Estimation of the percolation thresholds in ternary lobenzarit disodium–dextran–HPMC hydrophilic matrices tablets: Effects of initial porosity

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ABSTRACT

The aim of this work is to estimate the excipient percolation threshold for a new combined matrix native dextran (DT), series B110-1-2 (Mw 2×10^6): HPMC K4M CR: lobenzarit disodium (LBD) system and demonstrate the advantages of this ternary system with respect to previously reported binary dextran:LBD and HPMC:LBD tablets. The formulations studied were prepared with different amounts of excipient (DT:HPMC, 4:1 (wt/wt) for all tablets and relative polymer/drug particle size of 4.17) in the range of 10–70% (wt/wt). Dissolution studies were carried out using the paddle method (100 rpm) and one face water uptake measurements were performed using a modified Enslin apparatus. The Higuchi's models as well as the non-linear regression were employed as empiric methods to study the released data. Values of diffusion exponent $0.588 < n < 0.784$ (Korsmeyer equation) for dissolution profile and water uptake mechanism $0.715 < n < 0.960$ (Davidson and Peppas equation) suggests anomalous or complex mechanisms in all cases. The critical points in ternary tablets were reduced from 44.75% (v/v) of excipient (correspond to purely native dextran) to 22.34% (v/v) (corresponding to mixture native dextran:HPMC, 4:1, wt/wt). The initial porosity (IP) of hydrophilic matrices above the values of 20% has an important influence on the percolation threshold as well as on establishment of the gel barrier responsible for the controlled release from the DT:HPMC:LBD tablets.

1. Introduction

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 in the pharmaceutical field by Leuenberger et al. (1987) to improve the characterization of solid dosage forms. In this first definition, through the compaction process to form a pharmaceutical tablet, a site-percolation and a bond-percolation may be observed.

The sites can be occupied by particles or pores and bonds can exist between neighbouring particles. This theory assumes that at a specific solid/pores composition in the tablet, i.e., when particles or pores form a continuous network in the system, a sudden change in the tablet properties (release rate, mechanical properties, etc.) is observed. This particular ratio corresponds to the percolation threshold (Holman and Leuenberger, 1991).

In a binary pharmaceutical tablet, two percolation thresholds are expected: the drug and the excipient percolation threshold. A cluster is defined as a group of neighbour-occupied sites in a lattice (Stauffer and Aharony, 1992). 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. 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 (Miranda et al., 2006a,b; Fuertes et al., 2006).

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 (Castellanos Gil

et al., 2006a; Campos Aldrete and Villafuerte Robles, 1997; Tahara et al., 1995).

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. Coming from renewable sources, polysaccharides have frequently also economical advantages over synthetic polymers. Polysaccharides are usually non-toxic, biocompatible and show a number of peculiar physico-chemical properties that make them suitable for different applications in drug delivery systems (Coviello et al., 2007; Robyt, 1986).

Hydroxypropyl methylcellulose has been employed extensively as hydrophilic matrix former in oral controlled release dosage forms for different drugs. Its popularity can be attributed to the polymer's non-toxic nature, small influence of processing variables on drug release, ease of compression, and its capability to accommodate high levels of drug loading (Bettini et al., 1994).

The percolation theory has been applied to describe controlled release inert matrix systems (Caraballo et al., 1993). Recently we started to apply the percolation theory to the study of HPMC hydrophilic matrix systems. Miranda et al. demonstrated experimentally the influence of the particle size of the components on the percolation threshold in HPMC hydrophilic matrices (Miranda et al., 2006a,b, 2007c; Fuertes et al., 2006) and some evidence of the influence of the initial porosity in the formation of the gel layer (sample-spanning cluster of excipient) were achieved.

Lobenzarit disodium (LBD) 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. It is administered orally in the form of tablets and its daily dosage is 240 mg (80 mg three doses per day) (Ohsugi et al., 1985).

The objective of the present work was to estimate the excipient percolation threshold for a new combined matrix native dextran (DT), series B110-1-2 (Mw 2×10^6): HPMC K4M CR: LBD system, to characterize its release kinetics and to demonstrate the advantages of this ternary system with respect to previously reported binary dextran:LBD tablets (Castellanos Gil et al., 2008b). At the same time the influence of the initial porosity (IP) of hydrophilic matrices in the range 0–30% on the release and percolation behaviour was analyzed.

2. Materials and methods

2.1. Materials

Commercial native Dextran B512-F (Mw 5 000 000–40 000 000, according to manufacturer's data and Mw 22 000 000, according to viscometer analysis (Castellanos Gil et al., 2008c)) was obtained from Sigma (Saint Louis, USA) and used as reference polymer.

High molecular weight native dextran (B110-1-2, Mw 2 000 000 (Castellanos Gil et al., 2008c)) was obtained from the Center of Studies of Sugar Cane (Havana, Cuba). Lobenzarit disodium (LBD) was prepared in the Synthesis Laboratory at the Center of Pharmaceutical Chemistry (Cuba). Hydroxypropyl methylcellulose (HPMC) with a viscosity grade 4000 cps (Methocel K4M CR) was obtained from Colorcon (Kent, England). Other chemicals and reagents were of analytical grade.

2.2. Preparation of matrix tablets

The polymers were sieved (Retsch type Vibro, Germany), the granulometric fractions 150–200 μm were employed and Carr's index (CI) was calculated. The drug was not sieved but its mean particle size was measured as 42 ± 0.61 μm using a He–Ne laser diffraction system (Malvern Instr., type Matersize x, 1.2 b, UK). The apparent particle density of LBD (2.159 g/cm^3) and polymers (1.330 g/cm^3 for DT and 1.285 for HPMC K4M CR) has been calculated using an air pycnometer (Quantachrome type Stereopynometer spy-3, USA) and not very different values to those reported in the literature were achieved (Novoa et al., 1996; Fuertes et al., 2006).

