Application of a New Mathematical Method for the Estimation of the Mean Surface Area to Calculate the Percolation Threshold of Lobenzarit Dissodium Salt in Controlled Release Matrices

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One of the practical handicaps for the application of the percolation theory to estimate the percolation threshold of drugs in controlled release systems is the fact that the dissolution studies must be carried out so that only one surface of the tablet is exposed to the dissolution medium. The aim of this work is to estimate the percolation threshold of the antiarthritic drug lobenzarit dissodium (LBD) in inert matrices prepared with the excipients Ethocel® 100 and Eudragit® RS-PO (10—75% w/w). Release assays were performed using the paddle method. The whole surface of the tablets was exposed to the dissolution medium. For the first time, a new mathematical method is developed to transform the amount of drug released in amount released per surface area in order to calculate the percolation thershold of LBD. The mathematical method proposed allows to calculate, using a new equation, the evolution of the mean surface area ($O_{(t)}$). The new method was validated and three novel results were achieved: A constant value of ($O_{(t)}$) at critical time (θ) in the matrices ($O_{(\theta)}=1.272\ cm^2$); a linear relationship between initial surface area ($O_{(0)}$) and critical time; and a linear relationship between $O_{(t)}$ and time. Employing the values of $O_{(t)}$, it was possible to calculate for the first time, the percolation threshold (p_{c1}) for LBD in Ethocel® 100 ($p_{c1}=0.280\pm0.102$) and Eudragit® RS-PO ($p_{c1}=0.344\pm0.07$) matrices.

Key words percolation theory; lobenzarit dissodium salt; inert matrices critical time; mean surface area

The Higuchi square root law[1] has been used by many researchers who have corroborated its ability for describing the dissolution profiles of a soluble drug from an inert matrix.

There are three assumptions in the derivation of the Higuchi's law. The first one is that the two-dimensional cross-sectional porosity has the same mean as the volumetric porosity and that the dissolving substance is sufficiently diluted. The second is the existence of a sink condition dissolution test, and the third one is that the surface area from which the release takes place is constant.[2]

Nevertheless, a deviation in the applicability of the square root law was demonstrated. The profiles analysed have shown a change in the Higuchi's slope at a determined time.

Farhadieh (1971)[3] concluded that this fact is related to the geometrical form of the matrices, a flat tablet shows a linear relationship during a longer time than a spherical tablet. Fessi[2] assumed that the change in the profile is due to a modification in the release mechanism that appears when the tablet has been completely penetrated by the dissolution liquid. From this moment the Higuchi law is not valid and the dissolution performs according to a simple diffusion model. The time required for the change in the dissolution process is called the critical time. Finally, Stam[4] concluded that for tablets with high porosity (low hardness) the change in the slope is probably due to a change in the release mechanism, but for tablets with low porosity the differences in density in the tablets are responsible for the change in slope.

On the other hand, the percolation theory has been applied to optimise controlled release inert matrices. Bonny and Leuenberger explained the changes in dissolution kinetics of a matrix controlled release system over the whole range of drug loading, on the basis of percolation theory.[5] Taking into account the Higuchi model and the percolation theory, these authors derived a mathematical model for the estimation of the percolation thresholds in inert matrices.[5,6] Since these initial communications, the new percolation model has been applied to optimise controlled release matrices.[7,8]

According to the percolation model proposed, to calculate the percolation thresholds of drugs, the dissolution assay must be performed keeping only one side of the tablet exposed to the dissolution medium. In this sense, the matrices are embedded into paraffin before the beginning the dissolution assay. This fact supposes a practical disadvantage for the application of this method to estimate the percolation threshold in the pharmaceutical industry.

The objective of this work is to calculate the percolation thershold of LBD in Ethocel® 100 and Eudragit® RS-PO from release assay in which the total surface of the tablets was exposed to the dissolution medium. For this reason, it was necessary to develop a new mathematical method to transform the amount of drug release (mg) in the dissolution assay, in amount of drug release per surface area (mg/cm^2). Obviously this transformation must take into account the changes in the drug/water interface during the dissolution assay.

