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Application of percolation theory in the study of an extended release Verapamil hydrochloride formulation

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ABSTRACT

The percolation theory studies the critical points or percolation thresholds of the system, where one component of the system undergoes a geometrical phase transition, starting to connect the whole system. The objective of the present paper was to study the existence of critical points governing the water and drug transport inside hydroxypropylmethylcellulose (HPMC) hydrophilic matrix systems obtained with different polymer viscosity grades. For this purpose, extended release formulations of Verapamil HCl, have been prepared and studied. The percolation theory has been applied for the first time to multi-component hydrophilic matrices. The materials used to prepare the tablets were Verapamil HCl, four different viscosity grades of HPMC, microcrystalline cellulose, lactose, magnesium stearate and colloidal silicon dioxide NF. 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. From the point of view of the percolation theory, the optimum concentration for all the studied polymers, to obtain a hydrophilic matrix system for the controlled release of Verapamil HCl is higher than 20% (v/v) HPMC. Above 20% (v/v) HPMC, an infinite cluster of excipient would be formed, ensuring uniform hydration, maintaining integrity of the system and controlling the drug release.

1. Introduction

A matrix tablet is the simplest and most cost-effective method to develop and manufacture an extended release (ER) dosage form. A typical ER matrix formulation consists of a drug, release retardant hydrophilic polymer, one or more excipients (as fillers or binders), flow aid (glidant) and a lubricant. Other functional ingredients such as buffering agents, stabilizers, solubilizers and surfactants may also be included to improve or optimize the release or/and stability performance of the formulation system. Hydrophilic matrices are flexible technologies to obtain desired release profiles for a wide range of drugs, with cellulose ethers, and in particular hypromellose (hydroxypropylmethylcellulose, HPMC) being the polymers of choice for their formulations (Rajabi-Siahboomi and Jordan, 2000).

The percolation theory studies the critical points or percolation thresholds of the system, where one component of the system undergoes a geometrical phase transition, starting to connect the whole system. At the percolation thresholds the influence of the formulation factors usually undergoes sudden changes. Therefore, the knowledge of these points as well as their relationship with the main factors affecting the behaviour of the system will result in a robust, safer formulation and faster development.

In recent studies (Caraballo and Leuenberger, 2004; Miranda et al., 2006a,b, 2007; Fuertes et al., 2006) the existence of critical points affecting the water uptake and the release behaviour of hydrophilic matrices has been observed. Nevertheless, these works have been performed employing binary systems, i.e., tablets composed solely with the hydrophilic matrix forming excipient (polymer) and the drug.

The objective of the present paper is to study for the first time in a typical multi-component ER formulation, the existence of critical points governing the water and drug transport inside hydrophilic matrix systems prepared from HPMC with different viscosity grades. Various ER formulations of Verapamil HCl were prepared and studied. Then the percolation theory was applied to these multi-component hydrophilic matrices.

2. Materials and methods

2.1. Materials

The following materials were used in the study: Verapamil HCl (Recordatti, Italy), METHOCEL™ K100 LV CR, METHOCEL™ K4 M CR, METHOCEL™ K15 M CR and METHOCEL™ K100 M CR

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Table 1
The composition and concentration of materials used in matrix formulations

	Batch VX1		Batch VX2		Batch VX3		Batch VX4		Batch VX5	
	%	Tablet (mg)	%	Tablet (mg)	%	Tablet (mg)	%	Tablet (mg)	%	Tablet (mg)
Verapamil HCl	30	180.0	30	180.0	30	180.0	30	180.0	30	180.0
HPMC	10	60.0	20	120.0	30	180.0	35	210.0	40	240.0
MCC	40	240.0	30	180.0	20	120.0	15	90.0	10	60.0
Lactose	19	114.0	19	114.0	19	114.0	19	114.0	19	114.0
SiO_2	0.5	3.0	0.5	3.0	0.5	3.0	0.5	3.0	0.5	3.0
Mg stearate	0.5	3.0	0.5	3.0	0.5	3.0	0.5	3.0	0.5	3.0
Total	100	600.0	100	600.0	100	600.0	100	600.0	100	600.0

(manufactured by Dow Chemical Company and supplied by Colorcon, UK), lactose (Safic-Alcan, Spain), microcrystalline cellulose (MCC, Mingtai Chemical, Spain), magnesium stearate (Acofarma, Spain), colloidal silicon dioxide NF (Acofarma, Spain).

