the drug release kinetics, the fit of the data corresponding to 5–70% drug release to the Zero order Eq. (1), Higuchi Eq. (2) (Higuchi, 1963), Korsmeyer Eq. (3) (Korsmeyer et al., 1983) and Peppas and Sahlin Eq. (4) (Peppas and Sahlin, 1989) models were studied:

$$\frac{Q_t}{Q_\infty} = kt \quad (1)$$

$$\frac{Q_t}{Q_\infty} = bt^{1/2} \quad (2)$$

$$\frac{Q_t}{Q_\infty} = kt^n \quad (3)$$

$$\frac{Q_t}{Q_\infty} = k_d t^m + k_r t^{2m} \quad (4)$$

where Q_t/Q_∞ = fraction of drug released; b = Higuchi's slope; k = kinetics constant of the Korsmeyer model; n = diffusional exponent which depends of the release mechanism and the shape of the device; k_d = diffusional constant of Peppas and Sahlin model; k_r = relaxation constant of Peppas and Sahlin model; m = diffusional exponent which depends on the geometrical shape of the releasing device through its aspect ratio.

2.5. Water uptake studies

The water uptake studies were performed using the modified Enslin apparatus. The water uptake through one side of the tablet at each time was read from a precision balance (Scaltec SBC 31) linked to a chart recorder and a personal computer, during 12 h employing deionizated water. This test was performed in three replicates.

The Davidsons and Peppas (Davidson and Peppas, 1986) model Eq. (5) was applied to these data to determine the mechanism and

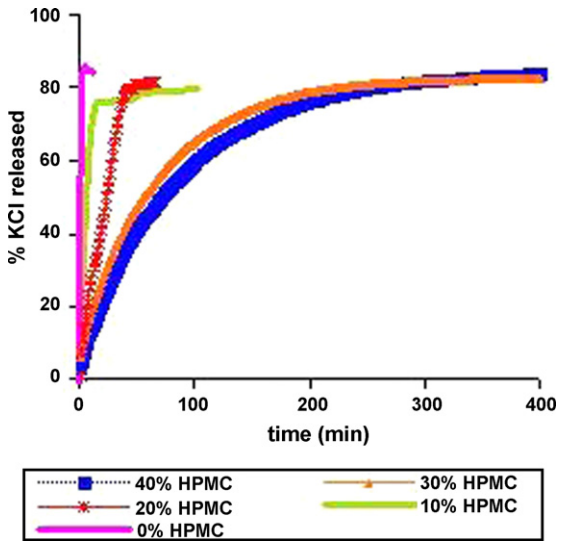

Fig. 2. Dissolution profiles of the binary hydrophilic matrix systems elaborated with KCl–HPMC.

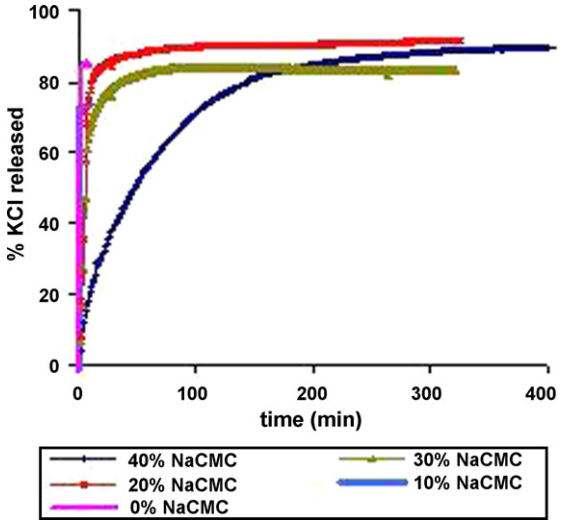

Fig. 3. Dissolution profiles of the binary hydrophilic matrix systems elaborated with KCl–NaCMC.

the rate of water uptake:

$$w = k_s t^n \quad (5)$$

where w = weight gain of the swelled matrix (water/dry polymer); k_s = kinetic constant of water penetration; t = penetration time; n = exponent which depends on the water penetration mechanism.

2.6. Estimation of the percolation threshold

In order to estimate the percolation threshold, the behaviour of several properties of the system has been studied. In our case the behaviour of the kinetic parameters Higuchi's slope "b" and normalized Higuchi's slope, was studied as a function of the volumetric fraction of each component at time zero.

A linear regression has been performed as an approximation for estimating the trend of the parameter. To estimate the percolation threshold the percentage of the drug release and the amount of the drug release normalized with the volumetric fraction of the drug (q/F_{KCl}) have been plotted vs. the square root of the time.

Some matrix surfaces were examined using a scanning electron microscope (SEM) (Philips type XL-30) with a backscattering electrons detectors (BSE) was employed to study the excipient and drug particles after compaction.

In order to study the existence of combined percolation thresholds on the ternary hydrophilic matrix systems the obtained data were plotted using the Matlab program.

