ELSEVIER

International Journal of Pharmaceutics 115 (1995) 217–224

international journal of pharmaceutics

# Percolation effects in matrix-type controlled drug release systems

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Received 13 May 1994; accepted 20 July 1994

**Abstract**

From experimental evidence it is well known that the bioavailability of controlled release systems, i.e., the percentage of the dose absorbed by the body, is often reduced compared to a corresponding dosage form with immediate release. In the case of inert matrices, a water-soluble drug is embedded in a finely dispersed state in an insoluble carrier material and released by diffusion. In the present work such systems are described by percolation theory. Based on a Bethe lattice model the amount of drug substance 'trapped' in the matrices, which determines the reduction of bioavailability, is calculated in a straight-forward way from the volume-to-volume ratio of drug and matrix material. To check the use of the model, matrix tablets are prepared with caffeine as a model drug and ethyl cellulose or hydrogenated castor oil as carrier materials, and their drug release is determined in vitro. The experimental findings are in good agreement with the values predicted from the percolation model. The most pronounced reductions of bioavailability are observed if the volume-to-volume ratio of drug and matrix substance is below a percolation threshold.

*Keywords:* Percolation theory; Bethe lattice; Controlled drug release; Bioavailability; Non-swellable matrix; Ethyl cellulose; Hydrogenated castor oil

## 1. Introduction

Percolation theory is based on the formation of clusters and on the existence of a site or bond percolation phenomenon (Stauffer and Aharony, 1992). For simplicity, particles of type A (substance A) and type B (substance B) are assumed to form binary powder mixtures, which are compressed to rectangular tablets of volume *abc* with a minimum porosity $\epsilon_0$ and where the original particles A and B are randomly distributed. In this model, particles of type A are identified as primary clusters of molecules of a crystalline, hard, brittle drug substance A, which is well soluble in water, and particles of type B are assumed to be primary clusters of molecules of a water-insoluble, inert, soft, plastic material B. During the compression process, different types of bonds (A-A, B-B, A-B) between the particles are formed. Thus, after compression the primary

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*SSDI* 0378-5173(94)00266-5

particles A and B lose their identity and in the case of zero porosity the final tablet can be imagined as a volume *abc* spanned by a virtual lattice (e.g., cubic), where all lattice sites are randomly occupied forming clusters of substance A or substance B. It is evident that if the drug load (occupation probability $p$ of substance A) and the amount of the inert matrix substance B (occupation probability $1-p$) are varied, percolation phenomena occur. If the amount of substance B is not sufficient to form a coherent matrix, the tablet disintegrates in water. On the other hand, in the case of a dominant amount of substance B, the dissolution of the drug substance A leads to a carcass which still contains an important amount of trapped drug particles not accessible by the solvent. The model established fulfils all conditions to apply the concepts of percolation theory.

## 2. Theory

### 2.1. Percolation thresholds in a matrix tablet

The fate of a drug molecule within a matrix-type controlled release system is identical to the situation of the 'ant in the labyrinth' (De Gennes, 1976), which is trying to escape. The labyrinth consists of randomly distributed sites, which are accessible or not accessible by the solvent. The accessible sites are on the one hand drug particles connected to the 'infinite cluster', i.e., the interpenetrating network between the drug substance and the matrix material spanning the whole tablet volume, and on the other hand clusters of drug particles connected to the surface of the finite size tablet. If the initial porosity $\epsilon_0$ of the tablet is equal to zero, inaccessible sites consist of insoluble material of the matrix-forming substance and of clusters of drug particles totally encapsulated by the insoluble matrix material. It can be well imagined that the critical drug load $\epsilon_c$, i.e., the site percolation threshold of the drug substance A, depends on the original particle size distributions of the substances A and B.

