

Percolation theory, conductivity and dissolution of hydrophilic suppository bases (PEG systems)[☆]

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Abstract

We investigated the conductivity of binary mixtures of different volume to volume ratios of liquid polyethylene glycol 200 (PEG 200) and solid PEG 6000. The conductivity was measured using a specially designed cell, which could be filled with the sample to be analysed. The results were analysed by the help of the percolation theory and its basic equation: $X = S(p - p_c)^q$ with $X = \gamma$ the conductivity and $X = k$ the dissolution rate constant of binary mixtures with p the concentration of PEG 200 including Mepyraminmaleat as a marker substance. The intrinsic dissolution rate was determined spectrophotometrically. The simultaneous determination of the critical exponent q and the percolation threshold p_c of the conductivity experiment yielded the following values $q = 1.83 \pm 0.05$ and $p_c = 11.6 \pm 1.1\%$ with a squared correlation coefficient $R^2 = 0.9986$. For $q = \mu = 2.00$ fixed the percolation threshold is equal to $p_c = 8.4 \pm 1.3\%$ with $R^2 = 0.9984$. Thus if the same percolation threshold $p_c = 8.4 \pm 1.3\%$ is adopted for the dependence of the dissolution process q becomes equal to $q \approx \mu = 1.94 \pm 0.045$. $R^2 = 0.9991$. This result is in excellent agreement with the theoretical prediction that the permeability of a porous network scales in the same way as the conductivity. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Most of the saturated organic polymers, such as polyethylene or polyvinyl chloride, have a very low specific conductivity of $\approx 10^{-18}$ S/cm. They

are classified as insulators. Unsaturated polymers or polymers with a very complex structure might have higher conductivities of $\approx 10^{-3}$ – 10^{-2} S/cm and are classified as conductors. Polyethylene glycols are saturated polymers, nevertheless their conductivity in air is relative high i.e. in the range of $\approx 10^{-10}$ S/cm. The high conductivity can be explained by an ionic process where protons are available and transported along the polymer chain. Conditions for such a process are proton accepting atoms (for example oxygen atoms) and/

[☆] Dedicated to Professor Dr B.C. Lippold for his 60th birthday.

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or low melting temperature (chain flexibility) (Binks and Sharples, 1968). The evidence of chain flexibility can also be recognised by the fact that polyethylene glycols in the molten state conducts electricity better than in the solid state (Craig, 1989).

The concepts of percolation theory have a wide application in many disciplines of sciences (Stauffer, 1985). In the pharmaceutical technology it is possible to explain the formation (Leu and Leuenberger, 1992) and the properties of tablets (Luginbühl and Leuenberger, 1994) or to describe the release kinetics from drugs out of inert matrix tablets (Bonny and Leuenberger, 1991). Only a few attempts were made to apply percolation theory to semisolid drug systems like ointments or suppositories. Tarabishi (1995) studied the physical properties of mixtures consisting of PEG 200 and PEG 6000 and interpreted the results with the concepts of percolation theory.

Percolation theory deals with the number and properties of clusters on virtual two, three or higher dimensional lattices. It is possible to distinguish different types of percolation like site, bond, site-bond, directed, continuum and others. Close to the percolation threshold a property X of the system follows the scaling law of the percolation theory. The following relationship expresses the scaling law (Stauffer, 1985).

$$X = S|p - p_c|^q \quad (1)$$

In Eq. (1) X represents a property studied, p the occupation probability, p_c the percolation threshold, S a proportional constant, and q the

critical exponent. It is not possible to give an analytical form for the constant S , because of the lack of knowledge about the cluster size distributions (size and shape) in most systems. Two types of critical exponents can be distinguished (Sahimi, 1994). In the first group are the so-called topological exponents listed. They mainly describe the number, structure, or size of clusters. These exponents are completely universal, i.e. they are independent of the percolation type, the lattice type or the microscopic details of the system, and depend only on the dimension of the system. The other group consists of the so-called transport exponents. They describe physical properties like the conductivity, the permeability, or the elasticity of a system. These exponents are also largely universal. In some cases however they depend not only on the dimension of the system but also on the percolation type (Feng et al., 1987). Table 1 shows some well-known critical exponents.

