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Percolation theory – a novel approach to solid dosage form design

H. Leuenberger, B.D. Rohera and Ch. Haas
School of Pharmacy, University of Basle, Basle (Switzerland)

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Summary

Percolation theory has become a very important concept in various fields of research and application. The impact of this concept on solid dosage form design is presented on the basis of our research findings where compacts of binary mixtures of active substances and excipients have been studied. It can be demonstrated that a major change in the properties of the compact is related to the percolation threshold p_c in the binary system. Thus p_c determines the minimum concentration of an excipient (e.g. microcrystalline cellulose) to design a hydrophilic controlled release dosage form. In the case of a solid dispersion excipient, such as polyethylene glycol 8000 (PEG), p_c is responsible for the onset of dissolution control by PEG. Thus in order to properly design the dosage form, concentration of PEG has to exceed p_c. On the other hand, in the case of classical dosage forms, disintegrants only show disintegrant activity for concentrations below p_c. In many cases p_c can be determined experimentally by simple means.

Introduction

What is a percolation threshold?

Percolation theory is an important new field of multidisciplinary research dealing with clusters of randomly occupied sites in a lattice (Stauffer, 1985). The lattice may be atomic sites in a crystal or a lattice of trees in a forest. In the case of a suitable pharmaceutical dosage form consisting of a binary mixture of substances A and B, the lattice is formed by particles of type A or type B. The theoretical percolation threshold depends on the type of lattice formed and indicates at what concentration of substance A it dominates in the system A/B or vice versa. The situation can easily be compared (Leuenberger, 1985) to a dispersion of oil droplets in water: there is a percolation threshold where, with an increasing amount of the lipophilic phase, system o/w turns into a system w/o. The critical concentration depends on the packaging of the oil and water droplets, i.e. on the type of lattice. Thus it is essential to realise which of the two substances, oil or water, forms the continuous phase. As a consequence, percolation threshold controls major properties of the system

TABLE 1

Selected percolation threshold for 3-dimensional lattices (Stauffer, 1985) as volume-to-volume ratio

Lattice type	Site	Bond
Diamond	0.428	0.388
Simple cubic	0.3117	0.2492
Body-centred cubic	0.245	0.1785
Face-centred cubic	0.198	0.119

Correspondence: H. Leuenberger, School of Pharmacy, University of Basle, Totengässlein 3, CH-4051 Basle, Switzerland.

studied. From the theoretical point of view it is possible to distinguish between "site percolation" and "bond percolation". Table 1 summarises known percolation thresholds for 3-dimensional lattices (Stauffer, 1985).

The lattice types mentioned in Table 1 are idealised systems, e.g. balls of equal size, which differ only in colour (i.e. substance A and B).

In practice, where we often have a rather broad particle size distribution of both types of particles (A and B), it is difficult to predict the type of lattice. To take into account the shape and surface roughness of the particles, it is useful to apply the concept of fractal dimensions (Mandelbrot, 1983; Family and Landau, 1984; Pape et al., 1985). It does not matter whether clusters are formed by droplets, particles or holes (Kaye, 1983). Percolation theory can be applied as an entrance to problems where fractal dimensions are involved. A prerequisite for fractal dimensions is the presence of self-similar particle size distributions. The existence of self-similarity in the growth pattern of pharmaceutical granules could be shown elsewhere (Imanidis et al. 1985). Bond and site percolation can be defined as follows: a pair of two particles A (see Fig. 1A) may be described as a cluster of *size two*, because two neighbouring *sites* are occupied. On the other hand, the same pair of particles can be described as a "cluster" of *size one*, as only *one bond* between the particles is effective (see Fig. 1B). Thus for each type of lattice there is a site and a bond percolation threshold.

In the case of gelation phenomena the formation of gel-point corresponds to a bond percolation threshold (see Fig. 1C); in the two-dimensional space, i.e. square lattice, $p_c = 0.5$.