3. Results and discussion

3.1. Dissolution studies

As Fig. 1 shows, binary and ternary formulations were compressed employing potassium chloride as drug model. In order to have a reference, the dissolution and water uptake behaviour of the binary matrix systems KCl–HPMC and KCl–NaCMC and the corresponding critical points were studied in a first step. Then, the ternary systems KCl–HPMC–NaCMC shown in Fig. 1 were studied. The data corresponding to 100% KCl tablets were also obtained for comparison purposes.

3.1.1. Binary hydrophilic matrix systems KCl–HPMC

The dissolution studies for the binary KCl–HPMC systems are shown in Fig. 2, where an important change in the drug release profiles between 20 and 30% (w/w) HPMC can be appreciated. The kinetic analysis of the release data confirms this change. Table 1 shows the values obtained from Higuchi's, Korsmeyer and Peppas–Sahlin models. As it can be observed, the Higuchi's slope, b (6.67–15.31% $min^{-1/2}$), and the Korsmeyer diffusional exponent n (0.504–0.870), increase between 20 and 30% (w/w) HPMC for these binary systems. This indicates a change in the drug release mechanism from diffusional to a relaxation or erosion controlled release. The values of the Peppas and Sahlin constants confirm this change on the drug released mechanism. The diffusional constant, k_d decreases (7.016–0.765% min^{-m}) whereas the relaxational constant, k_r increases (0.1520–2.7640% min^{-2m}). Therefore both, drug release profiles and the kinetic analysis confirm the existence of a critical point between the concentrations 20 and 30% (w/w) HPMC, corresponding to 29–41% (v/v) HPMC.

3.1.2. Binary KCl–NaCMC hydrophilic matrix systems

The dissolution studies for the binary systems prepared with KCl–NaCMC are shown in Fig. 3. The figure shows a change in the drug release profiles between 30 and 40% (w/w) NaCMC. The kinetic analysis (Table 1) of the drug release profiles shows that the matrix containing 40% (w/w) NaCMC shows a low value for the Higuchi's slope, b with respect to the matrix containing 30% (w/w) NaCMC. In the case of the Korsmeyer's diffusional exponent, n, the batch 3 (40%, w/w NaCMC) shows a value close to 0.5. With respect to the Peppas–Sahlin model, the diffusional constant, k_d (6.663 min^{-m}) is higher than the relaxational constant, k_r (0.328% min^{-2m}) indicating that for this matrix system containing 40% NaCMC the drug release process is mainly governed by diffusion.

On the other hand, the drug release profiles from the matrices containing between 10 and 30% (w/w) NaCMC showed a fast drug release rate compared to the 40% (w/w) NaCMC formulation. The Korsmeyer's diffusional exponent is near 1 for the case of 30% (w/w) NaCMC and $n > 1$ for 10% and 20% (w/w) NaCMC. In the case of Peppas and Sahlin model, k_r shows very high values indicating that the drug release is governed by the relaxation of the chains of the polymer or by the erosion of the matrix system. This analysis confirms the existence of a critical point between 30 and 40% (w/w) NaCMC, corresponding to the 39–54% (v/v) of NaCMC.

3.1.3. Ternary hydrophilic matrix systems KCl–HPMC–NaCMC

Ternary hydrophilic matrix systems were prepared (see Fig. 1) and their drug release behaviour was studied in order to investi-

Table 1
Kinetic parameters for the Zero order, Higuchi, Korsmeyer and Peppas–Sahlin models calculated for the binary and ternary hydrophilic matrix tablets.