Ternary mixtures DT:HPMC:LBD keeping ratio DT:HPMC always as 4:1 (wt/wt), were prepared with varying polymer's mixture contents (10%, 15%, 20%, 30%, 40%, 50%, 60% and 70%, wt/wt) (for volumetric fraction see Table 1) and with a constant amount of the drug (150 mg dosage) without any further excipient. Binary system DT:LBD was prepared with the same polymer amount (range 10–70%, wt/wt) with respect to LBD according to previously reported data (Castellanos Gil et al., 2008b). Table 1 also shows the composition of the studied batches as well as the tablet thicknesses ($n = 12$). Tablet components were mixed for 3 min (optimal mixing time) using a Turbula mixer (Basel, Switzerland).

Tapped density and bulk density of polymers and mixtures were determined according to European Pharmacopoeia (PhEur 4, 2002). Approximately 100 ml of powder is gently poured into a tare graduated cylinder and the initial volume and weight of the material is recorded. The graduated cylinder is placed on a tapped density tester and the final volume is recorded after 500 taps (SBS model. VOL-1 tap density tester) and Carr's index was obtained (Eq. (1)).

Percent compressibility index

$$= 100 \times \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \qquad (1)$$

The mixtures were compressed with a F. RASSANT (France) hydraulic press fitted with a 10 mm diameter flat punch. After some time (around 10 s) the formed tablets were ejected from the punch. Based on previous studies where the influence of compression force was studied as a function of the reduction in volume of dextran placebo tablets, compression force 14 kN was applied for all experiments in order to minimize initial porosity of tablets (Castellanos

Table 1
Properties of LBD tablets (dosage 150 mg) at various amounts of polymers mixture DT:HPMC (4:1, wt/wt).

Batch (total excipients %, v/v)	DT (%, v/v)	HPMC (%, v/v)	[a]Tablet weight (mg)	[a]Tablet thickness (mm)
DT:HPMC-10 (10.81)	8.59	2.22	166.1 ± 0.9	1.480 ± 0.031
DT:HPMC-15 (15.89)	12.63	3.26	176.2 ± 2.1	1.600 ± 0.025
DT:HPMC-20 (22.34)	17.75	4.59	187.5 ± 1.1	1.618 ± 0.060
DT:HPMC-30 (33.10)	26.30	6.80	214.2 ± 0.9	1.878 ± 0.063
DT:HPMC-40 (43.55)	34.60	8.95	250.0 ± 1.4	2.213 ± 0.065
DT:HPMC-50 (53.89)	42.81	11.09	300.0 ± 1.3	2.683 ± 0.056
DT:HPMC-60 (63.65)	50.57	13.08	375.2 ± 1.3	3.407 ± 0.047
DT:HPMC-70 (68.62)	54.52	14.10	500.1 ± 1.9	4.916 ± 0.078

[a] Values expressed the mean of experimental ± RSD values for 12 samples.

Gil et al., 2008b,c). Furthermore in order to analyze the influence of IP, different and adequate compression forces (range 2–30 kN) were applied to obtain IP of tablets in the range 0–30%, respectively. All the tablets were tested for friability (Erweka, mod. TAD, Germany).

2.3. In vitro drug release studies

Dissolution studies were carried out at $37 \pm 0.5\,^{\circ}$C in 900 ml of distilled water, in a USP apparatus (SotaxAT7 Smart, Teknokroma, Spain) using the paddle method. The rotation speed was kept constant at 100 rpm. Release of LBD was detected by UV spectrophotometric method at 360 nm during 8 h. 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 carried out by analyzing solutions containing several concentrations of LBD in five replicates. Furthermore, these solutions were analyzed by triplicate on five different days ($n = 15$). The results showed a good linearity ($r^2 = 0.9940$), with appropriate precision (CV <2%) and accuracy values ($\geq 98.98\%$). The absence of interference of dextran and HPMC was checked by comparing the data obtained from pure substance LBD and from samples spiked with polymer (Castellanos Gil et al., 2006a, 2008b,c).

The mechanism of drug release was analyzed according to, Higuchi (Eq. (2)), Korsmeyer (Eq. (3)) and Peppas-Sahlin (Eq. (4)) equations:

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

$$\frac{Q_t}{Q_\infty} = K \cdot t^n \tag{3}$$

where Q_t/Q_∞ is the fraction of drug released; k_h 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. 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 $n = 1.0$ show a case II (purely erosion/relaxation controlled) drug release.

$$\frac{Q_t}{Q_\infty} = K_d \cdot t^m + K_r \cdot t^{2m} \tag{4}$$

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 (Ritger and Peppas, 1987).

2.4. 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 which is placed on a precision balance (Scatlec SBC 31, 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 percent (wt/wt) of penetrated fluid with respect to dry polymer. The kinetics of the water uptake into hydrophilic matrices was analyzed according to Davidsons and Peppas model using

the following equation:

$$W = K_s \cdot t^n \tag{5}$$

Being W the weight gained 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 (Davidson and Peppas, 1986).

2.5. Estimation of the percolation threshold

In order to estimate the percolation threshold, the behaviour of the kinetic parameters (k_h, K and K_r/K_d, respectively) and normalized kinetic constants with respect to volumetric fraction and volumetric fraction plus IP were studied.