Experimental

The antiarthritic drug lobenzarit dissodium (LBD) (Centro de Química Farmacéutica, La Habana, Cuba) was used in a dose of 150 mg. Eudragit® RS-PO (Degussa, Barcelona) and Ethocel® 100 (Dow Chemical, Barcelona) were employed as matrix-forming materials. The mixtures (Table 1) were compressed on an excentric machine (Bonals AM-T 300) without any further excipient. Cylindrical tablets were obtained by direct compression at the maximum pressure accepted by the formulations.

The *in-vitro* release assay was performed in the USP 25th apparatus (Turu Grau, model D-6) using the paddle method (75 rpm) and the total surface of the tablet were exposed to the dissolution medium (dearated water, 900 ml at 37±0.5 °C). The amount of LBD released was detected by the increase in conductance of the dissolution medium using a Crison micro CM-2201 digi-

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Table 1. Quantitative Composition of the Formulations

LBD (% w/w)	25	30	40	50	60	70	75	80	83	87	90
Polymers (% w/w) (Eudragit® RS-PO and Ethocel® 100)	75	70	60	50	40	30	25	20	17	13	10

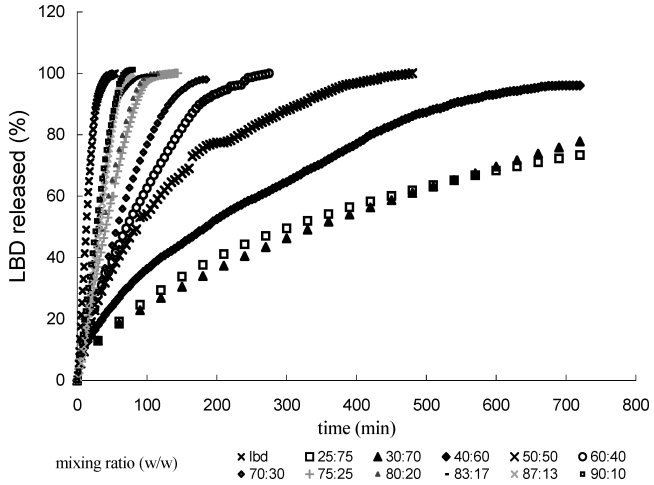

Fig. 1. Amounts of Drug Released *vs*. Time for Tablets Prepared with Different Loading of LBD in Ethocel® 100 Matrices

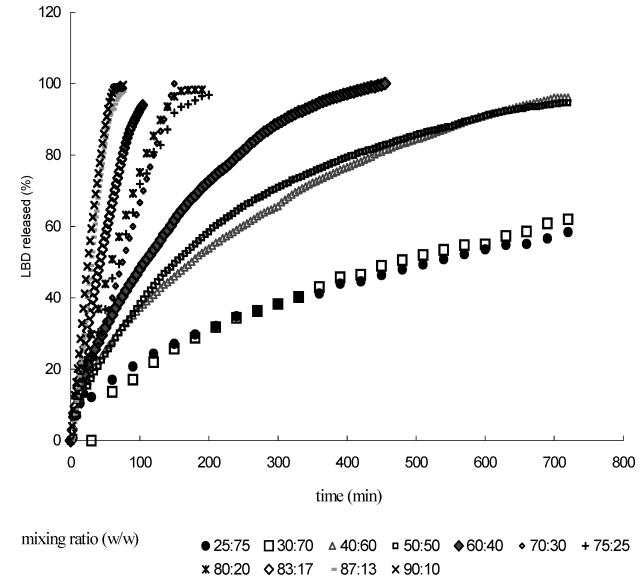

Fig. 2. Amounts of Drug Released *vs*. Time for Tablets Prepared with Different Loading of LBD in Eudragit® RS-PO Matrices

tal conductivity-meter linked to a chart recorder and an IBM-compatible personal computer. The validation of the analytical method as well as a preformulation study of the LBD were previously reported.[9]

Results and Discussion

Matemathical Procedure Figures 1 and 2 show the dissolution profiles of LBD in Ethocel® 100 and Eudragit® RS-PO matrices respectively. As it can be appreciated, a lower release rate was obtained for Eudragit® RS-PO than for Ethocel® 100 matrices.

The square root plots were performed for all lots by plotting the amount of LBD released (mg) *versus* the square root of time ($min^{1/2}$). With the exception of lots consisting of 70 and 75% polymers, a change in the Higuchi's slope was observed in every release profile.