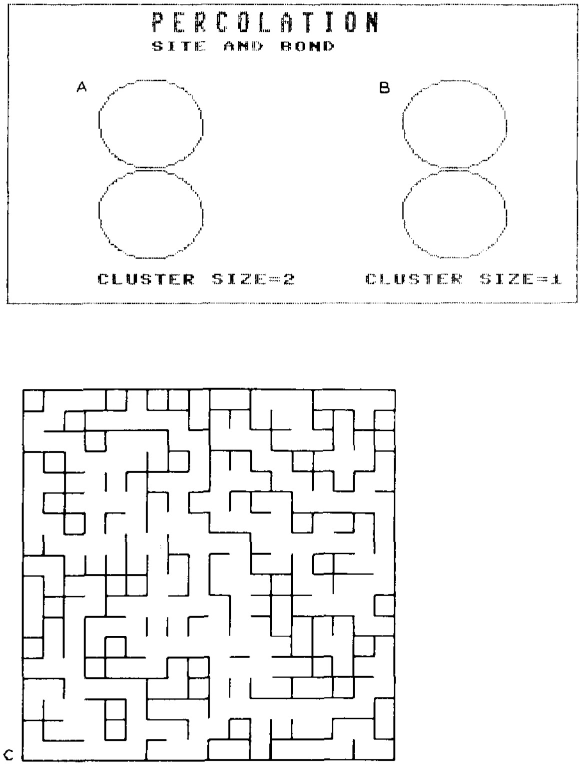

Fig. 1. A and B: site and bond percolation (Stauffer, 1985). 1C: example of percolation at the gel point, $p = 1/2$, in a square lattice. Each bond which has been formed is shown as a short line connecting two monomers; the monomers are not shown. One sees some nearly "infinite" macromolecules, where infinity means that they span the whole sample. Each bond is formed with probability p (Stauffer et al., 1982).

Materials and Methods

Materials and experimental methods are described in detail elsewhere (Leuenberger, 1980; Rohera, 1985; Leuenberger and Rohera, 1986; Haas, 1986). In Table 2 the physical characteristics of the compressed powder material are compiled. In order to keep the experimental conditions as constant as possible, tablets were compressed on a Universal Testing Instrument (model TT-DM, Instron, High Wycombe, U.K.) instead of a tabletting machine modified to take a 11 mm diameter tablet punch and die system (Rohera, 1985). The starting material used to study disintegration properties and the intrinsic dissolution rate of compacts of binary powder mixtures is characterised in Table 3. The powder material was compressed (Haas, 1986) on a single punch machine (Korsch EKO; punch diameter 10 mm, 50 tablets/min).

TABLE 2

Physical characteristics of starting materials (Rohera, 1985)

Substance	True density (g/cm^3)	Poured density (g/cm^3)	Tapped density (g/cm^3)	Particle size analysis (RRS-B distribution)		Surface area (cm^2/g)	Loss on drying (%)
				n	d'(μm)		
Caffeine (anh.) powder	1.458	0.331	0.476	2.43	34.0	5235	0.1
Magnesium stearate	1.048	0.184	0.347	2.46	32.3	26795	2.5
Polyethylene glycol (4000)	1.213	0.516	0.725	2.82	45.7	1782	0.4
Sodium lauryl sulphate	1.258	0.192	0.269	3.11	39.8	18063	0.5
Sodium stearate	1.089	0.250	0.431	2.68	34.9	17338	1.5

TABLE 3

Physical characteristics of starting material (Haas, 1986)

Substance	True density (g/cm^3)	Poured density (g/cm^3)	Tapped density (g/cm^3)	Mean density μm)	Loss on drying (%w/w)
Caffeine anhydrous	1.44	0.48	0.56	666	0.1
Potassium chloride	1.98	1.05	1.19	345	0.3
Microcrystalline cellulose (Avicel PH 102, FMC)	1.58	0.32	0.42	108	4.6
Lactose cryst. (DMV, Veghel)	1.61	0.72	0.90	144	0.6
Polyethylene glycol 8000	1.21	0.5	0.67	210	0.4
PVPP XL (GAF)	1.18	0.31	0.40	110	4.3
Starch 1500 (Colorcon)	1.48	0.63	0.77	142	10.8

Properties of tablets, compressed from binary powder mixtures

Compressibility and compactibility of powder systems

The term "compressibility" is defined as the ability of a powder to decrease in volume under pressure, and the term "compactibility" is defined as the ability of the powdered material to be compressed into a tablet of specified strength (Leuenberger, 1982). The following compaction/compression equation was used (Leuenberger, 1980; Leuenberger et al., 1981):

$$P = P_{\max}(1 - \exp(-\gamma \cdot \sigma_c \cdot \rho_r)) \qquad (1)$$

Parameter $P_{\max}$ is equal to the theoretically maximum possible deformation hardness at $\sigma_c \cdot \rho_r \rightarrow \infty$ with σ_c = compressional stress and ρ_r = relative density = $1-\epsilon$ where ϵ = porosity. Thus $P_{\max}$ describes compactibility and the second parameter, termed "compression susceptibility", describes compressibility as was shown mathematically (Leuenberger and Jetzer, 1984). The compression of binary mixtures consisting of brittle (caffeine anh.) and plastic materials (polyethylene glycol, sodium stearate, magnesium stearate), yielded, for

