The Role of the Drug/Excipient Particle Size Ratio in the Percolation Model for Tablets

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Purpose. In previous papers, a linear relationship between drug particle size and drug percolation threshold was found in inert matrix tablets. The main objectives of the present work are: to study the influence of the excipient particle size on the drug percolation threshold and to investigate if the change in the drug percolation threshold is due either to the absolute or to the relative drug particle size.

Methods. Matrix tablets have been prepared using KCl (7 different particle size fractions) as a drug model and Eudragit® RS-PM (4 granulommetric fractions) as matrix forming material. *In vitro* release assays were carried out on the 66 lots of tablets. The drug percolation thresholds were estimated following the method of Bonny and Leuenberger.

Results. The particle size of the excipient has shown an opposite effect to the drug size on the drug percolation threshold. Nevertheless, the influence of drug and excipient sizes on the drug percolation threshold are of the same magnitude.

Conclusions. The drug percolation threshold depends linearly on the relative drug particle size. This finding is in agreement with percolation theory and can facilitate the use of the percolation threshold as a preformulation parameter to improve the pharmaceutical dosage forms design.

KEY WORDS: percolation theory; percolation threshold; inert matrix tablets; controlled release; drug/excipient particle size ratio.

INTRODUCTION

Percolation theory is a statistical theory that is able to explain the behavior of disordered systems. Many of the percolation models (site, bond, and site-bond percolation) assume the existence of a regular lattice underlying the system. In a binary mixture A/B, the sites or cells of this lattice can be occupied by the component A or B (1). The distribution of the particles of each component is random.

A cluster is defined as a group of neighbor occupied sites in the lattice (2). 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 (percolation theory deals with infinite lattices). One of the most important parameters of the percolation theory is the percolation threshold: the concentration of a component at which there is a maximum probability of appearance of an infinite cluster of this component.

Therefore, in a binary pharmaceutical tablet, two percolation thresholds are expected: the drug and the excipient percolation threshold. These percolation thresholds are critical concentrations where some tablet properties (percentage of drug released, release rate, mechanical properties, *etc.*) may undergo sudden changes (3).

Using these arguments, percolation theory makes the study of disordered (chaotic) systems possible and is being applied to an increasing number of scientific fields, for example, the flow of liquid in a porous medium, the mobility edge in amorphous semiconductors, or the polymer gelation (3).

In 1987, Leuenberger and his co-workers at the University of Basel (Switzerland) began to apply this theory in the pharmaceutical field, achieving interesting advances in the study of the mechanism of disintegration, the design of tablets, wet granulation process, and the behavior of controlled release systems (4–7).

In order to apply the simple random percolation models (site-bond percolation) to solid particulate forms, the requirement of an underlying regular-lattice must be fulfilled. Therefore, the components must have equal mean particle sizes. Evidently, this simplification cannot be assumed in most of the pharmaceutical systems.

Therefore, in order to avoid this problem, the continuum percolation model has been widely applied to pharmaceutical systems. This model dispenses with the regular lattice underlying the system, and is based in the volume fractions of the components (8–10). Nevertheless, in this manner, the influence of particle sizes cannot be appreciated.

In previous works, a quantitative study of the influence of the particle size of the drug on the drug percolation threshold has been carried out for 5 different drug particle sizes, keeping constant the excipient particle size. A linear relationship has been found in this study between the drug particle size and the drug percolation threshold (11).

In the present paper, this previous work (11) has been continued, studying the influence of the particle size of the excipient on the drug percolation threshold. The obtained results show that it is not the absolute particle size but the drug/excipient particle size ratio that is the main factor influencing the drug percolation threshold.

MATERIALS AND METHODS

Potassium chloride (Acofarma, Tarrasa, Barcelona) was used as a model water-soluble drug. A matrix-forming material, Eudragit® RS-PM (Hüls Española, Barcelona), was used. It is a hydrophobic, non-swelling acrylic polymer. Both compounds were sieved (Retsch type Vibro). The mean diameter of the particles of drug and excipient was measured using a He-Ne laser diffraction system (Malvern Instr., type Mastersizer x, 1.2b). Table I shows the composition of the studied formulations as well as the particle size of the employed substances.

