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Influence of two different types of excipient on drug percolation threshold

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Abstract

The application of the principles of percolation theory is providing a more rational pharmaceutical dosage form design. The drug percolation threshold is the parameter that provides a better description of the system according to this theory. In order to check the possibility of use the drug percolation threshold as a preformulation parameter, the influence of the main formulation factors is being studied. The aim of this work is to study the influence of the type of excipient on the drug percolation threshold. For this purpose, two excipients exhibiting very different mechanical behaviour have been selected. Inert matrices were prepared using Ethocel® 100 and Eudragit® RS-PM as excipients and KCl as a model drug. Release assays were performed using the rotating disk method. The drug percolation threshold was estimated employing the method of Leuenberger and Bonny. The following confidence intervals (95%) were obtained: $\epsilon_c = 0.3644 \pm 0.0641$ and $\epsilon_c = 0.3407 \pm 0.0345$ of total porosity for matrices containing Eudragit® RS-PM and Ethocel® 100, respectively. On the light of the obtained results, no significant differences were found on the drug percolation thresholds for two excipients having very different mechanical behaviour.

Keywords: Percolation theory; Percolation threshold; Inert matrices; Controlled release; Ethyl cellulose; Eudragit® RS-PM

1. Introduction

The percolation theory is a powerful tool that is applicable to a wide number of scientific disciplines. It was presented by Broadbent and Hammersley in 1957 to explain the behaviour of disordered systems (Hammersley, 1983). It was introduced in the pharmaceutical field by Leuenberger et al., in 1987, to the characterisation of solid dosage forms. This theory gives a better explanation to the mechanism of the formation of

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Table 1
Composition and tablet weight of the prepared inert matrices

Lot	Ethocel® 100 (%, w/w)	Eudragit® RS-PM (%, w/w)	KCl (%, w/w)	Tablet weight (mean, g)
1	70	—	30	0.595
2	60	—	40	0.598
3	50	—	50	0.598
4	40	—	60	0.593
5	30	—	70	0.591
6	20	—	80	0.589
7	—	70	30	0.595
8	—	60	40	0.598
9	—	50	50	0.590
10	—	40	60	0.598
11	—	30	70	0.598
12	—	20	80	0.599

a tablet and the mechanical and biopharmaceutical properties of compacts (Caraballo et al., 1993, 1994).

Using the concepts of the percolation theory, it has been found that the formation of a tablet can be considered as a site/bond percolation phenomenon (Leuenberger and Leu, 1992; Leu and Leuenberger, 1993).

Bond and site percolation can be defined as follows: a pair of two particles may be described as a cluster of size two, because two neighbouring sites are occupied (site percolation). On the other hand, the same pair of particles can be described as a cluster of size one, because there is only one bond between them (bond percolation). Thus for each type of lattice there is a site and a bond percolation threshold (Stauffer and Aharony, 1991, ch.1).

The concept of cluster can be defined as a group of neighbouring sites occupied by the same component. The concentration at which there is the maximum probability that a cluster just starts to percolate a tablet is termed the percolation threshold.

The lattice in a suitable pharmaceutical dosage form may be occupied by particles of type A or type B. The theoretical percolation threshold depends on the type of lattice formed and indicates since what concentration of A, this substance dominates the system A/B or vice versa (Bonny and Leuenberger, 1993).

In previous works we have checked the influence of the drug particle size on the drug percolation threshold in inert matrices, using KCl as drug and Eudragit® RS-PM as matrix-forming excipient. A linear relationship between the relative drug/excipient particle size ratio and the drug percolation threshold has been found for these systems (Caraballo et al., 1996; Millán et al., 1998).

In order to study the effect of the mechanical properties of the employed substances on the percolation threshold, two excipients exhibiting very different mechanical behaviour were employed, keeping constant the rest of the formulation factors. The selected excipients were Eudragit® RS-PM that exhibits a rigid behaviour, and Ethocel® 100, a plastic excipient.

Inert matrices were prepared with the selected excipients and its release behaviour was studied. The drug percolation threshold (p_{c1}) was calculated for the matrices containing either Ethocel® 100 or Eudragit® RS-PM.