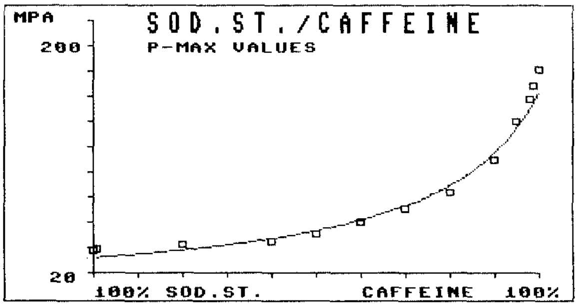

Fig. 2. Relation between compactibility parameters $P_{\max}$ and composition ratio (w/w) calculated on the basis of Eqn. 1 for individual mixtures. The line corresponds to Eqn. 3 and simultaneous evaluation of all data according to Eqn. 2.

different compositions, $P_{\max}$ values according to Eqn. 1, which could be predicted on the basis of $P_{\max}$ values known for the pure material (Leuenberger and Rohera, 1985). A typical example is given in Fig. 2. In the case of Fig. 2 the following equations and rules of additivity were applied (Leuenberger and Rohera, 1985):

$$P = P_{\max_{(\text{mixture})}} [1 - \exp(- [x \cdot \gamma_A + (1 - x)\gamma_B]\, \sigma_c \cdot \rho_r] \tag{2}$$

with the harmonic mean

$$P_{\max_{(\text{mixture})}} = \frac{P_{\max_A} \cdot P_{\max_B}}{x \cdot P_{\max_B} + (1 - x) P_{\max_A}} \tag{3}$$

where x, $1 - x$ = weight ratios for substance A, resp. B.

No significant deviation from model Eqn. 3 can be detected in Fig. 2. Thus the impact of a possible percolation threshold is not evident.

In the case of the compressibility parameter γ, the additivity rule derived earlier (Leuenberger, 1982) was shown to be correct (Jetzer et al., 1983) for materials which do not differ too much in their physicochemical properties (see Fig. 3). However, the additivity rule is only partially valid for binary mixtures consisting of hard, brittle and soft, plastic materials (Leuenberger and Rohera, 1986).

$$\gamma_{(\text{mixture})} = x \cdot \gamma_A + (1 - x) \cdot \gamma_B \tag{4}$$

The relation between the compressibility parameter γ and weight ratio x is still linear but shows at a critical ratio x a discreet change in the slope (see Fig. 4A–D). The different critical ratios demonstrate that, depending on type of material and type of packaging, the percolation threshold varies from binary mixture to binary mixture. As specific density of the organic materials studied do not differ very much, the weight-to-weight ratios were not converted into volume-to-volume ratios. Below the critical ratio of binary system A/B, compressional stress has the possibility of being transmitted from the upper to the lower punch through a continuous network of substance A. Thus substance B forms isolated clusters. With the increase of substance B in the system A/B, the number of clusters increase until a continuous phase of substance B is formed, i.e. the percolation threshold is reached. Above the percolation threshold, substance A and substance B can form in the 3-dimensional space a continuous network until substance A starts to appear only in the form of isolated clusters. For this reason a second percolation threshold may be visible in binary systems provided that the measurement principle allows quantification of the second critical concentration ratio. In most cases – like those investigated in this paper – only one percolation threshold, i.e. one critical concentration can be observed, as one of the substances A or B dominates and characterises the physicochemical properties below and above one of the two possible percolation thresholds. Thus the thickness of the tablet will change in relation to plasticity or brittleness of the substance A or B. Thus in the case of tablets compressed with identical load it is possible to detect the percolation threshold by a simple measurement of the change in the dimensions as a function of the weight ratio of substance A/B (see Fig. 5). Within the precision of measurement the critical ratio found in Fig. 5 is identical to that found in Fig. 4A.