The mixtures were compressed on an eccentric machine (Bonals A-300) without any further excipient. Cylindrical tablets with a weight of 600 mg and a diameter of 12 mm were prepared at the maximum compression force accepted by our formulations.

Dissolution studies were carried out in the USP 23 apparatus (Turu Grau, type D-6) using the rotating disc method so that only one surface of the tablet (0.79 cm^2) was exposed to the dis-

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Table I. Drug Loading, Drug Particle Size and β Property for Tablets Containing Different Eudragit® RS-PM Particle Sizes and 211 μm KCl

Lot	Eudragit® particle size (μm)	KCl (% w/w)	$\beta \cdot 10^3$
1	72	20	4.03
2	72	30	7.77
3	72	40	8.89
4	72	50	15.99
5	72	60	35.52
6	72	70	64.26
7	72	80	91.13
8	72	90	179.64
9	125	40	11.22
10	125	50	26.32
11	125	55	46.87
12	125	60	40.08
13	125	65	57.96
14	125	70	78.77
15	125	75	82.02
16	125	80	96.62
17	196	30	14.16
18	196	40	29.77
19	196	50	69.95
20	196	60	87.94
21	196	70	108.62
22	196	80	179.81
23	268	30	19.68
24	268	40	36.07
25	268	50	83.24
26	268	60	95.29
27	268	70	118.28
28	268	80	145.00

solution medium (deaerated water at 37 ± 0.5°C). The rotational speed was kept constant at 50 rpm. Release of KCl was detected by the increase in conductance of the dissolution medium using a Crison micro CM-2201 digital conductivity-meter linked to a chart recorder and a personal computer. The system provides one conductivity datum per s.

The drug percolation thresholds were calculated following the method reported by Bonny and Leuenberger (5,6). This drug percolation threshold corresponds to a critical porosity, ε_c, where the pore network, i.e., the initial pores and the pores filled up by the drug, just begins to span the whole matrix.

On the other hand, in order to calculate these theoretical porosities, the true density of KCl was taken from the literature (12), whereas the true density of Eudragit® RS-PM has been calculated experimentally using a mercury porosimeter (Porosimeter 4000 Fisons Instruments).

The method of Bonny and Leuenberger is based in the calculation of β, a property of the tablets derived from the diffusion coefficient. The tablet property, β, is defined as follows:

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

where b is the slope of the Higuchi plot, A the concentration of the dispersed drug in the tablet, and C_s the solubility of the drug in the permeating fluid. Above the drug percolation threshold, and below the excipient percolation threshold, the β property behaves as follows:

$$\beta = c(\varepsilon - \varepsilon_c) = -c\,\varepsilon_c + c\varepsilon$$

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

Plotting β vs. ε, the drug percolation threshold (ε_c) can be readily calculated as the point of intersection with the abscissa.

RESULTS AND DISCUSSION

The components of the pharmaceutical solid dosage forms usually have different particle sizes. Therefore, when the percolation model is applied to these systems, the particles cannot be considered to each occupy a lattice site.

In order to avoid this problem, the volume fraction of each component is usually employed. This strategy leads to continuum percolation models in which the particle size is assumed to have no influence on the percolation threshold.

Taking into account the more recent studies on this subject (9–11,14), this assumption does not hold. The particle size has showed to have an important influence on the percolation threshold. Therefore, it can be expected that this parameter has a notable effect on a great number of properties of the system. Furthermore, the influence of the drug particle size on the drug percolation threshold appears to be linear in the size range assayed (11,13).

As it has been discussed in previous papers (11,13), theoretical models are at the moment not developed enough to give an estimation of the type of influence that the particle size exerts on the characteristics of the system.

The main objective of this work is to investigate if the change of the drug percolation threshold reported in previous papers (11,13) is due either to the drug particle size or to the drug/excipient particle size ratio. For this purpose, 28 lots of tablets have been prepared keeping constant the drug particle size (211 μm) and using 4 different excipient mean particle sizes (72, 125, 196, and 268 μm). The rest of the conditions were similar to the previously assayed tablets (11,13) in which the drug percolation threshold was calculated for 7 drug particle sizes, keeping constant the excipient (Eudragit® RS-PM) particle size.