2.2. Matrix preparation

Table 1 lists the formulation used in this study. Initially, all materials, with the exception of magnesium stearate and colloidal silicon dioxide, were blended for 10 min in a Turbula mixer. Magnesium stearate and colloidal silicon dioxide were then added and blended for an additional period of 5 min. The mixtures (total weight 600 mg) corresponding to batch were directly compressed on an eccentric tabletting machine (Bonals A-300). Every mixture was compressed at the maximum compression force accepted by the formulation, using a 12-mm diameter die. Tablet hardness, weight, thickness and friability were measured for all the batches ($n = 10$ tablets).

The letter X in Table 1 can be replaced by the letter indicated in Table 2, in order to obtain the name of the lot of tablets prepared with each polymer fraction.

2.3. Determination of tablets volume and initial porosity

Tablet thickness and diameter were measured to ±0.001 mm using a 25-mm digital micrometer (Comecta, SA). The tablet volume was calculated by using the following equation:

$$V = \pi H \left(\frac{D}{2}\right)^2 \quad (1)$$

where V is tablet apparent volume and H and D are tablet thickness and diameter, respectively.

The initial porosity (ε_o) was determined by the known values of the volume and weight calculated by using the following equation:

$$\varepsilon_0 = \frac{V_{real} - V_{theor}}{V_{real}} \quad (2)$$

where V_{real} is the real volume of the tablet; V_{theor} is the theoretical volume of tablet which is obtained as the sum of the volumes of individual components (dividing the mass of each component by its real density).

Table 2
The name of the lot of tablets prepared with each polymer fraction

Polymer	Name of the lot
METHOCEL (HPMC) K100 LV CR	A
METHOCEL (HPMC) K100 M CR	B
METHOCEL (HPMC) K15M CR	C
METHOCEL (HPMC) K 4M CR	D

The numbers 1–5 change according to HPMC/MCC concentration.

2.4. Dissolution studies

Drug release was measured ($n = 3$) according to the requirements of "Verapamil HCl Extended Release Tablets" (Test 5) as outlined in the USP 26. The method employed the apparatus 2 (paddles), 50 rpm, and 900 ml of phosphate buffer solution pH 7.5. The percent of drug released was measured using UV spectrophotometry at a wavelength of 278 nm. Samples were withdrawn at 0, 15, 30, 60 and 90 min followed by 2, 3, 4, 6, 8 and 10 h.

The release rates from controlled release polymeric matrices can be studied using the zero-order model (Eqs. (3) and (4) proposed by Higuchi, 1963, Eq. (5) proposed by Korsmeyer et al. (1983), and Eq. (6) proposed by Peppas and Sahlin (1989). Linear and non-linear least squares fitting methods were used to determine the optimum values for the parameters present in each equation:

$$Q = kt \quad (3)$$

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

$$Q = k_1 t^n \quad (5)$$

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

where Q is the amount of drug remaining at time t; k is the zero-order release constant on Eq. (3) and the Higuchi rate constant on Eq. (4), k_1 is the Korsmeyer–Peppas kinetic constant; n is a diffusional exponent that depends on the release mechanism and on the shape of the swelling device tested (Ritger and Peppas, 1987). For thing slabs, values of $n = 0.5$ indicate Fickian release, values of $0.5 < n < 1.0$ indicate an anomalous (non-Fickian or couple diffusion/relaxation) drug release, whereas values of $n = 1.0$ indicate a case II (purely relaxation controlled) drug release. k_d is the diffusional constant; k_r is the relaxational constant and m is the diffusional exponent that depends on geometric shape of the releasing device through its aspect ratio.

2.5. Water uptake measurements

An Enslin apparatus was used for the study of water penetration. 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. The assay was performed using three tablets per lot. The absorption staged for a period of time (12 h) at a temperature of 37 ± 0.5 °C. The profiles of the liquid uptake were expressed as a weight gain of the swelled matrix, in grams of penetrant per grams of dry powder (Davidsons and Peppas, 1986), calculated as a ratio between the amount of the aqueous phase remaining in the swollen matrix for a given period of time and the initial weight of the dry matrix tablet. The mean profiles of the three measured tablets are shown in Fig. 2.