2. Materials and methods

Matrix tablets were compressed using an eccentric machine (Bonals A-300) with 12-mm flat-faced single punches. The tablets were prepared at the maximum compression force accepted by the formulation. Potassium chloride (Acofarma) was used as a model water-soluble drug. Ethocel® 100

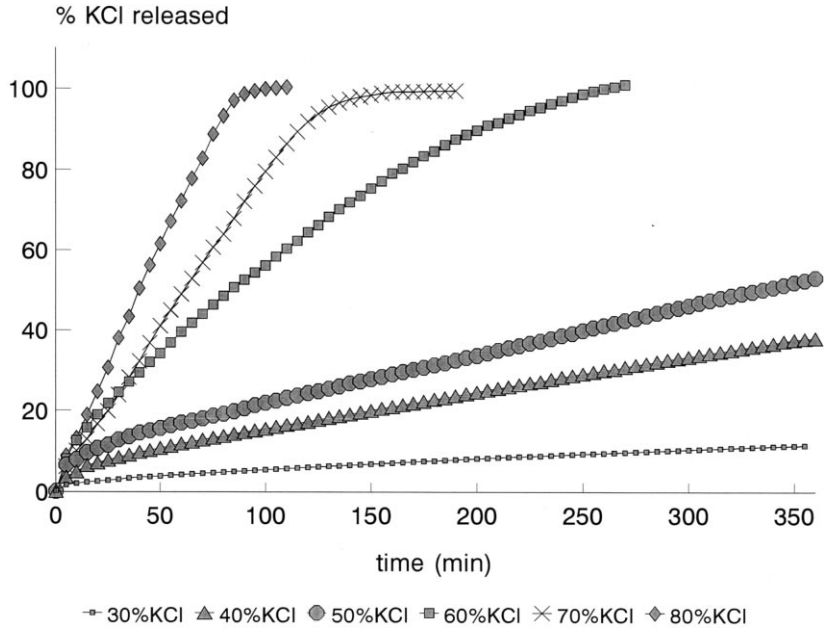

Fig. 1. Release profiles of tablets containing Ethocel® 100.

(Dow Chemical Company) and Eudragit® RS-PM were employed as matrix-forming materials. The ethyl cellulose is not affected by water. It takes up very little water from humid air or during immersion, and that small amount evaporates readily. Eudragit® RS-PM is a non-swelling, hydrophobic polymer.

The true density of Eudragit RS-PM was calculated measuring the total porosity of tablets prepared with pure Eudragit RS-PM by mercury intrusion porosimetry (Fisons Instruments, type 4000). The value of the true density of Ethocel® 100 (1.14 g/ml) was taken from the literature (Kent and Rowe, 1986).

The employed substances were sieved (Retsch, type Vibro) and the 50–100-μm granulometric fraction was selected for the drug substance. The particle size of the employed excipients (Eudragit® RS-PM and Ethocel® 100) was 100–150 μm.

Ten tablets were weighed (Mettler, type AE-50) and the mean value was calculated. Table 1 shows the drug and excipient content of the prepared formulations as well as the tablet weight (the theoretical tablet weight was 600 mg).

The tablets were embedded into paraffin leaving only one side accessible for the dissolution medium. The exposed surface to the medium was 1.13 cm^2. The drug release assay from the prepared tablets was carried out in the USP 23 apparatus (Turu Grau, model D-6) using a rotating disk method (50 rpm), and distilled water at 37 ± 0.5°C.

The KCl water-solubility and the insolubility in water of the excipients, make possible to use a conductimetric method to determine the drug released. The conductivity-meter (Crison micro CM-2201) was connected to a personal IBM computer. Tablets were assayed by triplicate. The method of Bonny and Leuenberger (1991) was employed to estimate the drug percolation threshold for tablets containing Eudragit® RS-PM and Ethocel® 100. This method uses the β-property:

$$\beta = -c\epsilon_c + c\epsilon$$

where c represents a constant, ϵ is the matrix porosity, due to initial tablet porosity and the drug content after leaching and ϵ_c denotes the critical porosity–drug percolation threshold.