On the other hand, in order to quantify more accurately the relationship between the particle size and the percolation threshold, the particle size of each fraction was measured for all the studied lots, using a He–Ne laser diffraction system. Furthermore, the true density of the excipient has been calculated experimentally using a mercury porosimeter. A true density of 1.235 g/cm^3 was obtained for Eudragit® RS-PM.

The prepared tablets were measured and weighted. *In vitro* release profiles were obtained following the experimental conditions described in the previous section. As an example, the obtained release profiles for tablets containing 211 μm KCl and 72 μm Eudragit® RS-PM are shown in Fig. 1. As can be observed in this figure, a change in the release profiles appear near 50% w/w KCl content. According to the percolation the-

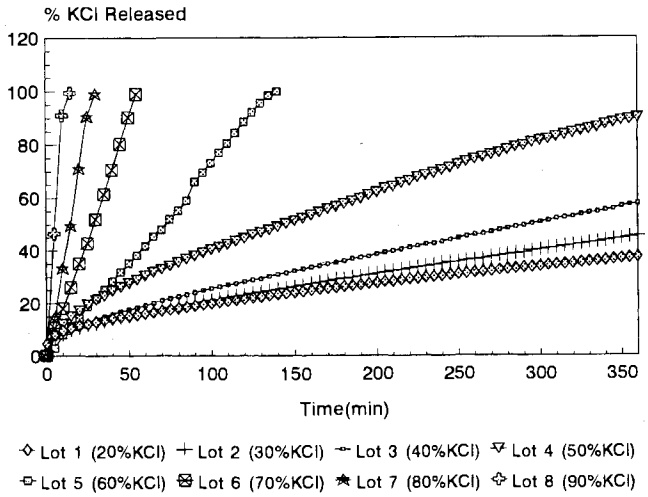

Fig. 1. Release profiles of tablets containing 72 μm Eudragit® particles.

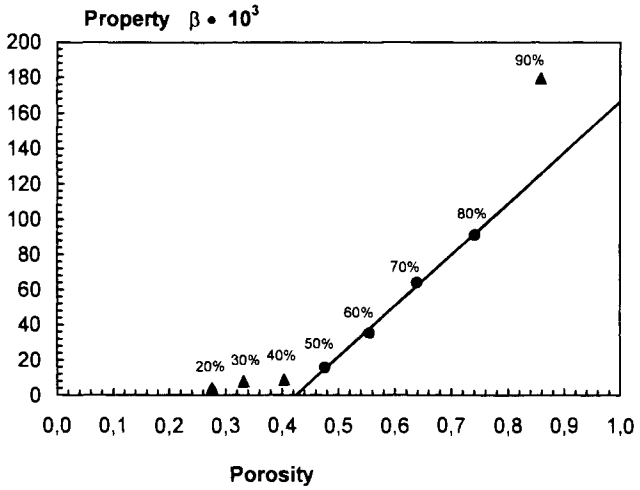

Fig. 2. Determination of the drug percolation threshold for the matrices containing 72 μm Eudragit® and 211 μm KCl particles.

ory, the drug percolation threshold, i.e., the volume fraction at which the drug starts to form an infinite cluster which percolates the whole tablet, must be close to the total porosity of this lot of tablets.

The drug percolation thresholds (p_{c1}) have been calculated following the method proposed by Bonny and Leuenberger, as described in the Materials and Methods section. Table II shows the values of the parameters involved in the calculation of β for the selected example, i.e., matrices with 72 μm Eudragit® RS-PM and 211 μm KCl. Plotting β vs. ε_c (see Fig. 2), the point of intersection with the abscissa is the critical porosity (ε_c) or percolation threshold.

According to the method of Bonny and Leuenberger (7), only the β values situated in the linear zone above the drug percolation threshold, p_{c1}, and below the excipient percolation threshold, p_{c2}, must be used to calculate ε_c. (Points plotted as black circles in Fig. 2.)