According to the fundamental equation of percolation theory (Eq. (6)), if these parameters behave as critical properties, we can expect that

$$X \propto S \cdot (p - p_c)^n \tag{6}$$

where X is the studied property; S is a constant; p is the volumetric fraction (or volumetric fraction plus IP) of the component; 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 non-linear behaviour as a function of the volumetric fraction of the excipients (plus or without initial porosity). Two (or three) linear regressions have been performed as an approximation for estimating the trend of the parameter, one regression line below and the other above the percolation threshold. The point of intersection between both regression lines has been taken as an estimation of the percolation threshold (Miranda et al., 2006a,b; Fuertes et al., 2006; Castellanos Gil et al., 2008b).

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

$$\varepsilon(\%) = 100 \times \left(\frac{Vt - (w \cdot \%\mathrm{LBD}/\rho\mathrm{LBD}) - (w \cdot \%\mathrm{DT}/\rho\mathrm{DT}) - (w \cdot \%\mathrm{HPMC}/\rho\mathrm{HPMC})}{Vt} \right) \tag{7}$$

where $\varepsilon(\%)$ is the initial porosity in percent; Vt is the tablets volume; w is the tablet weight; $\rho\mathrm{LBD}$, $\rho\mathrm{DT}$ and $\rho\mathrm{HPMC}$ are the drug, DT and HPMC density, respectively.

3. Results and discussion

3.1. Properties of binary and ternary matrix tablets at compression force 14 kN

Fig. 1 and Table 1 show IP, aspect ratio (ratio tablet diameter/tablet thickness), % (v/v) of excipients (DT + HPMC), tablet weight and tablet thickness obtained for the eight batches studies (DT:HPMC-10 up to DT:HPMC-70) applying 14 kN compression force (values for matrices DT:LBD were taken from previously reported data (Castellanos Gil et al., 2008b)). Carr's index is related to powder flowability, for which smaller values indicate better flowability. During the tabletting process, the enhancement of flowability could decrease the weight variation of tablets. On the other hand, the tensile strength of tablets is partly determined by the compressibility of the powder bed and the postcompression recovery of tablets. Greater compressibility or plastic deformation results in higher tensile strength of tablets. The extent of plastic deformation can be represented by yield pressure, for which a smaller value indicates a higher extent of plastic deformation. By contrast, the postcompression recovery of tablets leads to an increase in porosity accompanied by a decrease in tensile strength.
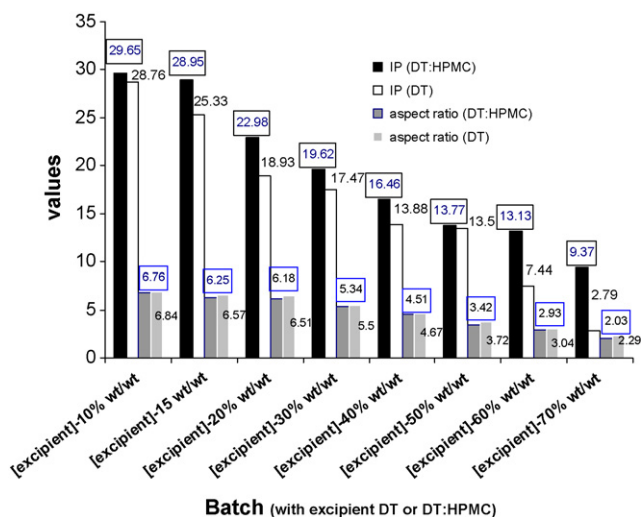
Fig. 1. Initial porosity and aspect ratio for binary and ternary tablets.

Packing/flow ratio (values of Carr's index, data showed in Fig. 2) became more favorable (CI become lower values) with the increasing of dextran's amount in binary and ternary systems. Lost due to friability for binary tablets (range 0.79–0.15%) were lower but in the same range as ternary system (range 0.94–0.25%). CI and IP for binary tablets were lower than for ternary systems, when tablets with equal % (v/v) excipients were compared. This can be due to the differences in compressibility index of dextran (CI = 18.8) and HPMC (CI = 24.6). As a consequence, when automatic machine will be in use, the tablets containing this granulate (HPMC) have to be manufactured at lower compression speed, in order to guarantee an accurate filling of the machine die.