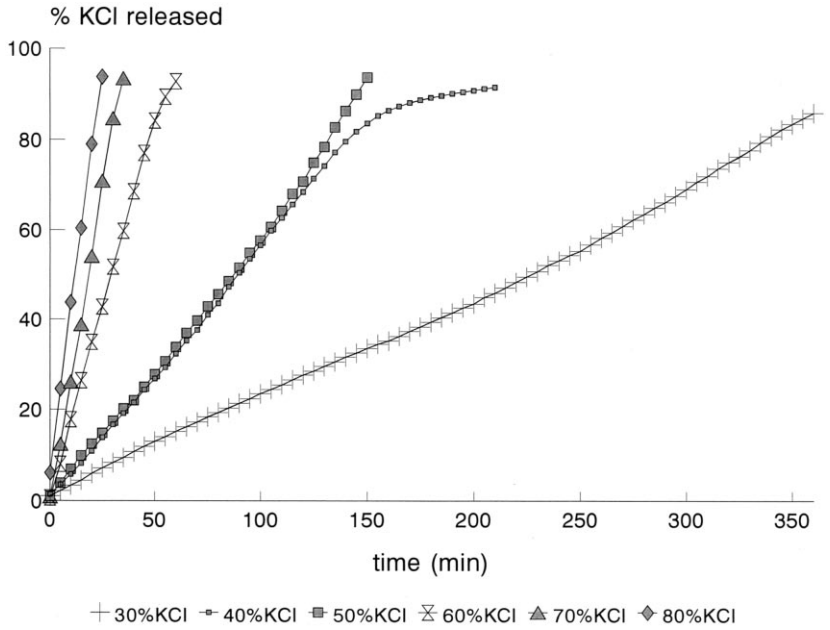

Fig. 2. Release profiles of tablets containing Eudragit® RS-PM.

β is defined as:

$$\beta = \frac{b}{\sqrt{2A - \epsilon C_s}}$$

where b is the slope of the Higuchi plot, A represents the concentration of the drug in each tablet, and C_s is the solubility of the drug in the dissolution medium (Bonny and Leuenberger, 1991).

Table 2
Values obtained for the β property for Ethocel® 100 and Eudragit® RS-PM tablets, as well as the parameters involved in its calculation

Lot	ϵ	$b \pm$ S.E.	r	n	P	A	β ($\times 10^3$)
1	0.268	0.00324 ± 3.2E-5	0.997	46	<0.0001	0.358	4.113
2	0.348	0.01076 ± 1.8E-4	0.994	46	<0.0001	0.496	11.55
3	0.424	0.01413 ± 2.5E-4	0.993	46	<0.0001	0.656	13.11
4	0.512	0.04003 ± 3.2E-4	0.999	36	<0.0001	0.834	32.85
5	0.611	0.05394 ± 1.7E-3	0.985	30	<0.0001	1.035	39.63
6	0.724	0.07378 ± 2.0E-3	0.995	15	<0.0001	1.257	49.13
7	0.319	0.01022 ± 3.1E-5	0.987	51	<0.0001	0.362	13.10
8	0.431	0.02331 ± 1.4E-4	0.978	23	<0.0001	0.469	26.44
9	0.480	0.02936 ± 1.7E-4	0.979	23	<0.0001	0.642	27.84
10	0.577	0.06406 ± 4.1E-4	0.994	7	<0.0001	0.784	54.91
11	0.650	0.09055 ± 4.9E-4	0.981	24	<0.0001	1.008	78.15
12	0.753	0.09814 ± 8.7E-4	0.964	18	<0.0001	1.221	66.57

ϵ, total porosity; b, Higuchi constant (g $min^{-1/2}$ cm^{-2}); r, correlation coefficient; n, number of cases; A, concentration of drug dispersed in the tablet (g cm^{-3}); β, tablet property ($g^{1/2}$ $cm^{-1/2}$ $min^{-1/2}$).