The connection of conductivity and percolation theory is well documented (Kirckpatrick, 1973; de Gennes, 1976; Clarkson and Smedley, 1988). It is possible to describe the behaviour of insulators/conductors mixtures by the ideas of percolation theory.

A pure insulator conducts no electrical current. The addition of only a small amount of conducting material changes nothing, as only a few separated finite conducting clusters are formed within the insulator matrix, which represents an infinite cluster. At a certain concentration of conducting material an infinite cluster is formed. At this concentration, the first (lower) percolation

Table 1
Selection of some well-known critical exponents

Exponent	Two dimensional	Three dimensional	Property connected with
<i>Topological exponents</i>			
α	-2/3	-0.62	Total number of clusters
β	5/36	0.41	Percolation probability
φ	43/18	1.8	Medium size of finite cluster
<i>Transport exponents</i>			
μ	1.3	2.0	Conductivity
ε	3.96	3.75	Elastic module
p	1.3	2.0	Permeability

threshold, the property of the system changes from insulator to conductor. Both compounds consist of infinite clusters and influence the conductivity of the whole system. Further increase of conducting material leads to higher values of conductivity until a critical concentration, the second (upper) percolation threshold, is reached, at which only the conducting material forms an infinite cluster, while the molecules of the insulator represent only finite clusters. The conductivity of the whole system depends only on the conducting material and the isolating material has no more an influence on the properties of the system.

1.1. Diffusion and conductivity

Diffusion and conductivity are very similar because both describe transport processes. In the case of diffusion molecules are transported in the case of conductivity it is an electrical charge. In this aspect the question arises, whether the conductivity is only due to electrons which are transported or whether ions can be transported as well. As the system consists of a solid and a liquid component ionic transport in the liquid system should play an important role too. In case of ionic transport the relation of the two terms is shown in Eq. (2) (Bunde and Roman 1996).

$$\gamma = \frac{1}{kT} e^2 n D_{\text{eff}} \quad (2)$$

where γ represent the specific conductivity, k the Boltzmann constant, T the absolute temperature, e the charge of the electrical carrier, n the concentration of the electrical carrier and D_{eff} the effective diffusion coefficient.

Due to the proportionality between γ and D_{eff} the critical exponents for the conductivity and for the effective diffusion coefficient D_{eff} are for n is constant equal.

$$\gamma \propto (p - p_c)^\mu \propto D_{\text{eff}} \quad (3)$$

Similarly, near p_c , the permeability P_m of a percolating network obeys the following scaling law

$$P_m \propto (p - p_c)^\mu \quad (4)$$

According to Fick's law the flux J of the intrin-

sic dissolution rate experiment under sink condition is proportional to P_m .

It has to be kept in mind, that the effective dissolution process takes only place after inhibition of the sample. It is assumed that the flux J scales as γ (Sahimi, 1994):

$$J \propto P_m \propto (p - p_c)^\mu \quad (5)$$

The transport exponent μ is largely universal. However for percolating continua the critical exponent can be different. In this work it is assumed that γ and J scale in an identical way.

Thus for the ratio γ/J we get the following relation:

$$\frac{\gamma}{J} \propto \text{constant} \quad (6)$$

For the practical evaluation of the parameters q (critical exponent) and p_c (percolation threshold) of Eq. (1) it has to be kept in mind that both parameters are correlated. Thus if the estimate of q is too high, a too low value of p_c is the consequence and vice versa.

Using a non-linear regression analysis both parameters can be determined simultaneously. It is of course also possible to keep one of the parameters fixed and to compare the resultant squared correlation coefficient R^2 describing the goodness of fit of Eq. (1). For the discussion of the results it is important to take into account to which extent the R^2 -values differ.

2. Experimental

2.1. Materials

Polyethylene glycol 200 (PEG 200, Fluka, Buchs, Switzerland, Batch 332636/1 295) with a medium molecular weight of 204 g/mol and density of 1.121 g/cm³ was used as the liquid compound. The solid compound was Polyethylene glycol 6000 (PEG 6000, Sandoz, Basle, Switzerland Batch 941506) with a medium molecular weight of 5814 g/mol, solidification point of 57°C and density of 1.197 g/cm³.