3.2. Release profiles and release kinetics at compression force 14 kN

Fig. 3 shows the dissolution profiles for tablets of LBD with DT-B110-1-2 (DT 10% to DT 70%, wt/wt, particle size 150–200 μm) and with DT:HPMC (always in ratio 4:1, wt/wt). The value for relative standard deviation was lower than 5% for all points measured ($n = 12$). Values for kinetic constants indicated that LBD release is faster in binary system (k_h binary system > k_h ternary system, for the same polymers content). This results agree well with our previous observation when a synergy in the ability to control the release of propranolol hydrochloride was observed when we used ratio DT:HPMC 4:1 (wt/wt) (Castellanos Gil et al., 2006a). The Higuchi's model as well as the non-linear regression of Korsmeyer
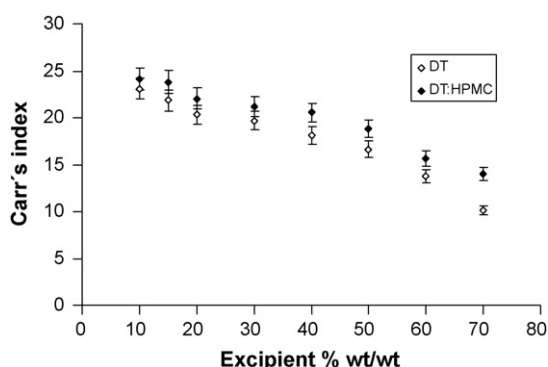
Fig. 2. Carr's index values as a function of % (wt/wt) DT and DT:HPMC.
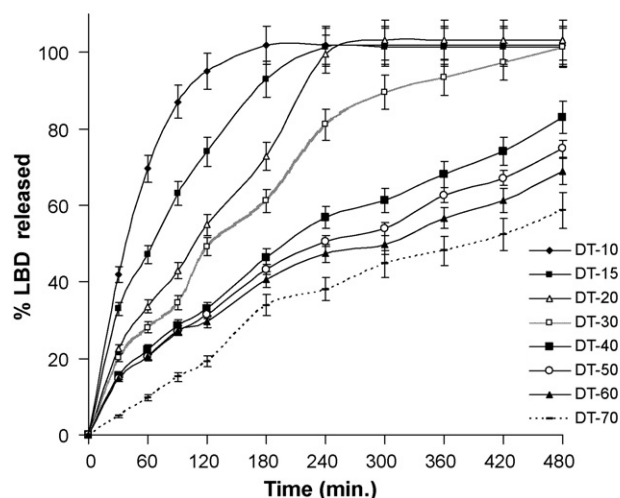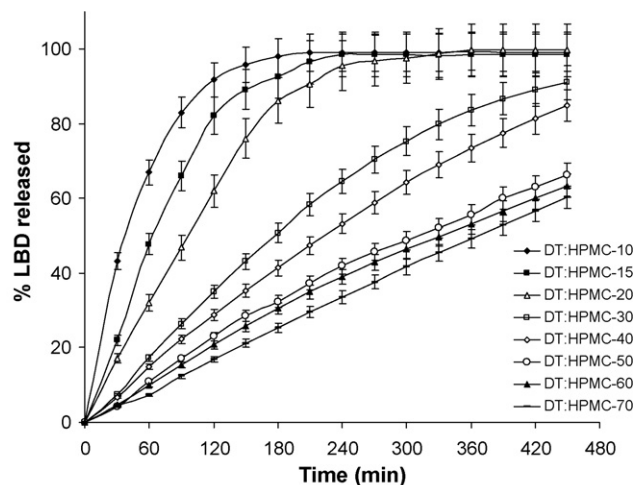
Fig. 3. Dissolution profiles for tablets prepared with different DT:HPMC and DT contents.

and Peppas-Sahlin was employed as empiric methods to study the released data. According to the aspect ratio obtained for all formulations, values of $0.432 < m < 0.465$ were found appropriate to be used in Eq. (4) (Ritger and Peppas, 1987). The results obtained are shown in Table 2.

Values of diffusion exponent $0.588 < n < 0.784$ (Korsmeyer equation) for dissolution profile of sparingly soluble drug correspond to anomalous diffusion mechanism and this well agrees with the results of other authors (Tahara et al., 1995; Miranda et al., 2006b). This can be also observed in Peppas-Sahlin equation. The model can identify the different contribution of the relaxation or erosion mechanism and of the diffusive mechanism. The values obtained for K_r were lower than K_d for all the dissolution profiles.

3.3. Water uptake assays 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 (Michailova et al., 2000). The characterization of water-sorption capabilities is the first step towards understanding the mechanisms of drug release from DT and DT:HPMC matrices.

The results of the water uptake measurements are shown in Fig. 4. An increase in the rate of water uptake/dry polymer can be observed when the excipients concentration decreases. A change in water uptake kinetic was found between 20% and 30% (wt/wt)

Table 2
Dissolution data for ternary and binary matrices prepared with DT:HPMC:LBD and DT:LBD.

Batch	Higuchi		
	k_h (%min$^{-1/2}$)	r^2	SQR
DT:HPMC-10	8.39	0.9980	5.74
DT:HPMC-15	6.45	0.9770	58.32
DT:HPMC-20	4.88	0.9710	50.35
DT:HPMC-30	3.57	0.9679	46.81
DT:HPMC-40	3.18	0.9739	64.10
DT:HPMC-50	2.76	0.9799	39.32
DT:HPMC-60	2.61	0.9778	39.36
DT:HPMC-70	2.36	0.9640	49.79

Batch	Korsmeyer				Peppas-Sahlin			
	K (%min^{-n})	n	r^2	SQR[a]	K_d (%min^{-m})	K_r (%min^{-2m})	r^2	SQR[a]
DT:HPMC-10	6.38	0.588	0.9999	1.08	7.04	0.86	0.9999	1.80
DT:HPMC-15	2.82	0.784	0.9991	4.19	3.95	0.67	0.9991	5.43
DT:HPMC-20	1.76	0.747	0.9990	3.42	2.40	0.57	0.9930	2.35
DT:HPMC-30	1.27	0.740	0.9999	0.68	1.78	0.34	0.9999	0.31
DT:HPMC-40	1.34	0.700	0.9992	3.18	2.08	0.25	0.9999	0.40
DT:HPMC-50	1.41	0.651	0.9999	3.43	2.14	0.21	0.9980	7.95
DT:HPMC-60	1.26	0.663	0.9991	1.28	1.93	0.23	0.9998	2.28
DT:HPMC-70	0.79	0.730	0.9999	2.83	1.09	0.28	0.9999	1.00

[a] Sum of squares residual; k_h, K, K_d and K_r: kinetic constants for each model; n: diffusional exponent of Korsmeyer model; m: exponent of Peppas-Sahlin model; r^2: coefficients of correlation for each model (applied compression force for all experiment 14 kN).

of excipients (for DT:HPMC:LBD tablets). This range corresponds to the critical point which has been observed in the release kinetics studies. Comparing these results with those obtained for DT:LBD, a reduction of amount of water uptaken was observed when a mixture of polymers was used. Nevertheless for short times (0–90 min) a faster water sorption was observed for ternary tablets with low polymer volumetric fractions. Different factors could be responsible for this behaviour, initial porosity (IP for ternary > IP binary mixtures), differences in hydrophilicity of polymers (DT > HPMC) and erosion of the tablets. Furthermore a reduction of around 10% (wt/wt) for the critical point has been obtained with respect to DT:LBD tablets (see Fig. 4).

