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Study of percolation thresholds in ternary tablets

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Abstract

One of the handicaps for the application of the principles of percolation theory in pharmaceutical systems is the fact that this theory has been developed for binary systems. The aim of this work is to study for the first time the existence and behaviour of the percolation thresholds in ternary pharmaceutical tablets. For this purpose, mixtures containing three substances with very different hydrophilicity and water-solubility—KCl, polyvinylpyrrolidone cross-linked (PVP-CL) and Eudragit® RS-PM—were prepared and compressed. The bulk and tapped densities of the mixtures as well as the hardness and in-vitro release behaviour of the tablets have been studied. The KCl percolation threshold has been estimated in the range 0.26–0.31 of total porosity. A range where PVP-CL percolates can be defined between 10 and 30% v/v. This influences the hardness of the tablet. On the other hand, the existence of a 'combined percolation threshold' of the sum of all the hydrophilic substances, i.e. KCl and PVP-CL, has been found at 35% v/v approximately. This fact is in agreement with previous results.

Keywords: Percolation theory; Percolation threshold; Ternary systems; Combined percolation threshold

1. Introduction

In 1957 Broadbent and Hammersley presented a statistical theory—Percolation theory—which was able to explain the behaviour of disordered systems (Broadbent and Hammersley, 1957; Hammersley, 1957).

Since these first works, Percolation theory has been fruitfully applied to a great number of scientific subjects as the spreading of fluids in porous media, the polymer gelation, the magnetization process, etc. (Zallen, 1983).

The Percolation theory is a statistical theory which 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 B. In random percolation

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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 neighbours (Domb, 1983). A cluster is defined as a group of neighbour occupied sites in the lattice and the probability at which a cluster just percolates a system (a tablet in our case) is termed percolation threshold.

Percolation theory was introduced in the pharmaceutical field by Leuenberger and his research group nine years ago (Leuenberger et al., 1987). This theory has been proved useful, especially for the characterization and design of binary dosage forms (Bonny and Leuenberger, 1991, 1993; Leuenberger et al., 1989a,b, 1992; Caraballo et al., 1993, 1994, 1995, 1996).

Bonny and Leuenberger (1991, 1993) explained the changes in the dissolution kinetic of a matrix controlled release system over the whole range of drug loadings on the basis of Percolation theory.

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 has been studied in a previous work (Caraballo et al., 1996), where a linear dependence of the percolation threshold on the drug particle size has been found. These results might be explained on the basis of correlated percolation models.

Another handicap is the fact that Percolation theory has been developed for binary mixtures (usually, drug delivery systems contain more than two components). In previous works, it was put

