Available online at www.sciencedirect.com
SCIENCE DIRECT
International Journal of Pharmaceutics 311 (2006) 75–81
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Study of the critical points of HPMC hydrophilic matrices for controlled drug delivery

Antonia Miranda *, Mónica Millán, Isidoro Caraballo

Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Seville, 41012 Seville, Spain

Received 27 July 2005; received in revised form 10 November 2005; accepted 9 December 2005
Available online 30 January 2006

Abstract

The knowledge of the percolation thresholds of a system results in a clear improvement of the design of controlled release dosage forms such as inert matrices. Despite hydrophilic matrices are one of the most used controlled delivery systems in the world, but actuality, the mechanisms of drug release from these systems continue to be a matter of debate nowadays. The objective of the present paper is to apply the percolation theory to study the release and hydration rate of hydrophilic matrices. Matrix tablets have been prepared using KCl as a drug model and HPMC K4M as matrix-forming material, employing five different excipient/drug particle size ratios (ranging from 0.42 to 2.33). The formulations studied containing a drug loading in the range of 20–90% (w/w). Dissolution studies were carried out using the paddle method and the water uptake measurements were performed using a modified Enslin apparatus. In order to estimate the percolation threshold, the behaviour of the kinetic parameters with respect to the volumetric fraction of each component at time zero, was studied. The percolation theory has been applied for the first time to the study of matrix type controlled delivery systems. The application of this theory allowed to explain changes in the release and hydration kinetics of these matrices. The critical points observed in dissolution and water uptake studies can be attributed to the excipient percolation threshold, being this threshold one of the main factors governing the gel layer formation and consequently, the drug release control from hydrophilic matrices.

Keywords: Gel layer; HPMC; Swelling; Percolation theory; Percolation threshold

1. Introduction

The hydrophilic matrices are one of the most used controlled delivery systems in the world, due to the simple technology and low cost. Its study is a difficult task due to its complex and disordered structure. A number of publications have reported studies about the mechanisms of drug release from hydrophilic matrices. Nevertheless, nowadays, the mechanisms of drug release from these systems continue to be a matter of debate (Ford et al., 1985a,b,c; Lee and Peppas, 1987; Bettini et al., 1994, 1997, 1998; Colombo et al., 1995, 2000; Siepmann et al., 1999, 2002; Siepmann and Peppas, 2000).

During the swelling process of the matrices prepared with buflomedil pyridoxal phosphate/HPMC K4M, Colombo et al. (1995), identified a "swelling front" that clearly separates the rubbery region from the glassy region and a second front, the "erosion front", which separates the matrix from the solvent. In addition, a drug diffusion front located between the swelling and erosion fronts and constituting the boundary separating solid from dissolved drug, was identified. A synchronization of the movement of these fronts has been shown to be responsible for the zero-order drug release from hydrophilic matrices (Pham and Lee, 1994).

Our research group is employing the percolation theory, a theory developed for the study of disordered media, in order to describe solid forms, in concrete controlled release inert matrix systems (Caraballo et al., 1993, 1996a,b, 2000; Millán et al., 1998; Melgoza et al., 1998, 2001; Espina-Márquez and Caraballo, 2004).

The percolation theory is a statistical theory that studies disordered or chaotic systems where the components are randomly distributed in a lattice. This theory has wide application in many scientific disciplines and was introduced by Leuenberger et al. in the pharmaceutical field in 1987 to improve the characterization of solid dosage forms (Caraballo et al., 1993,

* Corresponding author. Tel.: +34 954556136; fax: +34 954556726.
E-mail address: amirandal@us.es (A. Miranda).

0378-5173/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2005.12.012

1996a,b,c; Leuenberger et al., 1987; Holman and Leuenberger, 1988; Bonny and Leuenberger, 1991).

One of the most important parameters of percolation theory is the percolation threshold, where there is a maximum probability of appearance of an infinite or percolating cluster of a substance and some properties of the system change suddenly. A cluster is defined as a group of neighboring occupied sites in the lattice and is considered infinite or percolating when it extends from one 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 excipient. As a function of their relative volume ratio, 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 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 versus a desegregating device, etc.) (Stauffer and Aharony, 1992).

The objective of the present paper is to apply the percolation theory to study the release and hydration rate of hydrophilic matrices in order to contribute to the rationalization of the design of these controlled release systems and to obtain a better knowledge of the processes that occur during the release of the drug.

2. Materials and methods

2.1. Materials

Potassium chloride (Acofarma, Barcelona, Spain) was used as a model water-soluble drug. A matrix-forming material, hydroxypropyl methylcellulose (HPMC K4M, Colorcon S.A., Spain), a hydrophilic swelling polymer was used.

