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Study of critical points of drugs with different solubilities in hydrophilic matrices

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ABSTRACT

Hydrophilic matrices are one of the most popular controlled release systems in the World. It is well known that drug solubility increases the osmotic stress in hydrophilic matrices, resulting in higher swelling through the creation of microcavities and influencing the release rate. Drug solubility also affects the drug release mechanism, favouring the diffusion against the erosion mechanism. Nevertheless it has not been studied whether this can modify the critical points of the hydrophilic matrices.

The objective of the present work is to estimate the excipient percolation threshold in HPMC K4M hydrophilic matrices containing acetaminophen, theophiline and ranitidine·HCl, and to study the influence of the drug solubility on the excipient percolation threshold.

Dissolution assays were performed using the paddle method. Water uptake was examined using the modified Enslin apparatus. In order to estimate the excipient percolation threshold, the behaviour of the kinetic parameters versus the excipient volume fraction plus initial porosity, was studied.

The excipient percolation thresholds were situated between 24.8–25.8, 14.7–18.4 and around 31.2% (v/v) HPMC in theophiline, ranitidine·HCl and acetaminophen matrices, respectively.

On the other hand, using these and some previously reported values no relation has been found between drug solubility and excipient percolation threshold in hydrophilic matrices.

1. Introduction

Hydrophilic matrix tablets are among the most popular orally administered controlled release systems. Cellulose ethers are commonly employed swellable matrix polymers.

Polymer swelling, drug dissolution and matrix erosion are the phenomena leading to the drug release from swellable matrices, either on a macroscopic or on a molecular level (Hogan, 1989; Colombo et al., 1996; Bettini et al., 2001; Pham and Lee, 1994). Therefore, the basic mechanism of drug release such systems is governed by swelling/erosion and dissolution/diffusion. Thus, in swellable matrix tablets three fronts could be expected: the swelling front (the boundary between the still glassy polymer and its rubbery state), the diffusion front (the boundary in the gel layer between the solid, as yet undissolved, drug and the dissolved drug) and the erosion front the boundary between the matrix and the dissolution medium (Colombo et al., 1995; Bettini et al., 1994).

The influence of several factors on the properties and dissolution performance of the matrix system has been investigated. These factors include polymer content, substitution type and viscosity of the polymer, solubility and particle size of the drug, presence of other polymers and excipients, surface area and shape of the matrix tablets and process parameters such as method of incorporating raw materials, blending time, compression force, and conditions for dissolution studies (Sia Heng et al., 2001).

A number of publications have reported effect of drug solubility on the release from hydrophilic, monolithic matrices. Many authors have concluded that water-soluble drugs are released primarily by diffusion of dissolved drug molecules across the gel layer, while poorly water-soluble drugs are released predominantly by erosion mechanism (Ford et al., 1987; Ranga Roa et al., 1988; Kim, 1998; Velasco et al., 1999; Zuleger and Lippold, 2001).

The rate and amount of drug released from swellable matrices was dependent not only on drug dissolution but also on solid drug translocation in gel due to polymer swelling. In fact, as drug solubility decreased, the slower drug dissolution rate in the gel, reduced the swelling and the entanglement of the polymer chains and affected the resistance of gel towards erosion. As a consequence, the matrix became more erodible (Bettini et al., 2001).

On the other hand, the swelling/erosion process of polymer matrix controls the drug release behaviour. It has been reported that polymer swelling occurs as a result of osmotic stress exerted at the advancing glassy core/rubbery gel. When drug solubility increases, the enhanced osmotic stress accelerates water penetration into the matrix, resulting in a higher degree of polymer swelling and formation of more microcavities. Furthermore, the diffusivity of the drug in swelled gel increases when the solubility increases (Yang and Fassihi, 1997).

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Table 1
Dosage, drug particle size and drug true density for the hydrophilic matrices prepared with acetaminophen/theophiline/ranitidine·HCl as drug and HPMC K4M 150–200 μm as excipient.

Batch	Dosage (mg)	Drug particle size (μm)	Drug true density (g/cm^3)
Acetaminophen (A)	300	335.13 ± 107.53	1.496
Theophiline (T)	400	224.33 ± 90.91	1.802
Ranitidine·HCl (R)	300	208.24 ± 112.36	1.464

Percolation theory has been applied in the pharmaceutical field since 1987. It is a statistical theory that studies disordered or chaotic system where the components are randomly distributed in a lattice (Caraballo et al., 1993, 1994, 1996a,b; Leuenberger et al., 1987; Holman and Leuenberger, 1988; Bonny and Leuenberger, 1991). A cluster is defined as a group of neighbouring occupied sites in the lattice, being considered an infinite or percolating cluster when it extends from on side to the rest of the sides of the lattice, i.e. percolates the whole system (Stauffer and Aharony, 1992).

According to these ideas, a tablet, in its simplest approach, is regarded as a heterogeneous binary system formed by the active principle and an inert excipient. As a function of their relative volume ratios, one or both components constitute a percolating 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 at which there is the maximum probability of appearance of this continuous phase, is the percolation threshold (p_c) and represents a critical value for each system, close to which important changes can be observed, such as change in the release mechanism of the active agent or modification of the tablet structure (monolith vs. a desegregating device, etc.) (Stauffer and Aharony, 1992).

Our research group has employed widely the percolation theory in order to describe controlled release inert matrix systems (Caraballo et al., 1993, 1994; Melgoza et al., 1998, 2001; Millán et al., 1998; Espina-Márquez and Caraballo, 2004).

