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Research Article

Polymer Percolation Threshold in HPMC Extended Release Formulation of Carbamazepine and Verapamil HCl

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Abstract. The principles of the percolation theory were applied to further understand and design hydroxypropyl methylcellulose (HPMC) extended release matrix tablets containing carbamazepine and verapamil HCl. This statistical theory studies disordered or chaotic systems where the components are randomly distributed in a lattice. The application of this theory to study the hydration and drug release of hydrophilic matrices allows describing the changes in hydration and drug release kinetics of swellable matrices. The aim of this work was to study and develop extended release matrix formulations for carbamazepine and verapamil HCl, containing hypromellose (HPMC, METHOCEL™ Premium K100M CR) as rate controlling polymer using the concepts of percolation theory. The knowledge of the percolation threshold of the components of the matrix formulations contributes to improve their design. First, reducing the time to market and second, avoiding to formulate in the nearby of the percolation threshold, which will result in a lower variability. Therefore these formulations will be more robust when they are prepared at industrial scale. The HPMC percolation threshold for drugs with very different water solubilities was determined and it was shown that there was no significant influence of drug solubility on the HPMC critical concentration threshold (excipient percolation threshold). This may be related to the versatility and broad functionality of the swelling hydrophilic matrices.

KEY WORDS: carbamazepine; extended release; hydrophilic matrix; hypromellose; verapamil HCl; percolation theory.

INTRODUCTION

The high cost involved in the development of a new drug molecule has diverted the pharmaceutical companies to investigate various strategies in the development of new drug delivery systems (1). This is reflected by the large number of patents filed each year and by the commercial success of a number of extended release systems based on matrix technologies (2).

Hydroxypropyl methylcellulose (HPMC), a semi-synthetic cellulose ether polymer, is popular for the formulation of swellable extended release dosage forms. When in contact with water, HPMC hydrates rapidly and forms a gelatinous barrier layer around the tablet. The rate of drug release from HPMC matrix is dependent on various factors such as type of polymer, drug, polymer/drug ratio, particle size of drug and polymer, and the type and amount of fillers used in the formulation (3).

Carbamazepine (CBZ) is used for anticonvulsant and antineuralgic effects. CBZ is poorly soluble in water leading to erratic dissolution, oral absorption and therefore poor bioavailability (less than 70%). It has been reported that preparing the drug in a floating dosage form can control the extent of bioavailability for such a poorly water-soluble drug (4).

Verapamil hydrochloride is a calcium channel blocker commonly used for the treatment of hypertension, angina, and myocardial infarction. Due to its relatively short elimination half-life (4.2 h), the formulation of a controlled release dosage form is very useful (5).

Here, the principles of the percolation theory were applied to further understand and design HPMC extended release matrix tablets containing carbamazepine and verapamil HCl. Percolation theory represents a powerful concept which covers a wide range of applications in pharmaceutical technology (6). Previous works have demonstrated experimentally the influence of the particle size of the components on the percolation threshold in hydrophilic matrices, as well as the importance of the initial porosity in the formation of the gel layer (7–11).

Percolation theory is based on the formation of clusters and the existence of a site-and/or bond-percolation phenomenon. It can be applied if a system can be sufficiently well described by a lattice, where the sites are occupied at random, e.g., by particles (site-percolation), or in the case all sites are already occupied, where bonds between neighboring particles are formed at random (bond-percolation). Thus the formation of a tablet

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Table I. Composition for the Hydrophilic Matrices Prepared with Carbamazepine and Different Concentrations of HPMC K100M CR and Lactose

	Batch C1		Batch C2		Batch C3		Batch C4		Batch C5	
Formulation	%	(mg)	%	(mg)	%	(mg)	%	(mg)	%	(mg)
Carbamazepine	30	180.00	30	180.00	30	180.00	30	180.00	30	180.00
HPMC K100M CR	10	60.00	20	120.00	30	180.00	35	210.00	40	240.00
Lactose	40	240.00	30	180.00	20	120.00	15	90.00	10	60.00
MCC	19	114.00	19	114.00	19	114.00	19	114.00	19	114.00
SiO2	0.5	3.00	0.5	3.00	0.5	3.00	0.5	3.00	0.5	3.00
Mg stearate	0.5	3.00	0.5	3.00	0.5	3.00	0.5	3.00	0.5	3.00
Total	100	600.00	100	600.00	100	600.00	100	600.00	100	600.00

could be described by a site/bond-percolation phenomenon (12,13).

A cluster is defined as a group of neighbor-occupied sites in a lattice (14,15). When this cluster extends from one side to the rest of the sides of the lattice—percolates the whole lattice—it is considered as infinite or percolating cluster. Applied to a pharmaceutical tablet, it is obtained as a sample-spanning 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 of a component at which there is a maximum probability of appearance of a sample-spanning cluster of this component is named percolation threshold (16).