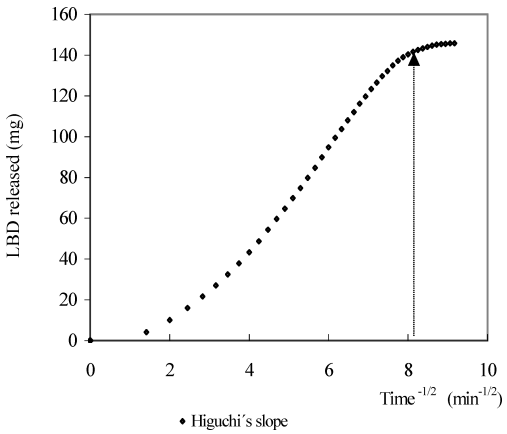

Fig. 3. Example of the Estimation of Critical Time (θ)
Corresponding the lot LBD : Ethocel® 100 of 90 : 10 w/w.

Table 2. Results of Critical Time Estimation

Composition LBD : polymers (w/w)	θ (min)	
	Ethocel® 100	Eudragit® RS-PO
25 : 75	≫720	≫720
30 : 70	≫720	≫720
40 : 60	670	700
50 : 50	515	550
60 : 40	220	440
70 : 30	165	275
75 : 25	110	170
80 : 20	110	150
83 : 17	64	94
87 : 13	67	68
90 : 10	68	66

As has been explained in the introduction section, the time corresponding to this change is denoted as "critical time" (θ). This parameter can be estimated by a visual change in the dissolution profiles.[2] An example of this estimation can be observed in Fig. 3. Table 2 summarises the results in the estimation of θ for all the studied lots. The higher the LBD load in the matrices, the lower the critical times determined. This is due to the decrease in the height of the matrices. As has been indicated, a fixed drug dose was employed (150 mg), therefore the tablet weight as well as the tablet volume decrease as the percentage of LBD increase.

Lai and Carstensen[10] have shown that for cylinders, there is a linear dependence with time of radius (r) and height (h) of the region containing solid drug, with common rate constant (k), as follows:

$$2r_{(t)}=2r_0-kt \quad (1)$$

$$h_{(t)}=h_0-kt \quad (2)$$

r_0: initial radius
h_0: initial height
k: height reduction rate constant (cm/min)

If $h_0<r_0$, k is determined as

$$k=\frac{h_0}{\theta} \quad (3)$$

θ: critical time

The mean surface area experienced by the diffusing species at time t is denoted by $O_{(t)}$ and is given by the following Eq. 2.

$$O_{(t)}=\frac{2\pi}{t}\int_0^t\left\{\left(r_0-\frac{k}{2}t\right)^2+\left(r_0-\frac{k}{2}t\right)(h_0-kt)\right\}dt \quad t>0 \quad (4)$$

According to Fessi, the diffusional cross section, $O_{(t)}$, at any time point will be determined as an average between the initial surface area ($O_{(0)}=2\pi r_0(r_0+h_0)$, the area of the initial cylinder, which is also the value limit of $O_{(t)}$ when t decreases to zero), and the surface area of the boundary of the ghost portion (L) as a function of time:

$$L_{(t)}=2\pi r^2_{(t)}+2\pi r_{(t)}h_{(t)} \quad (5)$$

$$O_{(t)}=\frac{L_{(t)}+O_{(0)}}{2} \quad (6)$$

In this paper, a simple method to calculate the values of mean surface area in matrices of LBD is proposed, through the direct integration of Eq. 4, which results in Eq. 7.

$$O_{(t)}=\frac{\pi}{2}(k^2t^2-(4r_0+h_0)kt+4r_0(r_0+h_0)) \quad (7)$$

Employing Eq. 7, it is possible for the first time to have an estimate of the mean surface area of the matrices as a function of time. This measure can be used to transform the amount of drug released (mg LBD) in amount of drug released per surface area (mg LBD/cm^2). Therefore, the proposed Eq. 7 can provide intrinsic release data whenever an intrinsic dissolution assay can not be carried out, as for example for tablets laving no flat sides.

In over case, these date have been used to estimate the percolation threshold of LBD following the method of Leuenberger and Bonny (see following section).

The results of mean surface area at critical time ($O_{(\theta)}$) using the proposed Eq. 7, are compared with the values obtained using the Fessi's method, which includes the use of Eqs. 1, 2, 3, 5 and 6.

