# Study of the Critical Points in Lobenzarit Disodium Hydrophilic Matrices for Controlled Drug Delivery

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**Percolation theory is a multidisciplinary theory that studies chaotic systems. It has been applied in the pharmaceutical field since 1987. The application of this theory to study the release and hydration rate of hydrophilic matrices allowed for first time to explain the changes in release and hydration kinetic of swellable matrices type controlled delivery systems. The objective of the present paper is to estimate the percolation threshold of HPMC K4M in matrices of lobenzarit disodium and to apply the obtained result to the design of hydrophilic matrices for the controlled delivery of this drug. The materials used to prepare the tablets were Lobenzarit disodium (LBD) and HPMC of viscosity grade K4M. The drug mean particle size was 42±0.61 $\mu$m and the polymer was sieved and 150—200 $\mu$m granulometric fraction was selected. The formulations studied were prepared with different excipient contents in the range of 10—80% 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. According to percolation theory, the critical points observed in dissolution and water uptake studies are attributed to the existence of an excipient percolation threshold. This threshold was situated between (18.58 to 24.33% v/v of HPMC). Therefore, the LBD-HPMC K4M matrices with a relative HPMC particle size of should be formulated with an excipient content above 24.33% v/v of HPMC, to obtain a control of the drug release from these systems.**

**Key words** percolation theory; lobenzarit dissodium; gel layer; HPMC; swelling; percolation threshold

The hydrophilic matrices are one of the most used types of Controlled Release Systems in the world. In comparison with other Controlled Release Devices, they have the advantage of their low cost and simple technology, that facilitates their application to an important sector of the population, as well as their safety against the dose dumping (accidental fast release of the whole drug dose).[1)] Another advantage of these matrices concerns the drug release kinetics. Using these systems, it is possible to obtain a variety of release kinetics, including in some cases zero-order release kinetics.[2)]

The study of hydrophilic matrices 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.[3—11)]

In recent works, our research group has applied 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.[12—14)]

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.[15—19)]

Our research group is employing the percolation theory in order to describe solid forms, in concrete controlled release inert matrix systems.[15,16,20—26)]

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.[27)]

The application of this theory to study the release and hydration rate of hydrophilic matrices allowed for first time to explain the changes in release and hydration kinetic of swellable matrices type controlled delivery systems.[12—14)] According to this theory, the critical points observed in dissolution and water uptake studies can be attributed to the existence of excipient percolation thresholds. The knowledge of these thresholds is very important to optimize the design of swellable matrix tablets. Above the excipient percolation threshold an infinite cluster of this component is formed, controlling the hydration and release rate. Below this threshold the excipient does not percolate the system and, as a consequence, the drug release can not be controlled. It has to be emphasized that the infinite cluster of excipient responsible for the drug release control must be present before the matrix is placed in the dissolution medium, *i.e.*, before the swelling process starts.[14)]

Lobenzarit disodium is a drug conceived for the treatment of rheumatoid arthritis. This drug produces an improvement of immunologic abnormalities and has a regulatory effect upon the antibody producing system.[28)] Its is administered orally in form of tablets and its daily dosage is 240 mg (80 mg three doses per day).

According to its pharmacokinetic and dosage characteristics and to the results obtained from the preformulation study carried out by our research team,[29)] it is a suitable candidate for the design of controlled release delivery systems.

The design of oral controlled release systems of lobenzarit disodium would present the advantage of less frequent dosing. This fact is very important in the case of a chronic disease, as is the rheumatoid arthritis.

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The objective of the present paper is to estimate the percolation threshold of HPMC K4M in matrices of lobenzarit disodium and to apply the obtained result to the design of hydrophilic matrices for the controlled delivery of this drug.

**Experimental**

The materials used to prepare the tablets were Lobenzarit disodium (LBD) prepared in the Synthesis Laboratory of the Center of Pharmaceutical Chemistry (Cuba) and hidroxypropyl methylcellulose of viscosity grade K4M (HPMC K4M, Dow Chemical Company), a hydrophilic, swelling polymer as matrix-forming material.