In a three-dimensional lattice it is known that there are two site percolation thresholds which define a volume-to-volume range of substance A to substance B where both percolate, i.e., form an interpenetrating network. Outside these thresholds, either substance A or substance B is percolating, while the partner substance is encapsulated forming isolated clusters ('A in B' or 'B in A' system). The percolation threshold depends on the type of lattice and the type of percolation. Examples for site percolation thresholds on three-dimensional lattices are 0.428 on a diamond lattice (coordination number $z = 4$), 0.312 on a simple cubic ($z = 6$) and 0.245 on a body-centered cubic lattice ($z = 8$) (Stauffer and Aharony, 1992). In case of a Bethe lattice approximation, the percolation threshold is identical to:

$$p_c = \frac{1}{z-1} \tag{1}$$

where $z$ is the coordination number (Stauffer and Aharony, 1992).

In a practical case, where e.g. very fine material A may be layered on coarse particles B, the thresholds are different from the above values in a three-dimensional or Bethe lattice, due to a non-random or correlated percolation phenomenon (Stauffer et al., 1982).

### 2.2. Dissolution kinetics from a matrix tablet

It is well known from percolation theory that the normal diffusion laws are not valid at and below the percolation threshold (Stauffer and Aharony, 1992). However, above the percolation threshold of the drug substance A, the dissolution kinetics obey the square-root-of-time law of Higuchi (1963):

$$Q(t) = b\sqrt{t} \tag{2}$$

with

$$b = \sqrt{DC_S(2A - \epsilon C_S)} \tag{3}$$

and

$$D = D_0\frac{\epsilon}{\tau} \tag{4}$$

where $Q(t)$ is the cumulative amount of drug substance dissolved per unit surface, $b$ the slope of Eq. 2, $D$ the apparent diffusion coefficient, $D_0$

the diffusion coefficient of the drug in the diffusion medium, $\epsilon$ the total porosity of the carcass, $\tau$ the tortuosity of the pore system of the carcass which diverges at the percolation threshold, $C_S$ the solubility of the drug in the dissolution medium, and $A$ the concentration of the drug substance dispersed in the tablet. If the initial porosity $\epsilon_0$ of the tablet is close to zero, the total porosity $\epsilon$ corresponds to the drug load expressed as volume-to-volume ratio.

Taking into account the concepts of percolation theory, the apparent diffusion coefficient $D$ obeys the following law close to $\epsilon_c$ (Stauffer and Aharony, 1992):

$$D = \chi D_0(\epsilon - \epsilon_c)^{\mu} \tag{5}$$

where $\chi D_0$ represents a scaling factor, $\epsilon$ the drug load, $\epsilon_c$ the critical drug load (i.e., the percolation threshold), and $\mu$ the conductivity exponent, which is 2.0 for a three-dimensional and 3.0 for a Bethe lattice, respectively (Stauffer and Aharony, 1992).

Eq. 2–5 can be used to calculate the following tablet property $\beta$ as a function of the drug load $\epsilon$ (Bonny and Leuenberger, 1991): For $\mu = 2.0$:

$$\beta = \frac{b}{\sqrt{2A - \epsilon C_s}} = \sqrt{\chi_d D_0 C_s}(\epsilon - \epsilon_{cd}) \tag{6}$$

For $\mu = 3.0$:

$$\beta^{2/3} = \sqrt[3]{\chi_b D_0 C_s}(\epsilon - \epsilon_{cb}) \tag{7}$$

Thus, the percolation thresholds $\epsilon_{cd}$ and $\epsilon_{cb}$ can be determined from the results of the dissolution experiments, assuming a three-dimensional or a Bethe lattice, respectively. Due to this concept, it is not necessary to keep the fitting parameter $\tau$ (tortuosity) of Eq. 4.