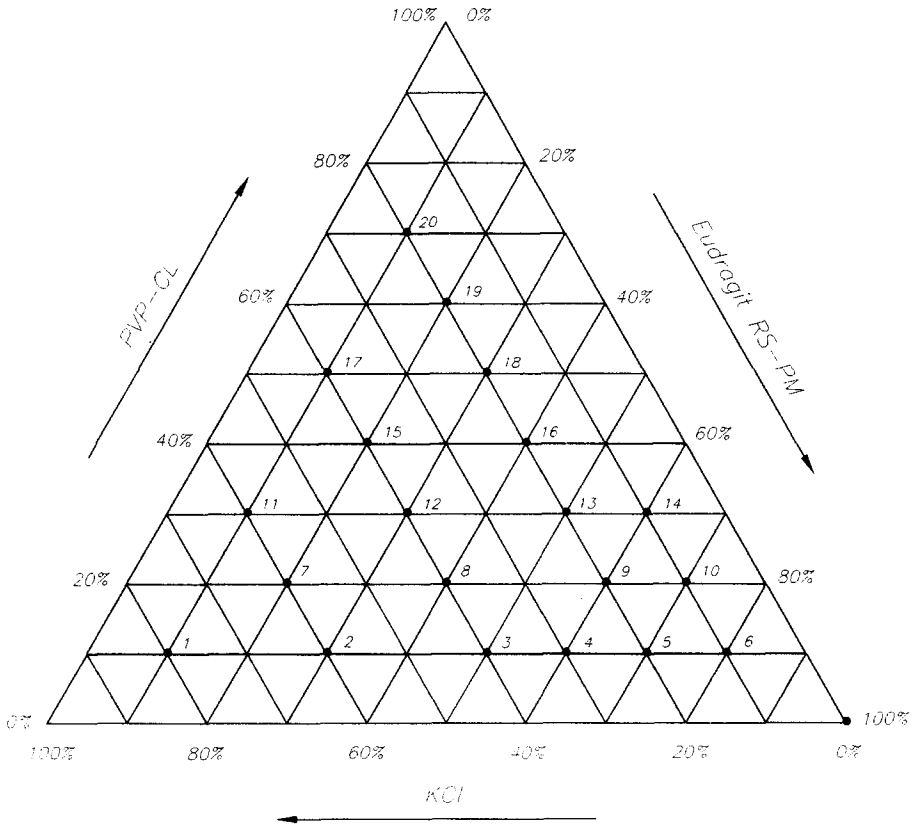

Fig. 1. Composition (% w/w) of the studied ternary mixtures.

forward as a hypothesis that multicomponent systems can be reduced to binary ones. This hypothesis led to acceptable results in the studied carteolol hydrochloride matrix systems (Caraballo, 1994).

The aim of the present work is to study the behaviour of ternary percolation thresholds in pharmaceutical dosage forms.

For this purpose, 20 mixtures of three substances with very different hydrophilicity and aqueous solubility—KCl, polyvinylpyrrolidone cross-linked (PVP-CL) and Eudragit® RS-PM—have been prepared. The bulk and tapped densities as well as the percentage of compressibility of these mixtures were measured.

Different weights of the prepared mixtures were compressed in order to obtain tablets of similar volume (0.39 cm^3) for the 20 formulations. Furthermore, the compression pressure was selected in order to obtain very similar and low porosities (≈ 2–4%).

The hardness of the tablets was determined and its in vitro release behaviour was evaluated on the basis of its dissolution efficiency (E_d) (Salvadó et al., 1987). No sharp percolation thresholds were found in these ternary systems for the employed components separately. Nevertheless, a percolation threshold has been found, which we have named as 'combined percolation threshold' of (KCl and PVP-CL) the hydrophilic components.

This finding is in agreement with previous results (Caraballo, 1994; Caraballo et al., 1994) and demonstrates that a multicomponent system can be reduced to a binary system on the basis of a common property.

2. Materials and methods

Potassium chloride (Acofarma, Tarrasa, E-Barcelona) was used as a model water-soluble and hydrophilic drug. Ternary mixtures of KCl with Eudragit® RS-PM (Industrias Sintéticas Curtex, E-Barcelona) and polyvinylpyrrolidone cross-

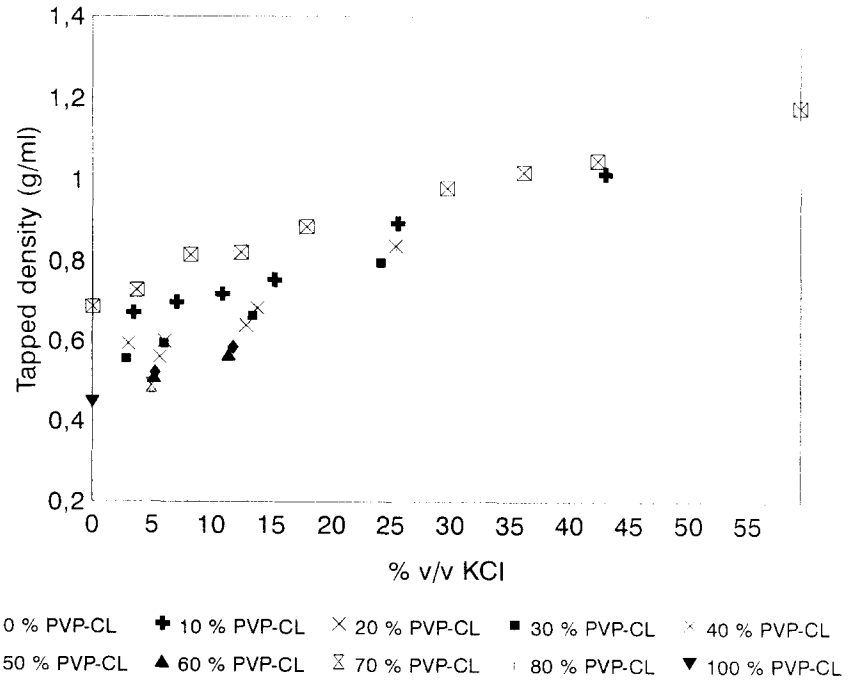

Fig. 2. Tapped density of the studied ternary mixtures as a function of their KCl volume fraction (%).

