Estimation of the Percolation Thresholds in Lobenzarit Disodium Native Dextran Matrix Tablets

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ABSTRACT

The objective of the present work is to estimate for the first time the percolation threshold of a new series of dextran (native dextran of high molecular weight [B110-1-2, Mw = 2×10^6]), in matrices of lobenzarit disodium (LBD) and to apply the obtained result to the design of hydrophilic matrices for the controlled delivery of this drug. The formulations studied were prepared with different amounts of excipient in the range of 20% to 70% wt/wt. Dissolution studies were performed using the paddle method (100 rpm) and one face water uptake measurements were performed using a modified Enslin apparatus. The Higuchi, zero-order, and Hixson-Crowell models as well as the nonlinear regression model were employed as empiric methods to study the release data. Values of diffusion exponent $0.563 < n < 0.786$ (Korsmeyer equation) for dissolution profile and water uptake mechanism $0.715 < n < 1$ (Davidson and Peppas equation) suggested anomalous or complex mechanisms. On the other hand, the contribution of the relaxation or erosion and of the diffusive mechanism in Peppas-Sahlin equation indicated that the main mechanism for drug delivery from tablets is swelling controlled delivery ($K_r/K_d < 1$). The critical points observed in kinetic parameters above 58.63% vol/vol of native dextran B110-1-2 plus initial porosity in the LBD-dextran matrices with a relative polymer/drug particle size of 4.17 were attributed to the existence of an excipient percolation threshold.

KEYWORDS: Dextran, lobenzarit, percolation, swelling, threshold.

INTRODUCTION

Among the numerous macromolecules that can be used for a swellable controlled release system, polysaccharides are extremely advantageous compared with synthetic polymers as they are widely present in living organisms and often are produced by recombinant DNA techniques. Coming from renewable sources, polysaccharides also frequently have economical advantages over synthetic polymers. Polysaccharides are usually nontoxic, biocompatible, and show several peculiar physicochemical properties that make them suitable for different applications in drug delivery systems.[1]

Dextrans can be defined as glucose homopolysaccharides that feature a substantial number of consecutive α-(1→6) linkages in their major chains, usually more than 50% of the total linkages. These α-D-glucans possess also side chains stemming from α-(1→2), α-(1→3), or α-(1→4) branch linkages.[2,3]

Drug release from swellable matrix tablets is based on the glassy-rubbery transition of the polymer, which occurs as a result of water penetration into the matrix. Therefore, the gel layer is physically delimited by the erosion (swollen matrix-solvent boundary) and swelling (glassy-rubbery polymer boundary) fronts.[4]

Water-soluble drugs are released primarily by diffusion of dissolved drug molecules across the gel layer, while poorly water-soluble drugs are released predominantly by erosion mechanisms.[5,6]

The factors influencing the release of drugs from hydrophilic matrices include viscosity of the polymer, ratio of the polymer to drug, mixtures of polymers, compression pressure, thickness of the tablet, particle size, pH of the matrix, entrapped air in the tablet, solubility of the drug, the presence of excipients or additives, and the mode of the incorporation of these substances.[7,8]

The principles of the percolation theory have been applied to design hydroxypropyl methylcellulose (HPMC) K4M controlled release matrix tablets containing lobenzarit disodium (LBD), KCl, and acyclovir.[9-11] Percolation theory is a statistical theory that studies disordered or chaotic systems where the components are randomly distributed in a lattice. It has wide application in many scientific disciplines and was introduced and later discussed in the pharmaceutical field by Leuenberger and coworkers in 1987 and 1996 to improve the characterization of solid dosage forms.[12,13]

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A cluster is defined as a group of neighbor-occupied sites in a lattice.[14] 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 a percolating cluster. Applied to a pharmaceutical tablet, the cluster 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 the appearance of a sample-spanning cluster of this component is the "percolation threshold." In a binary pharmaceutical tablet, 2 percolation thresholds are expected: the drug and the excipient percolation thresholds. These percolation thresholds are critical concentrations, where some tablet properties (percentage of drug released, release rate, mechanical properties, etc) may undergo sudden changes.[15] 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 (ie, before the swelling process starts).[9-11]

The knowledge of the percolation threshold of the components of the matrix formulations contributes to improving their design: first, to reduce the time to market; and second, to increase their robustness when they are prepared at industrial scale, avoiding the formulation near to the percolation threshold.

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.[16] It is administered orally in the form of tablets, and its daily dosage is 240 mg (80 mg, 3 doses daily).