Batch	% (w/w) KCl	% (w/w) HPMC	% (w/w) NaCMC	Zero order		Higuchi		Korsmeyer			Peppas and Sahlin		
				k_0 (% min^{-1})	r^2	b (% min$^{-1/2}$)	r^2	k (% min^{-n})	n	r^2	k_d (% min^{-m})	k_r (% min^{-2m})	r^2
7	60	40	0	0.3876	0.9400	6.3561	0.9934	4.5990	0.5500	0.9990	5.3900	0.2970	0.9980
11	70	30	0	0.4560	0.9334	6.6744	0.9933	6.4110	0.5040	0.9990	7.0160	0.1520	0.9990
14	80	20	0	1.9489	0.9973	15.3100	0.9834	3.2430	0.8700	1.0000	0.7650	2.7640	1.0000
16	90	10	0	5.7907	0.9717	29.1450	0.9966	10.2890	0.8000	0.9980	4.6310	6.2000	0.9980
17	100	0	0	81.311	0.9743	119.9900	0.9948	76.9490	1.0400	0.9950	−20.6040	97.7340	0.9960
3	60	0	40	0.5919	0.9574	7.6954	0.9983	5.9560	0.5440	1.0000	6.6630	0.3280	0.9990
8	70	0	30	10.1240	0.9984	41.0540	0.9867	11.1880	0.7430	0.9840	6.2140	5.5650	0.9830
12	80	0	20	11.4490	0.9695	48.9150	0.9361	3.8290	1.4440	0.9920	−23.0700	20.0710	0.9930
15	90	0	10	275.4100	0.9727	312.0600	0.9800	406.9220	2.1060	0.9830	−198.0460	10.9830	0.9930
17	100	0	0	81.311	0.9743	119.9900	0.9948	76.9490	1.0400	0.9950	−20.6040	97.7340	0.9960
1	40	30	30	0.3606	0.9575	6.2062	0.9961	3.1320	0.6110	0.9990	3.8270	0.4630	0.9990
2	50	30	20	0.2965	0.9355	5.6109	0.9917	3.7770	0.5590	0.9980	4.6030	0.2520	0.9980
4	60	10	30	0.4584	0.9523	6.8548	0.9967	4.6870	0.5620	0.9990	5.4820	0.3050	0.9990
5	60	20	20	0.4474	0.9576	6.9316	0.9971	3.4920	0.6150	0.9990	4.2730	0.4020	0.9980
6	60	30	10	0.501	0.9599	7.4618	0.9967	3.2580	0.6420	0.9990	3.8960	0.5080	0.9980
9	70	10	20	431.7200	0.9813	381.2500	0.9647	2496.3170	2.7770	0.9990	−267.1610	686.7880	0.9960
10	70	20	10	78.9420	0.9929	126.4200	0.9743	6.8520	1.5830	0.9990	65.0690	127.1070	0.9990
13	80	10	10	192.8900	0.9679	226.2600	0.9469	267.6710	2.1370	0.9920	−153.5320	334.3930	0.9940

k_0 (% min^{-1}) = zero-order constant; b (% min$^{-1/2}$) = Higuchi's slope; k (% min^{-n}) = kinetics constant of the Korsmeyer model, n = diffusional exponent, kd = diffusional constant of Peppas and Sahlin model, k_r = relaxation constant of Peppas and Sahlin model, and m = the exponent that depends on geometric shape of the releasing device through its aspect ratio.

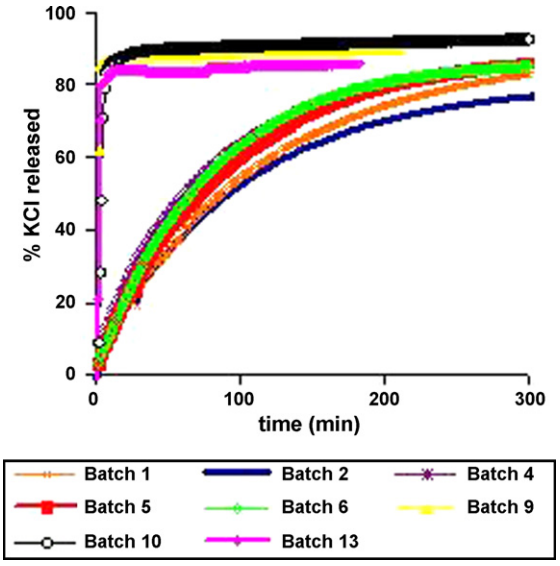

Fig. 4. Dissolution profiles of the ternary hydrophilic matrix systems elaborated with KCl–HPMC–NaCMC.

gate the existence of critical points. The drug release profiles were evaluated both visual and mathematically, taking into account the kinetic parameters obtained from the fitting of the obtained data to the main kinetic models. Fig. 4 shows the drug release profiles obtained from batches 1, 2, 4, 5, 6, 9, 10 and 13.

Two kinds of behaviours can be clearly appreciated in this figure. The first one, corresponding to batches 1, 2, 4, 5 and 6 shows a modified drug release, whereas the second one (batches 9, 10 and 13) shows a fast drug release, similar to conventional dosage forms. The kinetic analysis of the release profiles from batches 1, 2, 4, 5 and 6 (see Table 1) shows a good fit to Higuchi's model, the Korsmeyer's diffusional exponent, n, exhibits values near 0.5. Furthermore, the Peppas and Sahlin model shows higher absolute values of the diffusional constant k_d than the relaxational constant k_r. Therefore, the first behaviour observed in Fig. 4 can be related to a diffusion controlled release of the drug.

In the case of batches 9, 10 and 13, as it can be observed in Table 1, all the studied kinetic constants, i.e., the Higuchi's slope b, the kinetic constant k from Korsmeyer's model, and the Peppas and Sahlin model constants (k_d and k_r) showed higher values compared to the batches 1–6.

On the other hand, the exponent n of the Korsmeyer model shows values far away from 0.5. Furthermore, the values of the relaxation constant, k_r, for these lots (batches 9, 10 and 13) are higher than the values of the diffusion constant, k_d. This means that the drug release from these batches is governed by erosion/relaxation mechanisms.