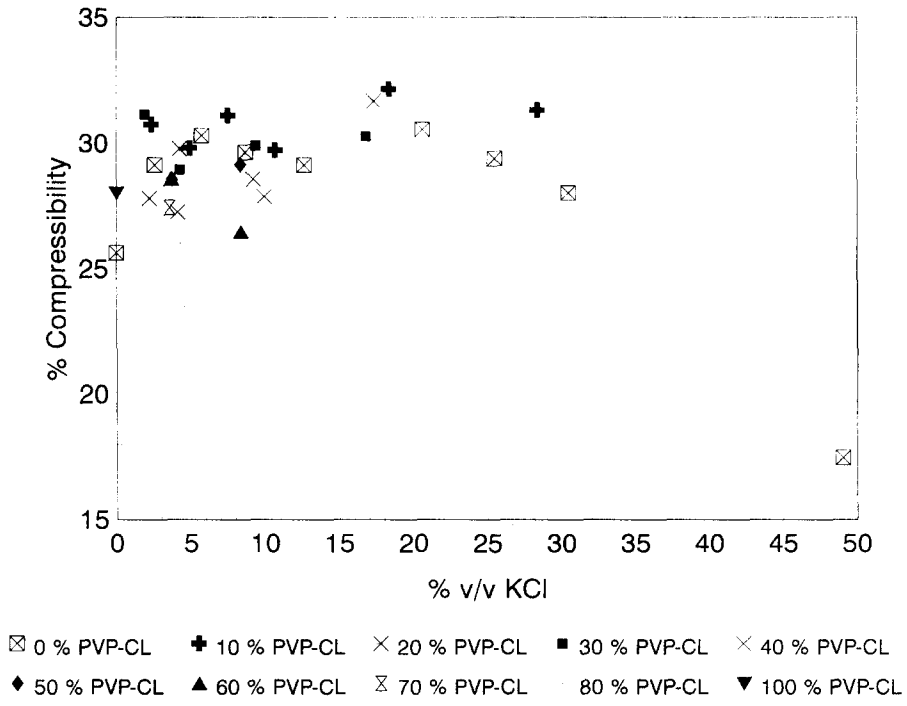

Fig. 3. Percentage of compressibility of the studied mixtures as a function of their KCl volume fraction (%).

linked (PVP-CL) (Basf, D-Ludwigshafen) have been prepared using a Turbula mixer (type T2C), with 5 min mixing time employed. All the three products were previously sieved (Retsch, type Vibro) and 90–180 μm granulometric fraction was selected for the three employed substances.

The bulk and tapped densities were determined by using 20 g of the different mixtures and a 50 ml volumetric cylinder. Three series of 1250 percussions (Engelsmann, D-Ludwigshafen) were used to calculate the tapped density of each formulation.

The percentage of compressibility of the mixtures was calculated following Eq. 1.

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

Different amounts of the mixtures were weighed (Mettler type PM-460) and compressed in a Zwick 1478 universal testing instrument with a compression force of 40 kN (421 MPa). This same instrument was used to calculate the hardness of the tablets.

Calculations were made in order to obtain approximately the same volume (0.39 cm^3) for all the tablets. The composition (w/w) of the 20 studied formulations is shown in Fig. 1. For example, lot 1 contains 80% w/w KCl, 10% w/w PVP-CL and 10% w/w Eudragit® RS-PM.

The diameter and height of the tablets were measured in ten replicates. The mean and the standard error for these measurements were calculated. These mean values were employed in order to calculate the tablet volume and the theoretical porosity.