In our study, the considered β values were those included in the following ranges of w/w KCl concentrations: 50–80%, 50–80%, 40–80%, 30–80% for tables containing 72, 125, 196, and 268 μm excipient mean particle size, respectively. Table III shows the obtained drug percolation thresholds as well as some statistical parameters from its determination.

It must be taken into account that the particle size of drug and excipient could change during the process due to fragmentation. Nevertheless, the substances used in this work are not brittle and, therefore, significant fragmentation is not expected.

Figure 3 shows the obtained drug percolation thresholds as a function of the mean drug particle size (line A) for lots with 125 μm mean diameter excipient. Furthermore, the drug percolation thresholds obtained for the lots where the drug particle size was kept constant (211 μm) have been also plotted in Fig. 3, as a function of its excipient particle size (line B).

As shown in this figure, linear changes in the drug percolation threshold were obtained by changing the particle size of both components of the binary system. Nevertheless, whereas the increase in the drug particle size produces an increase in the drug percolation threshold, for the excipient particle size, the contrary effect was observed, i.e., the larger the excipient particle size, the lower the drug percolation threshold.

These facts can be explained in terms of effectiveness of

Table II. Calculation of the Tablet Property β and Related Parameters[a] in Matrices Containing 72 μm Eudragit® RS-PM Particles

Lot	ε	b ± std. error	r	N	F	Prob.	A	β·10³
1	0.276	0.00237 ± 2.8E-5	0.9977	35	7277.05	<0.0001	0.223	4.03
2	0.331	0.00594 ± 7.6E-5	0.9966	43	6130.53	<0.0001	0.354	7.77
3	0.403	0.00814 ± 1.0E-4	0.9968	43	6409.6	<0.0001	0.492	8.89
4	0.476	0.01695 ± 1.9E-4	0.9976	40	8011.54	<0.0001	0.647	15.99
5	0.555	0.04275 ± 1.4E-3	0.9919	18	976.527	<0.0001	0.824	35.52
6	0.639	0.08614 ± 2.1E-3	0.9913	33	1751.96	<0.0001	1.040	64.26
7	0.741	0.13811 ± 5.5E-3	0.9890	16	636.63	<0.0001	1.281	91.13
8	0.858	0.30274 ± 5.7E-3	0.9993	6	2785.74	<0.0001	1.573	179.64

[a] ε: total porosity; b: Higuchi constant ($g \cdot min^{-1/2} \cdot cm^{-2}$); r: lineal correlation coefficient; n: number of cases; F: Snedecor ratio; A: concentration of drug dispersed in the tablet ($g \cdot cm^{-3}$); β: tablet property ($g^{1/2} \cdot cm^{-1/2} \cdot min^{-1/2}$).

Table III. Drug Percolation Thresholds (ε_c) for Tablets Containing Different Eudragit® RS-PM Particle Sizes and Statistical Parameters from Its Determination

Eudragit® Particle size (μm)	ε_c	Std. error	r	F	Prob.	N
72	0.425	0.014	0.9983	597.12	0.0017	4
125	0.371	0.027	0.9673	72.77	0.0004	7
196	0.334	0.044	0.9631	38.44	0.0085	5
268	0.280	0.026	0.9881	164.91	0.0002	6

the volume fraction of each component. The larger particles occupy several lattice sites each, whereas the volume of the lattice site will be identified with the mean volume of the minor particles. Therefore, a great particle can be considered as a cluster of *s* lattice sites which is occupied with a density of 100%, i.e., inside this particle, all the *s* lattice sites are occupied by same component.

The existence of these zones of high density implies the lower effectiveness of this component in order to percolate of whole system. In other words, an occupation density much lower than 100% (ever lower than 50% in 3D systems) (2) is enough to have a cluster of the same dimensions of the particles. This cluster contains a random mixture of both components and will allow the component to percolate the system in a similar way to the particle itself, employing less than *s*/2 lattice sites.

Therefore, this distribution of one component into clusters of 100% density (great particles) results in a lower effectiveness of this component to percolate the system. In this manner, a higher percolation threshold of this component is obtained.