Finally, the analysis of the release profiles obtained from the studied KCl–HPMC–NaCMC matrices indicates clearly the existence of a critical behaviour in these ternary hydrophilic matrices systems.

3.1.3.1. Ternary hydrophilic matrix systems with low drug loads. Ternary hydrophilic matrix systems with low drug loads were prepared (see Fig. 1, batches 18–28) between 5 and 20% (w/w) KCl. In percolation theory, two percolation thresholds are expected, the drug percolation theory and the excipient percolation threshold. Therefore, the existence of critical points and drug percolation threshold were studied on the release profiles obtained from the matrix systems.

The kinetic analysis of the drug release profiles obtained from the ternary hydrophilic matrix systems shows that there is not evi-

dence of a critical point on the matrices studied. In hydrophilic matrices the drug threshold is less evident that the excipient threshold which is responsible for the release control.

The analysis also shows that some of the matrix systems present zero order release properties and Korsmeyer's difussional exponent near to 1 or $n = 1$, at the concentrations: 60% (w/w) HPMC, 30% (w/w) NaCMC corresponding to batch 24, 65% (w/w) HPMC, 30% (w/w) NaCMC, batch 25 and 70% (w/w) HPMC, 20% (w/w) NaCMC batch 28.

3.2. Water uptake studies in binary and ternary hydrophilic matrix systems

The water uptake has been studied for many authors in order to explain the grade of hydration and swelling from the hydrophilic matrix systems (Michailova et al., 2000; Conti et al., 2007).

As it was described in previous sections, in the present work, the water uptake studies were carried out on the modified Enslin apparatus. In the KCl–HPMC binary mixtures, the transition can be located between the 20 and 30% (w/w) HPMC 29 and 41% (v/v) according to the increase in the swelling constant k_s.

In the case of the KCl–NaCMC binary systems. Profiles from slow swelling constant k_s (40%, w/w NaCMC) to a very fast swelling constant k_s (10%, w/w NaCMC) were observed. According to these water uptake profiles, the critical range for this property was located between 10 and 20% (w/w) NaCMC.

The water uptake profiles obtained from the ternary hydrophilic matrix systems show three different behaviours: (i) profiles with a slow swelling constant (batches 1 and 2), (ii) intermediate values of the swelling constant (batches 4, 5 and 6) and (iii) fast swelling constant (batches 9, 10 and 13) (Fig. 5). According to the Davidsons and Peppas model, the values of the swelling constant ranged from $k_s = 75{,}142–151{,}704$ for the studied ternary matrix systems.

The results obtained from the dissolution and water uptake studies confirm the existence of critical points in the studied binary and ternary hydrophilic matrices. In the following section the relationship of these points with percolation thresholds of the excipients will be discussed.

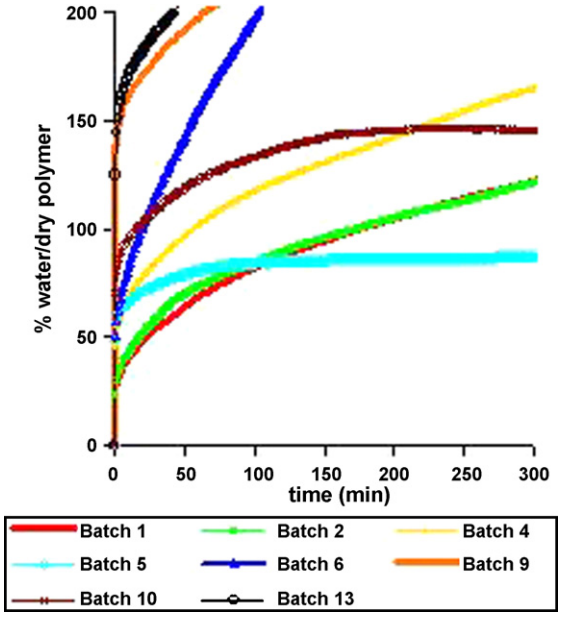

Fig. 5. Water uptake profiles of the ternary hydrophilic matrix systems containing KCl–HPMC–NaCMC.

3.3. Estimation of excipient percolation thresholds

The excipient percolation threshold is one of the main factors governing the gel layer formation and the control of the drug release from hydrophilic matrices. Above the excipient percolation threshold, a percolating cluster of this component exists and the gel layer is formed from the first moment, which is able to control the hydration and drug release rate.

Below the excipient percolation threshold, the excipients do not percolate the system and the drug release is not controlled by the gel layer, resulting in a faster release rate more similar to conventional dosage forms.

In order to estimate the percolation threshold, the evolution of the kinetic parameters Higuchi's slope, b; and normalized Higuchi's slope (b (g/cm^2)/% (v/v) of the excipient) as a function of the volumetric fraction of the excipient at time zero was studied on the binary as well as on the ternary hydrophilic matrix systems.