Figure 4 shows the results of this comparison. As it can be observed, constant values ($O_{(\theta)}=1.272$ cm^2) are achieved using the Eq. 7, either for matrices of Eudragit® RS-PO or Ethocel® 100. In contrast, employing the Fessi's equation the values decrease as the LBD load in the matrices increase.

The time required for height reduction from the initial value to zero is the critical time (Eq. 3). At this time, the geometry of the matrices changes from an initial cylindrical form to a plate. According to that, the results obtained applying the Fessi's guidelines can not be justified, specially considering that the initial height (h_0) decreases as the drug load increases. More expectable results (similar surface areas for the plates at the critical times) have been obtained employing the proposed equation.

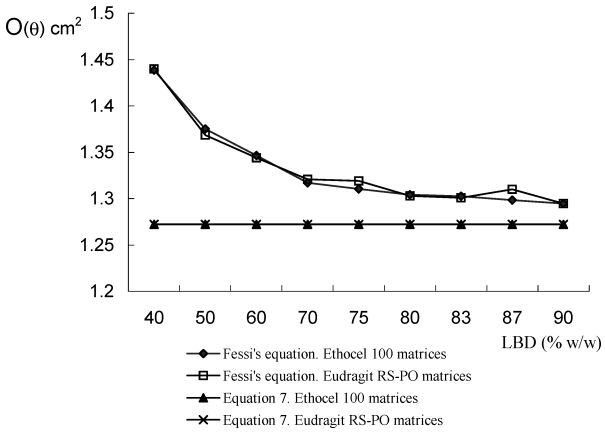

Fig. 4. Values of $O_{(\theta)}$ According to the Equations Studied

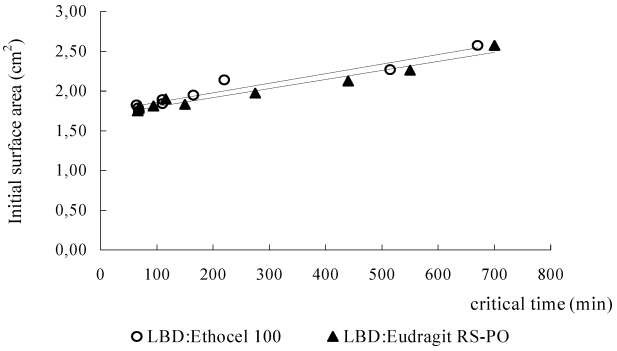

Fig. 5. Linear Relationship between Initial Surface Area and Critical Time

Table 3. Critical Times Extrapolated for Matrices with 70% and 75% Polymer Content, According to the Regression Lines Obtained

Composition LBD : polymer (w/w)	Excipient	$\theta_{(min)}$
25 : 75	Ethocel® 100	1560
	Eudragit® RS-PO	1518
30 : 70	Ethocel® 100	1171
	Eudragit® RS-PO	1183

Regression lines: Ethocel® 100: $O_{(0)}=1.207\cdot10^{-3}\pm(0.0001)\cdot(\theta)+1.735(\pm0.034)$, $n=9$, $r^2=0.942$.
Eudragit® RSPO: $O_{(0)}=1.162\cdot10^{-3}\pm(0.0001)\cdot(\theta)+1.676(\pm0.026)$, $n=9$, $r^2=0.965$.

In the matrices with high polymer ratio (70%, 75%) the experimental critical times (Table 2) and the corresponding mean surface area (Fig. 4) were not calculated, because the time necessary to achieve these points was longer than the dissolution assay (12 h).

However, in our work a linear relationship between the initial surface area and the critical time was found for Ethocel® 100 and Eudragit® RS-PO matrices (Fig. 5). Using the corresponding equation it has been possible to calculate the critical times in the lots with 70% and 75% polymer content (Table 3).