2.2. Preparation of matrix tablets

Both components were sieved (Retsch type Vibro). Table 1 shows the composition of the studied formulations, as well as the particle size of the employed substances. Then, the components were mixed using a Turbula mixer (Basel, Switzerland). The mixing time (3 min) was validated.

The mixtures were compressed using an eccentric machine (Bonals A-300, Barcelona, Spain) without any further excipient. Cylindrical tablets with a weight of 600 mg and a diameter of 12 mm were prepared at the maximum compression force accepted by our formulations.

2.3. In vitro drug release studies

Dissolution studies were carried out at $37 \pm 0.5\,^{\circ}C$ in 900 ml of distilled water, in a USP 26 apparatus (Turu Grau, type D-6) using the paddle method. The rotation speed was kept constant at 100 rpm. Release of KCl 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.

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

$$\frac{Q_t}{Q_\infty} = bt^{1/2} \tag{1}$$

$$\frac{Q_t}{Q_\infty} = kt^n \tag{2}$$

where Q_t/Q_∞ is the fraction of drug released, b and k are kinetic constants and n is the diffusional exponent which depends on the release mechanism and 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:

$$\frac{Q_t}{Q_\infty} = k_d t^m + k_r t^{2m} \tag{3}$$

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

2.4. Water uptake studies

Water uptake measurements were carried out using a modified Enslin apparatus.

The amount of water uptake at each time point was read from a precision balance (Scaltec SBC 31) linked to a chart recorder and a personal computer.

Table 1
Composition of the assayed tablets, KCl percentages, HPMC percentages and size fraction selected by sieving

Batch	Sieving fraction of KCl (μm)	Sieving fraction of HPMC (μm)	Range, KCl (%, w/w)	Range, HPMC (%, w/w)
A	50–100	150–200	20–90	10–80
B	150–200	150–200	20–90	10–80
C	200–250	150–200	20–90	10–80
D	150–200	50–100	20–95	5–80
E	150–200	200–250	20–90	10–80

The Davidsons and Peppas (1986) (Eq. (4)) model was applied to these data to determine the mechanism and the rate of water uptake:

$$w = k_s t^n \quad (4)$$

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

2.5. Estimation of the percolation threshold

In order to estimate the percolation threshold, the behaviour of the kinetic parameters (Higuchi's slope "b", normalised Higuchi's slope "b/% (v/v) of HPMC", relaxational constant of Peppas and Sahlin "k_r") with respect to the volumetric fraction of each component at time zero, was studied.

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 (Miranda, 2004).

3. Results and discussion

3.1. Study of release profile and release kinetics

In the present paper, 46 batches of tablets have been prepared using five different excipient/drug particle size ratios (ranging from 0.42 to 2.33). Table 1 summarizes the composition of the studied batches.

As an example, the obtained release profiles for tablets containing 50–100 μm KCl and 150–200 μm HPMC K4M are shown in Fig. 1. As it can be observed in this figure, an important change in the release profiles appears between 70 and 80% (w/w) KCl content.

The Higuchi's model as well as the non-linear regression of Korsmeyer and Peppas–Sahlin were employed to study the release data. The results obtained are shown in Table 2. As it can be observed both, the Higuchi's slope (11.38–21.96% $min^{-1/2}$) and the relaxational constant k_r of Peppas and Sahlin (1.068–4.803% min^{-2m}) underwent an important increase between matrices containing 70 and 80% (w/w) of drug. According to the Korsmeyer model, the kinetic constant k did not show an important change between matrices containing 70 and 80% (w/w) of drug (11.623–7.582% min^{-n}). Nevertheless, the diffusional exponent n indicated a change in the release mechanism. Drug loads between 20 and 70% (w/w) followed a diffusional kinetics (values $n \approx 0.5$), whereas drug loads between 80 and 90% (w/w) showed values of n close to 1, which suggests that the drug is released predominantly by erosion mechanism.

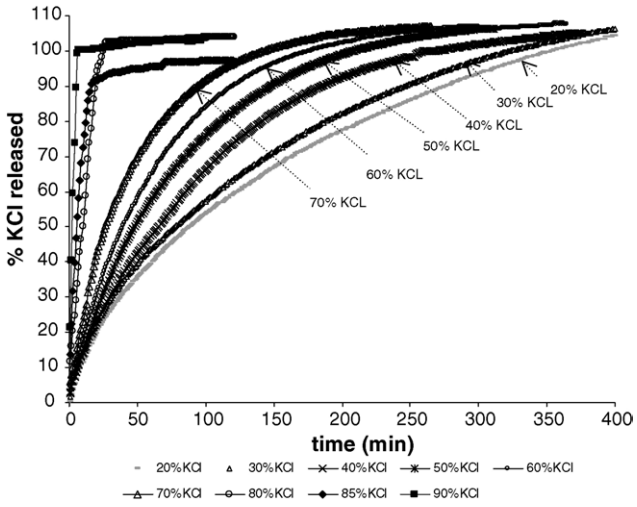

Fig. 1. Dissolution profiles for batch A (50–100 μm KCl and 150–200 μm HPMC K4M).