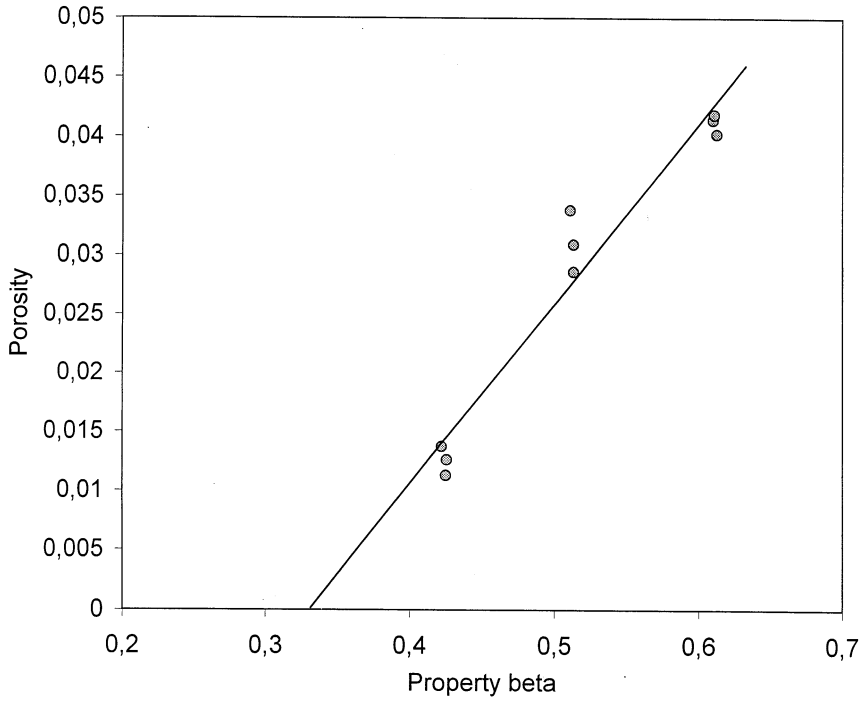

Fig. 3. Estimation of the drug percolation threshold (p_{c1}) for Ethocel® 100 matrices, employing the method of Bonny and Leuenberger.

3. Results and discussion

In order to study the influence of two different types of excipient on the drug percolation threshold, tablets with different drug loading and two different matrix-forming materials were prepared.

In previous works (Caraballo et al., 1996; Millán et al., 1998) it has been demonstrated that the particle size has an important influence on the percolation threshold. Therefore, in order to investigate the influence of the type of excipient, the particle size of both, drug and excipients was kept constant for all the studied tablets. The drug

Table 3
Statistical data from the regression analysis for the estimation of the percolation thresholds

	Ethocel® 100		Eudragit® RS-PM	
Correlation coefficient/n	0.971/9		0.933/7	
Regression coefficient ± S.E.	6.192 ± 0.574		3.897 ± 0.674	
Constant ± S.E.	0.341 ± 0.018		0.364 ± 0.033	
P (two-tail)	<0.005		<0.001	
Source	Regression	Residual	Regression	Residual
Sum-of-squares	0.049	0.003	0.030	0.005
DF	1	7	1	5
Mean-square	0.049	0.0004	0.030	0.0009
F ratio	116.41		33.39	

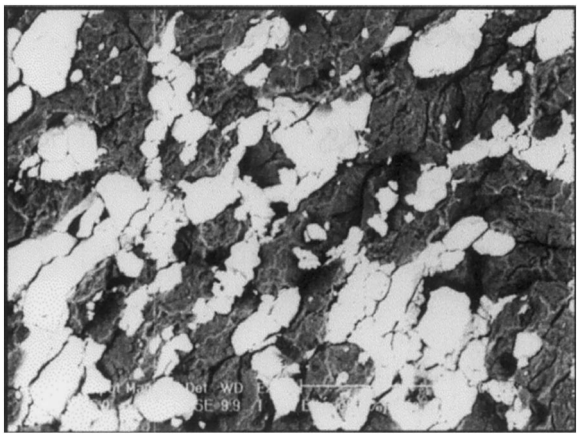

Fig. 4. SEM micrograph of a matrix tablet containing Ethocel® 100 and KCl (50:50%, w/w).

particle size was 50–100 μm and the excipient particle size was 100–150 μm. In vitro release assays were performed on these tablets. The release profiles of tablets containing Ethocel® 100 and Eudragit® RS-PM are shown in Figs. 1 and 2, respectively.