In order to validate the developed mathematical methodology, the assumption established by Fessi of an almost linear

Table 4. Validation of the Proposed Method

Lots[a]		Experimental values[b] of $O_{(0)}$ (cm^2)	Graphical values						
			N	Fessi's method[c]			Proposed method[d]		
				$O_{(0)}$ (cm^2)	γ	r^2	$O_{(0)}$ (cm^2)	γ	r^2
25 : 75	1	3.6191	24	3.5638	−0.0017	0.9944	3.5823	−0.0019	0.9979
	2	3.4975	24	3.4451	−0.0017	0.9945	3.4626	−0.0018	0.9980
30 : 70	1	3.1497	24	3.0870	−0.0016	0.9922	3.1079	−0.0018	0.9972
	2	3.096	24	3.0381	−0.0016	0.9928	3.0574	−0.0018	0.9974
40 : 60	1	2.5729	144	2.4777	−0.0016	0.9841	2.5094	−0.0019	0.9947
	2	2.5729	144	2.4860	−0.0016	0.9861	2.5150	−0.0018	0.9953
50 : 50	1	2.2704	144	2.1611	−0.0016	0.9774	2.2081	−0.0018	0.9942
	2	2.2619	144	2.1801	−0.0015	0.9853	2.2074	−0.0017	0.9951
60 : 40	1	2.1403	144	2.068	−0.0032	0.9866	2.0920	−0.0037	0.9954
	2	2.1623	144	2.031	−0.0015	0.9803	2.0627	−0.0017	0.9937
70 : 30	1	1.9481	37	1.9207	−0.0037	0.9958	1.9298	−0.0040	0.9984
	2	1.9735	62	1.9434	−0.0023	0.9955	1.9534	−0.0025	0.9983
75 : 25	1	1.8915	72	1.8598	−0.0050	0.9950	1.8704	−0.0054	0.9981
	2	1.9000	20	1.8746	−0.0033	0.9958	1.8831	−0.0036	0.9984
80 : 20	1	1.8406	23	1.8241	−0.0040	0.9975	1.8296	−0.0051	0.9990
	2	1.8321	20	1.8088	−0.0034	0.9961	1.8166	−0.0036	0.9985
83 : 17	1	1.8236	100	1.7800	−0.0071	0.9924	1.7946	−0.0079	0.9972
	2	1.8109	52	1.7939	−0.0053	0.9975	1.7996	−0.0057	0.9990
87 : 13	1	1.7869	75	1.7709	−0.0072	0.9977	1.7762	−0.0076	0.9991
	2	1.7829	66	1.7702	−0.0071	0.9980	1.7740	−0.0075	0.9991
90 : 10	1	1.7501	42	1.7353	−0.0065	0.9975	1.7390	−0.0069	0.9990
	2	1.7502	38	1.7357	−0.0067	0.9972	1.7405	−0.0071	0.9992

Graphical parameters from Eq. 8. *a*) 1, LBD: Ethocel® 100; 2, LBD: Eudragit® RS-PO. *b*) $O_{(0)}$ determined from the experimental measurement of r_0 and h_0 values, and calculated according to equation: $O_{(0)}=(2\pi r_0^2)+(2\pi r_0 h_0)$. *c*) $O_{(0)}$ determined from the graphical intercept according to Fessi's equation (Eq. 6). *d*) $O_{(0)}$ determined from the graphical intercept according to proposed equation (Eq. 7). γ=slopes. N=number of experimental points.

relationship between the diffusional cross section ($O_{(t)}$) *vs.* time was investigated (Eq. 8).

$$O_{(t)}=O_{(0)}-\gamma t \tag{8}$$

γ: regression constant

Table 4 shows the results obtained in the estimation of $O_{(0)}$ and γ, according to Eq. 8. The values of $O_{(t)}$ employed were calculated using either Eq. 6 or Eq. 7. Furthermore, the values of $O_{(0)}$ calculated from the experimental measurements of the tablet height and diameter, are shown in Table 4.

In all cases using Eq. 7 instead of Eq. 6, the estimated initial areas were more similar to the experimental values. Also, the regression coefficients obtained with the use of Eq. 7 were higher than those obtained with Eq. 6. This result allows us to verify the linear relationship between diffusional cross section ($O_{(t)}$) and time.

Aplication of the Mathematical Procedure to the Estimation of the Percolation Threshold of LBD Equation 7 has been used for the first time to estimate the surface area in inert matrices at each time point.

Finally, the Eq. 9 was established in order to transform apparent release data (mg LBD) in intrinsic release data (mg LBD/cm^2).

$$Q=\frac{Q_{(t)}}{O_{(t)}} \quad (\mathrm{mg/cm^2}) \tag{9}$$

$Q_{(t)}$: amount LBD released/time
$O_{(t)}$: surface area of LBD matrices/time

The Higuchi profiles were obtained by plotting Q (mg/cm^2, from Eq. 9) *vs. t*. The Higuchi slope (b) was determined for all lots (Table 5).