The objective of the present work was to estimate the percolation threshold of the new series native dextran B110-1-2 excipient (DT)[3,7,17] in LBD matrix tablets, and to characterize the release behavior of these hydrophilic matrices, in order to rationalize the design of these controlled release systems.

MATERIALS AND METHODS

Materials

Commercial native dextran B512-F (molecular weight [Mw] = 5 000 000 to 40 000 000, according to manufacturer's data, and Mw = 22 000 000, according to viscometer analysis)[7] was obtained from Sigma (St Louis, MO) and used as reference polymer. High molecular weight native dextran (B110-1-2, Mw 2 000 000)[7] was obtained from the Center of Studies of Sugar Cane (Havana, Cuba). Lobenzarit disodium (LBD) was prepared in the Synthesis Laboratory at the Cen-

ter of Pharmaceutical Chemistry (Havana, Cuba). Other chemicals and reagents were analytical grade.

Preparation of Matrix Tablets

The polymer was sieved (Retsch type Vibro, Haan, Germany) and the granulometric fractions 150 to 200 μm were employed. The drug was not sieved but its mean particle size was measured as 42 ± 0.61 μm using a He-Ne laser diffraction system (Mastersizer X, 1.2 b, Malvern Instruments, Malvern, UK). The true density of LBD, 2.159 g/cm^3, and dextran, 1.430 g/cm^3, were taken from the literature and from manufacturer reports.[18] The true density of drug and polymer also were calculated using an air pycnometer (Quantachrome Instruments, Stereopycnometer spy-3, Boynton Beach, FL) and similar values to the manufacturer's data were achieved.

Binary mixtures were prepared with varying polymer contents (20%, 30%, 40%, 50%, 60%, and 70% wt/wt) keeping constant the drug and excipient particle size without any further excipient. Table 1 shows the composition of the studied batches as well as the tablet thicknesses (n = 12). Both components were mixed for 3 minutes (optimal mixing time) using a Turbula mixer (Willy A. Bachofen AG Maschinenfabrik, Basel, Switzerland).

The mixtures were compressed with a PerkinElmer (Cambridge, UK) hydraulic press fitted with a 10-mm-diameter punch. After some time (~10 seconds), the formed tablets were ejected from the punch. Based on a previous study in which the influence of compression force was studied as a function of the reduction in volume of a dextran placebo tablet, compression force of 14 kN was applied for all experiments in order to minimize initial porosity of tablets.[3]

A scanning electron microscope (SEM) (Philips type S-4000, Eindhoven, The Netherlands) with a backscattering electrons

Table 1. Properties of the 150-mg LBD Tablets at Various Amounts of DT*

Batch	DT % (wt/wt)	Tablet Weight† (mg)	Tablet Thickness† (mm)
1	20	187.5 ± 1.7	1.534 ± 0.061
2	30	214.2 ± 1.5	1.817 ± 0.053
3	40	250.0 ± 1.2	2.139 ± 0.049
4	50	300.0 ± 1.0	2.683 ± 0.051
5	60	375.0 ± 1.8	3.283 ± 0.047
6	70	500.0 ± 1.0	4.357 ± 0.050

*LBD indicates lobenzarit disodium; DT, dextran B110-1-2 excipient.
†Values expressed as the mean of experimental ± relative standard deviation values for 12 samples.
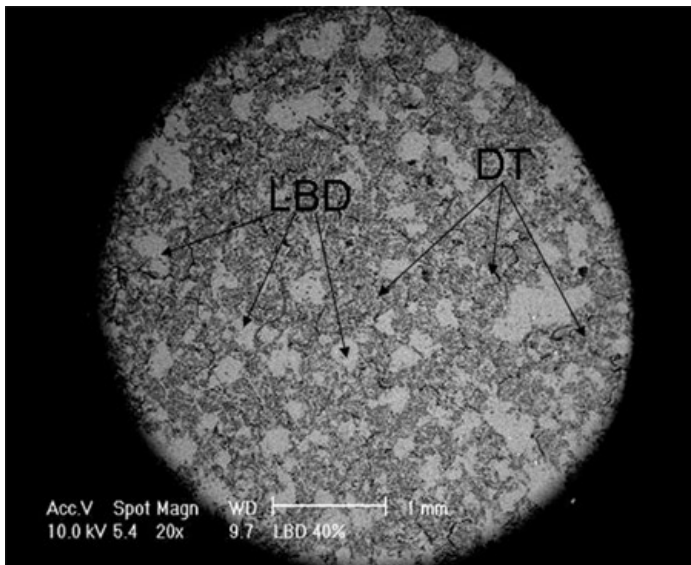
Figure 1. Scanning electron photomicrograph showing surface tablet of batch DT 60% wt/wt with infinite cluster of DT particles. DT indicates dextran B110-1-2 excipient. Original magnification ×20.

detector (BSE) was employed in order to study the tablet surface and to obtain an idea about formation of DT infinite cluster (Figure 1).