When the insoluble excipient has a plastic behaviour, it is expected to surround the drug particles and to reduce the number and size of the pores that are present in the tablet before the dissolution of the drug (initial porosity). Therefore, a decrease of the drug release rate is expected, due to a decrease in the effective coefficient of diffusion, D_{eff}. On the other hand, based on the percolation theory, it could be expected that when a plastic component of the system (component A) surround a rigid component (B), its percolation threshold, p_{cA}, will decrease due to a more effective distribution of this component to form an infinite cluster. In order to check this hypothesis, the drug percolation threshold has been estimated employing the method of Leuenberger and Bonny.

The values obtained for the β-property for Ethocel® 100 and Eudragit® RS-PM tablets, as well as the parameters involved in its calculation, are shown in Table 2. According to the method of Leuenberger and Bonny, when the property β of the tablets containing a bicoherent system, is plotted versus the total porosity, ϵ, the intercept with the abscissa gives an estimation of the drug percolation threshold ($\epsilon_c = p_{c1}$). Fig. 2 shows as an example the plot corresponding to the Ethocel® 100 matrices. In order to estimate the confidence intervals corresponding to the percolation thresholds, ϵ_c, it was necessary to introduce a slight modification in the treatment of the data: the critical porosity was obtained from a linear regression of the total porosity, ϵ versus the β-property. Fig. 3 shows as an example the plot corresponding to the Ethocel® 100 matrices. In this manner, it is possible to calculate a confidence interval for the critical porosity. The statistical data from the regression analysis for the estimation of the percolation thresholds are shown in Table 3: 95% confidence intervals of $0.3062 \leq \epsilon_c \leq 0.3753$ for Ethocel® 100 tablets and $0.3003 \leq \epsilon_c \leq 0.4286$ for Eudragit® RS-PM tablets were obtained. Both of them correspond to a drug particle size range of 50–100 μm. Furthermore, when the cross-section of the tablets is observed by SEM (see Figs. 4 and 5), it can be appreciated that an extensive fragmentation of the materials has not occurred during the compression process. It is important to determine this situation, because it has been demonstrated (Caraballo et al., 1996; Millán et al., 1998), that the particle size exerts a clear influence on the percolation threshold.

Therefore, in spite of the different mechanical properties of the selected matrix-forming excipi-

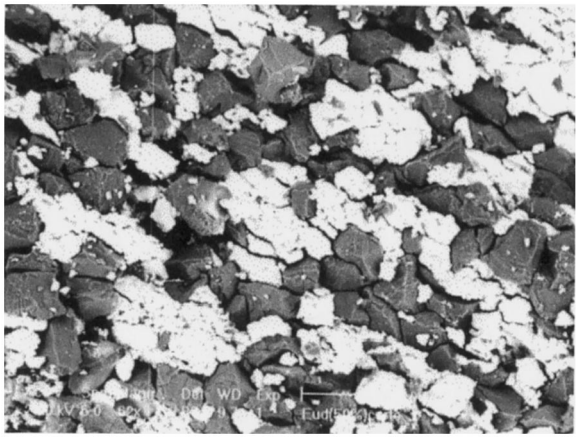

Fig. 5. SEM micrograph of a matrix tablet containing Eudragit® RS-PM and KCl (50:50%, w/w).

ents, and of the lower release profiles exhibited by the Ethocel® 100 matrices, the obtained confidence intervals show no significant differences between the drug percolation thresholds of these matrices.

On the basis of the obtained results, the mechanical properties of the excipient seems to have a low influence on the drug percolation threshold. If this result is confirmed to be valid, it may have an important practical impact: the percolation threshold of a drug may be valid for any (or at least a large number) of excipients. This fact will help to improve the pharmaceutical dosage forms design.

Nevertheless, further investigations are needed in order to know if the coating effect of the plastic excipient has been masked by the formulation factors. Furthermore, when more brittle substances are employed, it must be taken into account that an important fragmentation process can occur. This circumstance must be studied because it will change the percolation thresholds.

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