In recent works, we have applied, for the first time, the percolation theory to study the release and hydration rate of hydrophilic matrices. In order to control the release of a drug from a hydrophilic matrix, a percolating cluster of the polymer particles and pores have to be formed, because the initial porosity of hydrophilic matrices contribute to the establishment of the gel barrier responsible for the release control.

A linear relationship between a component percolation threshold (drug or excipient) and its relative particle size (drug/excipient in the case of the drug percolation threshold or excipient/drug in the case of the excipient percolation threshold) has been found. This relationship is valid for different drugs, excipients and systems (inert or hydrophilic matrix systems).

This finding can be of interest for the scientific community and supports the use of the percolation threshold (drug or excipient) as a preformulation parameter which can improve the pharmaceutical dosage form design.

Therefore, it is well known that drug solubility increases the osmotic stress in hydrophilic matrices, resulting in higher swelling

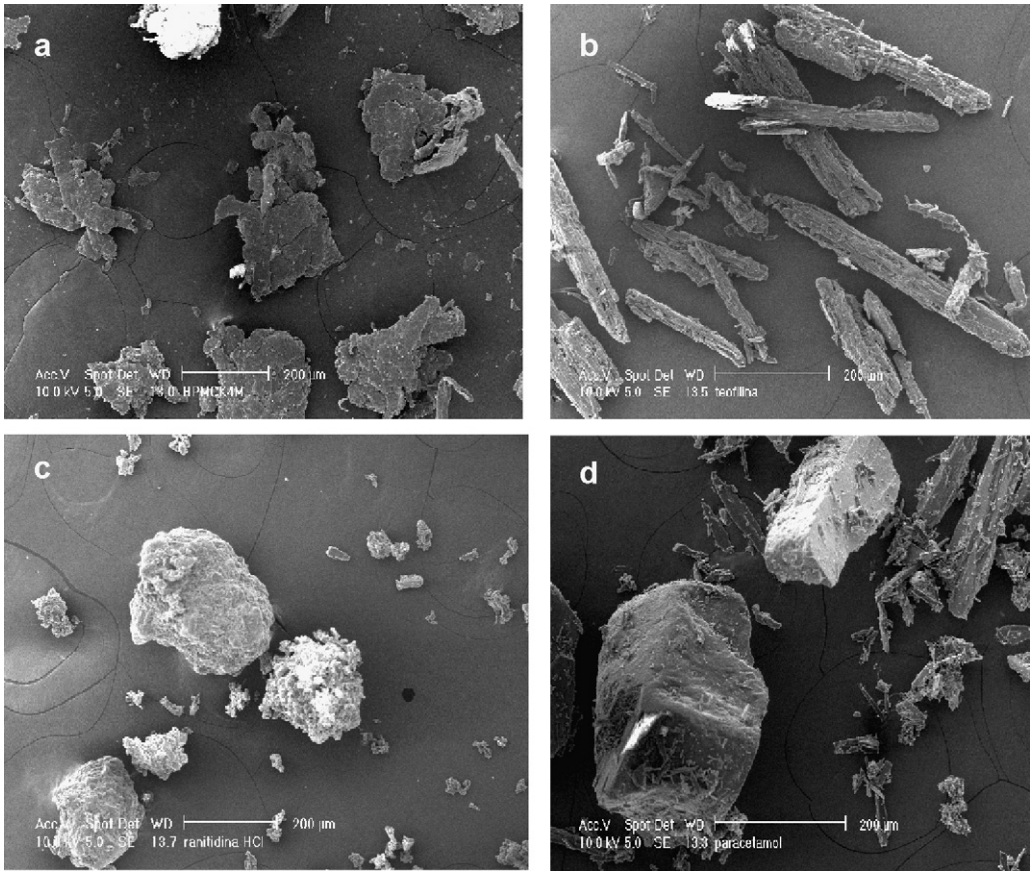

Fig. 1. SEM micrographs showing the particles before compaction: (a) HPMC K4M; (b) theophiline; (c) ranitidine·HCl; (d) acetaminophen.

Table 2
Composition, initial porosity and % (v/v) HPMC plus initial porosity for the hydrophilic matrices prepared with acetaminophen/theophiline/ranitidine·HCl as drug and HPMC K4M 150–200 μm as excipient.

Batches	% (w/w) drug	% (w/w) HPMC K4M	% (v/v) HPMC K4M	Initial porosity (ε)	% (v/v) HPMC plus initial porosity
Acetaminophen (A)					
A1	95	5	4.59	17.91	22.50
A2	90	10	8.93	19.79	28.72
A3	80	20	19.63	10.73	30.36
A4	70	30	29.13	10.61	39.74
A5	60	40	38.13	11.12	49.25
Theophiline (T)					
T1	95	5	5.66	15.05	20.71
T2	90	10	11.52	12.13	23.65
T3	80	20	22.39	11.66	34.05
T4	70	30	32.5	11.65	44.15
T5	60	40	40.33	15.12	55.45
Ranitidine·HCl (R)					
R1	95	5	5.40	0	5.40
R2	90	10	10.65	2.38	13.03
R3	80	20	19.86	8.13	27.99
R4	70	30	30.11	6.33	36.44
R5	60	40	38.41	9.34	47.75

through the creation of microcavities and influencing the release rate. It is also known that drug solubility affects the drug release mechanism, favouring the diffusion against the erosion mechanism. Nevertheless it has not been studied whether this can modify the critical points of the hydrophilic matrices.

The objective of the present work is to estimate the critical points of the excipient in HPMC K4M matrices containing acetaminophen, ranitidine·HCl and theophiline, as well as to study the influence of the drug solubility on the excipient percolation threshold, in order to rationalize the design of these controlled release systems.