In vitro drug release studies

Dissolution studies were performed at 37°C ± 0.5°C in 900 mL of distilled water, in a United States Pharmacopeia (USP) XXV apparatus (SotaxAT7 Smart, Teknokroma, Barcelona, Spain) using the paddle method. The rotation speed was kept constant at 100 rpm. Release of LBD was detected by UV spectrophotometer method at 360 nm during 8 hours. Three replicates of filtered samples, taken at different times, were performed for each determination, and the mean values were used to obtain the release profiles. The total amount of drug present in the tablets was calculated as the sum of the cumulative mass of drug released in the last sample and the mass of drug remaining (residue). The technique was previously validated. The validation method was performed by analyzing solution containing several concentrations of LBD in 5 replicates. Furthermore, these solutions were analyzed in triplicate on 5 different days (n = 15). The results showed a good linearity (r^2 = 0.9940), with appropriate precision (coefficient of variation [CV] <2%) and accuracy values (≥98.98%). The absence of interference of dextran was checked by comparing the data obtained from pure substance LBD and from samples spiked with polymer.[3]

The mechanism of drug release was analyzed according to Zero-Order (Equation 1), Higuchi (Equation 2), Hixson-Crowell (Equation 3), Korsmeyer (Equation 4), and Peppas-Sahlin (Equation 5) equations:

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

$$\frac{Q_t}{Q_\infty} = k_h \cdot t^{1/2}, \qquad (2)$$

$$\frac{Q_t}{Q_\infty} = (1 - k_w \cdot t)^{1/3}, \qquad (3)$$

$$\frac{Q_t}{Q_\infty} = K \cdot t^n, \qquad (4)$$

where Q_t/Q_∞ is the fraction of drug released; k_0, k_h, k_w, and K are kinetic constants; and n is a diffusional exponent that depends on the release mechanism and on the shape of the swelling device tested. 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; and values of n = 1.0 show a case-II (purely erosion/relaxation controlled) drug release.

$$\frac{Q_t}{Q_\infty} = K_d \cdot t^m + K_r \cdot t^{2m}, \qquad (5)$$

where 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.[19]

Water Uptake Studies

The process of water penetration into the hydrophilic matrix tablets was studied using a modified Enslin apparatus. This apparatus contains a fritted and a system to regulate the water level. When the tablet is placed on the fritted, the water is absorbed from a reservoir that is placed on a precision balance (Scatlec SBC 31, Goettingen, Germany). The amount of water uptake at each time point was read from the balance as weight loss in the reservoir. The balance is linked to a chart recorder and a personal computer. The rate of water penetration was expressed as the weight gain of the swelled matrix, in percentage wt/wt of penetrated fluid with respect to dry polymer.[20] The kinetics of the water uptake into hydrophilic matrices was analyzed according to the Davidsons and Peppas model by following equation:

$$W = K_S \cdot t^n, \qquad (6)$$

where W is the weight gained by the swelled matrix (water/dry polymer); K_S is the kinetic constant of water penetration; t is the penetration time; and n is the exponent that depends on the water penetration mechanism.[20]

Estimation of the Percolation Threshold

In order to estimate the percolation threshold, the behavior of the kinetic parameters with respect to the sum of the excipient volumetric fraction plus initial porosity (expressed in percentage) at time zero was studied. The following kinetic parameters have been included in this study: Higuchi's slope, Zero-order's slope (k_h and k_o, respectively), normalized k_h/% vol/vol of DT plus initial porosity, normalized k_o/% vol/vol of DT plus initial porosity, diffusional K_d and relaxational K_r constant of Peppas-Sahlin.[9]

According to the fundamental equation of percolation theory (Equation 7), if these parameters behave as critical properties, it is expected that

$$X \propto S \cdot (p - p_c)^n, \qquad (7)$$

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

The kinetic parameters studied show a nonlinear behavior as a function of the volumetric fraction of the DT plus initial porosity. 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.[9-11]

The initial porosity (IP) was calculated using the following equation:

$$\varepsilon(\%) = 100 \cdot \left(\frac{Vt - \left(\frac{w \cdot \%LBD}{pLBD} \right) - \left(\frac{w \cdot \%DT}{pDT} \right)}{Vt} \right), \qquad (8)$$

where $\varepsilon(\%)$ is the initial porosity in percentage; Vt is the tablets' volume; w is the tablet weight; $pLBD$ is the drug density; and pDT is the dextran density.

