Relationship Between Drug Percolation Threshold and Particle Size in Matrix Tablets

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Purpose. Since a previous qualitative study carried out by us showed the existence of an important influence of the particle size on the percolation thresholds and taking into account that the existing theoretical models can only provide qualitative explanation to this influence, the purpose of this work is to carry out the first quantitative study of the influence of the particle size over the drug percolation thresholds.
Methods. Matrix tablets have been elaborated using potassium chloride as drug model and Eudragit RS-PM as matrix forming material. Five different KCl particle size fractions have been employed whereas the Eudragit® RS-PM particle size was kept constant. *In-vitro* release assays were carried out for all the elaborated lots. The drug percolation thresholds were estimated following the method proposed by Bonny and Leuenberger.
Results. A linear relationship has been found between the drug particle size and the corresponding drug percolation threshold.
Conclusions. This finding confirms the results previously obtained in our qualitative study and has important repercussions in the design of pharmaceutical solid dosage forms. If this linear behaviour is general, the percolation threshold can soon become a useful preformulation parameter.

KEY WORDS: percolation theory; percolation threshold; inert matrix tablets; particle size; controlled release.

INTRODUCTION

In 1957 Broadbent and Hammersley (1) presented a statistical theory—percolation theory—which was able to explain the behaviour of disordered systems. Since these initial communications, percolation theory has been fruitfully applied to a great number of physical, chemical and biological problems as the flow of liquid in a porous medium, the polymer gelation, the glass transition or the confinement of quarks in nuclear matter.

Percolation theory was introduced in the pharmaceutical field in 1987 when, Leuenberger *et al.* (2) employed this theory in the characterization of solid dosage forms. After these initial applications, several investigations have demonstrated the usefulness of percolation theory in the pharmaceutical research (3–7).

This theory supposes the existence of a regular lattice underlaying the system. In a binary mixture A/B, the sites—or cells—of this lattice can be occupied by the component A or by the component B. In random percolation models, the occupation of the sites is random, i.e. each site is occupied by the component A or B independent of the occupation *status* of its neighbors (8).

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A cluster is defined as a group of neighbor occupied sites in the lattice (8) and the probability at which a cluster just percolates a system (a tablet in our case) is termed the percolation threshold.

In 1991, Bonny and Leuenberger (3) explained the changes in dissolution kinetic of a matrix controlled release system over the whole range of drug loadings on the basis of percolation theory. Furthermore these authors derived a model for the estimation of the percolation thresholds from the diffusion behaviour.

Nevertheless, there are still some handicaps for the application of this theory in the rationalization of the pharmaceutical design. One of these handicaps is the requirement of an underlaying regular-lattice. Usually, drug delivery systems contain substances with different particle sizes. Therefore the particles can not be considered as occupying a lattice site each one.

This problem can be avoided by using not a lattice sites ratio but a volume ratio. So, all the studies of pharmaceutical systems on the basis of percolation theory dealt with the volume fractions of the components. In this manner, the percolation thresholds were calculated as critical volume fractions (2–7).

Nevertheless, the influence of the particle size of the components on the percolation thresholds can not be explained alone by using a volume fraction i.e. that tablets with the same total porosity are equivalent.

A qualitative study of the influence of the particle size on the percolation threshold in inert matrix tablets has been carried out by us in a previous paper (5) showing that substances having the higher particle size need a higher concentration to percolate the tablet. Furthermore, some authors have reported very low percolation thresholds when very fine powders were employed (6, 9).

Since at present theoretical models cannot provide a quantitative information about how the particle size can change the percolation threshold, in the present paper the first quantitative study of the influence of the particle size on the drug percolation threshold has been carried out.

A linear relationship has been found between the drug particle size and the corresponding drug percolation threshold. This new finding is in agreement with the results previously obtained in the qualitative study and can have important repercussions in the design of pharmaceutical solid dosage forms.

MATERIALS AND METHODS

Matrix tablets were prepared in the same conditions reported for the qualitative study (5). Potassium chloride (Acofarma, Tarrasa, E-Barcelona) was used as a model water-soluble drug. Eudragit® RS PM (Industrias Sintéticas Curtex, E-Barcelona), a hydrophobic, non-swelling acrylic polymer was employed as matrix-forming material. Both compounds were sieved (Retsch, type Vibro) to obtain the desired granulometric fractions. Table I show the drug loading and the drug particle size of the 46 elaborated formulations. The Eudragit® particle size was kept constant (100–150 μm).