2. Materials and methods

2.1. Materials

Hydroxypropylmethyl cellulose (HPMC, Methocel K4M) was supplied by Colorcon S.A., Spain. Theophylline anhydrous was purchased from Roig Farma, Tarrasa, Barcelona; acetaminophen from Roig Farma, Tarrasa, Barcelona and ranitidine·HCl from Acofarma, Tarrasa, Barcelona.

2.2. Tablet manufacturing

The polymer was sieved (Retsch type Vibro) and the 150–200 μm granulometric fraction was employed. The drug was not sieved, i.e. the whole drug powder was employed. Nevertheless, the mean drug particle size was measured by sieving (see Table 1).

A scanning electron microscope (SEM) (Philips type XL-30) with a back scattering electrons detector (BSE) was employed in order to study the excipient and drug particles before compaction (Fig. 1).

The components were mixed using a Turbula mixer (Basel, Switzerland).

Binary mixtures were prepared with varying drug contents (60, 70, 80, 90 and 95%) keeping constant the drug and excipient particle size. Table 2 shows the composition of the studied batches. The mixtures were compressed on an eccentric machine (Bonals A-300) without any further excipient. Cylindrical tablets with different dosage (Table 1) and a diameter of 12 mm were prepared at the maximum compression force accepted by the formulations.

2.3. Drug solubility

The drug solubilities are shown in Table 3. The equilibrium solubility water values of acyclovir, theophiline and acetaminophen has been calculated in purified water. Excess of drug was added in aqueous medium. Then, the samples were shaken continuously in a water bath (Selecta Rotaterm) maintained at 37 °C for seven days. After this time, the samples were filtered through 0.45 μm pore size Millipore filters. The concentration of the filtrates was measured by UV-spectroscopy by triplicate, after the necessary dilutions.

Ranitidine·HCl, lobenzarit disodium and KCl solubility has been taken from the literature (Miranda et al., 2006a; Mirmehrabi et al., 2004).

2.4. Drug and excipient true density

The true density of the drugs has been calculated using an air pycnometer (Quantachrome type Stereopynometer spy-3). The results obtained are shown in Table 1. The true density of HPMC K4M, 1.316 g/cm^3, has been taken from the literature (Pharmaceutical Press and American Pharmaceutical Association, 2003).

2.5. Dissolution profiles

Dissolution studies were carried out in the USP 2 (paddle) as described in USP 26th (Turu Grau, type D-6) at 100 r.p.m. and 900 ml of distilled water as dissolution medium at 37 ± 0.5 °C, during 12 h.

The drug release was determined by UV-spectroscopy at 272 nm for theophiline and 244 nm for acetaminophen. The ranitidine·HCl release was detected by the increase in conductance of the dissolution medium using a Crison micro CM-2201 digital conductivitymeter linked to a chart recorder and a personal computer.

Table 3
Drug solubility obtained at 37 °C.

Drugs	Solubility (mg/ml)
Theophiline	11.32
Acetaminophen	27.39
Ranitidine·HCl	660
Acyclovir	2.5
Lobenzarit disodium	42
KCl	357

Dissolution studies were performed in three replicates for each batch of tablets.

The release kinetics mechanism was analysed according to the equations of zero order (Eq. (1)), Higuchi (1963) (Eq. (2)), Korsmeyer et al. (1983) (Eq. (3)) and Peppas and Sahlin (1989) (Eq. (4)).

$$\frac{Q_t}{Q_\infty} = k_0 \cdot t \quad (1)$$

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

$$\frac{Q_t}{Q_\infty} = k \cdot t^n \quad (3)$$

where Q_t/Q_∞ is the fraction of drug released; k_0, k_H and k are kinetic constants; n is a exponent which depends on the release mechanism and on the shape of the swelling device tested (Ritger and Peppas, 1987). For thin slabs, values of $n = 0.5$ indicate Fickian release, values of $0.5 < n < 1.0$ indicate an anomalous (non-Fickian or coupled diffusion/relaxation) drug release, whereas values of $n = 1.0$ indicate a case II (relaxation-erosion controlled) drug release.

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

where Q_t/Q_∞ is the fraction of drug released; k_d is the diffusional constant; k_r is the relaxational constant and m is the diffusional exponent which depends on the geometrical shape of the releasing device through its aspect ratio (Peppas and Sahlin, 1989).

2.6. Water uptake studies

The rate of dissolution medium uptake by the polymer was examined using the 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 dynamics of the water uptake was expressed as the weight gain of the swelled matrix, in g penetrant/g dry polymer. The Davidson and Peppas (1986) (Eq. (5)) model was applied to these data to study the mechanism and the rate of water uptake.

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

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 (Davidson and Peppas, 1986).

2.7. Estimation of the percolation threshold

In order to estimate the percolation thresholds, the behaviour of the kinetic parameters (Higuchi's slope "$k_{H''}$, normalised Higuchi's slope "k_H/% (v/v) of HPMC", relaxational constant of Peppas and Sahlin "$k_{r''}$) with respect to the volumetric fraction plus initial porosity (see Table 2) of each component at time zero, was studied (Miranda et al., 2007).

The initial porosity was calculated using the following equation:

$$\varepsilon = V_T - \left(\frac{w\ \%\text{drug}}{\rho_d}\right) - \left(\frac{w\,\%\text{excipient}}{\rho_e}\right) \quad (6)$$

where ε is the initial porosity; V_T is the total volume; w is tablet weight; ρ_d the drug density and ρ_e the excipient density.