### 2.3. Amount of drug substance trapped in the matrix

The fraction of sites $Q_c$ not connected to the 'infinite network' of the drug substance (i.e., sites of trapped drug substance and sites occupied by the matrix substance) can only be calculated in a straight-forward way in the case of a Bethe lattice approximation. The amount $Q_c$ depends on the coordination number $z$ and the site occupation probability $p$ (Stauffer and Aharony, 1992). It can be calculated from a recursion relation for the probability $Q_B$ that a site is not connected to infinity by one of the $z$ branches:

$$Q_c = (1-p) + pQ_B^z \tag{8}$$

with

$$pQ_B^{(z-1)} - Q_B + (1-p) = 0 \tag{9}$$

In the present model, $p$ is equal to the drug load $\epsilon$, and $p_c$ is equal to the percolation threshold on the Bethe lattice, i.e., $p_c = \epsilon_{cb}$. Based on Eq. 9, $Q_B$ can be determined for different coordination numbers: (a) $z = 3$ ($\epsilon_{cb} = 0.5$):

$$Q_B = \frac{1-\epsilon}{\epsilon} \tag{10}$$

(b) $z = 4$ ($\epsilon_{cb} = 0.33$):

$$Q_B = \sqrt{\frac{1}{4} + \frac{1-\epsilon}{\epsilon}} - \frac{1}{2} \tag{11}$$

(c) $z = 5$ ($\epsilon_{cb} = 0.25$):

$$Q_B = \sqrt[3]{\frac{1}{2}u + \sqrt{\frac{1}{4}u^2 + \frac{8}{729}}} + \sqrt[3]{\frac{1}{2}u - \sqrt{\frac{1}{4}u^2 + \frac{8}{729}}} - \frac{1}{3} \tag{12a}$$

with

$$u = \frac{7}{27} + \frac{1-\epsilon}{\epsilon} \tag{12b}$$

(d) $z = 6$ ($\epsilon_{cb} = 0.2$):

$$Q_B = -\frac{1}{2}\sqrt{x - \frac{3}{4}} + \sqrt{\frac{1}{4}\left(\frac{1}{2} + \sqrt{x - \frac{3}{4}}\right)^2 - \left(\frac{1}{2}x - \sqrt{\frac{1}{4}x^2 + \frac{1-\epsilon}{\epsilon}}\right)} - \frac{1}{4} \tag{13a}$$

with

$$x = \sqrt[3]{v + \sqrt{v^2 + w^3}} + \sqrt[3]{v - \sqrt{v^2 + w^3}} + \frac{1}{3} \tag{13b}$$

where

$$v = \frac{10}{27} + \frac{5}{6} \cdot \frac{1-\epsilon}{\epsilon} \tag{13c}$$

and

$$w = \frac{2}{9} + \frac{4}{3} \cdot \frac{1-\epsilon}{\epsilon} \qquad (13d)$$

(e) For $z \to \infty$, $Q_B$ as well as $Q_c$ can be approximated by $1-\epsilon$, giving a straight line in a plot of $Q_c$ vs $\epsilon$.

The fraction of drug $Q_r$ trapped in the matrix can easily be calculated from $Q_c$ as follows:

$$Q_r = \frac{Q_c - (1-\epsilon)}{\epsilon} \qquad (14)$$

In Table 1, the values for $Q_c$ are compiled for the coordination numbers $z = 3$, $z = 4$, $z = 5$ and $z = 6$ and increasing drug loads $\epsilon$. Eq. 10–13 were used to calculate $Q_B$, from which $Q_c$ was determined by means of Eq. 8.

## 3. Materials and methods

Granulated anhydrous caffeine (Sandoz Pharma Ltd, Basel, Switzerland) with a mean particle size of 387 $\mu$m was used as a water-soluble model drug. Ethyl cellulose (Ethocel® 7 mPa s, Fluka Ltd, Buchs, Switzerland) and the lipid material hydrogenated castor oil (Cutina® hr, Sandoz Pharma Ltd, Basel, Switzerland) were chosen as water-insoluble, non-swellable matrix-forming excipients. The mean particle sizes were 259 and 30 $\mu$m for the ethyl cellulose and the hydrogenated castor oil, respectively.