The drug was not sieved but its mean particle size was measured as $42\pm0.61\,\mu$m using a He-Ne laser diffraction system (Malvern Instr., type Matersize x, 1.2 b). The polymer was sieved (Restch type Vibro) and 150—200 $\mu$m granulometric fraction was selected.

Binary mixtures were prepared with different excipient contents (10, 15, 20, 30, 40, 50, 60, 70, 80% w/w) keeping constant the dose of the drug (150 mg of LBD) (see Table 1). Both components were mixed for 3 min (optimal mixing time) using a Turbula mixer.

The mixtures were compressed with an eccentric machine (Bonals A-300) without any further excipient. Cylindrical tablets with a diameter of 9 mm (lots between 10—50% w/w of excipient) and a diameter of 12 mm (lots 60, 70 and 80% w/w of the HPMC) were prepared at the maximum compression force accepted by our formulations.

Dissolution studies were carried out at $37\pm0.5$ °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 LBD 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 mechanism of drug release was analysed according to Higuchi (1963) (Eq. 1),[30] Korsmeyer (1983) (Eq. 2)[31] and Peppas–Sahlin (1989) (Eq. 3) equations,[32]

$$\frac{Q_t}{Q_\infty} = b \cdot t^{1/2} \tag{1}$$

Table 1. Composition of the Assayed Tablets

| Lot | LBD (mg) | HPMC % (w/w) |
|---|---|---|
| 1 | 150 | 10 |
| 2 | 150 | 15 |
| 3 | 150 | 20 |
| 4 | 150 | 30 |
| 5 | 150 | 40 |
| 6 | 150 | 50 |
| 7 | 150 | 60 |
| 8 | 150 | 70 |
| 9 | 150 | 80 |

$$\frac{Q_t}{Q_\infty} = K \cdot t^n \tag{2}$$

where $Q_t/Q_\infty$ is the fraction of drug released; $b$ and $K$ are kinetic constants; $n$ is a diffusional exponent that depends on the release mechanism and on the shape of the swelling device tested.[33] 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.

$$\frac{Q_t}{Q_\infty} = K_d \cdot t^m + K_r \cdot t^{2m} \tag{3}$$

where $Q_t/Q_\infty$ is the fraction of drug released; $K_d$ 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.

Water uptake measurements were carried out using a modified Enslin apparatus. The amount of water uptaken at each time point was read from a precision balance (Scaltec SBC 31) linked to a chart recorder and a personal computer.

The Davidsons and Peppas (1986) (Eq. 4)[34] model was applied to these data to study the mechanism and the rate of water uptake.

$$w = K_s \cdot t^n \tag{4}$$

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

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, was studied.

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

$$X \propto S \cdot (p - p_c)^q \tag{5}$$

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.

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.[14]

## Results and Discussion

**Study of Release Profiles and Release Kinetics** Figure 1 shows the percentage of drug released from the studied matrices. As it can be observed in this figure, two important changes in the release profiles appear between 10—15% w/w of HPMC and between 20—30% w/w of HPMC.