RESULTS AND DISCUSSION

Release Profiles and Release Kinetics

Figure 2 shows initial porosity (in percentage), aspect ratio, and percentage vol/vol of DT obtained for the 6 batch studies (DT 20% wt/wt to DT 70% wt/wt, respectively). In this case,
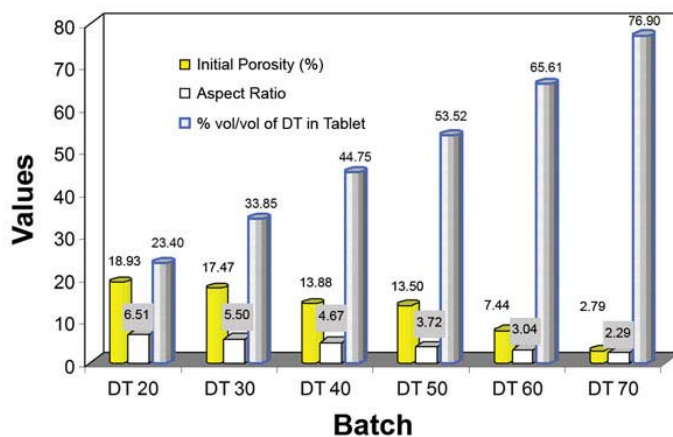

Figure 2. Initial porosity, aspect ratio, and % vol/vol DT in tablet for batches DT 20% to DT 70%, wt/wt. DT indicates dextran B110-1-2 excipient.

critical values of porosity for variant DT 70% wt/wt were achieved (2.79%). Figure 3 shows dissolution profiles for tablets of LBD with DT-B110-1-2 (DT 20% to DT 70% wt/wt, particle size 150-200 μm). The value for relative standard deviation was lower 5% for all points measured (n = 12).

The Higuchi, Zero-Order, and Hixson-Crowell models as well as the nonlinear regression of Korsmeyer and Peppas-Sahlin were employed as empiric methods to study the released data. The results obtained are shown in Table 2. As can be observed, the Hixson-Crowell model does not fit at all the dissolution profile, indicating that erosion is not the main mechanism ($r^2 < 0.650$).

For batch DT 20% wt/wt and DT 30% wt/wt, the dissolution profile fit better to the Zero-Order model ($r^2 = 0.945$ and $r^2 = 0.920$, respectively) than the Higuchi model ($r^2 = 0.883$ and $r^2 = 0.892$, respectively). In this case, tablets have very small thickness (ie, longer aspect ratio compared with batches DT 40% wt/wt to DT 70% wt/wt; Figure 2), and drug diffusion is much faster than the movement of glassy rubbery interface; thus a zero-order release profile is expected, similar as occurs for a slab system.[21]

The matrix system DT 70% wt/wt showed an n value very close to 1.0 (zero-order kinetics), and an increase in the total period of drug release was observed. As in all of these experimental cases, the drug release profile is determined by the profiles of medium infiltration into the matrix tablet and the erosion profile of the matrix. Minimizing the porosity of the matrix system in DT 70% wt/wt (initial porosity 2.79%) also decreased interstitial channels, and consequently decreased diffusion (litter increment of the ratio K_r/K_d) and lower drug release can be observed even from the initial time (Figure 3 and Table 2).
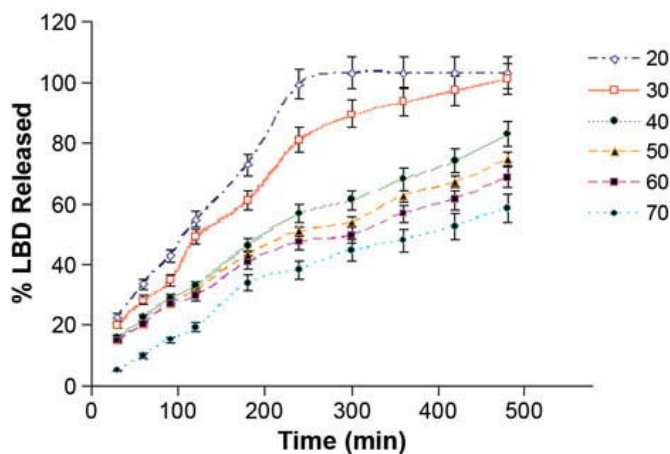
Figure 3. Dissolution profiles for tablets prepared with different DT contents. DT indicates dextran B110-1-2 excipient; LBD indicates lobenzarit disodium.