Therefore, the results obtained from the study of the release profiles as well as the release mechanism indicated the existence of a critical point situated between 20 and 30% (w/w) of HPMC K4M (70–80% (w/w) of KCl). This critical point could be related to the existence of an excipient percolation threshold. This would mean that above 30% (w/w) HPMC K4M, a percolating cluster of the excipient would be obtained which controls the drug release. The polymer swells in contact with an aqueous liquid and forms a gel layer, which spreads the whole tablet, controlling the drug release rate.

Below 20% (w/w) HPMC the excipient would not percolate the system and, as a consequence, the gel layer formed is less

Table 2
Dissolution data for batch A (50–100 μm KCl and 150–200 μm HPMC K4M)[a]

Lot	KCl (%, w/w)	Higuchi		Korsmeyer			Peppas and Sahlin		
		b (% $min^{-1/2}$)	r^2	k (% min^{-n})	n	r^2	k_d (% min^{-m})	k_r (% min^{-2m})	r^2
1	20	5.883	0.999	6.098	0.494	0.999	5.054	0.301	0.996
2	30	6.226	0.999	6.900	0.483	1.000	5.424	0.333	0.997
3	40	7.635	0.998	5.103	0.569	0.999	4.428	0.626	0.996
4	50	8.736	0.996	10.525	0.468	0.997	5.410	0.605	0.988
5	60	9.759	0.996	6.545	0.576	0.998	5.009	0.905	0.994
6	70	11.385	0.994	11.623	0.496	0.995	6.652	1.068	0.987
7	80	21.962	0.978	7.582	0.801	0.990	5.163	4.803	0.990
8	85	27.219	0.998	29.956	0.474	0.999	13.148	4.281	0.991
9	90	55.310	0.995	28.923	0.754	0.999	2.024	20.229	0.999

[a] b, Higuchi's slope; k, kinetics constant of the Korsmeyer model; n, diffusional exponent; k_d, diffusional constant of Peppas and Sahlin model; k_r, relaxational constant of Peppas and Sahlin model; m, diffusional exponent that depends on geometric shape of the releasing device through its aspect ratio.

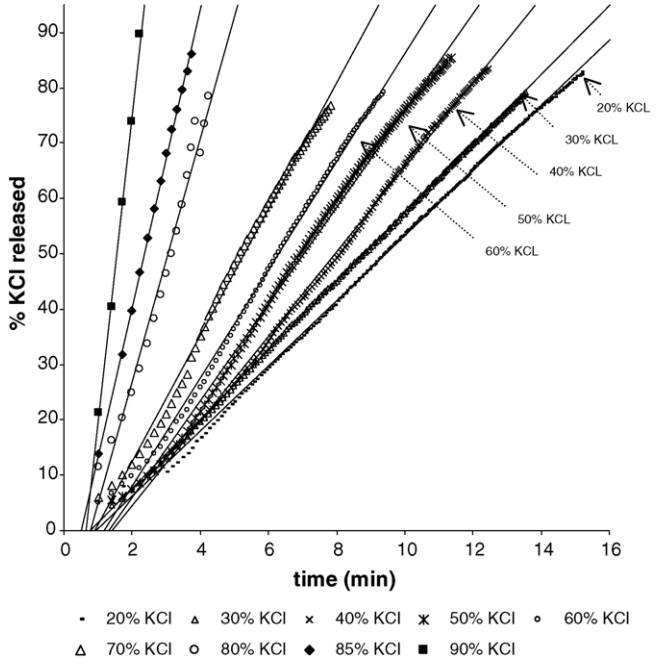

Fig. 2. Percentage of drug released vs. square root of the time for batch A (50–100 μm KCl and 150–200 μm HPMC K4M).