As discussed in Section 3.1.1, the release behaviour from the binary KCl/HPMC matrices shows a critical point between 20 and 30% (w/w) HPMC, corresponding to the range 29–41% (v/v) HPMC. As it was stated in Section 3.2, the water uptake behaviour of these systems also shows a critical point in this range. It has to be realized that water uptake and release behaviour are different processes, therefore, two different percolation thresholds could be obtained. Furthermore, following the Enslin methodology, the water uptake was measured through only one face of the tablets, whereas the drug release takes place through the whole surface of the tablets. Notwithstanding the above, the fact that water uptake and drug release show a critical point in the same range reinforces the location of the excipient percolation threshold for the binary KCl–HPMC matrices between 29 and 41% (v/v) HPMC.

With respect to the KCl–NaCMC binary matrices, there is a disagreement between the drug release (see Section 3.1.2) and the water uptake studies (Section 3.2). Obviously in this case, we have to focus on the percolation threshold for the release properties, which are the objective of this study. Therefore, we can locate the excipient percolation threshold for the binary KCl–NaCMC hydrophilic matrices between 39 and 54% (v/v) NaCMC.

Fig. 6 shows the Higuchi's slope, b; and the normalized Higuch's slope values plotted as a function of the volumetric fraction of the excipient for the binary and ternary hydrophilic matrix systems studied.

Analyzing Fig. 6, we can observe two behaviours, which go from very high values (represent by triangles) to very low values (represent by square) for the Higuchi's slope as well as for the normalized Higuchi's slope.

As it can be appreciated in Fig. 6, there is not a critical drug concentration governing the release properties, but a critical excipient barrier. This critical excipient barrier, could be located in the range from 54 to 61% (v/v) (60–70%, w/w) KCl (Fig. 8). Above this critical barrier, excipients percolating cluster allows the formation of the gel layer from the first moment and the matrices show controlled drug release.

Recent studies of our research group have found on binary matrices that the drug effective surface is not the only factor that influences the drug release as was mentioned by Salomón and Doelker (1979). There are other parameters as the excipient percolation threshold influencing the drug release from these systems (Miranda et al., 2006). Therefore, the percentage of the drug release and the amount of the drug release normalized with the volumetric fraction of the drug (q/F_{KCl}) have been plotted vs. the square root of the time to estimate the excipient percolation threshold on binary and ternary matrices (Fig. 7a and b). Different groups of lines clearly different can be observed. The groups of lines show important changes: (1) an important change can be appreciated between the batches 11 and 14, which corresponds to HPMC percolation

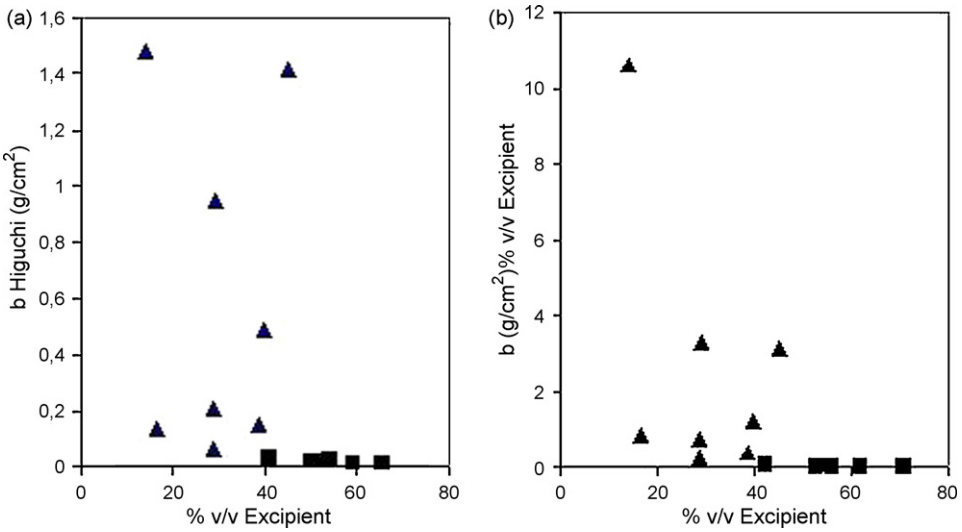

Fig. 6. (▲) High values of Higuchi's slope and (■) low values of Higuchi's slope for the binary and ternary hydrophilic matrix systems elaborated with KCl–HPMC–NaCMC. (a) Higuchi's slope vs. percentage of the excipient for the binary and ternary hydrophilic matrix systems. (b) Normalized Higuchi's slope vs. percentage of the excipient volumetric fraction for the binary and ternary hydrophilic matrix systems.

threshold for the binary systems, (2) the change observed between batches 3 and 8 corresponding to NaCMC percolation threshold for the binary systems and (3) for the ternary systems, it could be observed a change between the batches 4 (60%, w/w KCl, 10%, w/w HPMC, 30%, w/w NaCMC), 5 (60%, w/w KCl, 20% w/w, HPMC, 20% w/w, NaCMC) and 6 (60%, w/w KCl, 30%, w/w HPMC, 10%, w/w NaCMC) respective to the batches 9 (70%, w/w KCl, 10%, w/w HPMC, 20%, w/w NaCMC) or 10 (70%, w/w KCl, 20%, w/w HPMC, 10%, w/w NaCMC). The regressions presented have the same slope as the results presented from the study of the drug release profiles and in agreement with the results mentioned in previous sections. Therefore, the formation of the excipient critical barrier could be appreciated on the drug release properties and located as is shown in Fig. 8.