The experimental methods were described in detail in previous publications (Bonny and Leuenberger, 1991, 1993). From binary mixtures of the caffeine and the matrix substances round, flat tablets with a weight of $400 \pm 1$ mg and a diameter of 11 mm were prepared by direct compression. With regard to the initial porosity $\epsilon_0$ of the tablets, the volume-to-volume ratio of the drug load ranged from 0.21 to 0.90 (i.e., 10 to 90% w/w of caffeine) for the matrices of ethyl cellulose ($\epsilon_0$ between 0.13 and 0.09) and from 0.10 to 0.94 (i.e., 10 to 95% w/w of caffeine) for the matrices of hydrogenated castor oil ($\epsilon_0$ between 0.03 and 0.07). The drug release from the matrix tablets was measured with a flow-through cell using distilled water of 37°C as a dissolution medium. The dissolution test was performed during 8 h, as in human beings a period of 6–8 h is considered as the average residence time of a controlled release dosage form in the small intestine, where the drug needs to be released to become available for a passive absorption into the biological system.

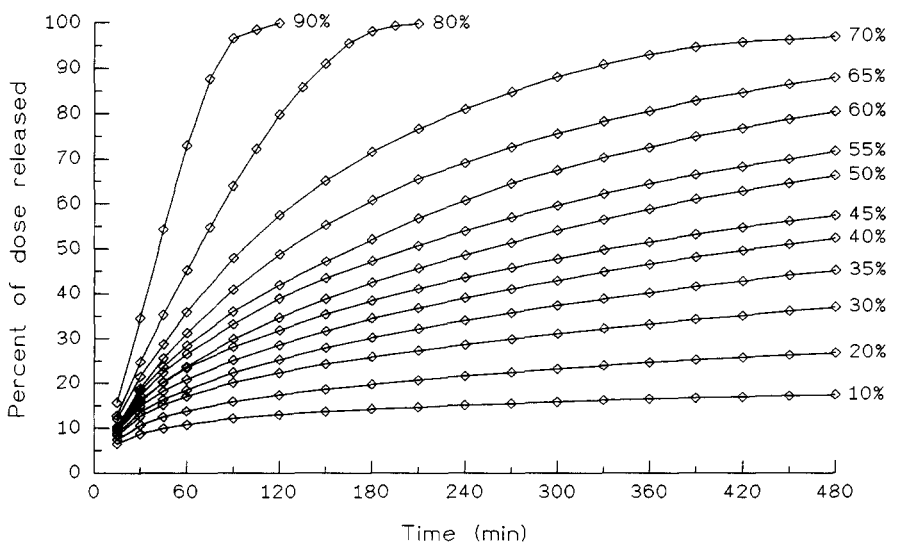


Fig. 1. Cumulative drug release in vitro from matrix tablets consisting of different ratios of caffeine and ethyl cellulose. The label of the dissolution profiles corresponds to the initial caffeine content (in % w/w) of the tablets.