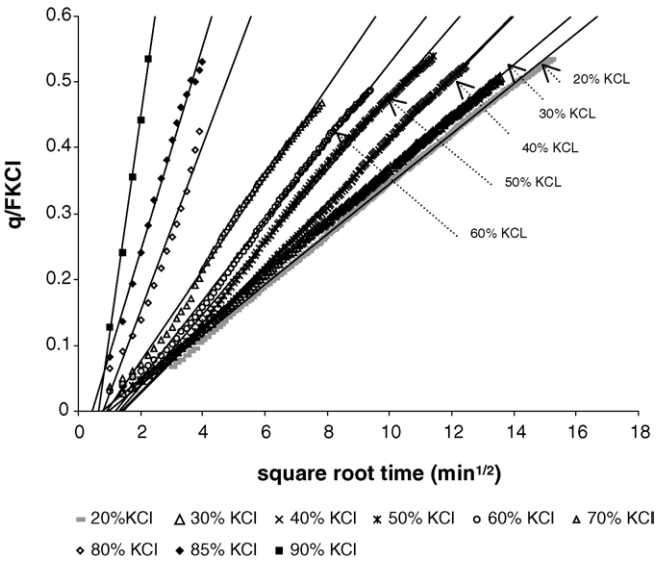

Fig. 3. Amount of drug released/volumetric fraction of the drug vs. square root of the time for batch A (50–100 μm KCl and 150–200 μm HPMC K4M).

coherent and soluble substances may act as channelling agents, resulting in a failure of the release control. The drug is release predominantly by the erosion mechanism. It has to be emphasized that this critical point is expressed as the concentration of excipient in dry state, i.e. before the matrix is placed in the dissolution medium.

According to Ford et al. (1985a,b,c), the most important factor affecting the rate of release from HPMC matrices is the drug/HPMC ratio. An increase in polymer concentration causes an increase in the viscosity of the gel layer as well as the formation of a gel layer with a longer diffusional path, decreasing the drug release rate. Nevertheless, this theory does not explain the existence of the critical points, where the kinetic properties undergo important changes. According to percolation theory these changes can be attributed to the modification of the matrix structure close to percolation thresholds.

On the other hand, according to Salomón and Doelker (1979) the higher the drug load, the higher the release rate, due to the larger effective surface exposed by the drug in the matrix. In order to investigate this hypothesis, the percentage of the drug released (Fig. 2) and the amount of the drug released normalised with the volumetric fraction of the drug (q/F_{KCl}) (Fig. 3) have been plotted versus the square root of the time. The percentage of the drug released and the amount of the drug release were normalised with its volumetric fraction, because the fraction of the external surface occupied by a component depends on its volumetric fraction.

In case the drug effective surface was the only factor that influences on the drug release rate, the regressions presented in Fig. 3 should have the same slope. Two groups of the lines clearly different can be observed in Fig. 3. A change can be appreciated between 20 and 30% (w/w) HPMC content (70–80% (w/w) KCl). This fact is in agreement with the results obtained from the study of the release profiles (Fig. 1). Therefore, the results obtained indicate that the drug effective surface is not the only factor that influences the drug release; there are other parameters, as the excipient percolation threshold, influencing the drug release from these systems.

3.2. Study of water uptake profiles and swelling kinetics

The degree of hydration of the polymer is one of the factors determining the degree and velocity of drug release from the swellable matrices (Bettini et al., 1997; Michailova et al., 2000, 2001). In this section, a study of the hydration rate of the matrices has been carried out.

As an example, the obtained water uptake profiles for tablets containing 50–100 μm KCl and 150–200 μm HPMC K4M are shown in Fig. 4. As it can be observed in this figure, when the drug loading of the matrices decreases, the hydration rate is lower. An important change in the water uptake profiles appears between 20 and 30% (w/w) HPMC (70–80% (w/w) KCl). In addition, the swelling kinetics parameters calculated by fitting the water uptake data according to the Davidsons and Peppas model, showed an important decrease in the swelling constant (from $k = 228.67$ to $k = 73.12$) between matrices containing 20 and 30% (w/w) of HPMC.

These changes observed in the water uptake profiles and in the swelling constants (k) could be due to the percolation threshold of the excipient. This would mean that above 30% (w/w) HPMC, an infinite cluster of excipient would be formed. When the polymer swells in contact with an aqueous liquid, forms a gel layer around the whole tablet, controlling the hydration rate.