Values of the diffusion exponent 0.563 < n < 0.786 (Korsmeyer equation) for the dissolution profile of sparingly soluble drug correspond to anomalous diffusion mechanism; these results are in good agreement with other authors.[3,10] This can be also observed in Peppas-Sahlin equation. The model can identify the different contributions of the relaxation or mechanism erosion and of the diffusive mechanism. In Equation 5 (Peppas-Sahlin), the values obtained for K_r were lower than K_d for all dissolution profiles.

The central element of the release mechanism in swellable systems is the gel-layer formation around the matrix in response to water penetration. Phenomena such as water penetration, polymer swelling, drug dissolution and diffusion, and matrix erosion govern the gel-layer formation and, consequently, the drug release rate. In addition, the viscosity of a polymer has a great influence on the erosion rate, which can be adjusted by using different viscosity grades of polymers or by combining different kinds of polymers.[3,7]

The main mechanism for drug delivery from DT tablets is swelling-controlled delivery (K_r/K_d < 1, for all experiments; Table 2). For batch DT 40% to DT 70% wt/wt, hydrogels may undergo a swelling-driven phase transition from a glassy state where entrapped molecules remain immobile to a rubbery state where molecules rapidly diffuse. In these systems, the rate of molecule release depends on the rate of gel swelling. Drug-loaded DT tablets are 3-dimensional, hydrophilic matrices that are usually stored in a dry, glassy state. After oral administration, DT polymer absorbs liquid and a rapid glassy-to-rubbery phase transition occurs once the glass transition temperature (Tg) is reached, causing the systematic release of loaded drugs. The drug release rates are modulated by the rate of water transport and the thickness of the gel layer. Taking into account the drug solubility of LBD, the prevalence of the swelling vs erosion mechanism can be expected.

Water Uptake Assays and Swelling Kinetics

Since the favorable properties of hydrogels stem from their hydrophilicity, the characterization of their water-sorption capabilities is the first step toward understanding the mechanisms of drug release from swellable matrices.

Table 2. Dissolution Data for Matrices Prepared With LBD/DT (150-200 μm)*

Batch DT% (wt/wt)	Higuchi			Zero-Order			Hixson-Crowell		
	k_h (%min$^{-1/2}$)	r^2	(SQR)	k_0 (%min^{-1})	r^2	(SQR)	k_w (%min$^{-1/3}$)	r^2	(SQR)
20	5.440	0.883	(92.9)	0.429	0.945	(43.4)	8.100	0.667	(1450.3)
30	4.529	0.892	(53.7)	0.356	0.920	(41.4)	10.116	0.596	(1213.9)
40	3.524	0.967	(17.9)	0.255	0.869	(30.6)	7.435	0.579	(1331.1)
50	3.188	0.977	(9.7)	0.174	0.807	(81.3)	8.262	0.529	(1215.8)
60	2.948	0.986	(4.7)	0.160	0.742	(85.1)	8.854	0.496	(1111.7)
70	2.405	0.897	(37.7)	0.134	0.938	(22.6)	10.297	0.103	(1347.6)

Batch DT % (wt/wt)	Korsmeyer				Peppas and Sahlin			
	K (%min^{-n})	n	r^2	(SQR)	K_d (%min^{-m})	K_r (%min^{-2m})	r^2	(SQR)
20	1.299	0.786	0.988	(12.28)	1.929	0.429	0.991	(8.8)
30	1.300	0.749	0.984	(10.60)	1.956	0.336	0.986	(8.8)
40	1.697	0.629	0.996	(2.60)	2.606	0.147	0.995	(3.2)
50	1.806	0.600	0.996	(2.02)	2.649	0.142	0.995	(2.4)
60	2.062	0.563	0.994	(2.06)	2.838	0.124	0.994	(2.3)
70	0.528	0.766	0.979	(8.57)	0.577	0.254	0.976	(9.7)