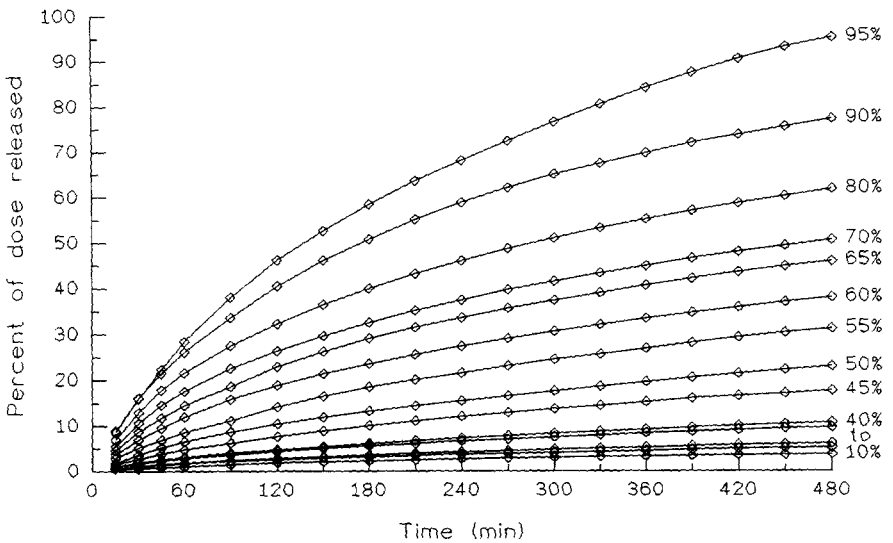


Fig. 2. Cumulative drug release in vitro from matrix tablets consisting of different ratios of caffeine and hydrogenated castor oil. The label of the dissolution profiles corresponds to the initial caffeine content (in % w/w) of the tablets.

## 4. Results and discussion

### 4.1. Percolation thresholds

The results of the in vitro drug release from the matrices of the two types of investigated matrices are plotted in Fig. 1 and 2. Based on Eq. 6, i.e., a three-dimensional lattice, the percolation threshold $\epsilon_{cd}$ for the matrices of ethyl cellulose was calculated as $0.29 \pm 0.01$ with $r^2 = 0.9942$ (squared correlation coefficient of the fit) and for the matrices of hydrogenated castor oil as $0.30 \pm$

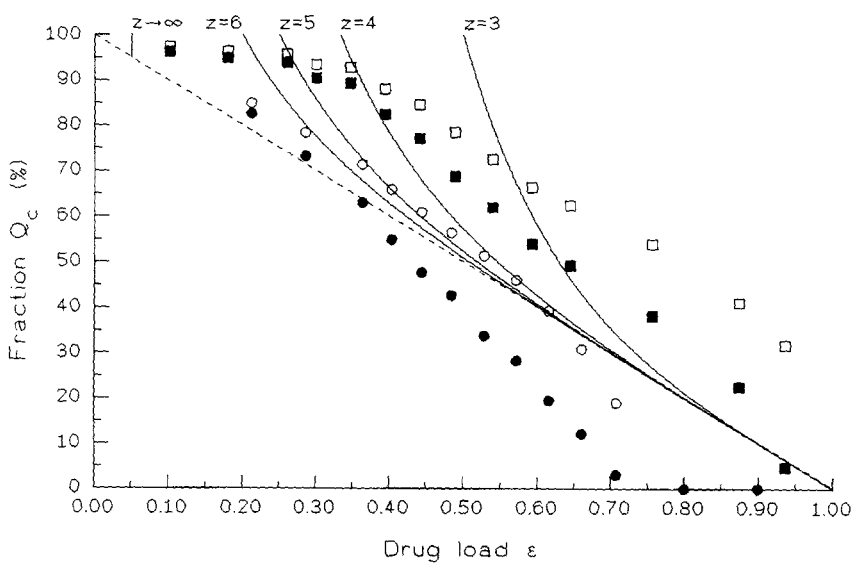


Fig. 3. Fraction of sites $Q_c$ not connected to the 'infinite network' vs the drug load $\epsilon$ for different coordination numbers $z$ according to Table 1 and limit for $z \to \infty$ (dashed line). The symbols mark the percentage of the dose remaining in the investigated matrix tablets after different dissolution times. Matrices: ethyl cellulose after 4 h (○) and 8 h (●), hydrogenated castor oil after 4 h (□) and 8 h (■).