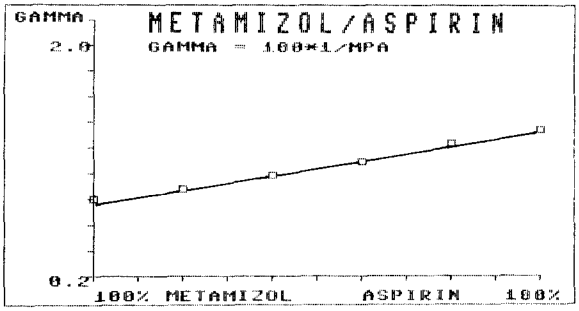

Fig. 3. Relation between compressibility parameter γ and composition ratio (w/w) for binary mixtures of aspirin FC and metamizol (Jetzer et al., 1983).

Disintegration time and percolation threshold

In the case of binary mixtures between an active substance and a disintegrant, such as microcrystalline cellulose, cross-linked polyvinylpyrrolidone, physically modified corn starch, etc., disintegrating activity can only take place below a critical concentration (Haas, 1986). Above this

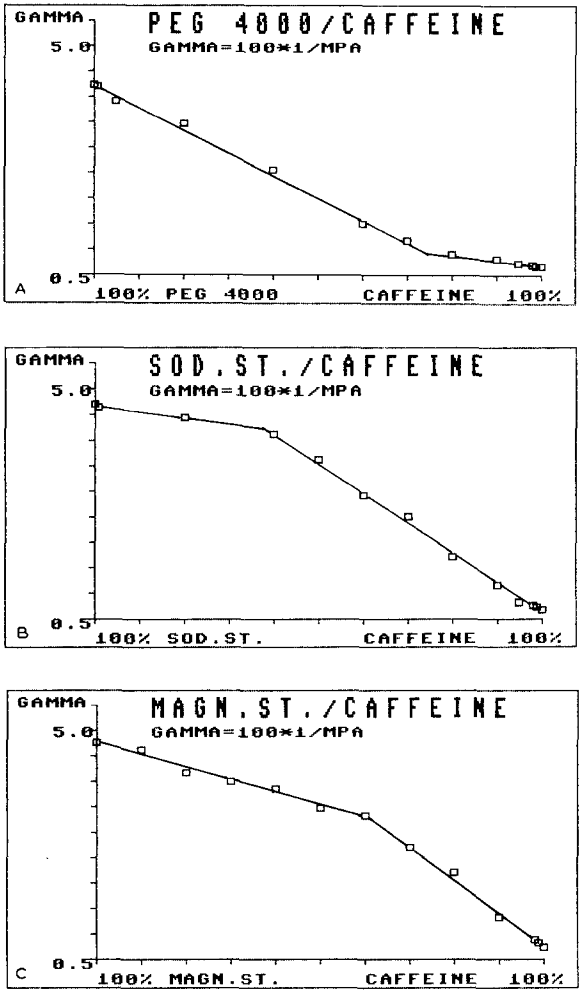

Fig. 4. A–C: relation between compressibility parameter γ and composition ratio (w/w) for binary mixtures consisting of brittle and plastic material. In case of mixtures caffeine with polyethylene glycol 4000 the percolation threshold is at about 75% w/w caffeine. Mixtures of caffeine with sodium stearate or magnesium stearate show a percolation threshold at about 40% w/w, resp. 60% w/w caffeine.

concentration, i.e. percolation threshold, the hydrophilic excipient coats for the active substance present themselves as clusters or finely dispersed particles and act as a slow release agent. As a consequence, disintegration time is increased many times (see Fig. 6A–D). Again the percolation threshold dramatically changed the properties of the tablet.

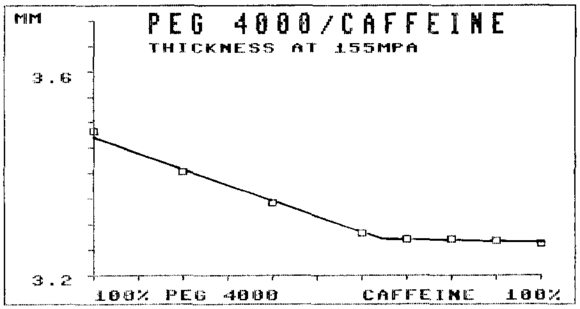

Fig. 5. Relation between thickness of the compact and composition ratio (w/w) for a binary mixture of caffeine with polyethylene glycol 4000 (cf. Fig. 4A) with constant tablet mass (= 400 ± 0.2 mg).