*LBD indicates lobenzarit disodium; DT, dextran B110-1-2 excipient; SQR, sum of squares residual; k_h, k_0, k_w, K, K_d, and K_r, kinetics constants; n, diffusional exponent of the Korsmeyer model; m, diffusional exponent of Peppas and Sahlin model; r^2, coefficient of correlation for each model.
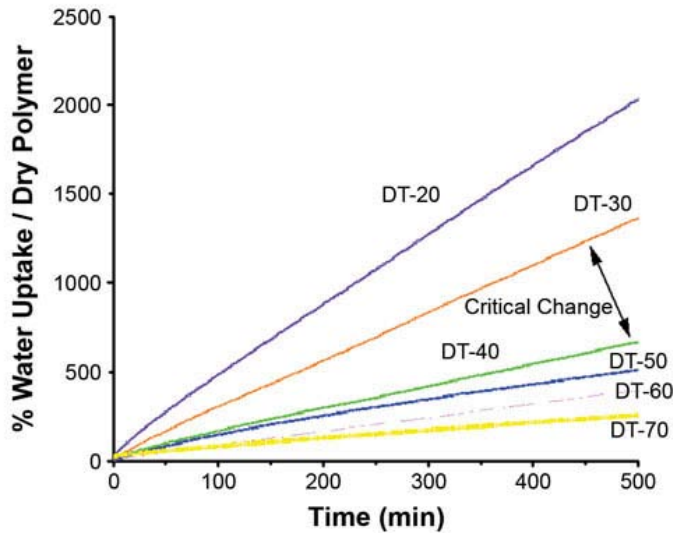
Figure 4. Water uptake profiles for tablets prepared with different DT contents. DT indicates dextran B110-1-2 excipient.

The results of the uptake water measurements are shown in Figure 4. An increase in the rate of water uptake can be observed when the DT concentration decreases. A critical point was found between 30% and 40% wt/wt of excipient. This range corresponds with the critical point which has been observed in the release profile studies.

The water uptake data were subjected to the Davidson and Peppas model to calculate the rate of water penetration. The results are shown in Table 3. Lower values of initial porosity (<3%) for batch DT 70% wt/wt have an important role because of difficult water penetration (K_s= 0.73% min$^{-0.715}$). In addition, the high value of swelling constant (K_s= 20.60% min$^{-0.960}$) for DT 20% wt/wt suggests burst swelling or water uptake. The exponent for all cases is $0.715 < n < 1$, which suggests an anomalous or complex behavior (the rate of diffusion of the liquid is relatively higher than that of relaxation of the polymer segment) and agrees well with previously discussed kinetic results.

Table 3. Water Uptake Data for Matrices Prepared With LBD/DT (150-200 μm)*

| Batch | DT % wt/wt | Davidson and Peppas | | |
		K_s (%min^{-n})	n	r^2
1	20	20.60 ± 0.06	0.715	0.993
2	30	2.00 ± 0.05	1.000	0.999
3	40	4.98 ± 0.06	0.819	0.995
4	50	3.39 ± 0.05	0.844	0.996
5	60	2.35 ± 0.09	0.850	1.000
6	70	0.73 ± 0.09	0.960	1.000

*LBD indicates lobenzarit disodium; DT, dextran B110-1-2 excipient; K_s, kinetic constant of water penetration; t, penetration time; n, diffusional exponent that depends on the water penetration mechanism; r^2, coefficient of correlation.
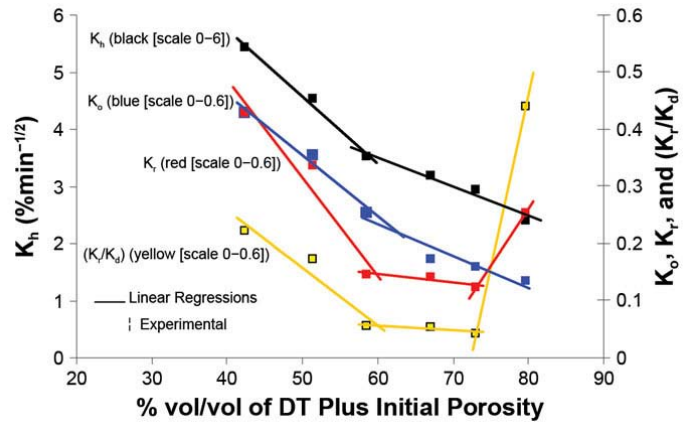

Figure 5. Evolution of different kinetic constants as a function of the DT volumetric fraction plus initial porosity. DT indicates dextran B110-1-2 excipient.

Estimation of the Excipient Percolation Threshold

When percolation theory is applied to binary pharmaceutical systems, 2 percolation thresholds are expected; the drug percolation threshold and the excipient percolation threshold. In hydrophilic matrices, the drug threshold is less evident than the excipient threshold, which is responsible for the release control.[9]

Recent studies have found 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. This cluster conditions the release kinetics of the drug.[9-11]