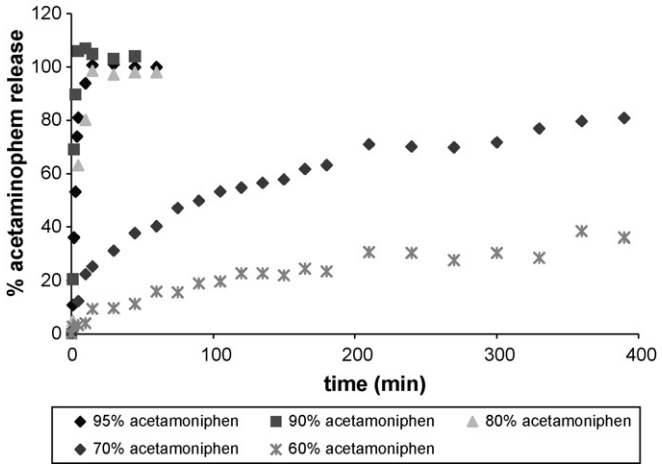

Fig. 2. Percent release profiles of acetaminophen matrix tablets with a total drug content of 95, 90, 80, 70 and 60% prepared with acetaminophen/HPMC K4M (150–200 μm).

According to the fundamental equation of percolation theory (Bonny and Leuenberger, 1991), if these parameters behave as critical properties, we can expect that

$$X \propto S \times (p - p_c)^q \quad (7)$$

where X is the studied property; S is a constant; p is the volumetric fraction of the component, p_c is the percolation threshold, $(p - p_c)$ is the distance to the percolation threshold and q is a critical exponent.

The kinetic parameters studied show a non-linear behaviour as a function of the volumetric fraction of the excipient.

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 (Espina-Márquez and Caraballo, 2004; Miranda et al., 2006a, 2007).

3. Results and discussion

3.1. Kinetics of the in vitro drug release

Figs. 2–4 illustrate the dissolution profiles of acetaminophen, theophiline and ranitidine·HCl, respectively. These figures show that lower excipient loads result in faster release rates. Furthermore, important changes in the release rate as a function of the

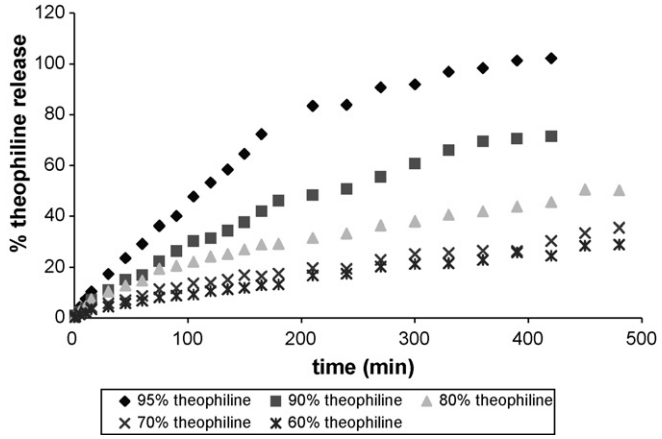

Fig. 3. Percent release profiles of theophiline matrix tablets with a total drug content of 95, 90, 80, 70 and 60% prepared with theophiline/HPMC K4M (150–200 μm).

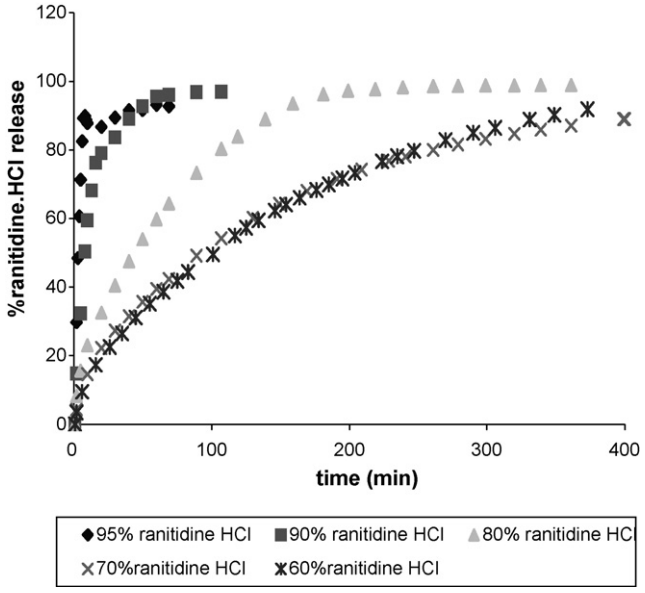

Fig. 4. Percent release profiles of ranitidine·HCl matrix tablets with a total drug content of 95, 90, 80, 70 and 60% prepared with ranitidine·HCl/HPMC K4M (150–200 μm).

polymer load can also be observed in the figures. These changes are better observed in the kinetic parameters calculated from the release profiles (Table 4). These critical points can represent the transition between fast and controlled drug release. The existence of this critical point can be attributed to the excipient percolation threshold.

Acetaminophen matrices (Fig. 2, Table 4) show very clearly the two different behaviours previously mentioned. In the first behaviour, the release was controlled by the fully hydrated gel layer. In these systems, the diffusion of the drug from the hydrophilic gel structure has an important influence on the drug release. This is indicated by different facts: the better fit of the drug release kinetics to the Higuchi equation than to the zero order equation, the n values of Korsmeyer–Peppas equation being close to 0.5 and the higher value of k_d with respect to k_r in Peppas–Sahiln equation. After the transition point, a second behaviour can be observed; the tablet allows the free dissolution of the drug directly in contact with the dissolution medium. A sufficient gel layer is not established from the first moment, leading to uncontrolled drug release. As a consequence, the Higuchi release rate increases from 4.30 to 35.44% $min^{-1/2}$.