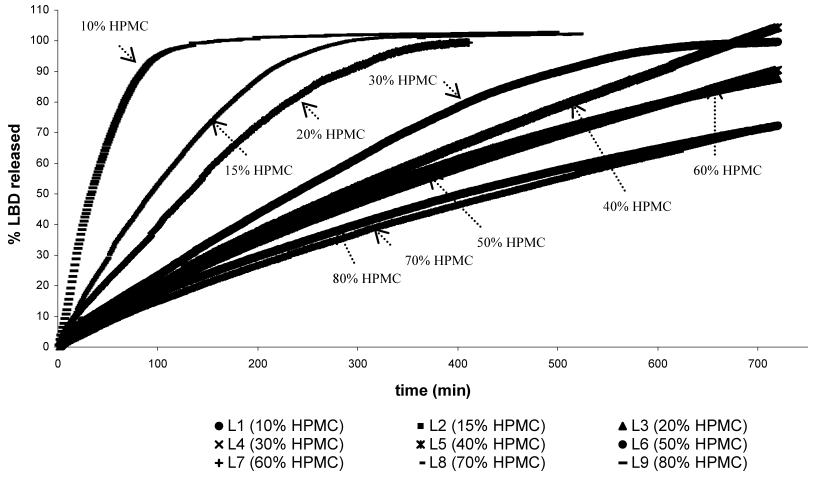


Fig. 1. Dissolution Profiles for Tablets Prepared with Different Excipient Contents

Table 2. Dissolution Data for Matrices Prepared with LBD/HPMC K4M (150—200 $\mu$m)

| Lot | HPMC % (w/w) | Higuchi | | Korsmeyer | | | Peppas–Salhin | | |
|---|---|---|---|---|---|---|---|---|---|
| | | $b$ (% min$^{-1/2}$) | $r^2$ | $K$ (% min$^{-n}$) | $n$ | $r^2$ | $K_d$ (% min$^{-m}$) | $K_r$ (% min$^{-2m}$) | $r^2$ |
| 1 | 10 | 12.741 | 0.998 | 15.877 | 0.460 | 0.998 | 3.911 | 1.050 | 0.983 |
| 2 | 15 | 7.819 | 0.996 | 3.126 | 0.649 | 0.999 | −1.15[a)] | 1.508 | 1.000 |
| 3 | 20 | 6.764 | 0.988 | 1.459 | 0.742 | 0.996 | 1.116 | 0.494 | 0.995 |
| 4 | 30 | 5.056 | 0.986 | 0.620 | 0.808 | 0.999 | 0.398 | 0.387 | 0.998 |
| 5 | 40 | 4.539 | 0.991 | 0.706 | 0.763 | 1.000 | 0.517 | 0.313 | 0.999 |
| 6 | 50 | 4.024 | 0.996 | 0.849 | 0.714 | 1.000 | 0.943 | 0.262 | 0.999 |
| 7 | 60 | 6.963 | 0.998 | 2.023 | 0.591 | 0.999 | 1.571 | 0.164 | 0.994 |
| 8 | 70 | 3.309 | 0.997 | 0.633 | 0.726 | 1.000 | 0.605 | 0.202 | 0.999 |
| 9 | 80 | 3.570 | 0.997 | 1.243 | 0.629 | 0.999 | 1.205 | 0.187 | 0.997 |

$b$, 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; $m$ is the diffusional exponent that depends on geometric shape of the releasing device through its aspect ratio. *a*) The negative values obtained for $K_d$ in lot 2 should be interpreted in terms of a diffusion process insignificant compared to the relaxation mechanism.

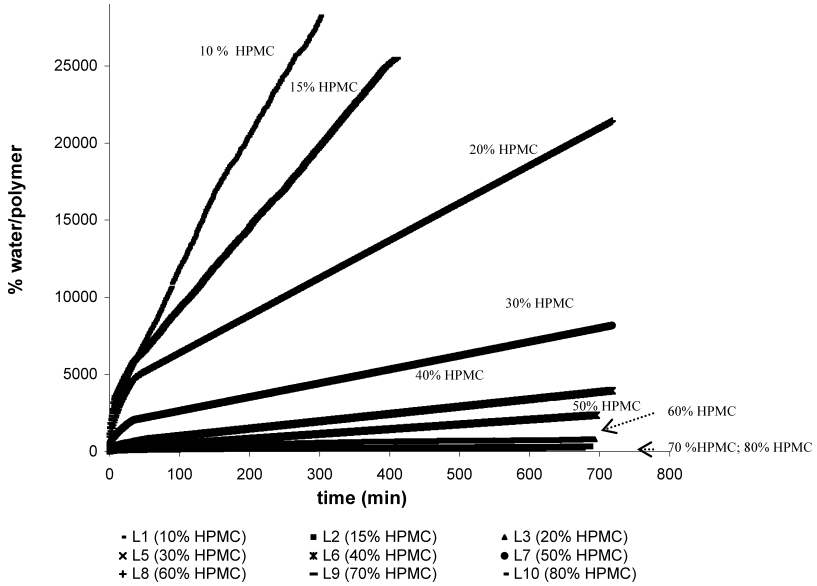


Fig. 2. Water Uptake Profiles for Tablets Prepared with Different Excipient Contents