2.2. Methods

2.2.1. Preparation of the conductivity cell

The conductivity was measured with an impedance analyser (HP 4284A, Hewlett Packard, Widen, Switzerland) taking into account the cell constant of the measuring unit (See Eq. (7)) All measurements were made with alternating current (Frequency $f = 100$ kHz). The same instrument can be used to measure the static dielectric constant due to the rather low frequency f . Thus in a first approximation γ represents the d.c. conductivity. In this respect it is important to realise that the relative change in the current γ as a function of the content of PEG 200 is more important than the absolute value. Before starting a measurement, the conductivity cell stands for 12 h in a desiccator under vacuum. To start a measurement the susceptance of the empty cell had to be smaller than 8 nS, otherwise the cell was put back in the desiccator for another 12 h. The conductivity of the different mixtures can be calculated using Eq. (7).

$$\gamma = G \times k \quad (7)$$

γ is conductivity (Siemens/cm); G is susceptance (Siemens, S); k is the Cell constant (0.0067 cm^{-1})

As the conductivity between $p = 0\%$ (V/V) of PEG 200 and the percolation threshold p_c should be zero by definition, the value of $\gamma(p_c) = \gamma_0$ was deducted from the values $\gamma(p)$ for $p = p_c$. Thus for the evaluation of Eq. (1) the values $(\gamma - \gamma_0)$ were used, i.e. the conductivity, which originates from the percolation of PEG 200.

2.2.2. Preparation of the samples

2.0 g of the tested volume to volume ratios of PEG 200 and PEG 6000 were filled in a lock-up vial. The vial was allowed to stand for 15 min in a water bath at $70 \pm 1^\circ\text{C}$. After 15 min the mixture was taken out of the water bath and mixed for 2 min on a mixer (Vortex Genie 2, Scientific Industries Inc., Bohemia, USA). To eliminate air bubbles that arise during the mixing, the mixtures stand for another 2 min in the water bath. Afterwards the mixture was poured out in the cylindrical conductivity cell (Fig. 1). The conductivity cell was closed and cooled down within 1 h to room

temperature. The conductivity of the samples was determined after 24 h of storage at room temperature. 17 binary mixtures with PEG 200 contents between 0 and 100% (V/V) were prepared in the same manner.

2.2.3. Preparation of the samples for the dissolution test

For the determination of the intrinsic dissolution rate of PEG 200 a marker (Mepyraminmaleat, MM, Sigma, Buchs, Switzerland, Batch Nr. 75 H 1030, Analytical grade) was used. This marker substance could be easily dissolved in PEG 200.

An 0.75% (V/V) solution of MM in PEG 200 was prepared. The required amount of this solution was added to molten PEG 6000. This mixture stands for 10 min in a water bath ($T = 70 \pm 1^\circ\text{C}$). Subsequently the mixture was taken out of the water bath and mixed for 2 min with a Vortex Genie 2 (Scientific Industries Inc. Bohemia, USA). To eliminate air bubbles that arise during mixing, the mixture stands for another 2 min in the water bath. Afterwards 3 ± 10 mg of the mixture was poured out in a cylinder (height: 2.0 cm, diameter: 2.9 cm) closed on the one side by aluminium foil. After the solidification of the mixture, which takes about 20 min, the remaining space of the cylinder was filled with molten paraffin. This preparation procedure leads to discs of the suppository bases mixtures of about 3 mm height and a surface area of 26.42 cm^2 . 16 binary mixtures with contents of PEG 200 between 0 and 90% (V/V) were prepared in the same manner. It has to be kept in mind, that the drug remains dissolved in PEG 200 and that the solid fraction PEG 6000 is free of drug after preparation of the samples. Before starting the dissolution rate, the aluminium foil was taken away from the above-described filled cylinder. This procedure leaves only one surface of the PEG mixtures free to the dissolution medium (water $37 \pm 0.5^\circ\text{C}$). The determination of the dissolution rate was performed under sink conditions using a rotating disc method. The rotation speed was kept constant on 100 rpm. The MM concentration in the medium was registered spectrophotometrically at 244 nm (Perkin Elmer, Type Lambda so, Rotkreuz, Switzerland).

