A New Wet Conductivimetric Method To Estimate the Drug Percolation Threshold

Álvaro Espina-Márquez[1] and Isidoro Caraballo[1,2]

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Purpose. The main objectives of this work are to study the behavior of fluid imbibition into a consolidated matrix through a wet invasive conductivimetric technique, to investigate if the changes in the behavior observed can be related to the drug percolation threshold, and to use this technique for its estimation.

Methods. Matrix tablets were prepared using five sieving fractions of KCl and Eudragit RS-PM. *In vitro* release assays were carried out on 45 batches. The drug percolation thresholds were estimated following the method of Leuenberger and Bonny, and the results were compared to the obtained employing the conductivimetric technique described in this paper.

Results. The wet conductivimetric technique and the standard method provided similar results for the estimation of the percolation threshold. The presented technique also provides quantitative information about the consolidated matrix.

Conclusions. A new apparatus has been developed for the study of the conductivimetric behavior of matrix tablets during water uptake. This technique provides measurable parameters of fluid penetration and can be used to estimate the drug percolation threshold, providing similar results to the Leuenberger and Bonny method and being clearly faster.

KEY WORDS: controlled release; inert matrix tablets; percolation theory; wet conductivimetric estimation of the percolation threshold.

INTRODUCTION

Percolation theory and fractal geometry have an increasing number of applications in pharmaceutical technology. The concepts of fractal dimension and fractal reaction dimension, D_R, for the dissolution (1–3) are improving the understanding of the processes involved in the *in vivo* dissolution of a drug (2,4). Therefore they provide a better characterization and prediction of the biopharmaceutical properties of drugs.

On the other hand, the percolation theory is explaining the existence of critical points in pharmaceutical formulations that normally can be related to percolation thresholds of a component of the formulation (5–7). The knowledge of these critical points and the corresponding percolation thresholds is of great importance to optimize the design of a pharmaceutical dosage form. For example, inert matrices should be formulated above the drug percolation threshold (to allow the complete release of the drug) and below the excipient percolation threshold (to obtain a controlled release and to avoid disintegration). Furthermore, in order to prepare robust formulations, the neighborhood of the percolation thresholds should be avoided; otherwise a little change in the concentration of one component can cause a high variability in the properties of the formulation (6).

The relevance of the percolation thresholds has been widely accepted since its application as a tool in pharmaceutical dosage form design. This use is based on the method for the estimation of the percolation threshold developed by Leuenberger and Bonny (7). This standard method implies single-sided dosage form release in a dissolution medium.

Previous work has been carried out on the dry conductivimetric analysis of matrices below and above the percolation threshold (8). The authors indicate the existence of a change in the conductivimetric properties at or around the percolation threshold. Nevertheless, as the authors also indicate, this dry conductivimetric technique is of limited use, due to its inherent design. Some of the limitations are the difficulty found in preparing the thin laminated samples required, and the fact that the method can only be used with highly conductive solids due to the dry state of the sample. The thickness of the samples should be around 1 mm, for tablets containing sodium chloride. For less conducting substances, a lower maximum thickness is expected. On the other hand, it has to be realized that due to the nature of the results obtained (conducting/isolator), the dry conductivimetric technique did not allow the estimation of the percolation threshold; it only provides an indication of whether the sample is above or below the percolation threshold.

Therefore, one of the main handicaps for the estimation of the drug percolation threshold is that the standard method implies very time-consuming measurements of the active component and costly equipment. In addition, if more components of the formulation dissolve in the medium, the determination and estimation of the percolation threshold is further complicated. These facts are responsible for the reluctance of application of the principles of the percolation theory in the pharmaceutical field, and more particularly in solid dosage form design.

The first objective of the current work was to design an apparatus for the study of the conductivimetric behavior when the matrix is subjected to the imbibing of a solvent through one side and to define the diffusion pattern that occurs. The second objective was to investigate if the wet conductivity profiles obtained can be related to the relative position of the matrix with respect to the drug percolation threshold ($p < p_c$, $p = p_c$, $p > p_c$).

The third objective of this work was to define measurable parameters that can be obtained from the wet conductivity profiles and investigate if these parameters can be used in the estimation of the drug percolation threshold. For this pur-

[1] Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Seville, c/o Professor García González, 2.41012 Seville, Spain.