The Higuchi's model as well as the non-linear regression of Peppas and Peppas–Sahlin were employed to study the release data. The results obtained are shown in Table 2. As it can be observed in this table, the Higuchi's slope (12.741 to 7.819% min$^{-1/2}$), Korsmeyer's rate constant (15.877 to 3.126% min$^{-n}$) and the relaxational constant $K_d$ of Peppas–Sahlin (3.911 to −1.15% min$^{-m}$) underwent an important decrease between matrices containing 10 and 15% w/w of excipient.

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 10—15% w/w of HPMC K4M, related to the excipient percolation threshold. This means that above 15% w/w HPMC K4M, a percolating cluster of the excipient has been formed which controls the drug release from the matrices studied. 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 15% w/w HPMC the excipient does not percolate the system, and as consequence, the drug release is not controlled.

**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.[11,35,36)] In this section a study of the hydration rate of the matrices has been carried out, in order to obtain more information about the critical points observed in the study of drug release.

The obtained water uptake profiles are shown in Fig. 2. As it can be observed in this figure, when the drug loading of the matrices decreases, the hydration rate is lower. Two important changes in the water uptake profiles appear between 20—30% w/w of HPMC and between 10—20% w/w of HPMC. In addition, the swelling kinetic parameters calculated by fitting the water uptake data according to the Davidsons and Peppas model, showed two important decreases in the swelling constant (see Table 3). A first decrease situated between matrices containing 20—30% w/w of HPMC (from $k$=306.720 to $k$=154.891) and a second decrease between 10—20% w/w of HPMC (from $k$=414.254 to $k$=306.720).

According to the results obtained of the study of the hydration rate "only", the excipient percolation threshold should be situated between 10—20% w/w of HPMC or be-

tween 20—30% w/w of HPMC, but providing the results obtained of the release study, can say that the excipient percolation threshold is close to 15% w/w of HPMC. The results obtained from the studies of the release rate and hydration rate, show the existence of critical points related to an excipient percolation threshold, being this thresholds one of the main factors that govern gel-layer formation and, consequently, the control of the drug release from hydrophilic matrices.

**Estimation of the Excipient Percolation Threshold** The excipient percolation thresholds have been estimated as described in Experimental

In order to estimate the percolation threshold, the evolution of the measured kinetic parameters ("*b*" Higuchi's slope, "*b*/%v/v of HPMC" Higuchi's slope normalized, "$K_r$" relaxational constant of Peppas–Sahlin) as a function of the volumetric fraction of the excipient at time zero, was studied. The results obtained are shown in Fig. 3.

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

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

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.

As indicated in Experimental two linear regressions have been performed as an approximation for estimating the percolation threshold as the point of intersection between both regressions. In the case of the relaxation constant of Salhin, this method can not be applied. Nevertheless, an important change can be observed close to 24.33% v/v of HPMC (Fig. 3c).

The values of the excipient percolation threshold estimated for all the batches studied, based on the behaviour of the kinetic parameters, are shown in Table 4.

As this table shows, the excipient percolation threshold for the studied hydrophilic matrices is situated between 18.58 and 24.33% v/v of HPMC.

In conclusion, according to percolation theory, the critical points observed in dissolution and water uptake studies are attributed to the existence of an excipient percolation threshold. This threshold was situated between (18.58 to 24.33% v/v of HPMC). Therefore, the LBD-HPMC K4M matrices with a relative HPMC particle size of should be formulated with an excipient content above 24.33% v/v of HPMC, to obtain a control of the drug release from these systems.