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. The high value of swelling constant (K_S = 17.31% min$^{-0.903}$) for DT:HPMC-10 suggests burst swelling. The exponent for all cases is in the range 0.735 < n < 1 which suggests an anomalous or complex behaviour (the rate of diffusion of the liquid is relatively higher than that of relaxation of the polymer segment). This behaviour agrees well with the previously discussed kinetic results. For DT:HPMC-50 (corresponding to 42.81%, v/v DT plus 11.07%, v/v HPMC, respectively) an small change of the system was achieved, i.e., a litter increment of K_S values (K_S = 4.24 ± 0.05) with a respective reduction in exponent (n = 0.772) values. In this case the percolation threshold corresponding to pure DT (around 44.75%, v/v (Castellanos Gil et al., 2008b)), could be the possible reason for these phenomena.

3.4. Estimation of the excipient percolation threshold

When percolation theory is applied to binary pharmaceutical systems, two percolation thresholds are expected; the drug

Fig. 4. Water uptake profiles for tablets prepared with different DT:HPMC and DT contents.

Table 3
Water uptake data for binary and ternary matrices prepared with different polymer contents (10–70, wt/wt).

Batch	K_s (%min^{-n})	n	r^2	SQR[a]
DT:HPMC-10	17.31 ± 0.86	0.903	0.9990	94.39
DT:HPMC-15	11.10 ± 0.66	0.901	0.9999	73.08
DT:HPMC-20	7.40 ± 0.45	0.903	0.9999	86.39
DT:HPMC-30	3.59 ± 0.76	0.955	0.9990	46.09
DT:HPMC-40	2.83 ± 0.32	0.877	0.9999	24.45
DT:HPMC-50	4.24 ± 0.05	0.772	0.9991	4.56
DT:HPMC-60	1.09 ± 0.29	0.948	0.9999	2.01
DT:HPMC-70	0.73 ± 0.73	0.735	0.9960	21.60

K_s: kinetic constant of water penetration; t: penetration time; n: diffusional exponent which depends on the water penetration mechanism, r^2: coefficient of correlation.

[a] Sum of squares residual (applied compression force 14 kN).

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 (Miranda et al., 2006a,b; Fuertes et al., 2006). According to Miranda's et al. results, the percolation threshold for LBD is around 56% (v/v) of active pharmaceutical ingredient (this value was obtained near to the batch DT:HPMC-15, where % (v/v) polymers = 15.91% and IP = 28.95% and batch DT-15, where % (v/v) polymer = 16.62% and IP = 25.33%, respectively).

In order to estimate the percolation threshold of the mixture of excipients DT:HPMC (ratio 4:1, wt/wt), the evolution of the release parameters has been studied as a function of the sum of the excipient volumetric percentage alone or added with the initial porosity (IP). Fig. 5 shows changes in the different kinetic parameters as well as in the normalized kinetic parameters as a function of % (v/v) of excipients and % (v/v) of excipients plus IP. Two linear regressions have been performed as an approximation. The percolation threshold has been estimated as the point of intersection

between both regression lines ($X1$). 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 Higuchi's slope, as well as K and the ratio K_r/K_d underwent an important change between DT:HPMC:LBD-20 and DT:HPMC:LBD-30 Aexcipient percolation threshold. This means that between 22.34% (v/v) and 33.10% (v/v) of polymers mixture DT:HPMC (4:1, wt/wt), a percolating cluster of the excipients would be obtained which results in a control of the drug release. Opposite to the Higuchi's model parameters, the kinetic constants derived from non-linear methods show a second change around DT:HPMC:LBD-50 (see K and K_r/K_d values, Fig. 5 and Tables 2 and 4).

According to percolation theory, the studied properties show a critical behaviour as a function of the volumetric fraction of the components. A critical point (for intersection of linear regression, see Table 4) has been found between 21.08% and 25.17% (v/v) of DT:HPMC (corresponding to the range 44.75–47.66%, v/v of DT:HPMC plus IP). This fact indicates that above this range an

Fig. 5. Evolution of different kinetic and normalized kinetic constants as a function of the excipients volumetric fraction plus and without IP.

Table 4
The values of the excipients percolation thresholds, according to the kinetic and normalized kinetic parameters used.