For mixtures of KCl with microcrystalline cellulose (Avicel PH 102, FMC) the disintegration time and percolation threshold are a function of the compressional stress (Fig. 6A). In contrast to other types of disintegrants, cross-linked PVP exhibits disintegration activity even at concentrations above the percolation threshold. Maximum disintegration time (= 160 s) is found at the percolation threshold at higher compressional stress (255 MPa). No percolation threshold can be detected for a low compressional stress (127 MPa).

Intrinsic dissolution rate and percolation threshold

In order to investigate the effect of the accompanying excipient on the dissolution rate of the active substance, binary mixtures were compressed (Haas, 1986). The tablets were embedded into paraffin leaving only one side accessible for the dissolution medium. The tablets were mounted on a stirrer to enable measuring of the intrinsic dissolution rate at a defined stirring rate.

The intrinsic dissolution rate constant k can be calculated from the slope of the zero-order dissolution rate (see e.g. Carstensen, 1977). To quantify a possible enhancement or slowdown of the dissolution rate constant by the effect of the environment (excipient), a ratio F was defined as follows:

$$F = \frac{k(x) \cdot 100\%}{x} \Big/ k(x = 100\%) \qquad (5)$$

where $k(x)$ = intrinsic dissolution rate constant

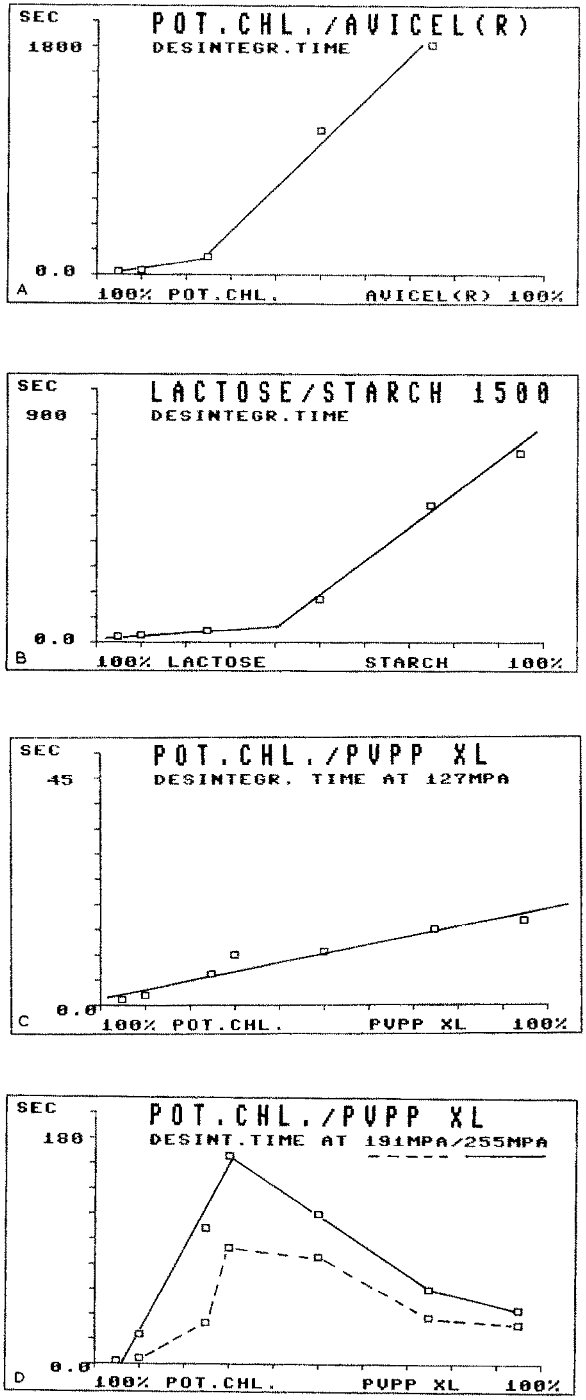

Fig. 6. A–D: relation between disintegration time and composition ratio (w/w) of the disintegrants microcrystalline cellulose, (A), starch 1500 and PVPPXL for tablets compressed at 127 MPa (C) and at 191 MPa, respectively, at 255 MPa (D).