As it was previously mentioned, this critical point is expressed as the concentration of excipient in dry state, i.e. before the matrix is placed in the dissolution medium. The obtained values are in the range of previously estimated per-

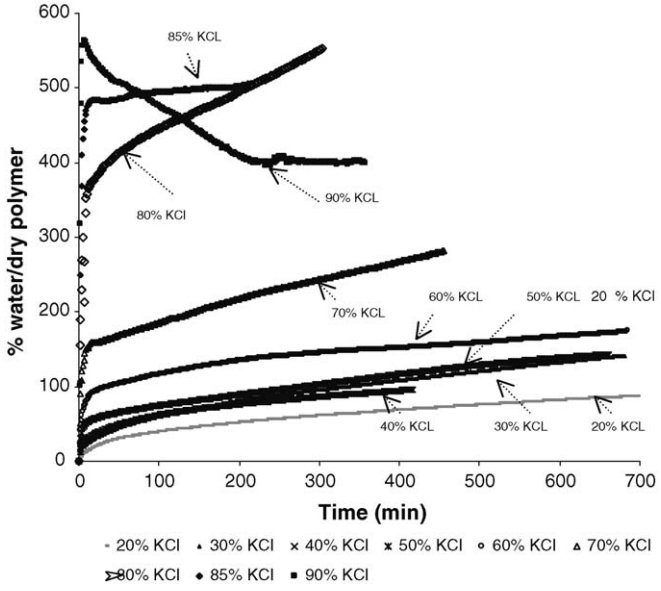

Fig. 4. Water uptake profiles for batch A (50–100 μm KCl and 150–200 μm HPMC K4M).

colation thresholds for particulates components in a tablet (inert matrices).

Therefore, the results obtained from the studies of the release and hydration rate for all the tested batches, demonstrate the existence of critical points which can be related to the excipient percolation thresholds, being these thresholds one of the main factors governing the gel layer formation and consequently, the drug release control from hydrophilic matrices.

3.3. Estimation of excipient percolation thresholds

In order to estimate the percolation threshold, the evolution of the measured kinetic parameters ("*b*" slope of Higuchi, "*b*/% (v/v) of HPMC" slope of Higuchi normalized, "k_r" relaxational constant of Peppas and Sahlin) as a function of the volumetric fraction of the excipient at time zero was studied (Miranda, 2004). As an example, the results obtained for tablets containing 50–100 μm KCl and 150–200 μm HPMC K4M are shown in Fig. 5. The percolation thresholds for the rest of the batches have been estimated using the same methodology.