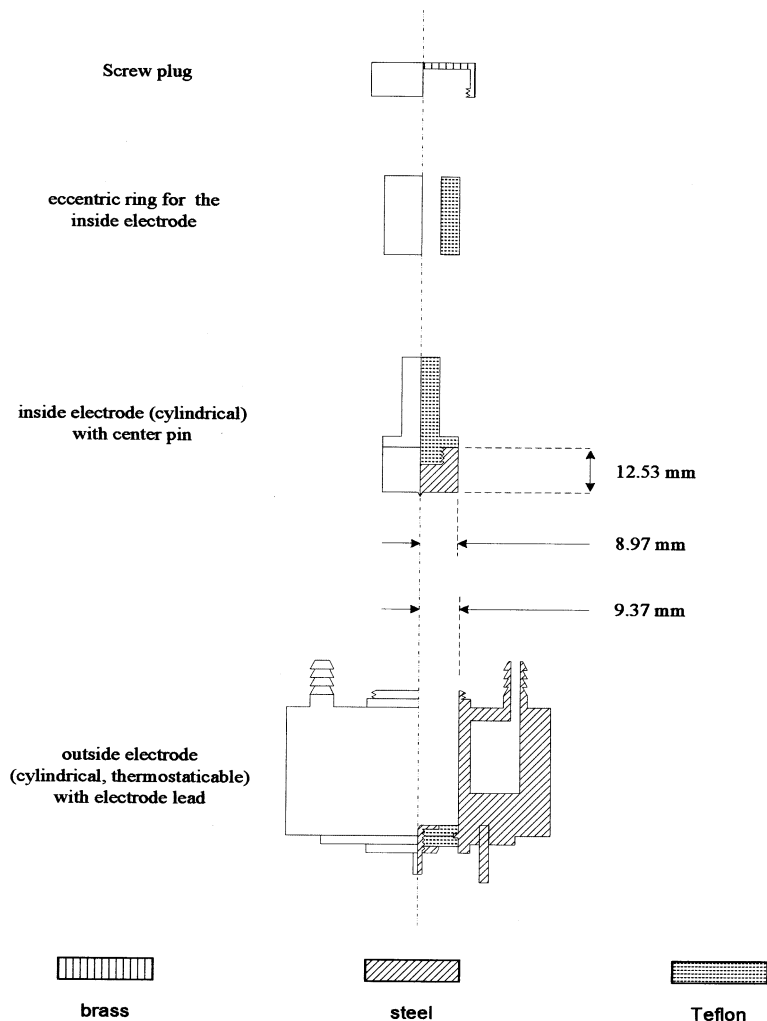


Fig. 1. Schematic presentation of the conductivity cell

To determine the percolation effect of PEG 200, the intrinsic dissolution rate constant of PEG 200 (with the marker) was determined at the percolation threshold p_c . Thus between the range of 0% (V/V) PEG 200 and the percolation threshold p_c , the flux J has to be zero, i.e. only the $J(p) - J(p_c)$ for $p = p_c$ were evaluated.

3. Results and discussion

3.1. Conductivity

For each volume to volume ratio three samples were measured. The calculated conductivities are shown in Table 2. Fig. 2 shows the results as a plot (mean value \pm RSD). The value for the

conductivity of pure PEG 6000 is compared to the results of Binks and Sharples (1968) too high. A possible explanation for this fact is that he had used very pure PEG 6000 for his measurements and the measurements were carried out under vacuum. We used commercially available PEG 6000 without further purification and our measurements were not carried out under vacuum. This procedure was

Table 2
Results of the conductivity measurement^a

% PEG 200 (m/m)	% PEG 200 (V/V)	$\gamma \pm s_{\text{abs}}$	s_{rel}
0	0	92.0 ± 4.2	4.6
2.5	2.66	204.1 ± 4.7	2.3
5	5.32	272.9 ± 1.6	0.6
7.5	7.97	305.1 ± 15.8	5.2
10	10.61	358.5 ± 2.1	0.6
15	15.86	387.9 ± 26.4	6.8
20	21.07	413.4 ± 14.0	3.4
30	31.40	469.3 ± 16.3	3.5
40	41.58	560.0 ± 29.3	5.2
50	51.64	670.8 ± 33.4	5.0
60	61.56	844.3 ± 38.8	4.6
70	71.36	994.7 ± 30.9	3.1
80	81.03	1184.5 ± 49.3	4.2
85	85.82	1379.2 ± 43.7	3.2
90	90.58	1641.3 ± 5.1	0.3
95	95.30	1898.9 ± 6.9	0.4
100	100	2173.4 ± 96.5	4.4

^a γ is the conductivity (nS/cm); s_{abs} is the absolute standard deviation (nS/cm); s_{rel} is relative standard deviation (%).