The dissolution studies were carried out in the USP XXII apparatus (HETO, mod. MA 6 VS) using the rotating disc method at 37 $\pm$ 0.5°C. The rotational speed was kept constant at 50 rpm. The KCl released was calculated by a conductometric method as described in previous papers (Caraballo et al., 1993).

Table 1
Weight, volume and theoretical initial porosity of the studied ternary tablets

Lot	Weight (mg)	Volume (ml) ± S.E. ($n = 10$)	Theoretical ϵ_0 (%) ± S.E. ($n = 10$)
1	638	0.3914 ± 7.15E-4	2.9 ± 0.18
2	556	0.3905 ± 5.56E-4	2.7 ± 0.14
3	492	0.3929 ± 6.29E-4	3.3 ± 0.16
4	466	0.3908 ± 4.76E-4	2.8 ± 0.12
5	442	0.3920 ± 6.15E-4	3.1 ± 0.15
6	420	0.3907 ± 3.75E-4	2.7 ± 0.09
7	552	0.3929 ± 1.02E-3	3.3 ± 0.25
8	490	0.3944 ± 9.63E-4	3.6 ± 0.24
9	440	0.3924 ± 5.10E-4	3.2 ± 0.13
10	419	0.3934 ± 4.80E-4	3.4 ± 0.11
11	550	0.3883 ± 8.79E-4	2.1 ± 0.22
12	488	0.3916 ± 6.76E-4	2.9 ± 0.17
13	438	0.3898 ± 4.55E-4	2.5 ± 0.11
14	417	0.3927 ± 6.94E-4	3.2 ± 0.17
15	485	0.3878 ± 8.56E-4	2.0 ± 0.22
16	437	0.3903 ± 4.13E-4	2.7 ± 0.10
17	483	0.3961 ± 9.16E-4	4.1 ± 0.22
18	435	0.3963 ± 5.24E-4	4.1 ± 0.13
19	433	0.3943 ± 4.61E-4	3.6 ± 0.11
20	431	0.3967 ± 5.20E-4	4.2 ± 0.13

3. Results and Discussion

Percolation theory deals with the volume of the components instead of its weight because it is the volume of a component which determines if it can percolate the sample, i.e. if there is a cluster of this component connecting all the sides of the sample.

When Percolation theory has been applied to binary systems, two percolation thresholds have been considered. The first percolation threshold, i.e. the percolation threshold of the drug substance, p_{c1}, and the second percolation threshold, p_{c2}. This last parameter corresponds to the probability, or drug volume ratio, at which the excipient ceases to percolate the tablet.

Therefore, these two drug percolation thresholds can be referred to as drug percolation threshold, p_{c1}, and excipient percolation threshold, p_{c2}, respectively.

In ternary systems A, B, C, several percolation thresholds can be expected: the percolation thresholds of each substance, p_A, p_B and p_C, and those we have referred to as 'combined percolation threshold'. The percolation thresholds of the substances, individually considered, are the probabilities or volume fractions at which one of the substances starts to percolate the sample.

On the other hand, we have defined the 'combined percolation threshold' of several components, two components in ternary systems, as the volume fraction at which these components, jointly considered, start to percolate the sample. So, in ternary systems, the 'combined percolation threshold' of the components B and C, p_{BC}, is related to the second percolation threshold of the component A, p_{2A} (see Eq. 2).

$$p_{BC} = 1 - p_{c2A} \tag{2}$$

3.1. Powder mixtures

The bulk and tapped densities as well as the percentage of compressibility of the mixtures were calculated as it has been indicated in the previous section. The obtained results were plotted versus the KCl, PVP-CL and Eudragit® RS-PM volume fractions. As an example, the behaviour of the