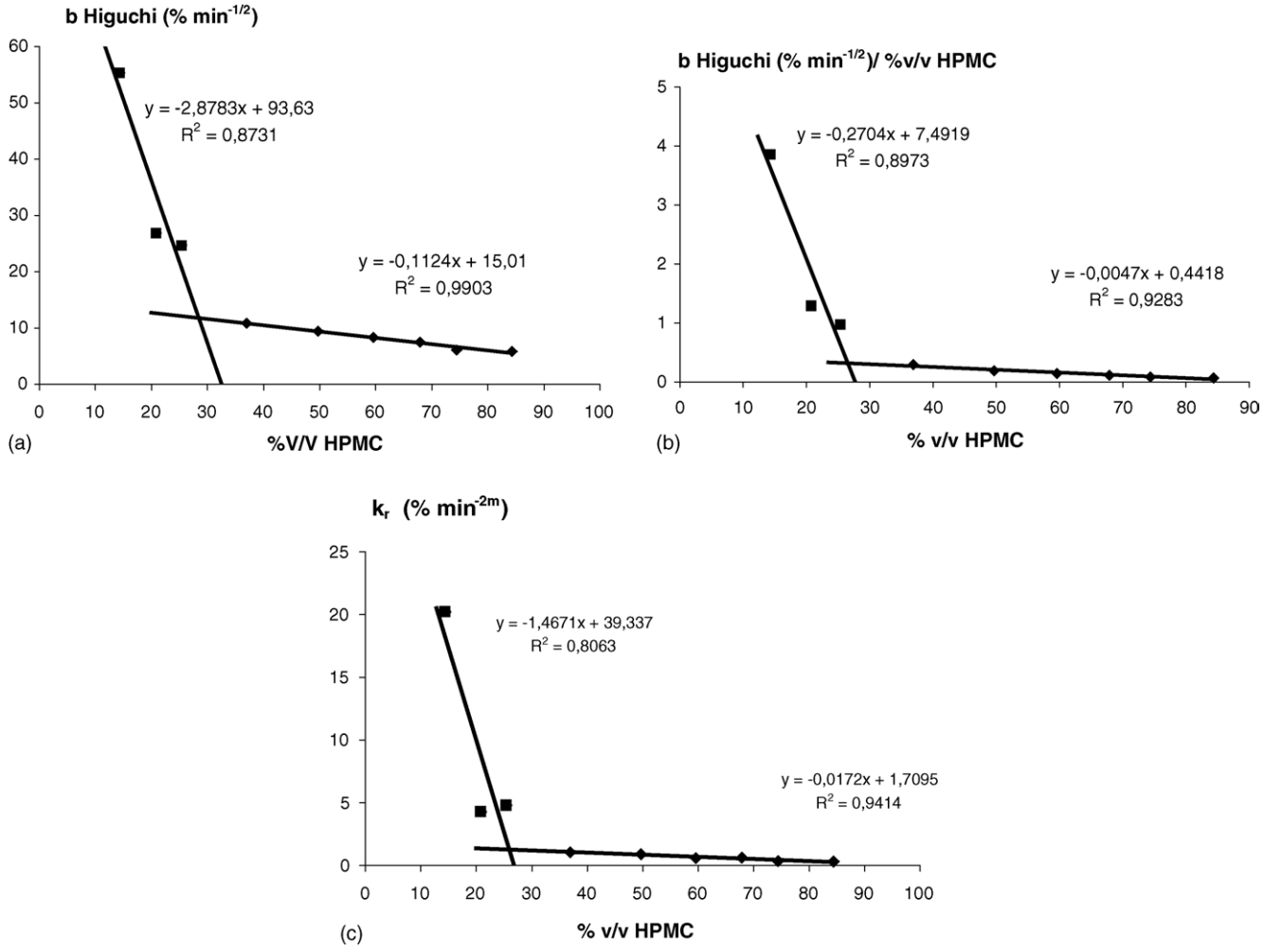

Fig. 5. (a) Higuchi slope's; (b) Normalized Higuchi slope's; (c) Relaxational constant of Peppas and Sahlin vs. percentage of the excipient volumetric fraction for batch A (50–100 μm KCl and 150–200 μm HPMC K4M).

Table 3
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 (% $min^{-1/2}$)	$Y_1 = -2.87x + 93.63$	0.873	$X = 28.42$
		$Y_2 = -0.11x + 15.01$	0.980	
	Higuchi's slope (% $min^{-1/2}$)/% (v/v) HPMC	$Y_1 = -0.27x + 7.49$	0.897	$X = 26.53$
		$Y_2 = -4.7 \times 10^{-3}x + 0.44$	0.928	
	Relaxational constant, k_r (% min^{-2m})	$Y_1 = -1.72 \times 10^{-2}x + 1.709$	0.941	$X = 25.95$
		$Y_2 = -1.46x + 39.33$	0.806	
B	Higuchi's slope (% $min^{-1/2}$)	$Y_1 = -2.18x + 75.82$	0.820	$X = 29.09$
		$Y_2 = -0.12x + 15.21$	0.874	
	Higuchi's slope (% $min^{-1/2}$)/% (v/v) HPMC	$Y_1 = -0.21x + 6.13$	0.846	$X = 27.64$
		$Y_2 = -4.9 \times 10^{-3}x + 0.44$	0.959	
	Relaxational constant, k_r (% min^{-2m})	$Y_1 = -1.39 \times 10^{-3}x + 1.34$	0.695	$X = 29.43$
		$Y_2 = -0.63x + 19.49$	0.778	
C	Higuchi's slope (% $min^{-1/2}$)	$Y_1 = -2.74x + 90.34$	0.955	$X = 29.61$
		$Y_2 = -0.075x + 11.30$	0.919	
	Higuchi's slope (% $min^{-1/2}$)/% (v/v) HPMC	$Y_1 = -0.23x + 6.87$	0.916	$X = 27.81$
		$Y_2 = -3.4 \times 10^{-3}x + 0.33$	0.973	
	Relaxational constant, k_r (% min^{-2m})	$Y_1 = -7.75 \times 10^{-3}x - 0.29$	0.916	$X = 28.20$
		$Y_2 = -1.17x + 33.20$	0.865	
D	Higuchi's slope (% $min^{-1/2}$)	$Y_1 = -1.92x + 45.12$	0.897	$X = 19.61$
		$Y_2 = -0.036x + 8.092$	0.901	
	Higuchi's slope (% $min^{-1/2}$)/% (v/v) HPMC	$Y_1 = -0.33x + 6.73$	0.875	$X = 19.24$
		$Y_2 = -3.2 \times 10^{-3}x + 0.30$	0.883	
	Relaxational constant, k_r (% min^{-2m})	$Y_1 = -4.33 \times 10^{-3}x - 0.12$	0.737	$X = 18.34$
		$Y_2 = -0.39x + 7.21$	0.819	
E	Higuchi's slope (% $min^{-1/2}$)	$Y_1 = -2.49x + 76.49$	0.990	$X = 26.88$
		$Y_2 = -0.077x + 11.54$	0.906	
	Higuchi's slope (% $min^{-1/2}$)/% (v/v) HPMC	$Y_1 = -0.20x + 5.73$	0.990	$X = 26.71$
		$Y_2 = -0.0038x + 0.35$	0.896	
	Relaxational constant, k_r (% min^{-2m})	$Y_1 = -4.08 \times 10^{-3}x + 4.56 \times 10^{-3}$	0.863	$X = 33.22$
		$Y_2 = -0.43x + 14.57$	0.643	

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

$$X \propto S(p - p_c)^q \quad (5)$$

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

As the percolation theory predicts (Eq. (5)), the kinetic parameters studied show a non-linear behaviour as a function of the volumetric fraction of the excipient.