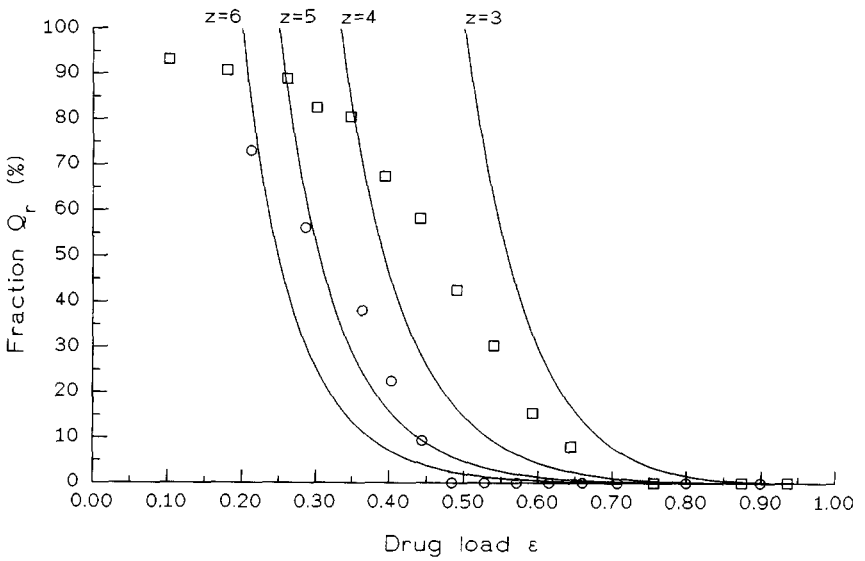


Fig. 4. Fraction of drug $Q_r$ 'trapped' in the matrix vs the drug load $\epsilon$ for different coordination numbers $z$ according to Eq. 14 and percentage of the dose remaining in the matrices of ethyl cellulose (○) and hydrogenated castor oil (□) extrapolated for a dissolution time of 24 h.

0.01 with $r^2 = 0.9947$. These percolation thresholds are in good agreement with the mentioned theoretical value of 0.312 on a simple cubic lattice with a coordination number $z = 6$. The calculation of $\epsilon_{cb}$ based on a Bethe lattice according to Eq. 7 led to a value of $0.21 \pm 0.01$ for both matrices ($r^2 = 0.9987$ and 0.9969, respectively). This value is close to the theoretical percolation threshold of 0.20 on a Bethe lattice with the same coordination number 6. The outlined results,

Table 1
Fraction of sites $Q_c$ as a function of the drug load $\epsilon$ for different coordination numbers $z$, i.e., different percolation thresholds $\epsilon_{cb}$

| Drug load ($\epsilon$) | Fraction of sites ($Q_c$) (%) | | | |
|---|---|---|---|---|
| | $z = 3$ ($\epsilon_{cb} = 0.50$) | $z = 4$ ($\epsilon_{cb} = 0.33$) | $z = 5$ ($\epsilon_{cb} = 0.25$) | $z = 6$ ($\epsilon_{cb} = 0.20$) |
| 0.20 | 100.0 | 100.0 | 100.0 | 100.0 |
| 0.25 | 100.0 | 100.0 | 100.0 | 87.3 |
| 0.30 | 100.0 | 100.0 | 85.8 | 77.6 |
| 0.35 | 100.0 | 93.7 | 75.0 | 69.7 |
| 0.40 | 100.0 | 78.3 | 66.3 | 62.9 |
| 0.45 | 100.0 | 66.7 | 58.9 | 56.7 |
| 0.50 | 100.0 | 57.3 | 52.4 | 51.0 |
| 0.55 | 75.1 | 49.5 | 46.4 | 45.5 |
| 0.60 | 57.8 | 42.6 | 40.8 | 40.3 |
| 0.65 | 45.1 | 36.5 | 35.4 | 35.1 |
| 0.70 | 35.5 | 30.8 | 30.2 | 30.1 |
| 0.75 | 27.8 | 25.4 | 25.1 | 25.0 |
| 0.80 | 21.2 | 20.1 | 20.0 | 20.0 |
| 0.85 | 15.5 | 15.0 | 15.0 | 15.0 |
| 0.90 | 10.1 | 10.0 | 10.0 | 10.0 |
| 0.95 | 5.0 | 5.0 | 5.0 | 5.0 |

which can only be interpreted in a qualitative way, indicate the trend that the percolation threshold plays an important role.