Therefore, the results of the kinetic analysis as well as the visual observation of the release profile indicate a critical point in the release rate and mechanism between matrices containing 70 and 80% (w/w) of drug (20–30%, w/w of excipient).

The study of the release profiles of the theophiline containing matrices (Fig. 3, Table 4) seem to indicate a critical point between 10 and 20% (w/w) of HPMC K4M. Although, in this case, the data are less clear than in the case of acetaminophen matrices, the Higuchi's slope and the zero order constant, undergo an important increase between matrices containing 80 and 90% (w/w) of drug (10–20%, w/w of excipient).

Finally, the release profiles obtained for hydrophilic matrices formulated with ranitidine·HCl (Fig. 4, Table 4) also show two behaviours in the drug release control. Firstly, tablet containing 90 and 95% (w/w) of drug do not show control of the drug release. Secondly, matrices containing 60 and 70% (w/w) of drug, control the ranitidine·HCl release, whereas, the behaviour of the matrices containing 80% (w/w) of drug, suggest that this batch (20%, w/w of excipient) has been formulated very close to the excipient percolation threshold.

3.2. Water uptake

The obtained water uptake profiles for tablets containing acetaminophen, theophiline and ranitidine·HCl, respectively and HPMC K4M 150–200 μm as excipient, are shown in Figs. 5–7. As it can be observed in these figures, critical points appear in the water uptake profiles in the same range than the previously obtained in release studies (between 80 and 90% (w/w) of theophiline, 80–90% (w/w) of ranitidine·HCl and 70–80% (w/w) of acetaminophen matrices).

The kinetic study performed fitting the water uptake data to the Davidsons and Peppas model, confirms the previous results, showing an important decrease in the swelling constant between matrices formulated before and after the critical point (see Table 5).

3.3. Effect of the drug solubility

HPMC K4M matrix tablets with 70% drug load have been selected to study the effect of the drug solubility because all these batches contain the excipient percolating cluster that is one of the main factors governing the gel-layer formation and consequently, the

Table 4
Kinetic constants k_0, k_H, k, n, k_d and k_r. Values based on Eqs. (1)–(4), calculated in the range of 5–70% drug release for all the batches studied[a].

Batches	% (w/w) drug	Zero order equation		Higuchi equation		Korsmeyer–Peppas equation			Peppas and Sahlin equation		
		k_0	r^2	k_H	r^2	k	n	r^2	k_d	k_r	r^2
A1	95	20.62	0.994	61.89	0.995	14.51	1.182	0.998	−16.5	29.56	0.999
A2	90	34.52	0.947	95.46	0.976	27.97	1.098	0.988	−20.5	46.64	0.990
A3	80	0.815	0.869	35.44	0.951	16.07	0.723	0.973	8.903	7.194	0.970
A4	70	0.247	0.927	4.304	0.987	8.233	0.396	0.999	7.368	−0.112	0.999
A5	60	0.057	0.924	1.806	0.958	2.111	0.479	0.994	2.268	0.025	0.994
T1	95	0.404	0.998	6.516	0.976	0.913	0.850	0.999	0.789	0.566	>0.999
T2	90	0.170	0.976	4.251	0.992	1.124	0.699	0.999	1.800	0.188	0.998
T3	80	0.081	0.966	2.471	0.993	1.539	0.567	0.999	2.134	0.064	0.999
T4	70	0.059	0.985	1.870	0.973	0.492	0.689	0.997	0.847	0.095	0.997
T5	60	0.051	0.991	1.681	0.985	0.307	0.738	0.999	0.486	0.111	0.999
R1	95	13.70	0.981	50.35	0.995	17.32	0.891	0.999	−0.20	0.124	0.998
R2	90	4.835	0.983	25.66	0.994	9.545	0.779	0.999	5.303	5.034	0.999
R3	80	0.698	0.976	8.111	0.999	6.390	0.545	>0.999	7.012	0.311	>0.999
R4	70	0.311	0.964	5.450	0.999	4.518	0.530	>0.999	5.268	0.155	>0.999
R5	60	0.318	0.974	5.576	0.998	5.398	0.488	0.982	4.298	0.289	>0.999

[a] k_0 (% min^{-1}), zero order constant; k_H (% $min^{-1/2}$), Higuchi's slope; k (% min^{-n}), kinetic 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, diffusional exponent that depends on geometric shape of the releasing device through its aspect ratio.

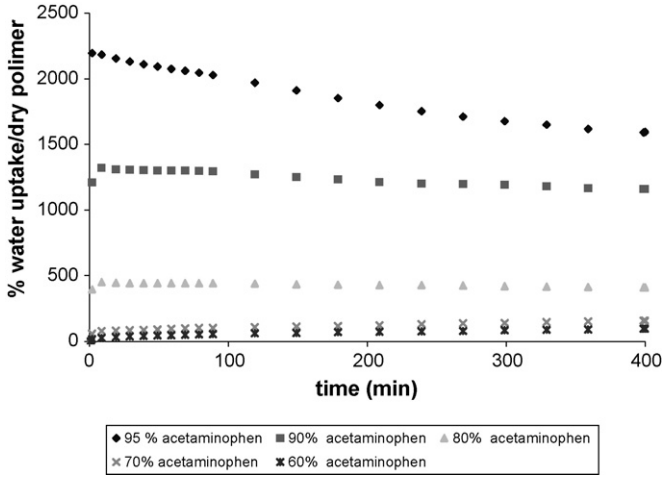

Fig. 5. Water uptake profiles for tablets prepared with acetaminophen/HPMC (150–200 μm).