The mixtures were compressed on an eccentric machine (Bonals A-300) without any further excipient. Cylindrical tablets (600 mg) were prepared at the maximum compression force accepted by the formulations.

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Table I. Drug Loading, Drug Particle Size and β Property for All the Tested Formulations

Lot	KCl particle size (μm)[a]	KCl (% p/p)	$\beta \cdot 10^3$
1	50–100	30	1.615
2	50–100	40	3.298
3	50–100	50	3.531
4	50–100	55	4.289
5	50–100	57	6.184
6	50–100	60	6.982
7	50–100	65	6.586
8	50–100	70	8.685
9	50–100	75	8.265
10	50–100	80	8.559
11	100–150	10	0.444
12	100–150	20	0.851
13	100–150	30	1.263
14	100–150	40	3.521
15	100–150	50	6.711
16	100–150	60	5.381
17	100–150	65	7.727
18	100–150	70	10.02
19	100–150	75	8.277
20	100–150	80	14.38
21	100–150	90	19.98
22	150–200	40	1.407
23	150–200	50	3.332
24	150–200	55	5.957
25	150–200	60	5.113
26	150–200	65	7.407
27	150–200	70	10.09
28	150–200	75	10.24
29	150–200	80	12.41
30	200–250	40	1.531
31	200–250	50	3.349
32	200–250	55	5.831
33	200–250	60	8.631
34	200–250	65	7.985
35	200–250	70	8.339
36	200–250	75	11.32
37	200–250	80	13.42
38	250–300	40	1.006
39	250–300	50	1.988
40	250–300	55	4.694
41	250–300	60	6.030
42	250–300	65	6.366
43	250–300	70	8.488
44	250–300	75	12.11
45	250–300	80	14.24
46	250–300	85	16.36

[a] The excipient particle size was 100–150 μm for all the formation.

The *in-vitro* release assay of the elaborated tablets was performed in the USP XXII apparatus (Turu Grau, model D-6) using the rotating disk method (50 rpm) so that only one surface of the tablet (0.72 cm^2) was exposed to the dissolution medium (deaerated water at 37 ± 0.5 °C).

The amount of KCl released 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 an IBM-compatible personal computer.

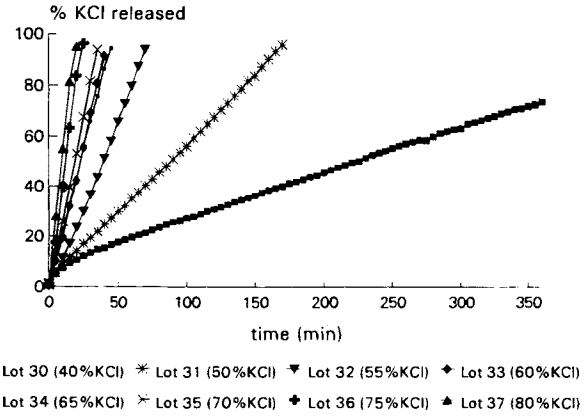

Fig. 1. Release profiles of tablets containing 200–250 μm KCl particles.

The drug percolation thresholds were calculated following the method reported by Bonny and Leuenberger (3, 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 load, just begins to span the whole matrix.

This method 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:

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

being b 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 behave as:

$$\beta = -C \cdot \epsilon_C + C \cdot \epsilon$$

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

RESULTS AND DISCUSSION

As it has been mentioned in the first section, a qualitative study of the influence of the particle size on the percolation thresholds in matrix systems has been carried out in previous works (5). Particle size showed a clear influence on the percolation thresholds. The substances having the higher particle size needed a higher concentration to percolate the tablet. This fact cannot be explained by random percolation.

In 1993, Bonny and Leuenberger (6) reported a very low percolation threshold (6% v/v) obtained using an excipient with very little particle size. These authors affirm that correlated percolation models can provide a theoretical explanation for this fact.

Correlated percolation models consider that the distribution of the components in the system is not completely random.