Scanning electron microscopy (SEM) was employed as an auxiliary technique, in order to study the excipient and drug particles in the matrices. Fig. 9 shows two SEM micrographs corresponding to the tablet side facing, 60% (w/w) and 70% (w/w) of drug, using the BSE detector at the same magnification.

As an example, it were examined two batches, batches 5 (60%, w/w KCl–20%, w/w HPMC–20% NaCMC) and 9 (70%, w/w KCl–10%, w/w HPMC–20%, w/w NaCMC), which are located above and below the excipient critical barrier. In the ternary system containing 60% (w/w) KCl (Fig. 9a) an infinite cluster can be observed. The excipients particles (dark gray particles) begin to form a connective network from the left to the right and from the top to the bottom of the micrograph. In the matrix containing 70% (w/w) of KCl (Fig. 9b), the particles of the excipients (dark gray particles) seem to form isolated groups in the system.

Therefore, according to the different methods employed, a critical barrier is observed in the hydrophilic matrix systems studied.

As it was previously mentioned in Section 1, a combined percolation threshold was reported in ternary inert matrices by Caraballo (Caraballo et al., 1996). It corresponds to the maximum probability of appearance of a percolating cluster composed by the sum of two

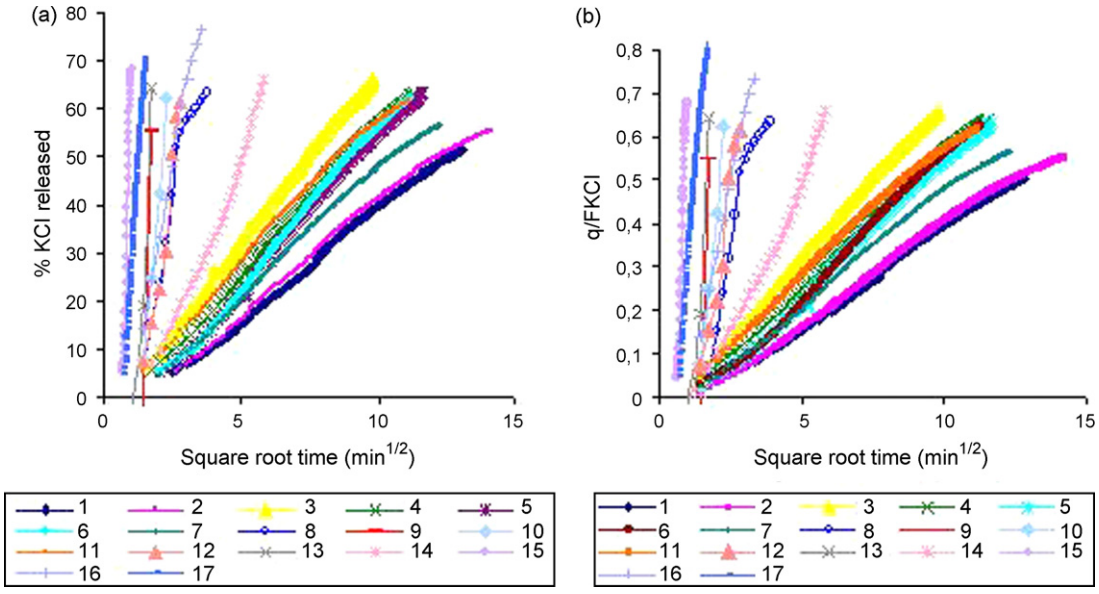

Fig. 7. (a) Percentage of drug released vs. square root of the time for the hydrophilic matrix systems. (b) Amount of drug released/volumetric fraction of the drug vs. square root of the time for the hydrophilic matrix systems.