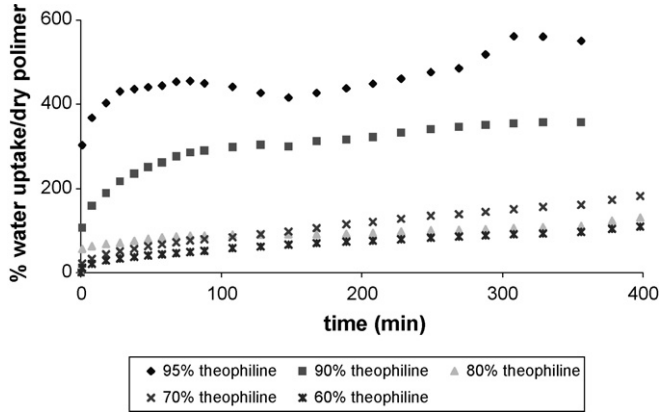

Fig. 6. Water uptake profiles for tablets prepared with theophiline/HPMC (150–200 μm).

drug release control from hydrophilic matrices. In order to study this fact, the data corresponding to hydrophilic matrices studied in previous work of our research group (Fuertes et al., 2006), have been included.

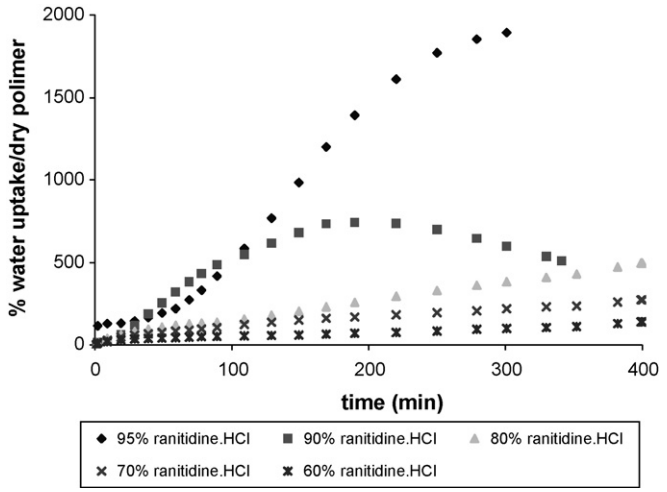

Fig. 7. Water uptake profiles for tablets prepared with ranitidine·HCl/HPMC (150–200 μm).

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

Batches	% (w/w) of drug	k_s	n	r^2
Davidsons and Peppas models				
A1	95	2735.951	−0.084	0.994
A2	90	1524.932	−0.047	0.997
A3	80	463.639	−0.017	0.998
A4	70	26.337	0.302	0.998
A5	60	8.544	0.408	0.999
T1	95	292.732	0.094	0.994
T2	90	116.881	0.194	0.999
T3	80	30.833	0.229	0.993
T4	70	6.136	0.565	0.999
T5	60	5.931	0.485	0.999
R1	95	3.100	1.145	0.993
R2	90	79.592	0.386	0.958
R3	80	7.929	0.674	0.993
R4	70	5.479	0.652	0.999
R5	60	0.696	0.884	0.992

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

There is evidence that the solubility of the drug affects significantly both the release rate and the release mechanism from hydrophilic matrices.

Fig. 8 and Table 6 show how lower drug solubilities result in slower and more linear release profiles. Therefore the main mechanism responsible for the drug release is the matrix erosion. Release of intermediate and highly soluble drugs (acetaminophen and ranitidine·HCl) was faster and purely Fickian (n close to 0.5).

These results are in agreement with the previously found by different authors (Ford et al., 1987; Kim, 1998; Velasco et al., 1999; Zuleger and Lippold, 2001). 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 mechanism. In fact, as drug solubility decreased, the slower drug dissolution rate in the gel layer allowed drug particles to be transported close to the matrix erosion front. The presence of solid particles in the gel reduced the swelling and affected the resistance of the gel towards erosion. As a consequence, the matrix became more erodible (Bettini et al., 2001).

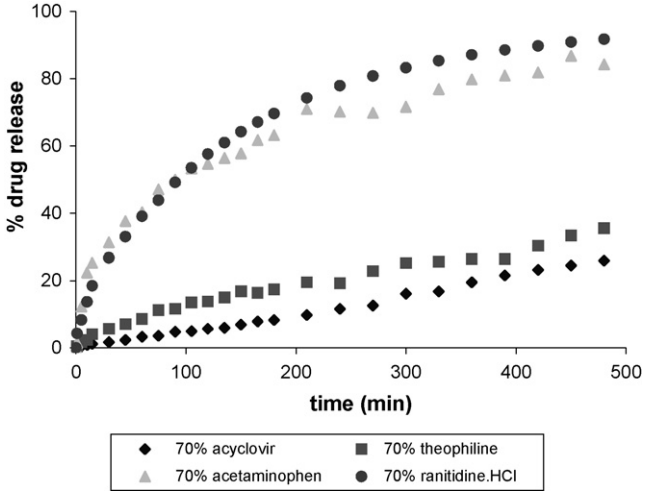

Fig. 8. Percent release profiles of different drugs studied, with a total drug content of 70% (w/w).

Table 6
Kinetic constants k_0, k_H, k; n, k_d and k_r. Values based on Eqs. (1)–(4), calculated in the range of 5–70% drug release for batches containing 70% of drug[a].