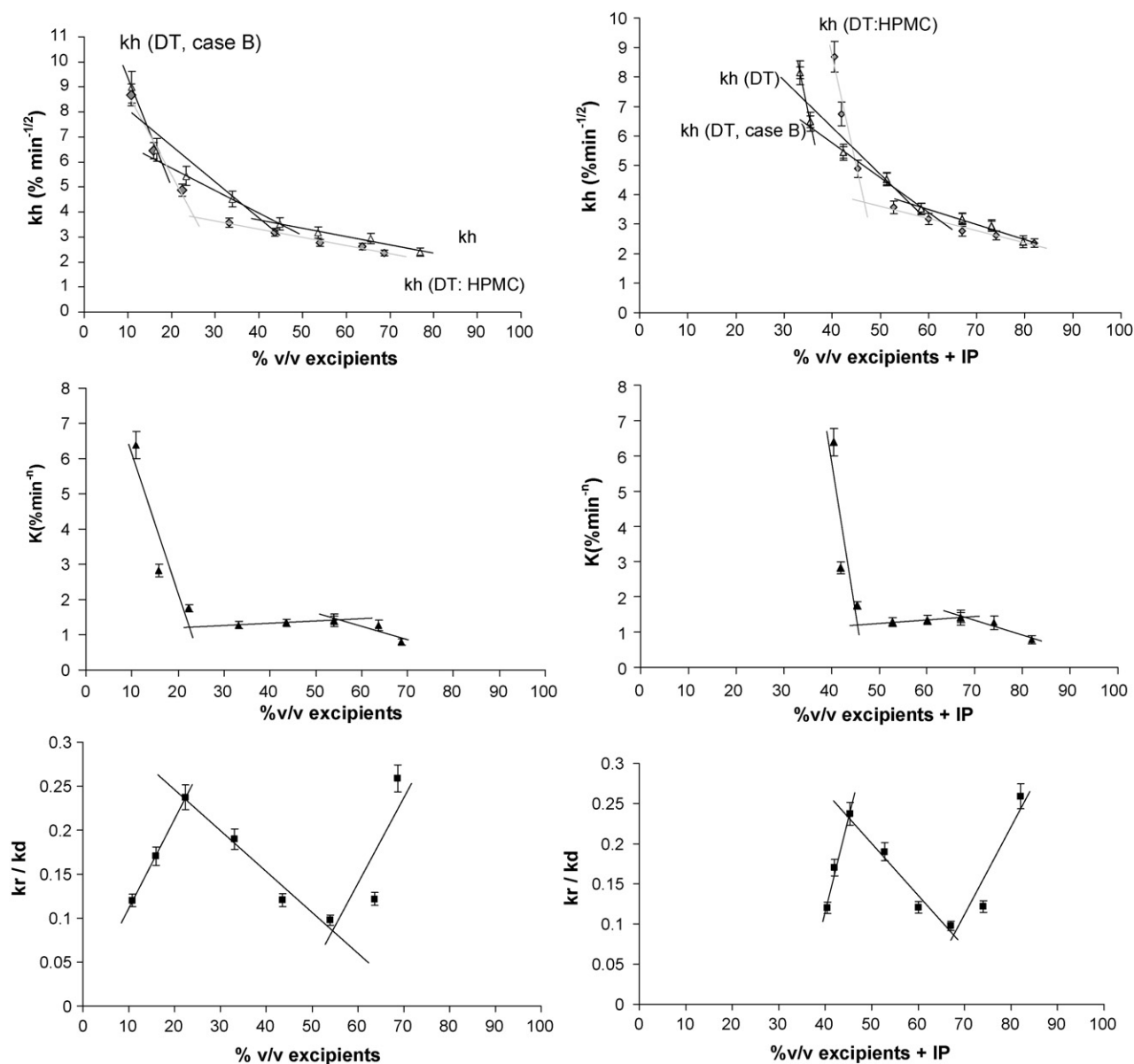| Kinetic parameters	Equations	r^2	[*]Intersection
(k_h) versus (%, v/v excipients)	$Y1 = -0.3257x + 11.998$	0.9720	$X1 = 25.17$
	$Y2 = -0.0328x + 4.6254$	0.9820	
$(k_h/\%,$ v/v excipients) versus (%, v/v excipients)	$Y1 = -0.0498x + 1.2894$	0.9449	$X1 = 23.48$
	$Y2 = -0.002x + 0.1666$	0.9483	
(K) versus (%, v/v excipients)	$Y1 = -0.3910x + 10.051$	0.8696	$X1 = 22.61$
	$Y2 = 0.0065x + 1.0624$	0.9997	
	$Y3 = -0.0388x + 3.5639$	0.7896	$X2 = 55.22$
$(K/\%,$ v/v excipients) versus (%, v/v excipients)	$Y1 = -0.0431x + 0.9888$	0.8426	$X1 = 22.12$
	$Y2 = -0.0006x + 0.0579$	0.9918	
	$Y3 = -0.0010x + 0.0784$	0.9324	$X2 = 53.94$
Ratio (K_r/K_d) versus (%, v/v excipients)	$Y1 = 0.0102x + 0.0097$	0.9998	$X1 = 22.24$
	$Y2 = -0.0046x + 0.3389$	0.9699	
	$Y3 = 0.0098x - 0.4472$	0.7101	$X2 = 54.59$
Ratio $((K_r/K_d)/(\%,$ v/v excipients)) versus (%, v/v excipients)	$Y1 = -0.00004x + 0.011$	0.8426	$X1 = 21.08$
	$Y2 = -0.0003x + 0.0161$	0.9227	
	$Y3 = 0.0001x - 0.00471$	0.9324	$X2 = 53.18$
(k_h) versus (%, v/v excipients + IP)	$Y1 = -0.7427x + 38.390$	0.9475	$X1 = 46.64$
	$Y2 = -0.0411x + 5.6655$	0.9652	
$(k_h/\%,$ v/v excipients + IP) versus (%, v/v excipients + IP)	$Y1 = -0.0209x + 1.0517$	0.9507	$X1 = 46.84$
	$Y2 = -0.0013x + 0.1336$	0.9549	
(K) versus (%, v/v excipients + IP)	$Y1 = -0.8436x + 39.573$	0.7516	$X1 = 45.46$
	$Y2 = 0.0095x + 0.7781$	0.9995	
	$Y3 = -0.0423x + 4.2997$	0.9371	$X2 = 67.98$
$(K/\%,$ v/v excipients + IP) versus (%, v/v excipients + IP)	$Y1 = -0.0218x + 1.0143$	0.7601	$X1 = 45.30$
	$Y2 = -0.0002x + 0.0358$	0.9928	
	$Y3 = -0.0008x + 0.0753$	0.9823	$X2 = 65.83$
Ratio (K_r/K_d) versus (%, v/v excipients + IP)	$Y1 = 0.0234x - 0.8194$	0.9811	$X1 = 44.75$
	$Y2 = -0.0068x + 0.5413$	0.9715	
	$Y3 = 0.0109x - 0.6522$	0.8852	$X2 = 67.42$
Ratio $((K_r/K_d)/(\%,$ v/v excipients + IP)) versus (%, v/v excipients + IP)	$Y1 = 0.0004x - 0.0149$	0.9608	$X1 = 47.66$
	$Y2 = -0.0002x + 0.0137$	0.9651	
	$Y3 = 0.0001x - 0.0065$	0.8599	$X2 = 67.33$