In order to estimate the percolation threshold of DT, the evolution of release parameters has been studied as a function of the sum of the excipient volumetric percentage plus initial porosity. Figures 5 and 6 show changes in the different
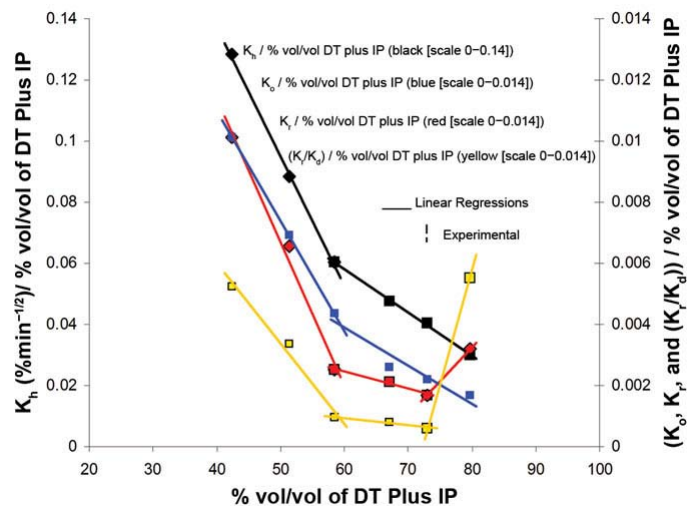

Figure 6. Evolution of normalized kinetic constants as a function of the DT volumetric fraction plus initial porosity (IP).

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

Kinetic Parameters	Equations	r^2	*Point of Intersection
Higuchi's slope ($\%min^{-1/2}$)	Y1 = −0.0511x + 6.5678 Y2 = −0.1182x + 10.492	0.9604 0.9909	X = 58.48
Higuchi's slope ($\%min^{-1/2}$) / %vol/vol DT plus initial porosity	Y1 = −0.0042x + 0.3076 Y2 = −0.0014x + 0.1420	0.9987 0.9983	X = 59.14
Zero-order's slope ($\%min^{-1}$)	Y1 = −0.0107x + 0.8886 Y2 = −0.0055x + 0.5653	0.9746 0.9166	X = 62.17
Zero-order's slope ($\%min^{-1}$) / vol/vol DT plus initial porosity	Y1 = −0.0004x + 0.0252 Y1 = −0.0001x + 0.0113	1.0000 0.9219	X = 61.96
Relaxational constant, k_r ($\%min^{-2m}$)	Y2 = −0.0172x + 1.1762 Y2 = −0.0015x + 0.2373	0.9332 0.8366	X = 59.80
Relaxational constant k_r ($\%min^{-2m}$) / %vol/vol DT plus initial porosity	Y1 = −0.0005x + 0.0302 Y2 = −0.00006 + 0.0058	0.9898 0.9862	X = 59.45
Ratio relaxational constant / diffusional constant (k_r/k_d)	Y1 = −0.0101x + 0.6623 Y2 = −0.0009x + 0.1071	0.9166 0.8468	X = 60.34
Ratio (k_r/k_d) / % vol/vol DT plus initial porosity	Y1 = −0.0003x + 0.0166 Y2 = −0.00002x + 0.0024	0.9824 0.9754	X = 58.71

*LBD indicates lobenzarit disodium; DT, dextran B110-1-2 excipient; X, values of intersection corresponding with values of % vol/vol of DT plus initial porosity of tablets (Figures 2 and 5); r^2, coefficient of correlation.

kinetic and normalized kinetic parameters as a function of percentage vol/vol of DT plus initial porosity. 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 behavior of the kinetic parameters, are shown in Table 4.

As percolation theory predicts, the studied properties show a critical behavior as a function of the volumetric fraction of the components. A critical point has been found at 58.63% vol/vol of DT plus initial porosity (corresponding to 44.75% vol/vol DT + 13.88% of initial porosity).

The results obtained from the kinetics analysis are in agreement with the release profiles, indicating a clear change in the release rate and mechanism from matrices containing 60% wt/wt of drug (40% wt/wt of DT). The existence of a critical point can be attributed to the excipient percolation threshold.

From the point of view of percolation theory, this finding means that above 40% wt/wt of DT, the existence of a network of DT (able to form a hydrated layer from the first moment) controls the drug release.

The percolation thresholds correspond to formulations showing a high variability in their properties as a function of the volume fraction of their components. Therefore, in order to increase the robustness of the formulation, the nearby percolation thresholds should be avoided.

The excipient percolation threshold is the border between a fast release of the drug (below the threshold) and a drug release controlled by the formation of a coherent gel layer (above the excipient percolation threshold). Therefore the knowledge of this threshold will allow us to avoid the preparation of several unnecessary lots during the development of a pharmaceutical formulation, resulting in a reduction of the time to market.

Dissolution profile of LBD from DT B110-1-2 (Mw 2×10^6) matrix tablets corresponds to anomalous mechanism. In these cases, both diffusion of the drug through the hydrate matrix and erosion of the matrix itself after the relaxation of polymer chain control the release of LBD from these formulations.