Batches	% (w/w) drug	Zero order equation		Higuchi equation		Korsmeyer–Peppas equation			Peppas and Sahlin equation		
		k_0	r^2	k_H	r^2	k	n	r^2	k_d	k_r	r^2
C[b]	2.5	0.057	0.995	1.7683	0.932	0.027	1.114	0.998	−0.81	0.202	0.997
T4	11.3	0.059	0.985	1.870	0.973	0.492	0.689	0.997	0.847	0.095	0.997
A4	22.3	0.247	0.927	4.304	0.987	8.233	0.396	0.999	7.368	−0.11	0.999
R4	660	0.311	0.964	5.450	0.999	4.518	0.530	1	5.268	0.155	1

[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, diffusional exponent that depends on geometric shape of the releasing device through its aspect ratio.
[b] Data corresponding to acyclovir hydrophilic matrices studied in previous work of our research group (Fuertes et al., 2006).

3.4. 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. In hydrophilic matrices the drug threshold is less evident than the excipient threshold which is the main responsible for the control of the drug release (Miranda et al., 2006a,b, 2007; Fuertes et al., 2006).

This research is focussed on the estimation of the critical points of the excipient but not on prediction of the drug transport properties for all polymer concentrations. Taking into account that the excipient percolation threshold is usually situated below 40% of excipient, tablets with polymer concentration up to 40% (w/w) have been prepared.

The excipient percolation threshold expressed as % (v/v) of excipient plus initial porosity (Miranda et al., 2007) was estimated using a graphical method (see Section 2.7). As the percolation theory predicts, the kinetic parameters studied show a non-linear behaviour as a function of the volumetric fraction of the excipient plus initial porosity.

As an example, the results obtained for tablets containing theophiline and HPMC K4M 150–200 μm are shown in Fig. 9. The percolation thresholds for the rest of the batches have been estimated using the same methodology.

As it can be observed in Fig. 9, 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, were situated between 24.8 and 25.8% (v/v) of HPMC in theophiline matrices, 14.7–18.4% (v/v) of HPMC in ranitidine·HCl matrices and around 31.2% (v/v) of HPMC in acetaminophen matrices (see Table 7).

The interpretation on the basics of percolation theory is the following: the percolation threshold defines the edge between two situations (existence of finite or percolating clusters of the component in a disordered system). The knowledge of these values for a particular system provides useful information about the drug release process. Bellow the excipient percolation threshold, the gel layer is not formed from the first moment, leading to a fast drug release process, not controlled by the excipient.

3.5. Study of the influence of the drug solubility on the excipient percolation threshold

In order to study the influence of the drug solubility on the excipient percolation threshold, firstly, the excipient percolation threshold (%, v/v of excipient plus initial porosity) was plotted versus the solubility of the different drug (mg/ml) studied in this paper as well as the data corresponding to hydrophilic matrices studied in previous works of our research group: KCl (Miranda et al., 2006a), lobenzarit disodium (Miranda et al., 2006b) and acyclovir (Fuertes et al., 2006).

As it can be observed in Fig. 10, the studied parameters do not show a clear relationship.

Previous work of our research group have shown that there is a linear dependence of the percolation threshold of one component

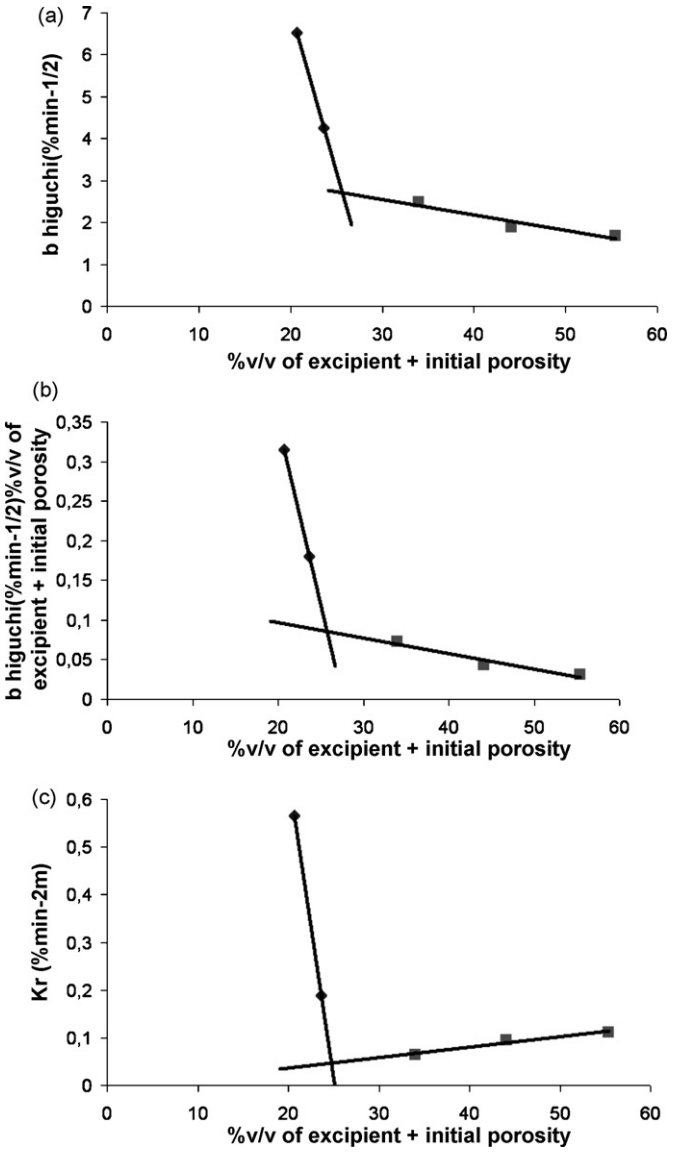

Fig. 9. (a) Slope of Higuchi, (b) slope of Higuchi normalized, (c) relaxational constant of Peppas–Sahlin versus percentage of the excipient volumetric fraction plus initial porosity for batch T (theophiline and 150–200 μm HPMC K4M).