The Bonny and Leuenberger method was used to estimate the percolation threshold (p_{c1}) of LBD in inert matrices.[5] Table 5 summarizes the parameters used to determine the apparent diffusion coefficient, Eq. 10, and the beta (β) property, Eq. 11.

$$D=\frac{b^2}{C_s(2A-\varepsilon C_s)} \tag{10}$$

$$\beta=\frac{b}{\sqrt{2A-\varepsilon C_s}} \tag{11}$$

D: diffusion coefficient of the drug
b: slope of the regression line in a plot of Q (mg/cm^2) *vs.* squared root of time
C_s: solubility of the drug in water (C_s=0.0423 mg/ml)
A: concentration of the dispersed drug in the tablet
ε: total porosity of the matrix

In a porous matrix, p_{c1} corresponds to a critical porosity (ε_c), where the pore network just begins to span the whole matrix. The equation proposed by these authors can be written as:

$$\beta=\frac{b}{\sqrt{2A-\varepsilon C_s}}=\sqrt{\chi D_0 C_s}\,(\varepsilon-\varepsilon_c) \tag{12}$$

$$\beta=c(\varepsilon-\varepsilon_c)=-c\varepsilon_c+c\varepsilon \tag{13}$$

ε_c: critical porosity of the matrix (lower percolation threshold)
χD_0: scaling facto

Figures 6 shows a plot of total porosity (ε) for the Ethocel® 100 matrices *vs.* the tablet property (β). The point of intersection with the ordenates corresponds to ε_c. Linear

Table 5. Calculation of the Tablet Property β

LBD[a] (% w/w)		ε_d	ε	A (g/cm^3)	b (g·cm^{-2}min$^{-1/2}$)	D (cm^2/min)	β (g$^{1/2}$cm$^{-1/2}$min$^{-1/2}$)
25 : 75	1	0.131	0.252	0.284	1.917	155.882	2.567
	2	0.138	0.272	0.300	1.771	125.997	2.308
30 : 70	1	0.164	0.273	0.355	2.334	184.385	2.792
	2	0.169	0.309	0.365	1.962	126.937	2.317
40 : 60	1	0.237	0.325	0.512	4.513	476.616	4.490
	2	0.244	0.357	0.528	4.189	398.552	4.105
50 : 50	1	0.309	0.414	0.668	5.277	499.295	4.595
	2	0.312	0.454	0.673	4.759	403.546	4.131
60 : 40	1	0.355	0.550	0.768	9.005	1267.283	7.321
	2	0.361	0.578	0.78	6.116	575.885	4.935
70 : 30	1	0.456	0.629	0.986	10.58	1360.265	7.585
	2	0.440	0.669	0.951	7.752	758.220	5.663
75 : 25	1	0.498	0.685	1.079	13.704	2085.328	9.391
	2	0.491	0.713	1.062	10.392	1219.318	7.181
80 : 20	1	0.543	0.742	1.173	14.606	2178.960	9.600
	2	0.551	0.758	1.191	11.071	1233.060	7.222
83 : 17	1	0.560	0.780	1.209	18.772	3492.984	12.155
	2	0.573	0.792	1.238	13.694	1815.064	8.762
87 : 13	1	0.600	0.830	1.296	18.787	3263.350	11.749
	2	0.605	0.842	1.306	19.522	3497.022	12.162
90 : 10	1	0.647	0.861	1.395	18.507	2940.596	11.152
	2	0.647	0.871	1.395	19.349	3214.783	11.661

a) 1, Ethocel® 100 matrices; 2, Eudragit® RS-PO matrices. ε_d: porosity due to dissolution; ε: total porosity of matrix; A: concentration of LBD dispersed in matrix; b: Higuchi's slope; D: apparent diffusion coefficient; β: tablet property; $C_s = 0.0423$ g/cm^3. f