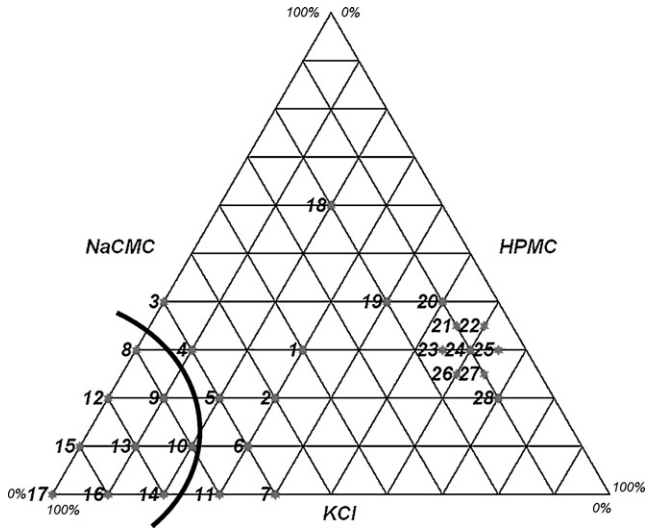

Fig. 8. ⋆ Composition % (w/w) of the studied batches of KCl and the critical barrier.

substances, i.e., the behaviour of the matrices was dependent on the value of the sum of the concentrations of these two substances. Nevertheless, it was independent on the individual concentration of each one of these substances.

In order to study the applicability of these concepts to the hydrophilic matrices studied in the present work, the obtained data are showed on a response surface plot using the program Matlab. Fig. 10 shows the evolution of one of the studied kinetic parameters, the Higuchi's slope, *b*, as a function of the volumetric fraction of both excipients (HPMC and NaCMC) at time zero. The batches plotted in Fig. 10 are the ternary hydrophilic matrix systems containing 40–80% (w/w) KCl.

In order to analyze this figure, two opposite patterns can be considered:

Pattern 1: ◺ Interchangeable excipients. This hypothesis supposes a full collaboration of both excipients in order to create the gel layer controlling the drug release from the hydrophilic matrices. In this case the concentrations of the hydrophilic polymers HPMC and NaCMC will be fully additive, i.e., the value of the Higuchi's slope, *b*, will be the same whenever the sum of the concentrations of both excipients will be the same, independent of the individual concentration of each one of the excipients. For example, we could expect the same release behaviour for a matrix containing

Table 2
% (v/v) of the components KCl, HPMC and NaCMC and Higuchi's slope values obtained for the ternary hydrophilic matrix systems.

Batch	% (v/v) KCl	% v/v HPMC	% v/v NaCMC	Higuchi slope "*b*" (g/cm^2)
1	29.2	33.8	31.5	0.013
2	39.4	36.5	22.7	0.015
4	53.9	13.8	38.8	0.022
5	54.3	27.9	26.0	0.022
6	53.5	41.3	12.8	0.024
9	62.5	13.8	25.7	1.416
10	61.3	27.0	12.6	0.491
13	73.3	14.1	13.2	0.952

10% HPMC + 20 NaCMC than for another containing 25% HPMC + 5% NaCMC.

In case that the obtained data would follow this pattern, the color lines in Fig. 10 will show that the critical barrier is a straight line forming a triangle together with the *X* and *Y*-axes.

Pattern 2: □ Independent excipients. This hypothesis supposes that at least the critical concentration of one of the excipients (HPMC or NaCMC) has to be reached in order to obtain the gel layer controlling the drug release, independently of the concentration of the other excipient. In this case, the critical barrier would be formed by two straight lines with an angle of 90°. They will form a square with the *X* and *Y*-axes.

Looking at Fig. 10, we can observe for example the behaviour of batches 9 and 10. These batches are near to the critical points. Despite the total polymer content is close to 39.5% (v/v) for both batches (see Table 2), their Higuchi's slope values are 1.416 and 0.49 respectively. Therefore, matrices having similar total polymer content, show very different drug release mechanism. These data do not fulfil the hypothesis depicted in Pattern 1, indicating that the excipients are not interchangeable.

In order to check the second hypothesis, which we have named by similar HPMC concentrations (27.9% and 27.0% respectively), the value of the Higuchi's slope is more than 22 times higher for batch 10 (see Table 2). Therefore we can affirm that the release behaviour of the matrices with the same amount of one of the polymers as Pattern 2, we can compare for example the batches 5 and 10. Despite they contain 27% (v/v), is not independent of the concentration of the other polymer.

Having a look to Fig. 10, it can observed that the isolines show an intermediate behaviour between the triangle corresponding to Pattern 1 and the square corresponding to Pattern 2. This confirms the previous results, indicating that HPMC and NaCMC show an intermediate collaboration between them in order to establish