The application of this theory to study the hydration and drug release of hydrophilic matrices allows explaining the changes in release and hydration kinetics of swellable matrix extended delivery systems.

The aim of this work was to study and develop extended release matrix formulations for carbamazepine and verapamil HCl, containing HPMC as rate controlling polymer, fillers using the concepts of percolation theory.

MATERIALS

Carbamazepine and verapamil HCl were supplied by Recordatti (Italy). METHOCEL™ K100M CR was supplied by Colorcon (Colorcon Ltd., UK). Lactose was purchased from Safic-Alcan (Spain) and microcrystalline cellulose from Mingtai Chemical (Spain). Magnesium stearate and colloidal silicon dioxide NF were purchased from Acofarma (Spain).

Preparation of Matrices

HPMC matrices were formulated according to Tables I and II. All the components except lubricant and glidant (magnesium stearate and colloidal silicon dioxide, respectively) were mixed for 10 min using a Turbula mixer (Basel, Switzerland). Then, lubricant and glidant were added in order to improve certain processing characteristics and mixed for further 5 min. The obtained powder mixtures were compressed into tablets, using direct compression method for all formulations in a Bonals A-300 (Barcelone, Spain) tabletting machine.

The resulting mixture was directly compressed to produce tablets of 600 mg using flat punches of 12 mm diameter.

The tablets were prepared at the maximum compression force accepted by our formulations, using manual feeding.

Determination of Matrix Volume

According to the percolation theory, the excipient percolation threshold is the volume fraction at which there is a maximum probability that the excipient starts to form an infinite clusters which percolates the whole tablet.

Therefore, it is mandatory to know the volume fraction occupied by every component.

Tablet thickness and diameter were measured to ± 0.001 mm using a 25-mm digital micrometer (Comecta, SA). The tablet volume was calculated according to Eq. 1:

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

Table II. Composition for the Hydrophilic Matrices Prepared with Verapamil HCl and Different Concentrations of HPMC K100M CR and Microcrystalline Cellulose

	Batch V1		Batch V2		Batch V3		Batch V4		Batch V5	
Formulation	%	(mg)	%	(mg)	%	(mg)	%	(mg)	%	(mg)
Verapamil·HCl	30	180.00	30	180.00	30	180.00	30	180.00	30	180.00
HPMC K100M CR	10	60.00	20	120.00	30	180.00	35	210.00	40	240.00
MCC	40	240.00	30	180.00	20	120.00	15	90.00	10	60.00
Lactose	19	114.00	19	114.00	19	114.00	19	114.00	19	114.00
SiO2	0.5	3.00	0.5	3.00	0.5	3.00	0.5	3.00	0.5	3.00
Mg stearate	0.5	3.00	0.5	3.00	0.5	3.00	0.5	3.00	0.5	3.00
Total	100	600.00	100	600.00	100	600.00	100	600.00	100	600.00

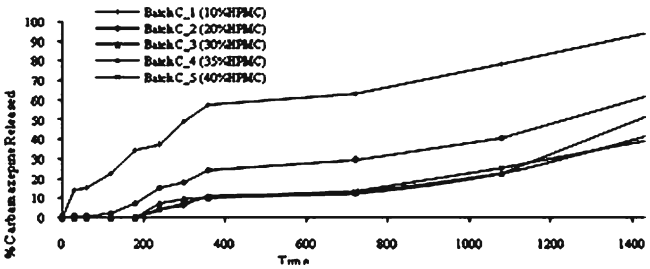

Fig. 1. Amount of carbamazepine released *versus* time for matrices with different concentrations of hydroxypropyl methylcellulose and lactose

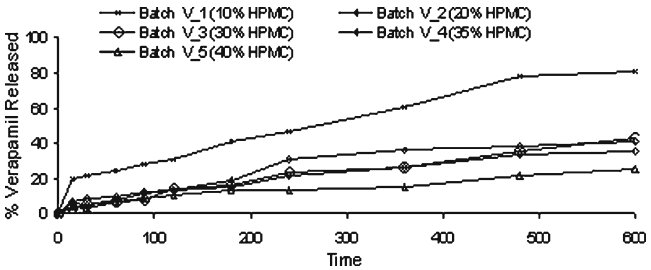

Fig. 2. Amount of verapamil HCl released *versus* time for matrices with different concentrations of hydroxypropyl methylcellulose and microcrystalline cellulose

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

Dissolution Studies

Dissolution Studies for Carbamazepine

Dissolution studies were performed at 37±0.5°C in 900 ml of distilled water, in a USP 26 using a rotating basket dissolution apparatus (Sotax Model 750D) at the rotation speed of 100±2 rpm. The sample (2 ml) was withdrawn at predetermined time interval. Samples were filtered and assayed using UV spectrophotometer (Agilent 8453) at 284 nm.