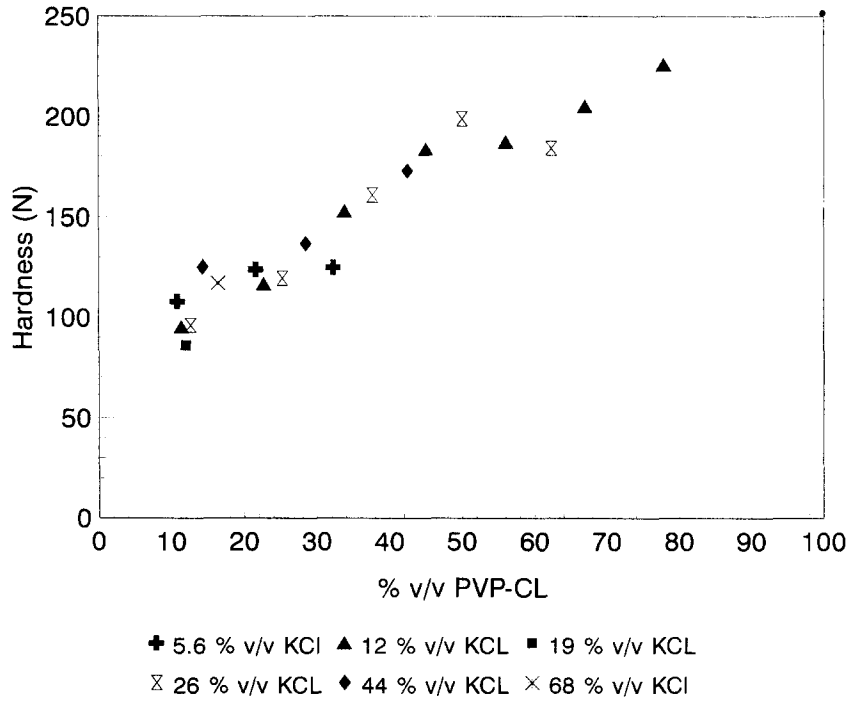

Fig. 4. Hardness of the ternary tablets as a function of their PVP-CL volume fraction (%).

tapped density and the percentage of compressibility as a function of the KCl% v/v is shown in Figs. 2 and 3. The bulk and tapped densities of the three pure components were also included in these figures for comparison purposes. The obtained results showed that the higher the concentration of KCl in the mixture is, the higher the bulk and the tapped densities are (see Fig. 2). The opposite effect was found in the case of PVP-CL whereas the Eudragit® RS-PM volume fraction showed no significant influence on these densities.

The study of the bulk and tapped densities and the percentage of compressibility of the powders showed no evidence of critical concentrations of any of the components. This fact may be due to the low influence of the percolation thresholds in ternary system on the studied parameters or to the low volume fractions of the components in most of the studied powder mixtures. These low concentrations are due to the high porosity of these powdered systems.

3.2. Tablets

Different amounts of the prepared ternary mixtures were compressed (see Table 1) in order to obtain tablets having approximately the same volume (0.39 cm^3). Furthermore, a high pressure (421 MPa) has been employed in order to obtain tablets with low initial porosities (2.0–4.2%). The tablet volumes and porosities obtained from ten measurements are shown in Table 1.

In this manner, it may be assumed that the influence of the initial porosity over the mechanical and release properties of the studied ternary tablets is low and does not produce significant differences between the different lots.

The PVP-CL can be expected to percolate the prepared tablets in a range between 10 and 30% v/v. As it can be observed in Fig. 4, this fact influences the hardness of the tablets. Above this percolation range, the hardness of the tablets increase with a higher slope as a function of the PVP-CL volume fraction.