The excipient percolation thresholds have been estimated as described in Section 2: two linear regressions have been performed as an approximation for estimating the percolation threshold as the point of intersection between both regression lines.

The values of the excipient percolation thresholds estimated for all the batches studied, based on the behaviour of the kinetic parameters, are shown in Table 3.

According to the results obtained, the excipient percolation threshold for tablets containing 50–100 μm KCl and 150–200 μm HPMC K4M is situated between 25.95 and 28.42% (v/v) of HPMC. This fact indicates that above this range an infinite cluster of the excipient has been formed, which controls the penetration of the liquid into the matrices and the release of drug from these systems.

4. Conclusions

The application of the percolation theory allowed us to explain the changes in the release and hydration kinetics of swellable matrix type controlled delivery systems. According to this theory, the critical points observed in dissolution and water uptake studies can be attributed to the excipient percolation threshold. The knowledge of these thresholds is important in order to optimize the design of swellable matrix tablets. Above the excipient percolation threshold an infinite cluster of this component is formed which is able to control the hydration and release rate. Below this threshold the excipient does not percolate the system and the drug release is not controlled.

The obtained excipient percolation thresholds (18.34–33.22% (v/v) of HPMC) are in the range of previously estimated percolation thresholds for particulate components in a tablet (inert matrices) (Caraballo et al., 1996a; Millán et al., 1998).

Acknowledgments

A part of this work has been supported by a Grant of the Andalusian Government "Junta de Andalucía": "Ayuda a la Investigación", resolution 4/2004. The authors also wish to express their gratitude to Colorcon S.A., Spain, for the supply of the polymer Methocel® K4M.

References

Bettini, R., Colombo, P., Massimo, G., Santi, P., Castellaini, P.L., Peppas, N.A., 1994. Moving fronts and drug release from hydrogel matrices. Proc. 21st Int. Symp. Control. Release Bioact. Mater. 21, 19–20.

Bettini, R., Colombo, P., Peppas, N.A., 1997. Drug concentration profiles during drug release from hydrophylic matrices. Proc. 24th Int. Symp. Control. Release Bioact. Mater. 24, 635–636.

Bettini, R., Peppas, N.A., Colombo, P., 1998. Polymer relaxation in swellable matrices contributes to drug release. Proc. 25th Int. Symp. Control. Release Bioact. Mater. 24, 36–37.

Bonny, J.D., Leuenberger, H., 1991. Matrix type controlled release systems. I. Effect of percolation on drug dissolution kinetics. Pharm. Acta Helv. 66, 160–164.

Caraballo, I., Fernández-Arévalo, M., Holgado, M.A., Rabasco, A.M., 1993. Percolation theory: application to the study of the release behaviour from inert matrix systems. Int. J. Pharm. 96, 175–181.

Caraballo, I., Fernández-Arévalo, M., Millán, M., Rabasco, A.M., Leuenberger, H., 1996c. Study of percolation thresholds in ternary tablets. Int. J. Pharm. 139, 177–186.

Caraballo, I., Millán, M., Rabasco, A.M., 1996a. Relationship between drug percolation threshold and particle size in matrix tablets. Pharm. Res. 13, 387–390.

Caraballo, I., Millán, M., Fini, A., Rodríguez, L., Cavallari, C., 2000. Percolation thresholds in ultrasound compacted tablets. J. Control. Release 69, 345–355.

Caraballo, I., Millán, M., Rabasco, A.M., Leuenberger, H., 1996b. Zero-order release periods inertmatrices. Influence of the distance to the percolation threshold. Pharm. Acta Helv. 71, 335–339.

Colombo, P., Bettini, R., Massimo, G., Castellani, P.L., Santi, P., Peppas, N.A., 1995. Diffusion front movement is important in drug release control from swellable matrix tablets. J. Pharm. Sci. 84, 991–997.

Colombo, P., Bettini, R., Santi, P., Peppas, N.A., 2000. Swellable matrices for controlled drug delivery: gel-layer behaviour, mechanism and optimal performance. Pharm. Sci. Technol. Today 3, 198–204.

Davidsons, G.M.R., Peppas, N.A., 1986. Solute and penetrant diffusion in swellable polymers. V. Relaxation-controlled transport in p(HEMA-co-MMA) copolymers. J. Control. Release 3, 243–258.