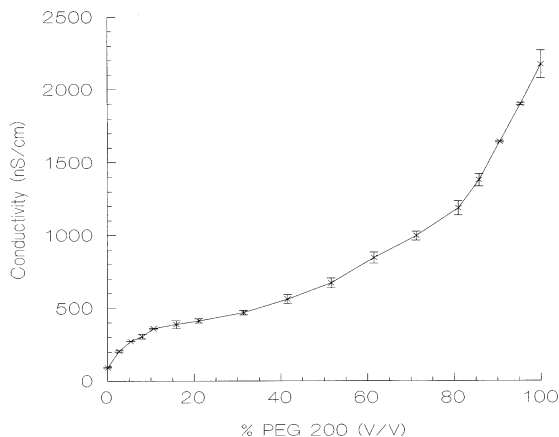


Fig. 2. Conductivity of the PEG 200/PEG 6000 system

enough exact for our intentions, because we wanted to investigate a system over the whole range of possible volume to volume ratios.

It is possible to distinguish three regions in Fig. 2. The first starts at 0% PEG 200 (V/V) and ends at $\approx 15\%$ (V/V). This region is characterised by a slight inconstant ascent of the conductivity. According to the percolation theory, the values of this region lead to the following interpretation. The small PEG 200 molecules (or chains) are only localised in finite clusters, while PEG 6000 builds an infinite network. In this special case where a solid and a liquid PEG is mixed together, no random distribution of the PEG 200 in the PEG 6000 happens. Goede (1983) found that in such systems the liquid PEG is first embedded at very special places between the large PEG 6000 chains. The single PEG 6000 chains are arranged in parallel as plate-like structures (lamellar) from which the hydroxyl end groups are rejected onto the surface. It is assumed that there exist regions vertical to the chains consisting of the terminal hydroxyl end groups, where the PEG 200 chains are first embedded. At a certain volume to volume ratio these regions are saturated with PEG 200. Above this volume to volume ratio a randomly distribution of the PEG 200 chains in the PEG 6000 starts. Goede (1983) Tarabishi (1995) found values of about 3–5% (V/V) PEG 200 for the saturation concentration. This special behaviour may be the explanation for the flattening values in the range of 5–10%. One could assume that the lower percolation threshold is localised in this region.

The second region starts at $\approx 10\text{--}15\%$ (V/V) PEG 200 and ends around the upper percolation threshold at $\approx 80\text{--}85\%$ (V/V) PEG 200. This region is characterised by a steadily increasing conductivity, which can be fitted by a quadratic model. Both compounds build infinite clusters. One could see that close to the second upper percolation threshold, the conductivity of the PEG 200 influences more and more the conductivity of the whole mixture.

Above the assumed upper percolation threshold at $\approx 85\%$ (V/V) PEG 200 there is a linear ascent of the conductivity. In this region only PEG 200 forms an infinite cluster, which is responsible for the conductivity of the whole mixture. PEG 6000

Table 3
Lower percolation threshold and critical exponents^a

Critical exponent	q	p_c	S	R^2
Conductivity 2 dimension	1.3	20.0 ± 1.8	3.52	0.991327
Conductivity 3 dimension	2.0	8.4 ± 1.3	0.16	0.998360
Free	1.83 ± 0.05	11.6 ± 1.1	0.34	0.998580

^a q , critical exponent; p_c , lower percolation threshold (% PEG 200 (V/V)); S , scaling factor; R^2 , squared correlation coefficient.

forms only small finite clusters and has no influence on the conductivity of the whole mixture. The consistency of the mixtures in this range of volume to volume ratios is semi-solid to liquid, while the consistency of the system below 80% (V/V) PEG 200 is rather solid. This gives an indication, that the upper percolation threshold can be expected at $\sim 80\%$ (V/V) PEG 200.