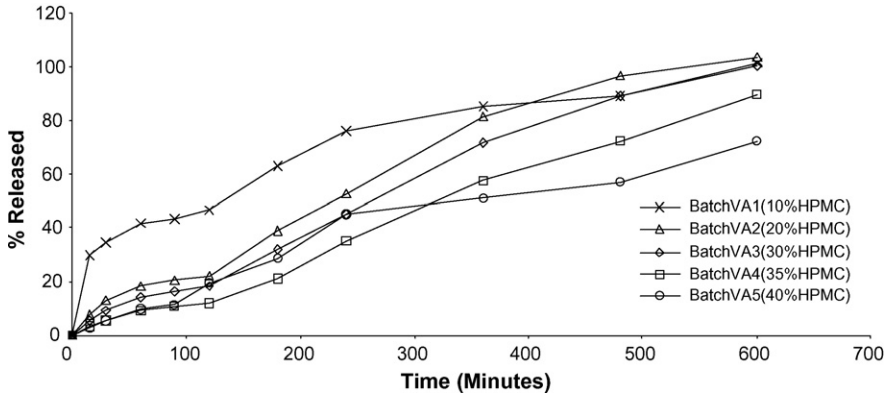

Fig. 1. Dissolution profiles for tablets prepared with different excipient contents.

2.6. 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–Sahlin "k_r") with respect to the volumetric fraction of each component at time zero, were studied (Fuertes et al., 2006; Miranda et al., 2006a,b, 2007).

According to the fundamental equation of percolation theory (Eq. (7)), if these parameters behave as critical properties, we can expect that

$$X \propto S(p - p_c)^q \tag{7}$$

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

2.7. Influence of relative excipient/drug particle size

For this specific study, the mean diameters of the particles of Verapamil HCl (μ = 138 μm; S.D. = 86 μm) and HPMC K100 LV CR (with 90% of particle below 140 μm) were calculated from the cumulative size distributions obtained after sieving (Retsch type Vibro). The relative polymer/drug particle size was calculated by dividing the mean diameter of polymer particles versus the mean diameter of the drug particles. The powders were used as were supplied (without size fraction) in all the formulations.

3. Results and discussion

3.1. Study of release profile and release kinetics

In this study, 20 batches of tablets were prepared using four different viscosity grades of HPMC with different ratios of HPMC and MCC. Table 1 summarizes the composition of the studied batches.

As an example, the release profiles for tablets containing Verapamil HCl and HPMC K100 LV CR are shown in Fig. 1. As it can be observed in this figure, an important change in the release profiles appears between 10 and 20% (w/w) HPMC content.

Dissolution profiles of batch VA (Verapamil HCl and HPMC K100LV CR) showed an important change between batch VA1 (10%, w/w of HPMC) and batch VA2 (20%, w/w of HPMC) (Fig. 1). When HPMC plus initial porosity concentration was above 21.76% (v/v) (20%, w/w of HPMC), the control of the water penetration and drug release is due to the relaxation of the polymer, whereas for lower HPMC plus initial porosity values (14.1%, v/v), the mechanisms of water penetration and drug release are diffusion-controlled (Table 3). This is indicated by the non-linear regression of Korsmeyer–Peppas and Peppas–Sahlin where the n value of Korsmeyer–Peppas equation was increased from 0.30 to 0.78 with increasing HPMC concentrations (Table 3). Furthermore, the relaxation constant k_r of Peppas–Sahlin was increased from negative values to 0.37% min^{-2m}. This behaviour is also shown by the better fit of the drug release kinetics to the zero-order model in Eq. (3). Therefore, below the excipient critical point, we obtain a fast decay of the drug release rate whereas above this point the release kinetics is much more similar to a constant release kinetics and therefore, more adequate for an ER system.