In case of swellable matrices consisting, e.g., of hydroxypropyl methylcellulose, the size and shape of the tablet change during the dissolution process and the drug load cannot be expressed as a constant volume fraction $\epsilon$. Because of the swelling property, the conditions to apply the concepts of percolation theory are not fulfilled and no percolation threshold can be determined.

### *4.2. Amount of drug trapped in the matrix*

In Fig. 3 the fraction of sites $Q_c$ not connected to the infinite network, i.e., sites consisting of either trapped drug substance or matrix material, as calculated in Table 1 are plotted for different coordination numbers $z$. The amounts of drug remaining in the matrices of ethyl cellulose and hydrogenated castor oil after 4 or 8 h of dissolution testing are comparable with the theoretical values of $Q_c$. This means that before complete release of the theoretically accessible drug, the amount remaining in the matrix depends on the total amount of not accessible sites. Thus, it can be assumed that the drug released is proportional to the accessible surface of the matrix carcass. This accessible surface is also influenced by the initial porosity $\epsilon_0$ of the matrix, which is higher in case of the ethyl cellulose matrices, leading to a faster drug release than from the matrices of hydrogenated castor oil.

To estimate the amounts of caffeine still trapped in the matrices after complete release, the dissolution data in Fig. 1 and 2 were extrapolated for an arbitrary dissolution time of 24 h by using the square-root-of-time law (Eq. 2). The resulting values are plotted in Fig. 4 and compared with the theoretical amounts of drug $Q_r$ trapped shown in Table 1. As the results may change considerably in three dimensions, the values for $Q_r$ calculated on the basis of a Bethe lattice have to be interpreted in a more qualitative way. In practice, the upper percolation threshold for the inert excipient is already reached for a drug load $\epsilon$ of 0.8, i.e., a 'matrix-type' controlled release dosage form disintegrates at a drug load of $\epsilon \geq 0.8$. Considering this fact, the values of $Q_r$ can be compared with the remaining drug contents extrapolated for 24 h from the in vitro dissolution test performed in water.

## 5. Conclusions

Summing up, it may be said that the presented model based on percolation theory allows a more rational design of matrix-type controlled release dosage forms. Assuming a Bethe lattice, the percolation thresholds of the investigated non-swellable matrices ethyl cellulose and hydrogenated castor oil were about 0.20, which corresponds to the percolation threshold on a Bethe lattice with the coordination number $z = 6$. As the model does not take into account dynamic changes of the matrix structure during the dissolution process, it cannot be applied to swellable matrices.

The fraction of the initial drug dose remaining in the matrices after different dissolution periods was compared to the theoretical values of $Q_c$, i.e., the fraction of sites not connected to the infinite network of drug substance, and to the values of $Q_r$, i.e., the fraction of drug substance trapped in the matrix. Though it was difficult to relate the experimental data to the values of $Q_c$ or $Q_r$ for a specific coordination number, a clear tendency was observed. As long as the accessible drug was only partially released, the amounts remaining in the matrix could be approximated by $Q_c$, which means that they are proportional to the inner surface of the matrix carcass. However, approaching the end of the dissolution process, the remaining drug amounts were in good agreement with the theoretically trapped amounts $Q_r$. Although only in vitro data were taken into account for this study, a comparison with in vivo bioavailability data does not offer advantages due to the relatively high variance of biological results.

Due to the outlined relationship, the bioavailability of a matrix-type controlled release system with a certain drug load $\epsilon$ can be estimated without performing any release test. In addition, it became obvious that for the development of a safe dosage form with optimal bioavailability it is

essential to keep a certain distance from the percolation thresholds.

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