By the help of the computer software SYSTAT for Windows (Version 5, 1992, Systat Inc., Second printing, Illinois, USA), it is possible to calculate the lower percolation threshold and the critical exponent of the system. Only the conductivity values of the samples between the supposed percolation thresholds were taken into account. The percolation thresholds are assumed to be at ≈ 15 and 75% (V/V) of PEG 200. By the help of the computer software, it is possible to describe the data points as a function in the form of:

$$\gamma - \gamma_{(u)} = S|p - p_c|^q \quad (8)$$

γ is conductivity (known); $\gamma_{(u)}$ is correction term to take into account the 'intrinsic' conductivity at the percolation threshold (lowest conductivity used for the calculation), (known); S is scaling factor (unknown); p is percentage PEG 200 (known); p_c is percentage PEG 200 at the percolation threshold (unknown); q is critical exponent (known or unknown)

The correction term was taken into account as the sample does not represent an infinite lattice and other molecules, which are not connected to the infinite cluster are responsible for an 'intrinsic' conductivity at the percolation threshold. These calculations were made for the conductivity exponents in two or three dimensions known from the literature. Beside these two exponents it is also possible to calculate simultaneously the critical exponent q and the percolation threshold p_c ,

which describes the data points best. The software calculates for each exponent the squared correlation coefficient (R^2) and Table 3 shows the results. It has to be kept in mind that the parameters q and p_c are correlated and it is not possible to determine q and p_c independently. Fig. 3 shows the results of Table 3 diagrammatically. The points represent the mixtures used, while the line represents the function that results by putting the values of Table 3 in Eq. (4). The value for the critical exponent is in good agreement with the one predicted by the literature for a three dimensional system. The percolation threshold and the critical exponent point to a three dimensional continuum system.

An excellent R^2 -value is obtained for the simultaneous calculation of q ($q = 1.83$) and p_c ($p_c = 11.6$) for the conductivity data. If q is fixed to $\mu = 2.0$ the R^2 -value is again an excellent one and not very different from the one obtained for $q = 1.83$. The lower value for p_c ($p_c = 8.4$) indicates a possible presence of a continuum percolation.

3.2. Diffusion and conductivity in the PEG 200/PEG 6000 system

Beside the determination of the conductivity in the PEG 200/PEG 6000 system there were also carried out some investigations upon the dissolution behaviour of this system. For this purpose the intrinsic dissolution rate of PEG 200 was determined (Siegmund, 1998). As the intrinsic dissolution rate J is proportional (under 'sink conditions' and constant rotation speed) to the permeability P_m of the percolating network, J scales as follows:

$$J \propto (p - p_c)^q \quad (9)$$

with, p is volume ratio of the component with the

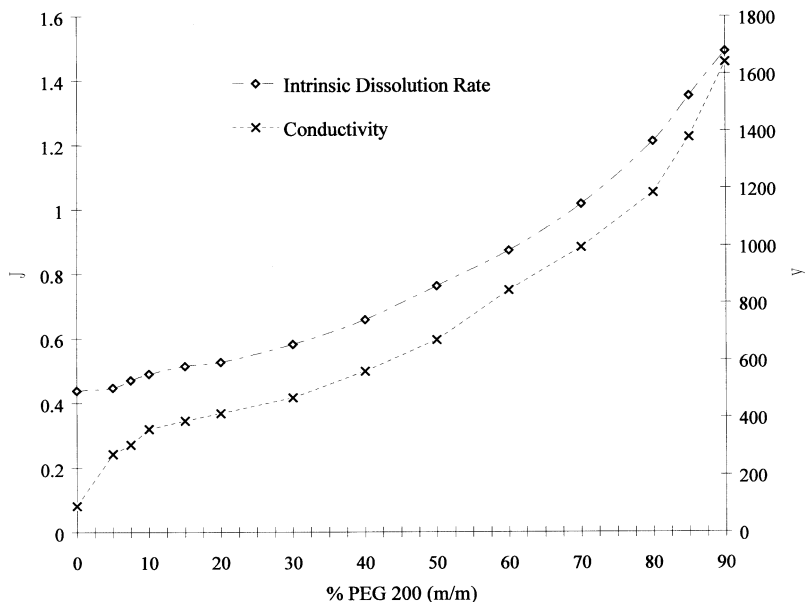


Fig. 4. Intrinsic dissolution rate and conductivity of the PEG 200/PEG 6000 system, J , dissolution rate (%/min cm²); γ , conductivity (nS/cm).

connection between dissolution and conductivity. If the ascent of the two curves follows the same power law a theoretical division of the two terms such as conductivity divided by the rate constant should lead to a constant.