Theoretical studies are needed to know the quantitative influence of this factor on the percolation threshold and on the rest of the system properties. A handicap for the development of such studies is the random structure of the percolation systems (15). At the moment, only experimental studies have been developed (11,13), indicating that the drug percolation threshold depends linearly on the drug particle size, at least in the size ranges assayed.

According to Percolation theory, an increase in the particle size of all the components of a finite system can be considered as equal to decreasing the sample size of the system.

Therefore according to the Percolation theory, the effect of a reduction in the drug particle size is similar to an increase in the excipient particle size in a binary system. In other words, it may be expected that the relative particle size of the component, but not its absolute particle size, will determine the characteristics of the system.

In order to study this fact, the obtained drug percolation thresholds have been plotted as a function of the drug/excipient particle size ratio of the matrices (see Fig. 4). A linear relationship has been found between the drug percolation threshold and the relative drug particle size. These results are in agreement with the above demonstrated theoretical model based on Percolation theory.

The obtained result may have important consequences in the pharmaceutical dosage forms design. If this behavior is general, the effect of a change in the drug particle size may be obtained by changing the excipient particle size. Furthermore, according to this relationship, if the drug percolation thresholds corresponding to at least two relative drug particle sizes are known, the drug percolation threshold may be predicted for other drug/excipient particle size ratios of these compounds. Nevertheless, it must be borne in mind that if more brittle substances are employed, the drug and/or excipient particle size may change due to fragmentation.

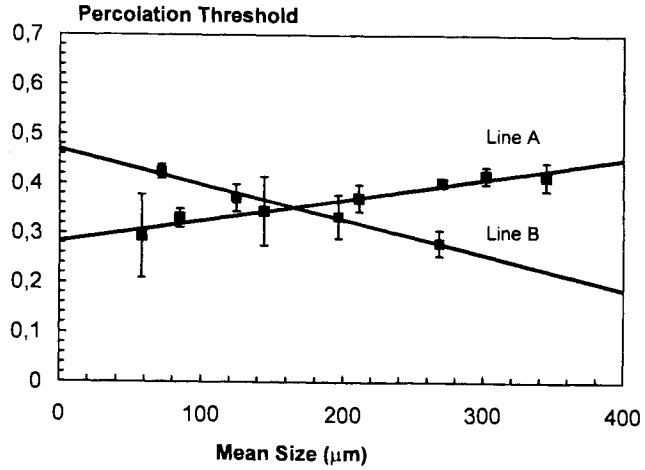

Fig. 3. Drug percolation threshold (mean ± SE) obtained as a function of the mean particle size of the drug (line A) and of the excipient (line B) employed.

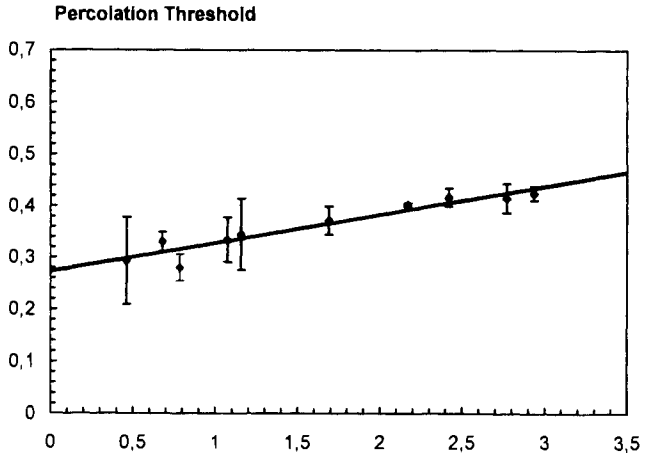

Fig. 4. Drug percolation threshold (mean ± SE) obtained as a function of the drug/excipient particle size ratio employed..

The main conclusion that the percolation threshold depends linearly on the drug/excipient particle size ratio is a new finding which can be of interest for the scientific community and supports the use of the drug percolation threshold as a preformulation parameter that can improve the pharmaceutical dosage form design.

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