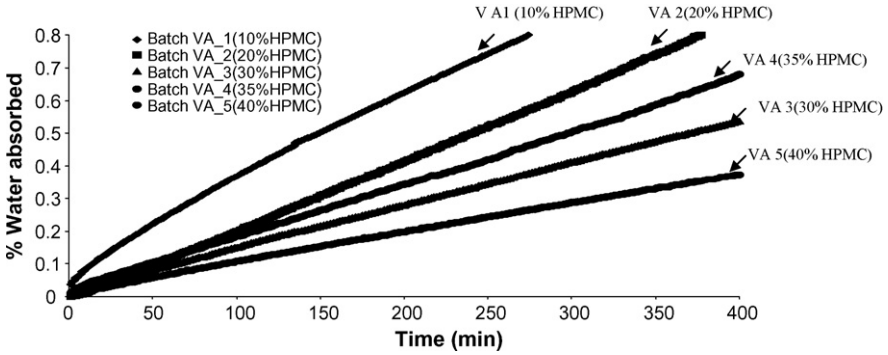

Fig. 2. Water uptake profiles for tablets prepared with different excipient contents.

Table 3
Kinetic parameters of Verapamil HCl release from the matrix tablets using HPMC K100 LV CR, Batch VA

Batch	Zero-order equation			Higuchi equation		Korsmeyer equation			Peppas y Sahlin equation		
	% (w/w) HPMC	K_0 (%t^{-1})	r^2	b (%$t^{-1/2}$)	r^2	K (%t^n)	n	r^2	K_d (%t^{-m})	k_r (%t^{-2m})	r^2
VA1	10	0.2638	0.7575	4.1781	0.9299	12.40	0.300	0.995	9.094	−0.297	0.993
VA2	20	0.1974	0.9699	3.195	0.9279	0.679	0.783	0.988	0.781	0.370	0.989
VA3	30	0.232	0.9788	3.2958	0.9688	1.146	0.702	0.997	1.372	0.360	0.998
VA4	35	0.1791	0.9818	3.4125	0.8983	0.232	0.959	0.993	−0.647	0.462	0.992
VA5	40	0.1798	0.9796	3.4263	0.8963	0.240	0.954	0.992	−0.590	0.460	0.991

b, Higuchi's slope; k, kinetics constant of the Kormeyer model; n, diffusional exponent; k_d, diffusional constant of Peppas and Sahlin model; k_r, relaxational constant of Peppas and Sahlin model, m is the diffusional exponent that geometric shape of the releasing device through its aspect ratio. The negatives values obtained for k_d in lot VA4 and VA5 should be interpreted in terms of a diffusion process insignificant compared to the relaxation mechanism.

3.2. Results of the analysis of the water penetration using Enslin apparatus

Water penetration into the matrix and drug release from the hydrated matrix are two different properties measured here. In addition, water uptake is measured through one side of the tablet and drug release through the whole surface of the tablet and therefore, may in theory have different percolation thresholds. Nevertheless, considering that similar transport processes are involved, a very similar percolation threshold could be expected for both properties.

The increase in polymer concentration is one of the factors affecting the water uptake and drug release rate from the swellable matrices.

As an example, the water uptake profiles for tablets containing Verapamil HCl and HPMC K 100 LV CR (Batch VA) are shown in Fig. 2. An important change in the water uptake profiles appears from 10 to 20% (w/w) polymer (14.1–21.8%, v/v of polymer plus initial porosity). When the HPMC loading of the matrices increases, the rate of water penetration (uptake) decreases. These changes in the water uptake profiles can be attributed to the percolation threshold of the excipient. Therefore, the results obtained from the release and water uptake profiles for all the tested batches, demonstrated for the first time in industrial formulations, the existence of critical points which can be related to the excipient percolation thresholds. These thresholds may be 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–Sahlin) as a function of the volumetric fraction of the excipient at time zero were studied (Fuertes et al., 2006; Miranda et al., 2006a,b, 2007).

As an example, the results for tablets containing Verapamil HCl and HPMC K 100 LV CR are shown in Figs. 3 and 4. The percolation thresholds for the rest of the batches have been estimated using the same methodology.

As the theory of percolation predicts (Eq. (7)), the kinetic parameters studied show a non-linear behaviour as a function of the volumetric fraction of the excipient. 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 4.