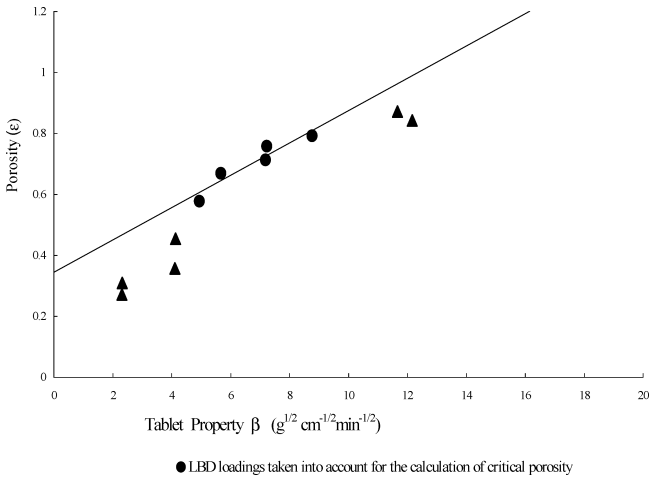

Fig. 6. Graphical Estimation of Percolation Threshold of LBD in Ethocel® 100 Matrices

According to the method of Leuenberger and Bonny, only the values showing a linear behaviour above the threshold (black circles) have been considered for the regression.

regression analysis yield values of: $\varepsilon_c = 0.280 \pm 0.102$ and $\varepsilon_c = 0.344 \pm 0.07$ for the Ethocel® 100 and Eudragit® RS-PO matrices respectively. These values correspond to drug contents between 30—40% w/w for both polymers: Ethocel® 100 and Eudragit® RS-PO. As can be observed in the release profiles (Figs. 1, 2), these ranges correspond to a transition from fast release to controlled release of the drug.

An estimation of the drug percolation threshold for these matrices has been carried out in a previous work,[11] based in the behaviour of the time to release 90% of the drug load ($t_{90\%}$). The obtained percolation ranges (27.31—32.55% v/v LBD for Ethocel® 100 matrices and 30.93—35.78% v/v LBD for Eudragit® RS-PO matrices) are in perfect agreement with the results obtained in the present study for the drug percolation thresholds using the proposed method.

Conclusions

A new method for the estimation of the difussional cross section ($O_{(t)}$) has been proposed and validated. This method provided results more similar to the experimental values than the previously existing procedures.

According to that, the values of the difussional cross section ($O_{(t)}$) in the matrices at each point can be used to transform the usually obtained apparent release data in drug released per surface area (intrinsic dissolution data). This transformation will facilitate the estimation of the drug percolation threshold using the method of Leuenberger and Bonny.[5,6]

The methodology proposed was validated in LBD controlled release matrices. The percolation thresholds estimated for LBD in Ethocel® 100 and Eudragit® RS-PO matrices were $p_{c1} = 0.280 \pm 0.102$ and $p_{c1} = 0.344 \pm 0.07$ (respectively) which corresponds to a random site percolation process in a three-dimensional lattice.

References

1) Higuchi T., *J. Pharm. Sci.*, **52**, 1145—1149 (1963).
2) Fessi H., Marty J. P., Puisiex F., Carstensen J. T., *Int. J. Pharmaceut.*, **1**, 265—274 (1978).
3) Farhadieh B., Borodkin S., Buddenhagen J. D., *J. Pharm. Sci.*, **60**, 209—212 (1971).
4) Stam A., Tritsch J. C., "Controlled Drug Release," Vol. 1, ed. by Rubinstein M. H., Ellis Horwood Limited, Chichester, 1987, pp. 54—63.
5) Bonny J. D., Leuenberger H., *Pharm. Acta Helv.*, **66**, 160—164 (1991).
6) Bonny J. D., Leuenberger H., *Pharm. Acta Helv.*, **68**, 25—33 (1993).
7) Caraballo I., Fernández-Arévalo M., Holgado M. A., Rabasco A. M., Leuenberger H., *Int. J. Pharm.*, **109**, 229—236 (1994).
8) Melgoza L. M., Rabasco A. M., Sandoval H., Caraballo I., *Eur. J. Pharm. Sci.*, **12**, 453—459 (2001).
9) Boza A., Caraballo I., Fernández M., Alvarez J., Rabasco A. M., *Int. J. Pharm. Adv.*, **1**, 429—442 (1996).
10) Lai T. Y. F., Carstensen J. T., *Int. J. Pharmaceut.*, **1**, 33—40 (1978).
11) Boza A., PhD Thesis, La Habana, 2002.