If for both processes, i.e. conductivity and dissolution an identical percolation threshold p_c is assumed, the critical exponents q_c (conductivity) and q_d (dissolution) become practical identical (Table 5). If the theoretically expected value of $q_c = 2$ for three dimensions is adopted a relatively low value for the percolation threshold $p_c = 8.4 \pm 1.3\%$ (v/v) for the conductivity experiment is calculated. If the same percolation threshold is adopted for the dissolution experiment a critical exponent $q_d = 1.94 \pm 0.04$ results. Analogous results are obtained for higher values of the percolation threshold p_c of the dissolution and conductivity experiment. Thus it is not surprising that the ratio $(\gamma - \gamma_0)/(J - J_0)$ yields a constant for the mixture samples between the lower and upper percolation threshold p_c (Table 5). It is important to keep in mind that γ_0 and J_0 correspond to the conductivity γ , respectively to the dissolution rate constant J at the lower percolation threshold. Thus the fraction of ‘background’ conductivity or

dissolution, which is not related to the percolation of PEG 200 in the PEG 200/PEG 6000 system, is deducted. The evaluation of data between 30% (V/V) and 70% (V/V) of PEG 200 assuming $p_c =$

Table 4

Intrinsic dissolution rate and conductivity of the PEG 200/PEG 6000 system^a

%PEG 200 (m/m)	$J \pm s_{\text{abs}}$	$\gamma \pm s_{\text{abs}}$	$(\gamma - \gamma_0)/(J - J_0)$
0	0.439 ± 0.012	92.0 ± 4.2	–
5	0.448 ± 0.018	272.9 ± 1.6	–
7.5	0.471 ± 0.013	305.1 ± 15.8	–
10	0.490 ± 0.015	358.5 ± 2.1	–
15	0.514 ± 0.024	387.9 ± 26.4	–
20	0.527 ± 0.03	413.4 ± 14.0	1961
30	0.582 ± 0.013	469.3 ± 16.3	1197
40	0.659 ± 0.04	560.0 ± 29.3	1187
50	0.763 ± 0.019	670.8 ± 33.4	1136
60	0.874 ± 0.016	844.3 ± 38.8	1268
70	1.017 ± 0.057	994.7 ± 30.9	1206
80	1.212 ± 0.049	1184.5 ± 49.3	–
85	1.354 ± 0.046	1379.2 ± 43.7	–
90	1.492 ± 0.084	1641.3 ± 5.1	–

^a J , dissolution rate (%/min cm²); γ , conductivity (nS/cm); s_{abs} , absolute standard deviation.

Table 5

Lower percolation threshold and critical exponents for conductivity and dissolution^a

Property	q	p_c	R^2
Conductivity ($\gamma - \gamma_0$)	1.83 ± 0.05	11.6 ± 1.1	0.99858
Dissolution ($J - J_0$)	1.71 ± 0.03	13.4 ± 0.5	0.99963
Conductivity ($\gamma - \gamma_0$)	2.00 (fixed)	8.4 ± 1.3	0.99910
Dissolution ($J - J_0$)	1.94 ± 0.04	8.4 (fixed)	0.99909
Conductivity ($\gamma - \gamma_0$)	1.75 ± 0.05	13.4 (fixed)	0.99857
Dissolution ($J - J_0$)	1.80 ± 0.03	11.6 (fixed)	0.99961

^a q , critical exponent; p_c , lower percolation threshold (% PEG 200 (V/V)); R^2 , squared correlation coefficient.

15% (V/V) yields for the ratio $(\gamma - \gamma_0)/(J - J_0)$ a mean value of 1199 ± 42 .

4. Conclusion

The results show, that the conductivity exponent $\mu = 2$ predicted by the literature is not only for ideal insulator/conductor mixtures valid but also for mixtures where both compounds conduct electricity. However it is important that a certain difference in the conductivity of the pure substances is detectable. This work shows that it is possible to describe selected properties of semi-solid drug systems with the concepts of percolation theory in a rigorous way. This approach helps to understand and to describe such systems in a better way. It was possible to show that the conductivity and the dissolution rate process can be successfully modelled by the basic equation of percolation theory and that both processes scale in an identical way with $\mu = q = 2$ in three dimensions.

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