The results show that the excipient percolation threshold for tablets containing Verapamil HCl and HPMC K 100 LV CR is between 14.1 and 21.76% (v/v) of HPMC plus initial porosity (Table 5). 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.

3.4. Influence of relative excipient/drug particle size

In previous papers, a linear relationship between drug percolation threshold and relative drug/excipient particle size was found in inert matrix tablets (Caraballo et al., 1996; Millán et al., 1998).

In recent works of our research group, a linear relationship between excipient percolation threshold and relative excipient/drug particle size was found in swelling binary system (Miranda et al., 2007). In other words, the excipient percolation threshold depends linearly on the relative excipient particle size. In order to examine this point, the excipient percolation thresholds have been plotted as a function of the excipient/drug particle size ratio of the multi-component formulations here, in Fig. 5.

As this figure shows, the batches with Verapamil HCl and HPMC of different types were in the same point in the X-axis, because the four types of excipient studied have the same particle size. All the polymers used here are METHOCEL CR grades with a particle size specification of 90% below 149 μm (Certificate of Analysis).

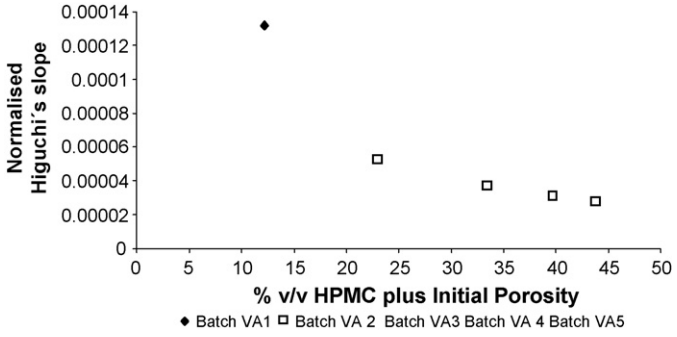

Fig. 3. Normalized Higuchi's slope vs. percentage of the excipient volumetric fraction plus initial porosity.

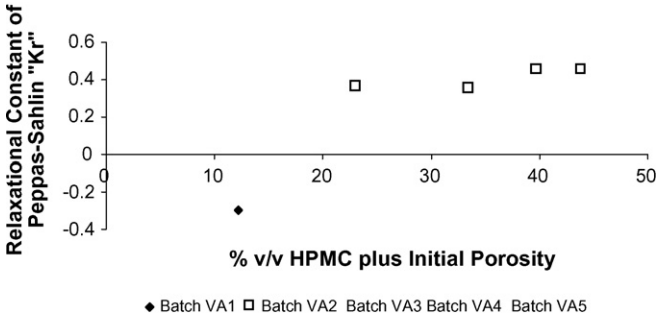

Fig. 4. Relaxational constant of Peppas–Sahlin vs. percentage of the excipient volumetric fraction plus initial porosity.

Table 4
The values of the excipient percolation threshold estimated for all the batches studied

	Batch VA1	Batch VA2	Batch VA3	Batch VA4	Batch VA5
Weight (g)	0.59	0.605	0.601	0.602	0.605
Drug w/w	0.3	0.3	0.3	0.3	0.3
HPMC (w/w)	0.1	0.2	0.3	0.35	0.4
Lactose	0.19	0.19	0.19	0.19	0.19
MCC	0.4	0.3	0.2	0.15	0.1
Mg stearate	0.005	0.005	0.005	0.005	0.005
SiO_2	0.005	0.005	0.005	0.005	0.005
Diameter (cm)	1.19	1.2	1.19	1.19	1.19
Thickness (cm)	0.403	0.401	0.422	0.437	0.439
Sur (cm^2)	4.757	4.782	4.876	4.970	4.983
Volume (cm^3)	0.448	0.454	0.469	0.486	0.488
A (g/cm^3)	0.395	0.400	0.384	0.372	0.372
Total porosity	38.206	36.138	37.512	38.982	38.383
% Initial porosity	4.163	1.638	4.396	6.949	6.337
%, v/v Verapamil HCl	34.043	34.500	33.116	32.033	32.046
%, v/v HPMC	9.927	20.121	28.971	32.693	37.379
%, v/v Lactose	16.115	16.331	15.676	15.163	15.169
%, v/v MCC	34.823	26.468	16.938	12.288	8.195
%, v/v Mg stearate	0.603	0.611	0.586	0.567	0.567
%, v/v SiO2	0.326	0.330	0.317	0.307	0.307
Density of Verapamil HCl	1.160	1.160	1.160	1.160	1.160
Density of HPMC	1.326	1.326	1.326	1.326	1.326
Density of lactose	1.552	1.552	1.552	1.552	1.552
Density of MCC	1.512	1.512	1.512	1.512	1.512
Density of Mg stearate	1.092	1.092	1.092	1.092	1.092
Density of SiO_2	2.020	2.020	2.020	2.020	2.020