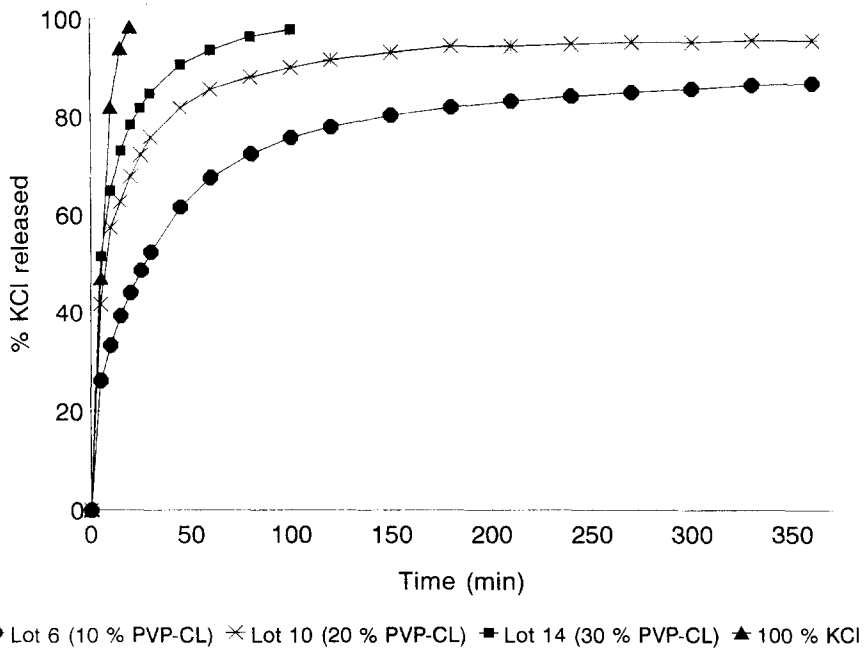

Fig. 5. Typical release profiles of the studied formulations. The release profile of a tablet containing 100% KCl is also plotted for comparison purposes.

On the other hand, the release behaviour of the prepared tablets were studied in order to find some evidence of percolation thresholds of the components in a ternary system. As an example, Fig. 5 shows the release profiles obtained from lots 6, 10 and 14 as well as from a 100% KCl tablet, for comparison purposes.

In order to evaluate the release behaviour and taking into account that the drug can be released from the studied tablets following different mechanisms, a no modelistic parameter as the dissolution efficiency, the area under the release profiles, (Salvadó et al., 1987) has been employed.

In the present study, the dissolution efficiency corresponding to 1 h (E_{d60}), has been calculated and employed.

The presence of a disintegrant as the PVP-CL at different concentrations exerts a great influence on the release profile of a tablet. This influence can mask the percolation thresholds of the other components of the formulation. Nevertheless, by plotting the E_d values as a function of the KCl volume fraction of the ternary tablets, two different regions can be observed (see Fig. 6). In the first one, the higher the KCl fraction, the higher the E_d values. In the second region, above 30% v/v KCl, the E_d values remain constant or even decrease.

The intersection of these two regions can be related to the KCl percolation threshold. It can be assumed that in this intersection, the KCl cluster starts to percolate the tablet. This percolating cluster exerts a positive influence on the E_d. However, in the second region, when this infinite cluster is already present, an increase in the KCl fraction does not clearly benefit the drug release.

Therefore, the cutoff of the two lines plotted in Fig. 6 is an estimation of the KCl percolation threshold, p_{KCl}. As tablets containing approximately 26% v/v of KCl are very close to the cutoff, it is not clear if these points belong to the first or second region. So, the situation of the cutoff depends on the inclusion of the tablets containing approximately 26% KCl in the first region (cutoff at 28% v/v KCl), in the second one (cutoff at 23% v/v KCl) or in both, the first and