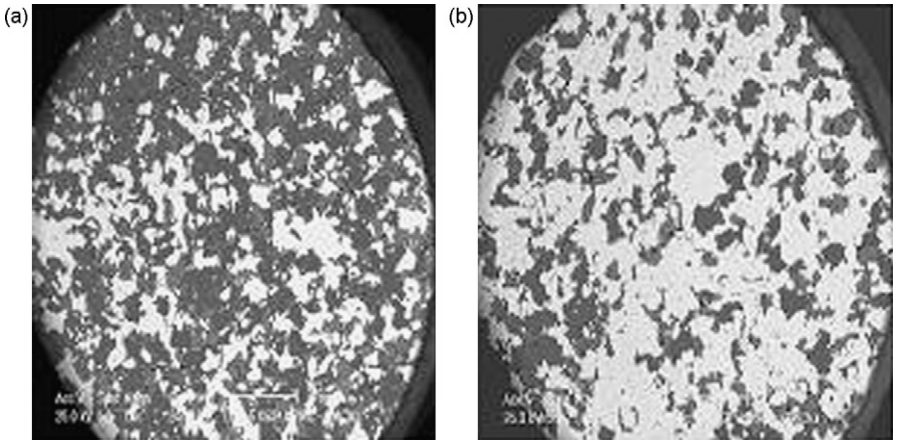

Fig. 9. SEM micrographs corresponding to the bottom side of the matrices, using a backscattering electrons (BSE) detector. The light gray particles correspond to KCl and the dark gray particles to the excipients HPMC and NaCMC. (a) Batch 5, matrices containing 60% (w/w) KCl–20% (w/w) HPMC–20% NaCMC. (b) Batch 9, matrices containing 70% (w/w) KCl–10% (w/w) HPMC–20% NaCMC.

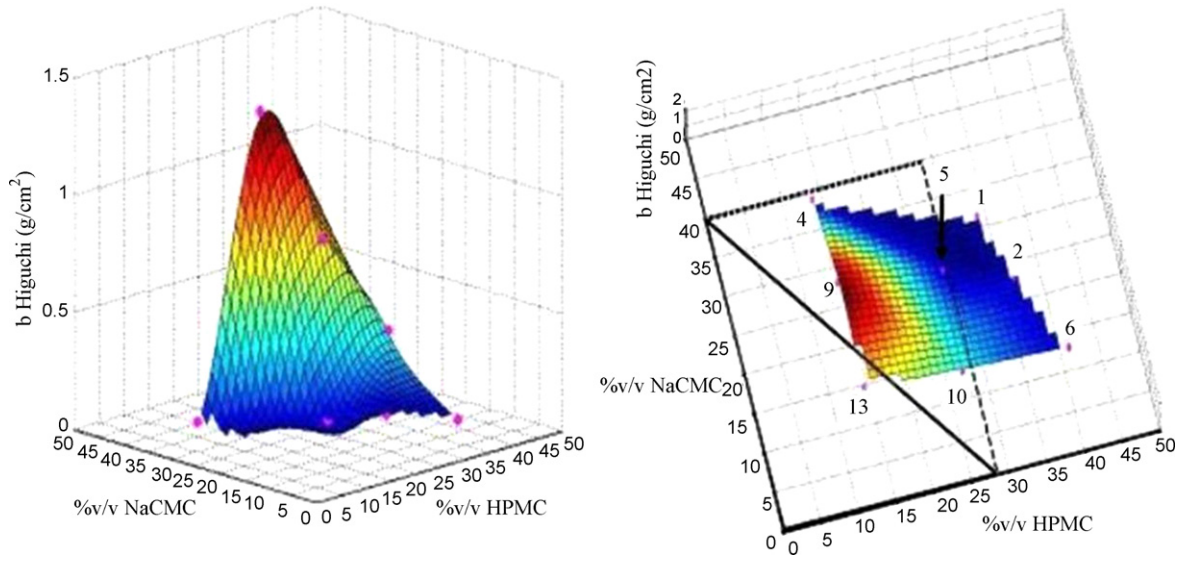

Fig. 10. Higuchi's slope vs. percentage of the both excipient volumetric fraction for the ternary hydrophilic matrix systems 1, 2, 4–6, 9, 10, 13.

the gel layer controlling the drug release. A full collaboration does not exist, so their concentrations cannot be considered as additive concentrations, in order to reach the critical range. Nevertheless this collaboration cannot be neglected, so the excipients cannot be considered as acting independently one of the other.

4. Conclusions

Applying the concepts of the percolation theory to binary KCl–HPMC and KCl–NaCMC hydrophilic matrices, the existence of critical points related to the excipient percolation threshold has been confirmed. The excipient percolation threshold for these binary hydrophilic matrices can be located between 29 and 41% (v/v) of HPMC and between 39 and 54% (v/v) of NaCMC, respectively.

These concepts have been applied for the first time to ternary hydrophilic matrices, showing the existence of a critical barrier between 54 and 61% (v/v) KCl (60–70%, w/w of KCl). HPMC and NaCMC do not have a combined percolation threshold in the studied ternary systems. Nevertheless, they show a partial collaboration between them in order to establish the gel layer. A possible explanation can be the existence of interactions between chemical groups of the polymers that avoids a complete collaboration between them.

The knowledge of this critical barrier will be useful in order to optimize the design of the ternary hydrophilic matrix systems. On the other hand it would be interesting to investigate whether this behaviour would be general for these important pharmaceutical excipients.

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