[*] Probability $p < 0.05$

infinite cluster of the excipients has been formed, which controls the penetration of the liquid into the matrices and the release of drug form these systems. For non-linear methods a second but less pronounced critical point was observed ($X2$ in Table 4) between 53.18% and 55.22% (v/v) DT:HPMC (65.83–67.98%, v/v DT:HPMC plus IP), this point corresponds to 42.81% (v/v) of pure DT polymer, i.e., dextran percolation threshold (Castellanos Gil et al., 2008b). On the other hand percolation threshold for LBD observed as inflexion point around 16.72% (v/v) of DT and 15.91% (v/v) of DT:HPMC was found easier from the Higuchi's slope representation (K_h) and even determined in DT batches (see Fig. 5 case B) as a similar value reported by Miranda et al.

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 70% (wt/wt) of drug (30%, wt/wt of DT:HPMC). The existence of a critical point can be attributed to the excipient percolation threshold.

3.5. Effect of tablets initial porosity

In practice, the percolation threshold of excipient is the most important for matrices system. Nevertheless, the percolation threshold of pores is also interesting to consider in the compaction process because the role of pores in swelling and erosion process (Holman and Leuenberger, 1991; Miranda et al., 2006a).

Above some compression force, the pores do not form anymore a continuous network. This is the percolation threshold of pores.

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 (Miranda et al., 2006a,b; Fuertes et al., 2006; Castellanos Gil et al., 2008b).

Batches for DT:HPMC-10 up to DT:HPMC-70, with three initial porosity ranges: 0–10%, 10–20% and 20–30% were studied. The data obtained from the corresponding dissolution assays were also fitted to Higuchi's model. Fig. 6 shows changes in the obtained kinetic parameters as a function of % (v/v) of excipients. The DT:HPMC thresholds were estimated as described in Section 2: two linear regressions have been performed. The percolation threshold has been estimated as the point of intersection between both regression lines.

When different IP series are compared, the values of k_h increased as increased IP. Nevertheless a not significant difference ($p < 0.05$) in percolation thresholds (intersection points $A = 21.98\%$, v/v excipients and $B = 21.99\%$, v/v excipients in Fig. 6) was achieved for series IP 0–10 and IP 10–20. Despite some statistical significance was found for the percolation threshold ($C = 24.17\%$, v/v excipients) of the matrices with 20–30% IP. As Fig. 6 shows, little difference has been found for the percolation threshold of tablets contain-
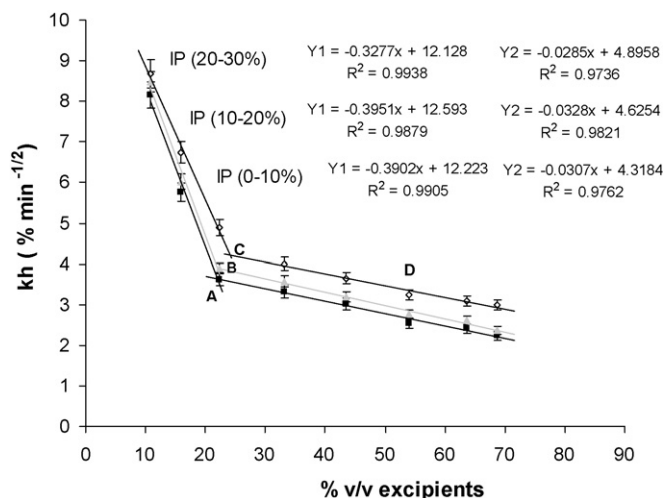
Fig. 6. Changes in the kinetic parameters as a function of % (v/v) of excipients for three series of IP (0–10%, 10–20% and 20–30% IP).

ing strong differences in initial porosity, and therefore in tablet hardness.

Batches DT:HPMC-50, have been supposed, according to the behaviour of the non-linear kinetic parameters (Korsmeyer and Peppas-Sahlin), to be very close to the percolation threshold of the pure dextran. In Fig. 6, these lots reflect a slight deviation from linearity (point D).

Minimizing the IP of the matrix system also decreased interstitial channels and, as a consequence decreases the diffusion rate. Therefore, a slower release of drug can be observed even from the initial time.

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 a number of unnecessary batches, during the development of a pharmaceutical formulation, resulting in a reduction of the time to market.