Espina-Márquez, A., Caraballo, I., 2004. A new wet conductivitymetric method to estimate the drug percolation threshold. Pharm. Res. 21, 875–881.

Ford, J.L., Rubistein, M.H., Hogan, J.E., 1985a. Formulation of sustained release promethazine hydrochloride tablets using hydroxypropylmethylcellulose matrices. Int. J. Pharm. 24, 327–338.

Ford, J.L., Rubistein, M.H., Hogan, J.E., 1985b. Propanolol hydrochloride and aminophylline release from matrix tablets containing hydroxypropylmethylcellulose. Int. J. Pharm. 24, 339–350.

Ford, J.L., Rubistein, M.H., Hogan, J.E., 1985c. Dissolution of a poorly water soluble drug, idomethacin, from hydroxypropylmethylcellulose controlled release tablets. J. Pharm. Pharmacol. 37, 33–40.

Higuchi, T., 1963. Mechanism of sustained-action medication-theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52, 1145–1149.

Holman, L.E., Leuenberger, H., 1988. The relationship between solid fraction and mechanical properties of compacts—the percolation theory model approach. Int. J. Pharm. 46, 35–44.

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P., Peppas, N.A., 1983. Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm. 15, 25–35.

Lee, P.I., Peppas, N.A., 1987. Prediction of polymer dissolution in swellable controlled-release systems. J. Control. Release 6, 207–215.

Leuenberger, H., Rohera, B.D., Haas, C., 1987. Percolation theory—a novel approach to solid dosage form design. Int. J. Pharm. 38, 109–115.

Melgoza, L.M., Rabasco, A.M., Sandoval, H., Caraballo, I., 2001. Estimation of the percolation thresholds in dextromethorphan hydrobromide matrices. Eur. J. Pharm. Sci. 12, 453–459.

Melgoza, L., Caraballo, I., Álvarez-Fuentes, J., Millán, M., Rabasco, A.M., 1998. Study of morphine percolation threshold in Eudragit® RS-PM matrices. Int. J. Pharm. 170, 169–177.

Michailova, V., Titeva, S.T., Kotsilkova, R., Krusteva, E., Minkov, E., 2000. Water uptake and relaxation processes in mixed unlimited swelling hydrogels. Int. J. Pharm. 209, 45–56.

Michailova, V., Titeva, S.T., Kotsilkova, R., Krusteva, E., Minkov, E., 2001. Influence of hydrogel structure on the processes of water penetration and drug release from mixed hydroxypropylmethylcellulose/thermally pregelatinized maxy maize starch hydrophilic matrices. Int. J. Pharm. 222, 7–17.

Millán, M., Caraballo, I., Rabasco, A.M., 1998. The role of the drug/excipient particle size ratio in the percolation model for tablets. Pharm. Res. 15, 216–220.

Miranda, A., 2004. Estudio de puntos críticos para la optimización de matrices hidrófilas de liberación controlada. Aplicación a una formulación con Lobenzarit Disódico, PhD Thesis, University of Seville, Spain.

Peppas, N.A., Sahlin, J.J., 1989. A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. Int. J. Pharm. 57, 169–172.

Pham, A.T., Lee, P.I., 1994. Probing the mechanisms of drug release from HPMC matrices. Pharm. Res. 11, 1379–1384.

Ritger, P.L., Peppas, N.A., 1987. A simple equation for description of solute release. I. Fickian and non-fickian release from non-swellable devices in the form of slabs, sphere, cylinders or discs. J. Control. Release 5, 23–36, 1987.

Salomón, J.L., Doelker, E., 1979. Importance de la technologie et de la formulation pour le mécanisme de libération du chlorure de potassium contenu dans des matrices hydrophiles. Pharm. Helv. Acta 54, 82–85.

Siepmann, J., Kranz, H., Bodmeier, R., Peppas, N.A., 1999. HPMC-matrices for controlled drug delivery: a new model combining diffusion, swelling, and dissolution mechanisms and predicting the release kinetics. Pharm. Res. 16, 1748–1756.

Siepmann, J., Peppas, N.A., 2000. Hydrophilic matrices for controlled drug delivery: an improved mathematical model to predict the resulting drug release kinetics (the "sequential layer" model). Pharm. Res. 7, 1290–1298.

Siepmann, J., Streubel, A., Peppas, N.A., 2002. Understanding and predicting drug delivery from hydrophilic matrix tablets using the "sequential layer" model. Pharm. Res. 19, 306–314.

Stauffer, D., Aharony, A., 1992. Introduction to Percolation Theory, 2nd ed. Burgess Science Press, London.