Table II. Calculation of the Tablet Property β and Related Parameters[a] in Matrices Containing (200–250 μm) KCl Particles

Lot	ϵ	b ± std. error	r	n	F	Prob.	A	$\beta \cdot 10^3$
37	0.2668	0.00144 ± 2.9E-5	0.9910	46	2407.3	<0.0001	0.489	1.531
38	0.3296	0.00370 ± 1.4E-4	0.9841	25	708.2	<0.0001	0.671	3.349
39	0.3860	0.00681 ± 4.7E-4	0.9817	10	212.7	<0.0001	0.751	5.831
40	0.4385	0.01067 ± 9.5E-4	0.9844	6	125.1	0.0004	0.842	8.631
41	0.5000	0.01034 ± 3.7E-4	0.9832	29	782.5	<0.0001	0.928	7.985
42	0.5549	0.01430 ± 54.7-4	0.9825	23	583.4	<0.0001	1.038	8.339
43	0.6187	0.01628 ± 9.3E-4	0.9779	16	305.7	<0.0001	1.144	11.32
44	0.6866	0.02018 ± 9.5E-4	0.9890	12	448.8	<0.0001	1.254	13.42

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

Therefore, the occupation of a lattice site by a component of the mixture is influenced by the occupation *status* of the neighboring sites. This interaction results in the obtention of ordered mixtures of the components.

The first model dealing with correlated percolation was developed by Coniglio (10) for the estimation of the magnetization probability in a system. In this model, the presence of up spin favors the obtention of up spins in the neighboring atoms. The model predicts that the component whose elements (atoms, molecules, particles, fractions of particles, etc.) are arranged in compact groups needs a higher concentration to percolate the system, i.e. this component has a higher percolation threshold. This conclusion is in agreement with the results obtained in previous papers (5–7).

Unfortunately, at present, correlated percolation models only provide a qualitative explanation of the influence of the particle size on the percolation thresholds (11–13). Therefore, the main goal of this work is to quantify for the first time the influence of the particle size on the percolation thresholds.

For this purpose, matrix tablets have been elaborated using potassium chloride as drug model and Eudragit® RS-PM as matrix forming material. As it can be seen in table I, five different KCl particle size fractions have been employed whereas the Eudragit® RS-PM particle size was kept constant.

In-vitro release assays were performed on all the elaborated lots. As an example figure 1 show the release profiles obtained from tablets containing 200–250 μm drug particles.

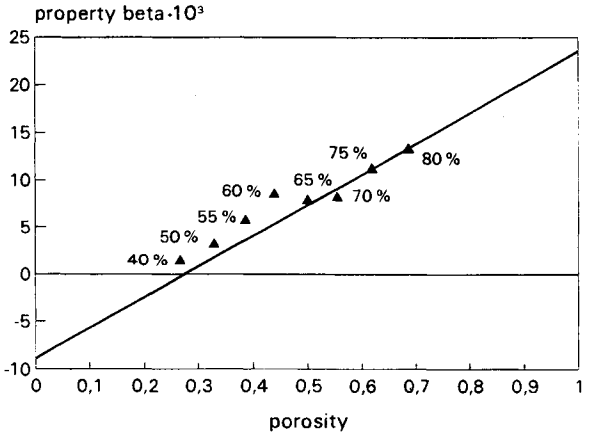

Fig. 2. Determination of the drug percolation threshold for the matrices containing 200–250 μm KCl particles.

According to the release profiles the drug percolation threshold expressed as w/w concentration, seems to undergo an important change as a function of the particle size. It appears to be very close to the 30 % w/w KCl for the lower drug particle size (50–100 μm) and increases gradually up to ≈ 50% w/w of drug loading for the higher KCl particle size (250–300 μm).

Nevertheless, it must be kept in mind that a part of this change in the drug percolation threshold expressed as weight concentration may be attributed to the different initial porosities of the matrices.

Due to the different technological characteristics of each particle size fraction, the matrices containing 50–100 μm KCl particles showed higher initial porosities than those containing coarser drug particles. Therefore, these first matrices have higher total porosities than tablets formulated with equal drug loadings (w/w) and coarser drug particles. So, from the w/w concentration data it is not possible to know if the faster release rate exhibited by these matrices is due to a change in the percolation threshold or only to their higher initial porosities. Employing the v/v ratio this problem can be excluded as the percolation threshold corresponds to the value of total porosity (expressed as critical volume fraction) where for the first time an infinite cluster of pores can be obtained (3, 5–7). As indicated in previous section, the total porosity includes the initial porosity and the porosity due to the dissolution of the drug because the sum of these porosities is responsible for the water penetration and the drug release.