Table 7
The values of the excipient percolation thresholds for all the batches studied, according to the kinetic parameters used.

Batches	Kinetic parameters	Equations	r^2	Point of the intersection
A	Higuchi's slope (% $min^{-1/2}$)	$Y_1 = -36.458x + 1142.6$	0.9999	$X = 31.16$
		$Y_2 = -0.2625x + 14.737$	0.9999	
	Higuchi's slope (% $min^{-1/2}$)/% (v/v) HPMC	The regressions could not be performed		
	Relaxational constant k_r (% min^{-2m})	The regressions could not be performed		
T	Higuchi's slope (% $min^{-1/2}$)	$Y_1 = -0.6366x + 3.6371$	0.8986	$X = 25.83$
		$Y_2 = -0.7716x + 22.50$	0.9999	
	Higuchi's slope (% $min^{-1/2}$)/% (v/v) HPMC	$Y_1 = -0.0020x + 0.356$	0.9260	$X = 25.74$
		$Y_2 = -0.0459x + 1.2659$	0.9999	
	Relaxational constant k_r (% min^{-2m})	$Y_1 = 0.0022x - 0.0072$	0.9547	$X = 24.75$
		$Y_2 = -0.1287x + 3.2326$	0.9999	
R	Higuchi's slope (% $min^{-1/2}$)	$Y_1 = -3.2343x + 67.83$	0.9999	$X = 18.4$
		$Y_2 = -0.0971x + 10.097$	0.8088	
	Higuchi's slope (% $min^{-1/2}$)/% (v/v) HPMC	$Y_1 = -0.9626x + 14.519$	0.9999	$X = 14.74$
		$Y_2 = -0.0057x + 0.4054$	0.8484	
	Relaxational constant k_r (% min^{-2m})	The regressions could not be performed		

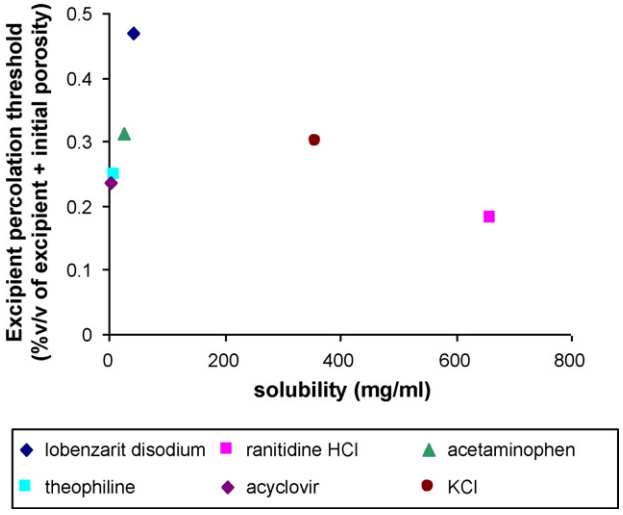

Fig. 10. Excipient percolation thresholds (expressed as %, v/v HPMC + initial porosity) versus the drug solubility in matrices containing acyclovir, theophiline, ranitidine HCl, acetaminophen, lobenzarit disodium and KCl.

on the relative particle size of this component (Millán et al., 1998; Fuertes et al., 2006).

In order to correct the influence of the different relative particle size studied, the values of the excipient percolation threshold have been divided by the excipient relative particle size. The obtained results have been plotted against the drug solubility (see Fig. 11). Even after this correction has been done, the obtained percolation thresholds are not related to the drug solubility. As it can be observed in Fig. 11, very different corrected percolation thresholds have been obtained for drugs having very similar water solubilities.

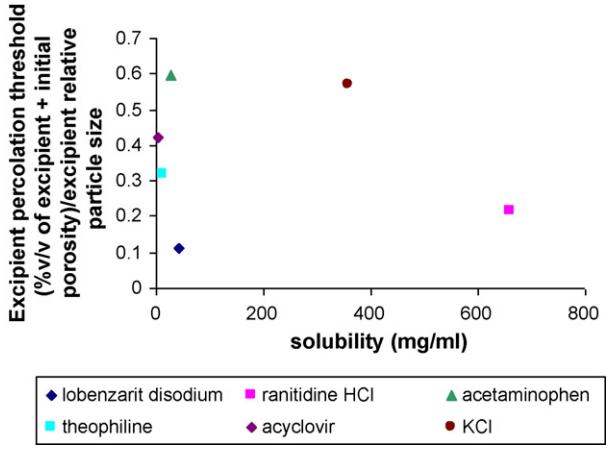

Fig. 11. Excipient percolation thresholds (expressed as %, v/v HPMC + initial porosity)/HPMC relative particle size versus the drug solubility in matrices containing acyclovir, theophiline, ranitidine·HCl, acetaminophen, lobenzarit disodium and KCl.

4. Conclusions

The critical points of the excipient have been estimated in theophilline, acetaminophen and ranitidine·HCl, hydrophilic matrices, based on their drug release and water uptake behaviour.

The knowledge of the percolation threshold of the components of the matrix formulations, especially of the excipient, in the case of hydrophilic matrices, contributes to improve their design.

Even using drugs with very different water solubilities, the excipient percolation threshold has been found to be independent on the solubility of the drug.

This result encourages the use of the excipient percolation threshold as a preformulation parameter, independent on the drug solubility, in order to rationalize the formulation of hydrophilic matrix systems, according to the guidelines of the regulatory authorities concerning Science-Based Formulation and Quality by Design.

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