Table 5
All the results for the Batch VA (Verapamil HCl and HPMC K100 LV CR)

Type of HPMC	Percolation threshold (%, w/w of HPMC)	Percolation threshold (%, v/v of HPMC)	Percolation threshold (%, v/v of HPMC plus initial porosity)
HPMC K100 LV CR (Batch VA)	10 and 20%	9.92 and 20.12%	14.1 and 21.76%
HPMC K100M CR (Batch VB)	10 and 20%	10.16 and 20.29%	12.05 and 21.09%
HPMC K15M CR (Batch VC)	10 and 20%	10.14 and 19.94%	12.19 and 22.42%
HPMC K4M CR (Batch VD)	About 20%	9.93 and 19.71%	23.35%

On the other hand, it can be observed that the formulations with Verapamil HCl are situated below the regression line corresponding to the previous works (Fig. 5).

According to these results, the critical points, for tablets containing Verapamil HCl and HPMC are situated between 10 and 20% (w/w) HPMC for the four viscosity grades of polymers studied. In this formulation, the content of microcrystalline cellulose (employed as filler) is very important (between 40 and 50%, w/w). The microcrystalline cellulose is a insoluble filler containing hydrophilic groups and in theory, can absorb water and help to establish the gel layer and to delay the release of drug.

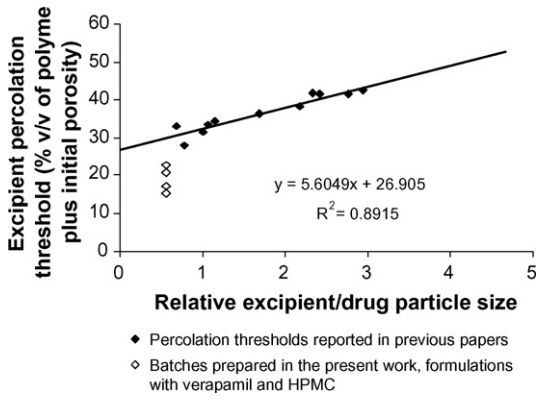

Fig. 5. Excipient percolation threshold vs. relative excipient/drug particle size.

On the other hand, the differences between the critical points obtained in this work for multi-component systems, and the results from previous works using binary systems, points out the possibility that the microcrystalline cellulose used as an insoluble filler, may help to establish the gel layer. If this hypothesis is confirmed by further studies, the presence of microcrystalline cellulose, would be responsible for the low values obtained for the excipient percolation threshold in the studied hydrophilic matrices, expressed as HPMC volume fraction.

4. Conclusions

Based on the percolation theory, the optimum concentration for all the polymers studied here, to obtain a hydrophilic matrix system for the controlled release of Verapamil HCl is higher than 20% (v/v) HPMC. Above 20% (v/v) HPMC, an infinite cluster of excipient would be formed, controlling the hydration, gel formation and the drug release.

For practical purposes and in order to reduce potential batch to batch inconsistency, all formulations containing about 30% (w/w) of HPMC polymer, fulfil this criteria, i.e., being clearly above 20% (v/v) of HPMC threshold and show consistent controlled drug release. Nevertheless, it must be taken into account that the change of the formulation components or the technological parameters, can result in a change in the relationship between w/w and v/v concentrations.

On the other hand, the results suggested the possibility that the microcrystalline cellulose may help establish the gel layer. The presence of microcrystalline cellulose may be responsible for

a reduction of the HPMC percolation threshold, i.e., in presence of microcrystalline cellulose a lower amount of polymer (HPMC) would be needed to obtain an ER system.

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