Therefore, the drug percolation thresholds have been calculated for each drug particle size. As described in the *materials and methods* section, the method proposed by Bonny and Leuenberger (3) has been used. This method has been already

Table III. Percolation Thresholds (ϵ_c) and Statistical Parameters from Its Determination

Particle size KCl (μm)	ϵ_c	Std. error	r	F	Prob	n
50–100	0.18297	0.03330	0.94448	41.317	0.001	7
100–150	0.22153	0.08554	0.67067	2.453	0.215	5
150–200	0.27167	0.03050	0.96041	30.587	0.005	5
200–250	0.27772	0.02224	0.97428	37.392	0.023	4
250–300	0.34537	0.01472	0.98941	88.265	0.003	4

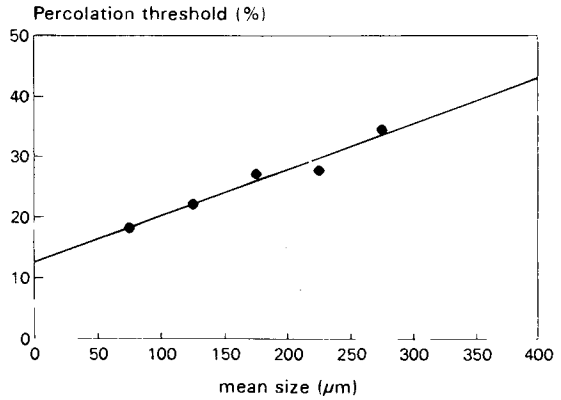

Fig. 3. Drug percolation thresholds obtained as a function of the mean drug particle size employed.

employed in previous works for the estimation of the critical probability in inert matrices (5, 6, 14).

As an example, the values of the parameters involved in the calculation of β for the matrices with 200–250 μm KCl are shown in table II. The values obtained for the β property for all the studied formulations were included in table I.

According to the method employed, the regression of the values of β corresponding to a bicoherent system which show a linear behaviour *versus* the distance to the percolation threshold, determines the drug percolation threshold (p_{cl}). In our study, the considered lots were those included in the following ranges of w/w concentrations: 40–70%, 50–75%, 60–80%, 65–80% and 65–80% for tablets containing 50–100 μm, 100–150 μm, 150–200 μm, 200–250 μm and 250–300 μm drug particle size, respectively. Figure 2 shows a typical plot of β as a function of the total porosity. The percolation threshold is determined by the intercept with the abscissa. Table III shows the estimated drug percolation thresholds as well as some statistical parameters from its determination.

When the obtained drug percolation thresholds were plotted *versus* the mean drug particle size employed, a linear relationship was obtained (see figure 3), which was not anticipated.

Several conclusions can be obtained from this new finding. First, this relationship confirms the results obtained in the qualitative study (5) and predicted by correlated percolation models. There is a clear influence of the drug particle size on the drug percolation threshold and this percolation threshold increases when coarser drug particles are employed.

Some authors suggest that the reason for the obtention of very low percolation thresholds can be the ordered powder mixing that is attributed to the adhesion of the little particles to the coarser ones (6, 15). This influence is expected to appear when there is an important difference in particle size between drug and excipient particles. On the other hand, the influence of the drug particle size on the percolation thresholds appears to be a continuous influence in this study and the initial mean particle size of drug and excipient do not differ in such a way that the smaller particles coat the coarser ones.

On the other hand it has to be kept in mind, that the excipient and drug particles in general change their shape and particle size during the compaction process. Thus it may be too speculative to make the conclusion that such a behaviour will be found in all cases of matrix formulations.

Nevertheless, if the linear relationship obtained for the first time in this study, is confirmed by further works as a general behaviour, the percolation threshold can soon become a useful preformulation parameter.

To summarize, the linear dependence of the percolation threshold on the mean particle size obtained in this work if generally valid represents an important progress in the application of Percolation theory in the pharmaceutical field. Thus these findings are very helpful in order to improve the design of matrix type dosage forms.

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