CONCLUSION

Binary controlled released tablet of lobenzarit disodium and native dextran B110-1-2 (Mw = 2×10^6) with a relative DT/LBD particle size of 4.17 should be formulated with DT

content above 40% wt/wt (volumetric fraction 44.75 vol/vol plus initial porosity) to obtain control of the drug release. This value corresponds to dextran's percolation threshold, and anomalous mechanism for water uptake and dissolution profile of LBD from this system can be expected.

ACKNOWLEDGMENTS

REFERENCES

1. Coviello T, Matricardi P, Marianecci C, Alhaique F. Polysaccharide hydrogels for modified release formulations. *J Control Release.* 2007;119:5–24.

2. Robyt JF. Dextran. In: Mark HF, Bikales NM, Overberger CG, Menges G, eds. *Encyclopedia of Polymer Science and Engineering.* New York, NY: John Wiley & Sons; 1986:752–767.

3. Gil EC, Colarte AI, El Ghzaoui A, Durand D, Delarbre JL, Bataille B. A sugar cane native dextran as an innovative functional excipient for the development of pharmaceutical tablets. *Eur J Pharm Biopharm.* In press.

4. Ferrero C, Muñoz-Ruiz A, Jiménez-Castellanos MR. Fronts movements as a useful tool for hydrophilic matrix release mechanism elucidation. *Int J Pharm.* 2000;202:21–28.

5. Tahara K, Yamamoto K, Nishihata T. Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose 2910. *J Control Release.* 1995;35:59–66.

6. Jamzad S, Tutunji L, Fassihi R. Analysis of macromolecular changes and drug release from hydrophilic matrix systems. *Int J Pharm.* 2005; 292:75–85.

7. Gil EC, Colarte AI, Bataille B, Pedráz JL, Heinämäki J. Development and optimization of a novel sustained-release dextran tablet formulation for propranolol hydrochloride. *Int J Pharm.* 2006;317:32–39.

8. Campos-Aldrete ME, Villafuerte-Robles L. Influence of the viscosity grade and the particle size of HPMC on metronidazole release from matrix tablet. *Eur J Pharm Biopharm.* 1997;43:173–178.

9. Miranda A, Millán M, Caraballo I. Study of the critical points of HPMC hydrophilic matrices for controlled drug delivery. *Int J Pharm.* 2006;311:75–81.

10. Miranda A, Millán M, Caraballo I. Study of the critical points in lobenzarit disodium hydrophilic matrices for controlled drug delivery. *Chem Pharm Bull (Tokyo).* 2006;54:598–602.

11. Fuertes I, Miranda A, Millian M, Caraballo I. Estimation of percolation thresholds in acyclovir hydrophilic matrix tablets. *Eur J Pharm Biopharm.* 2006;64:336–342.

12. Leuenberger H, Rohera BH, Haas C. Percolation theory—a novel approach to solid dosage form design. *Int J Pharm.* 1987;38:109–115.

13. Caraballo I, Fernandez Arévalo M, Millán M, Rabasco AM, Leuenberger H. Study of percolation thresholds in ternary tablets. *Int J Pharm.* 1996;139:177–186.

14. Stauffer D, Aharony A. *Introduction to Percolation Theory.* Washington, DC: Francis; 1992.

15. Zallen R. Percolation: a model for all seasons. In: Deutscher G, Zallen R, Adler J, eds. *Percolation Structures and Processes.* New York, NY: The American Institute of Physics; 1983.

16. Ohsugi Y, Nakano T, Ueno K. An immunopharmacological profile of lobenzarit disodium (CCA), a new immunomodulatory anti-rheumatic drug. *Int J Immunother.* 1985;2:85–92.

17. Castellanos GE, Caraballo I, Bataille B. Tablet design. In: Gad SC, ed. *Pharmaceutical Manufacturing Handbook.* Hoboken, NJ: John Wiley & Sons; In press.

18. Novoa H, Pellón R, Pomés P, Duque J. Crystal data and x-ray powder diffraction data of lobenzarit acid and lobenzarit disodium. *Powder Diffraction.* 1996;11:72–74.

19. Ritger PL, Peppas NA. A simple equation for description of solute release. I. Fickian and Non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *J Control Release.* 1987;5:23–36.

20. Davidson GWR III, Peppas NA. Relaxation-controlled transport in P(HEMA-co-MMA) copolymers. *J Control Release.* 1986;3:243–258.

21. Lin CC, Metters AT. Hydrogels in controlled release formulations: network design and mathematical modelling. *Adv Drug Deliv Rev.* 2006;58:1379–1408.