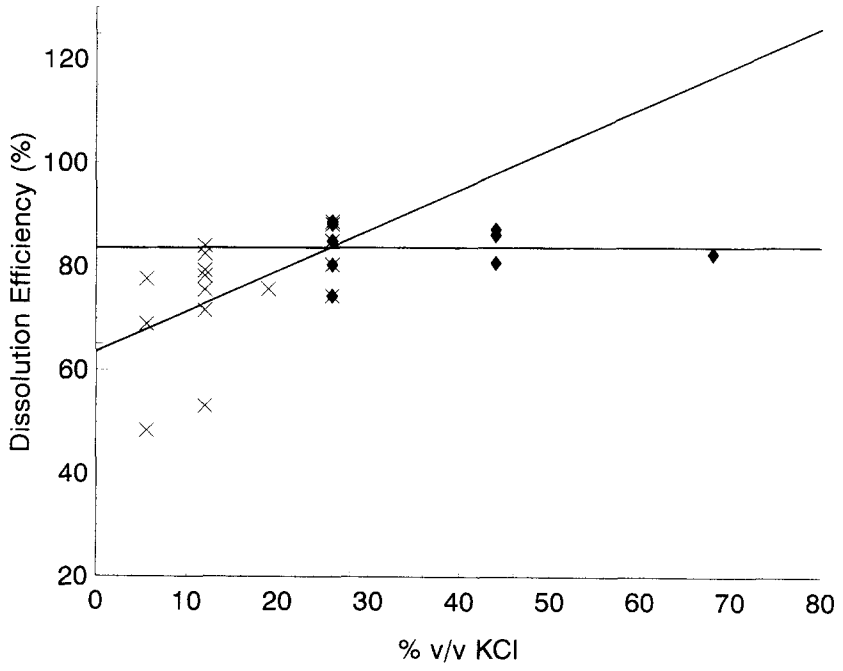

Fig. 6. Evolution of the dissolution efficiency (E_d) as a function of the percentage of KCl included in the tablet. The regression lines for the two regions cited in the text have been plotted. These straight lines show a cutoff at 26% v/v KCl (lots containing ~26% v/v of drug were included in both regions).

the second regions (cutoff at 26% v/v KCl) as Fig. 6 shows. In this manner, p_{KCl} can be estimated between 23 and 28% v/v of KCl.

Taking into account the mean porosity of the studied tablets ($3.12 \pm 0.596\%$), p_{KCl} can be estimated in the range 26–31% v/v of total porosity. The total porosity corresponds to the initial porosity added to the drug porosity after leaching (Bonny and Leuenberger, 1991) of the drug substance.

On the other hand, when the E_d values are plotted as a function of the Eudragit® RS-PM volume ratio (Fig. 7), a sudden decrease of this parameter appears at approximately 65% v/v of Eudragit® RS-PM.

This change does not correspond to the Eudragit® RS-PM percolation threshold but to the percolation threshold of the hydrophilic substances jointly considered. We have defined this threshold as the drug/disintegrant 'combined percolation threshold', $p_{KCl/PVP}$.

This clear decrease observed in the E_d values is due to the fact that above 65% v/v Eudragit® RS-PM volume fraction, the hydrophilic substances are in concentrations which do not allow them to percolate the tablets.

The existence of this 'combined percolation threshold' demonstrates that a multicomponent system can be reduced to a binary one by using a discriminating property. This result corroborates those obtained in previous papers (Caraballo, 1994; Caraballo et al., 1994).

In the light of the obtained results it can be concluded that Percolation theory is able to be applied to an increasing number of pharmaceutical systems giving a better explanation of these systems than 'classical theories' and allowing a more rational pharmaceutical solid dosage forms design.

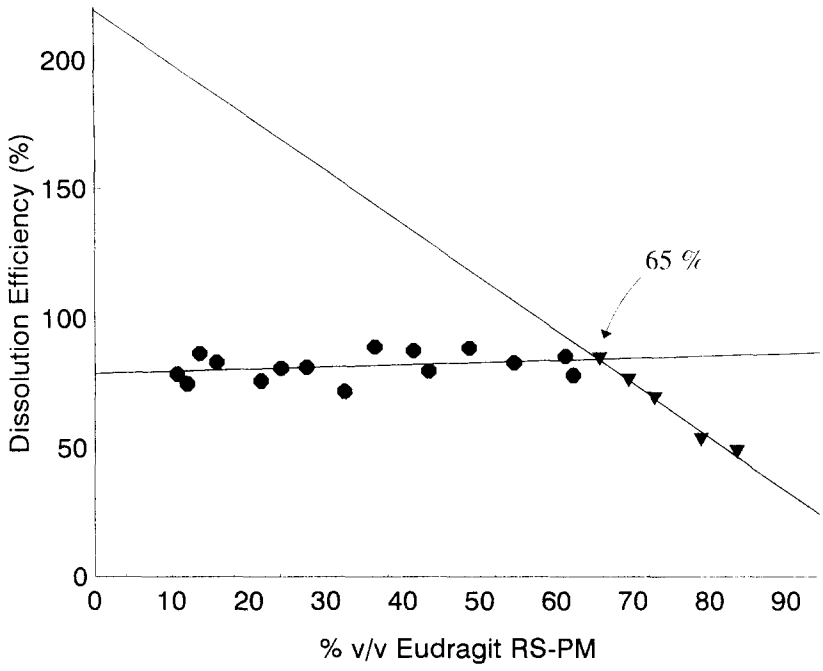

Fig. 7. Evolution of E_d of the studied tablets as a function of the Eudragit® RS-PM volume fraction (%).

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