4. Conclusion

Ternary controlled release tablets of lobenzarit disodium have been developed with a mixture of two polymers: native dextran B110-1-2 (Mw 2×10^6): HPMC K4M CR with a relative excipients/LBD particle size of 4.17. These systems should be formulated with polymer content above 20% (wt/wt) (corresponding to around 22.34%, v/v) to obtain a control of the drug release. This value corresponds to the percolation threshold of the excipients. Anomalous mechanism for water uptake and dissolution profile of LBD from these systems can be expected.

The employ of a mixture dextran:HPMC (4:1, wt/wt) resulted in a reduction of the percolation threshold from 44.75% to 25.17% (v/v) excipients, with respect to binary DT:LBD matrices. The ternary matrices showed better compressibility properties with respect to HPMC:LBD tablets. Initial porosity has an influence in the percent of lobenzarit disodium dissolved at each moment, nevertheless showed little influence in the excipient percolation threshold of the studied hydrophilic matrix tablets.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2009.07.013.

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	DThpmc20% w/	Thpmc30% w/	Thpmc40% w/	Thpmc50% w/	Thpmc60% w/	Thpmc70% w/	thpmc15% w/	Thpmc10% w/	Dt20% w/w	DT30% w/w	DT40% w/w	DT50% w/w	DT60% w/w	DT70% w/w	DT15% w/w	DT10% w/w
peso (g)	0,1875	0,2142	0,25	0,3	0,375	0,5	0,176	0,166	0,1875	0,2142	0,25	0,3	0,375	0,5	0,176	0,166
fármaco p/p(tanto por uno)	0,8	0,7	0,6	0,5	0,4	0,3	0,85	0,9	0,8	0,7	0,6	0,5	0,4	0,3	0,85	0,9
HPMC p/p(tanto por uno)	0,04	0,06	0,08	0,1	0,12	0,14	0,03	0,02	0	0	0	0	0	0	0	0
DT p/p(tanto por uno)	0,16	0,24	0,32	0,4	0,48	0,56	0,12	0,08	0,2	0,3	0,4	0,5	0,6	0,7	0,15	0,1
diámetro (cm)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
altura (cm)	0,1618	0,1871	0,2213	0,2683	0,3407	0,4916	0,16	0,148	0,1534	0,1817	0,2139	0,2683	0,3283	0,4357	0,152	0,146
sup (cm2)	0,785398	0,785398	0,785398	0,785398	0,785398	0,785398	0,785398	0,785398	0,785398	0,785398	0,785398	0,785398	0,785398	0,785398	0,785398	0,785398
volumen (cm3)	0,1270774	0,14694797	0,17380858	0,21072228	0,2675851	0,38610166	0,12566368	0,1162389	0,12048005	0,14270682	0,16799663	0,21072228	0,25784616	0,34219791	0,1193805	0,11466811
A (g/cm3)	1,18038301	1,02036118	0,8630184	0,71183739	0,56056933	0,38849872	1,19047922	1,28528397	1,24501937	1,05068562	0,89287504	0,71183739	0,58174222	0,43834283	1,25313602	1,3028906
poros. Total	77,6569495	66,8901929	56,4379506	46,1035323	36,3350941	31,3649607	84,0935355	89,1872518	76,5973803	66,1433205	55,2443588	46,4783918	34,389975	23,097749	83,3728082	89,1153668
% porosid inicial	22,9842764	19,6293693	16,4648891	13,1328334	10,3707897	13,370578	28,9532288	29,6558035	18,9308971	17,4779375	13,888405	13,5076929	7,44499017	2,79469982	25,3303801	28,7684191
%v/v fármaco	54,6726731	47,2608236	39,9730615	32,9706989	25,9643044	17,9943826	55,1403067	59,5314484	57,6664831	48,665383	41,3559538	32,9706989	26,9449848	20,3030491	58,0424281	60,3469476
%v/v HPMC	4,59293001	6,80618909	8,95479531	11,0791812	13,0872218	14,108903	3,26979873	2,22271331	0	0	0	0	0	0	0	0
%v/v DT	17,7501205	26,303618	34,607254	42,8172866	50,5776841	54,5261363	12,6366658	8,59003489	23,4026197	33,8566795	44,7556412	53,5216082	65,610025	76,902251	16,6271918	10,8846332
dens. Fco	2,159	2,159	2,159	2,159	2,159	2,159	2,159	2,159	2,159	2,159	2,159	2,159	2,159	2,159	2,159	2,159
dens. HPMC	1,285	1,285	1,285	1,285	1,285	1,285	1,285	1,285	1,285	1,285	1,285	1,285	1,285	1,285	1,285	1,285
dens. DT	1,33	1,33	1,33	1,33	1,33	1,33	1,33	1,33	1,33	1,33	1,33	1,33	1,33	1,33	1,33	1,33
dens. Relativa	0,77015724	0,80370631	0,83535111	0,86867167	0,8962921	0,86629422	0,71046771	0,70344197	0,81069103	0,82522062	0,86111595	0,86492307	0,9255501	0,972053	0,7466962	0,71231581
aspect ratio	6,18046972	5,34473544	4,51875282	3,72717108	2,93513355	2,03417413	6,25	6,75675676	6,51890482	5,50357733	4,67508181	3,72717108	3,04599452	2,29515722	6,57894737	6,84931507

	10%	15%
asp Ratio para dThpmc 10 y 15%	6,75675676	6,25
% POROSIDAD INiCIAL		

v/vDT+HPMC	22,3430505	33,1098071	43,5620494	53,8964677	63,6649059	68,6350393	15,9064645	10,8127482
v/vDT+HPMC + IP	45,3273269	52,7391764	60,0269385	67,0293011	74,0356956	82,0056174	44,8596933	40,4685516