New studies are needed in order to know the critical points governing the control of the drug release from hydrophilic

Table 3. Water Uptake Data Prepared with LBD/HPMC K4M (150—200 $\mu$m)

| | | Davidsons and Peppas | | |
|---|---|---|---|---|
| Lot | % w/w of HPMC | $K_s$ (% min$^{-n}$) | $n$ | $r^2$ |
| 1 | 10 | 414.254 | 0.738 | 0.999 |
| 2 | 15 | 381.011 | 0.694 | 0.999 |
| 3 | 20 | 306.720 | 0.640 | 0.998 |
| 4 | 30 | 154.891 | 0.597 | 0.998 |
| 5 | 40 | 31.112 | 0.733 | 0.999 |
| 6 | 50 | 12.668 | 0.796 | 0.999 |
| 7 | 60 | 55.940 | 0.408 | 0.999 |
| 8 | 70 | 17.804 | 0.449 | 1.000 |
| 9 | 80 | 12.765 | 0.374 | 1.000 |

$K_s$, kinetic constant of water penetration; $t$, penetration time; $n$, diffusional exponent which depends on the water penetration mechanism.

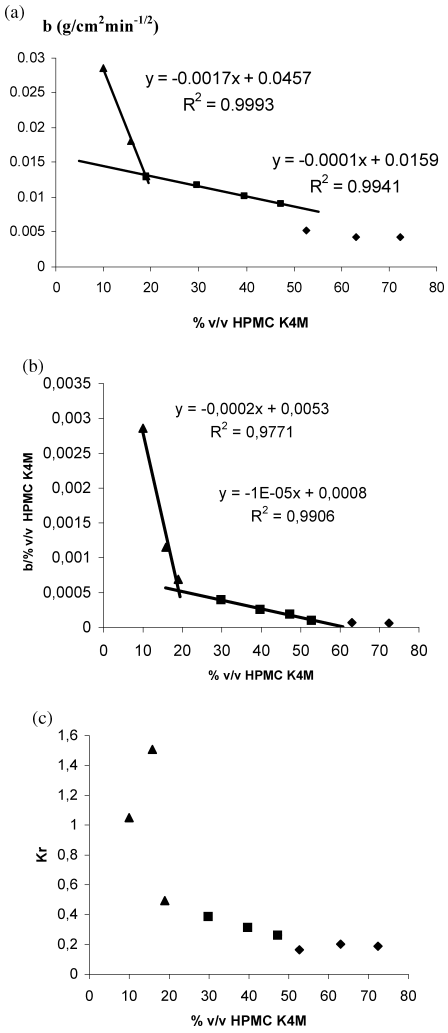


Fig. 3. (a) Higuchi Slope's, (b) Normalized Higuchi Slope's, (c) Relaxational Constant of Peppas–Sahlin *versus* Percentage of the Excipient Volumetric Fraction

Table 4. The Values of the Excipient Percolation Thresholds, According to the Kinetic Parameters Used

| Kinetic parameters | Equations | $r^2$ | Point of the Intersection |
|---|---|---|---|
| Higuchi's slope (g/cm$^2$) | $Y_1 = -1.15\times10^{-4}x + 0.0165$ | 0.990 | $X = 18.58$ |
| | $Y_2 = -1.73\times10^{-3}x + 0.0457$ | 0.995 | |
| Higuchi's slope (g/cm$^2$)/%v/v HPMC | $Y_1 = -1.24\times10^{-5}x + 7.64\times10^{-4}$ | 1.000 | $X = 19.12$ |
| | $Y_2 = -2.48\times10^{-4}x + 5.27\times10^{-3}$ | 0.988 | |
| Relaxational constant ($K_r$) | The linear regressions can not be performed | | Important change close to 24.33 |

matrices, one of the more widely used controlled release systems in the world.

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