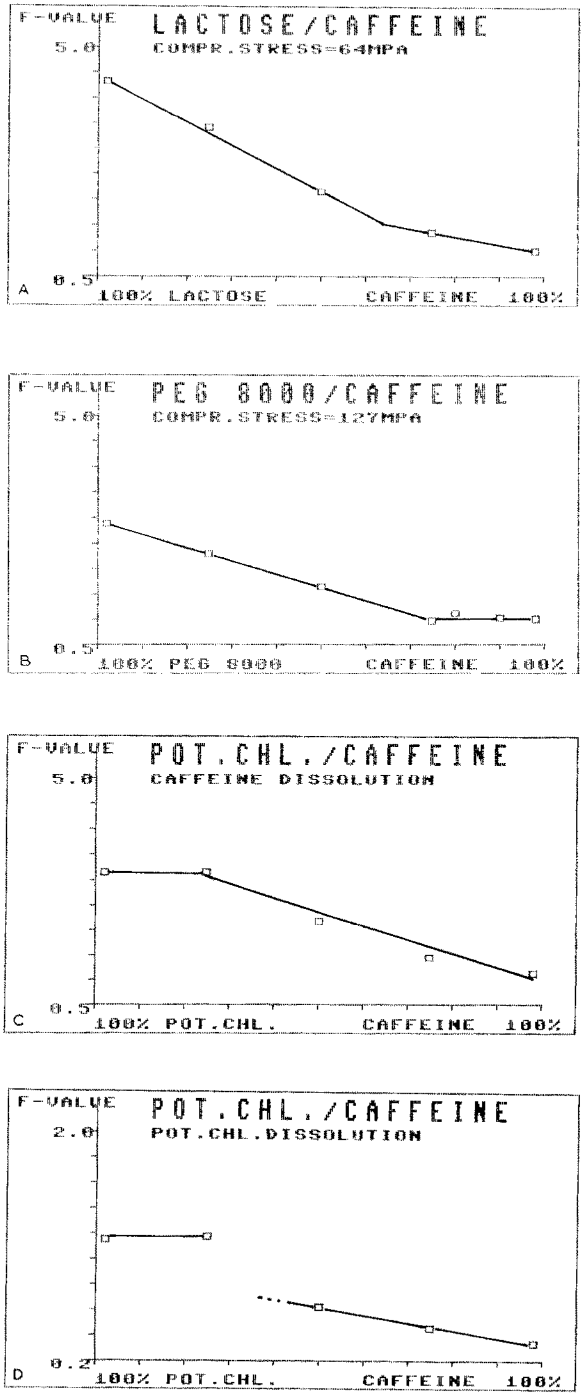

Fig. 7. A–D: Relation between intrinsic dissolution rate enhancement factor *F* and composition ratio for binary mixtures, i.e. mixture PEG 8000/caffeine (A), lactose/caffeine (B) and KCl/caffeine (C and D).

for concentration x of the active substance (in percent). Thus ratio F is normalised by the intrinsic dissolution rate constant $k(x = 100\%)$, i.e. for the pure substance. The value of $k(x = 100\%)$ did not change significantly as a function of the compressional stress for caffeine anhydrous (Haas, 1986). All the compacts consisting of binary mixtures show a percolation threshold. Caffeine dissolution is enhanced by a factor $F =$ ca. 4 for 2% w/w caffeine in lactose (Fig. 7A). In case of the mixture polyethylene glycol 8000 (PEG 8000) and caffeine, percolation threshold is at ca. 75% w/w caffeine. Thus below 75% w/w caffeine, caffeine dissolution is controlled by PEG 8000 (Fig. 7B).

The study of mixture KCl–caffeine (see Fig. 7C and D) permitted simultaneous measurement of the intrinsic dissolution rate for KCl (by measurement of conductivity) and for caffeine (by spectrophotometry). Caffeine dissolution was enhanced by a factor $F =$ ca. 3 below the percolation threshold (= ca. 25–30%) and is lowered to $F \approx 1$ for 98% caffeine (Fig. 7C). On the other hand, KCl dissolution enhancement is not present (factor $F \approx 1$) below the percolation threshold and is slowed down to ca. $F \approx 0.3$–0.4 above the percolation threshold (Fig. 7D).

Conclusions

The study of percolation theory, percolation thresholds, seems to be a promising new research area in pharmaceutics. It may provide an interesting and new tool for latter, i.e. a more rational and new solid dosage form design, including fast and slow release dosage forms.

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