Dissolution Studies for Verapamil HCl

Dissolution studies were performed using the paddle method rotating at 50 rpm. As dissolution medium, 900 ml of pH7.5 buffer was used at a temperature of 37±0.5°C (USP 26). The sample (2 ml) was withdrawn at predetermined time interval. Samples were filtered and assayed using UV spectrophotometer (Agilent 8453) at 278 nm.

Release Kinetics

The suitability of several equations, which have been reported in the literature, to define drug release mechanisms, was tested with respect to the release data. To analyze the mechanism of drug release from the matrix tablets, data obtained from the dissolution studies were analyzed according to Eqs. 2, 3, and 4 of the Higuchi model (1963), the Korsmeyer–Peppas model (1983), and Peppas–Sahlin (1989), respectively:

$$Q = K_H t^{0.5} \tag{2}$$

$$Q = K_K t^n \tag{3}$$

$$Q = K_d t^m + K_r t^{2m} \tag{4}$$

In all mathematical expressions, Q is the amount of the drug dissolved in time t; K_H is the Higuchi rate constant; K_K is the release constant; n is diffusional exponent that depends on the release mechanism, for matrix tablets, an n value of 0.5 indicates diffusion control and an n value of 1.0 indicates erosion or relaxation control (13); intermediate values suggest that at least two processes contribute to the overall release mechanism, K_d is the diffusional rate constant, K_r is the rate relaxational constant, and m, purely Fickian diffusion exponent for a device of any geometrical shape which exhibits controlled release.

Estimation of the Percolation Threshold

In order to estimate the percolation threshold, the behavior of the kinetic parameters (Higuchi's slope "b," normalized Higuchi's slope "b/%v/v of HPMC," relaxation constant of Peppas–Sahlin "Kr") with respect to the volumetric fraction of each component at time zero, were studied.

Table III. Carbamazepine Release Characterization Using Kinetic Parameters (Higuchi's Slope, Korsmeyer Model, and Peppas and Sahlin Model)

	Higuchi			Korsmeyer			Peppas and Sahlin		
Batch	% (p/p)	b (% $t^{-1/2}$)	r^2	K (% t^n)	n	r^2	K_d (% t^{-m})	K_r (% t^{-2m})	r^2
C1	10	2.652	0.925	2.510	0.503	0.986	3.245	0.047	0.985
C2	20	1.878	0.934	0.173	0.800	0.986	0.288	0.099	0.986
C3	30	1.637	0.766	0.000	1.632	0.955	−0.937	0.125	0.035
C4	35	1.413	0.869	0.003	1.315	0.977	−0.705	0.102	0.969
C5	40	1.408	0.925	0.008	1.170	0.989	−0.581	0.097	0.986

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

Table IV. Verapamil HCl Release Characterization Using Kinetic Parameters (Higuchi's Slope, Korsmeyer Model, and Peppas and Sahlin Model)

	Higuchi			Korsmeyer			Peppas and Sahlin		
Batch	% (*p*/*p*)	b (% $t^{-1/2}$)	r^2	K (% t^{n})	n	r^2	K_d (% t^{-m})	K_r (% t^{-2m})	r^2
V1	10	2.879	0.965	4.238	0.441	0.992	4.086	0.041	0.992
V2	20	1.827	0.956	0.985	0.594	0.987	1.452	0.088	0.987
V3	30	1.811	0.949	0.303	0.773	0.996	0.399	0.149	0.996
V4	35	1.558	0.975	0.599	0.644	0.997	0.972	0.090	0.996
V5	40	0.987	0.970	0.665	0.561	0.994	0.935	0.039	0.994

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

According to percolation theory, in case that these parameters behave as critical properties, we can expect a sudden change in the values of the parameters in the neighborhood of the percolation threshold.

RESULTS AND DISCUSSION

Carbamazepine Release Characterization

To study the effect of polymer concentration on drug release, five different formulations for each drug, having different concentrations of HPMC and filler, were developed. Figure 1 shows the effect of different concentrations of HPMC and lactose; 10/40, 20/30, 30/20, 35/15, and 40/10 (% *w*/*w* of HPMC K100M CR/lactose) on release rate of carbamazepine.

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 10% and 20% *w*/*w* of HPMC K100M CR, related to the excipient percolation threshold. This means that above 20% *w*/*w* HPMC K100M CR, a percolating cluster of the excipient has been formed which controls the drug release from the matrices. Furthermore, as it can be observed in this Table III, the Higuchi's slope (2.65% to 1.87% $min^{-1/2}$), Korsmeyer's rate constant (2.51% to 0.17% min^{-n}) and the diffusional constant K_d of Peppas–Sahlin (3.24% to 0.28% min^{-2m}) underwent an important decrease between matrices containing 10% and 20% *w*/*w* of polymer.

Verapamil HCl Release Characterization

Figure 2 shows the verapamil HCl release profiles from the HPMC matrices, where there is an important change in the release profiles between 10% and 20% *w*/*w* of HPMC K100M CR. This indicates that above 20% *w*/*w* HPMC K100M CR, a percolating cluster of the excipient (polymer) has been formed 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.

The Higuchi's model and the non-linear regression of Peppas and Peppas–Sahlin were employed to confirm this estimation. Table IV shows that the Higuchi's slope (2.87% to 1.82% $min^{-1/2}$), Korsmeyer's rate constant (4.23% to 0.98% min^{-n}) and the diffusional constant K_d of Peppas–Sahlin (4.06% to 1.45% min^{-2m}) underwent an important decrease between matrices containing 10% and 20% *w*/*w* of polymer.

According to the percolation theory, the existence of the critical points, where the kinetic properties undergo important changes, can be attributed to the modification of the matrix structure close to percolation thresholds.

Estimation of Excipient (Polymer) Percolation Thresholds

To estimate the excipient percolation threshold, normalized Higuchi rate constant was plotted *versus* the excipient volumetric fraction plus initial porosity. The evolution of these release parameters has been studied as a

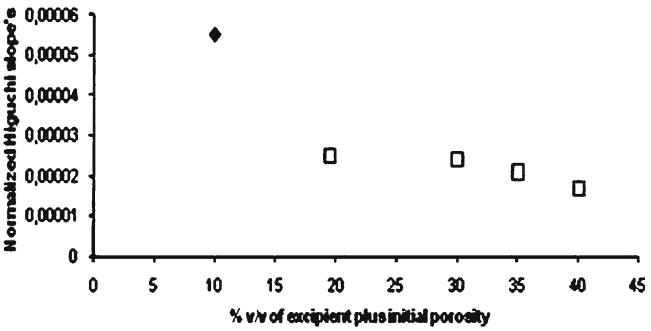

Fig. 3. Normalized Higuchi's slope *versus* percentage of the excipient volumetric fraction plus initial porosity for all the carbamazepine batches

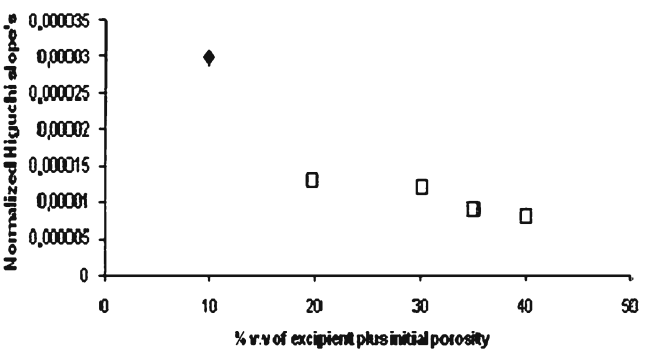

Fig. 4. Normalized Higuchi's slope *versus* percentage of the excipient volumetric fraction plus initial porosity for all the verapamil batches

function of the sum of the excipient volumetric percentage plus initial porosity. Recent studies have shown that the existence of a sample-spanning cluster of excipient plus pores in the hydrophilic matrix before the matrix is placed in contact with the liquid, conditions for the release kinetics of the drug (7–11).

The results for tablets containing carbamazepine and verapamil HCl are shown in Figs. 3 and 4.

According to the principles of the percolation theory, the critical points for both formulations are between 10% and 20% *w*/*w* of HPMC K100M CR (10.0% and 19.5% *v*/*v* HPMC K100M CR for carbamazepine tablets and 9.9% and 19.7% *v*/*v* for verapamil HCl tablets). 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. In order to ensure batch to batch consistency, it has been indicated that an HPMC use level of around 30% *w*/*w* in the formulation. It is important to note that in the case of the water-soluble drug, verapamil HCl, the matrix forming polymer (HPMC) was replaced in the formulations by a filler with very low water-soluble filler, MCC (Table II); whereas in the carbamazepine matrices, the HPMC was replaced by a freely water-soluble filler, lactose (Table I). Despite this important difference, the HPMC critical points appeared to lie in the same concentration range.

CONCLUSIONS

Formulations of HPMC matrices containing different drugs and fillers mixtures have been studied from the percolation theory point of view. The HPMC percolation threshold has been estimated in matrices containing drugs with very different water solubilities. Results showed that there was no significant influence of drug solubility on the HPMC critical concentration threshold (excipient percolation threshold). This may be indicative of the versatility and broad functionality of the HPMC percolation thresholds and therefore, of the robustness of this polymer to control the drug release from different formulations.

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