[2] To whom correspondence should be addressed. (e-mail: caraballo@us.es)

ABBREVIATIONS: A, concentration of drug in the tablet; b, Higuchi's slope; c, represents a constant; ε, total porosity of the tablet; ε_0, initial porosity of the tablet; ε_{csd}, drug percolation threshold estimated with the standard method; p_c, percolation threshold, expressed as occupation probability (% v/v); p_{c1}, drug percolation threshold, expressed as occupation probability (% v/v); $p_{c2} = p_{cExc}$, excipient percolation threshold (% v/v); ε_c, drug percolation threshold, expressed as critical porosity (% v/v); β or β-property, property related to the drug diffusion coefficient of each matrix; C_s, water solubility; C_{max}, maximum conductivity obtained from sample (Scm^{-1}); t_i, initial time: time to the initial imbibing phase (s); t_s, saturation time: time to the rapid imbibing phase or saturation phase (s); t_{max}, time to the maximum conductivity (s).

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pose, their behavior concerning the drug percolation threshold has been studied.

A method is proposed to estimate the percolation threshold based on this new wet conductivity technique. The pharmaceutical inert matrix tablets prepared have been examined employing the standard method (7) and compared with the new method proposed in this work. The obtained results show that conductivimetric analysis of solute penetration into a matrix is a useful tool in evaluating the percolation threshold.

MATERIALS AND METHODS

Potassium chloride (Acofarma, Barcelona, Spain) was used as a model water-soluble drug. Eudragit RS-PM (Hüls Española, Barcelona, Spain) a hydrophobic, inert, nonswelling acrylic polymer was used as matrix-forming material. Both compounds were sieved (Retsch type Vibro) to obtain the desired granulometric fractions. The mean diameter of the particles of drug and excipient were measured using a He–Ne laser diffraction system (Malvern Instruments, type Mastersizer x, 1.2b, Worcestershire, UK). Table I shows the composition of the studied formulations as well as the particle size of the used substances.

The mixtures were compressed with an eccentric tablet press (Bonals A-300, Barcelona, Spain). Cylindrical, flat, tablets, with a theoretical weight of 600 mg and a diameter of 12 mm were prepared at the maximum compression force accepted by the formulation. The particle size fractions, as well as the absolute and relative mean particle sizes for potassium chloride and Eudragit RS-PM are shown in Table I. In the conductivimetric assays the tablets were placed in the same orientation as they came out of the tablet press, that is, the lower punch side was exposed to the dissolution medium.

Dissolution studies were carried out with a USP 23 apparatus (Turu Grau, type D-6), employing the rotating disk method, in such a way that only one of the faces of the tablet (0.79 cm^2) was exposed to the dissolution medium (deaerated water at 37 ± 0.5°C). The rotating speed was kept constant at 50 rpm. The release of KCl was detected by the increase in conductivity of the dissolution medium using a Crison micro CM-2201 digital conductivity-meter linked to a chart recorder and a personal computer. The system provides one conductivity datum per second.

The drug percolation thresholds were calculated employing the method of Leuenberger and Bonny (7,9). This drug percolation threshold corresponds to a critical porosity, ε_c, where the pore network, that is, the initial pores and the pores filled up by the drug, just begins to span the whole matrix. In order to calculate these theoretical porosities, the true density of KCl was taken from the literature (10) whereas the true density of Eudragit RS-PM was obtained from previous mercury porosimetry measurements (Porosimeter 4000, Fisons Instruments).

The Leuenberger and Bonny method is based on the calculation of β, a property of the tablets derived from the diffusion coefficient. The tablet property, β, is defined as follows:

$$\beta = \frac{b}{\sqrt{2 \cdot A - \varepsilon \cdot C_s}} \quad (1)$$

Above the drug percolation threshold and below the excipient percolation threshold, the β property behaves as:

$$\beta = c(\varepsilon - \varepsilon_c) = -c\,\varepsilon_c + c\varepsilon \quad (2)$$

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

The conductivimetric studies were carried out using the apparatus illustrated in Fig. 1. The matrix was exposed to the dissolution medium (water at room temperature) and a 20-s timer incorporated to a water detector electrode activated the data acquisition program. This "lag time" was previously determined when the calibration of the apparatus was carried out. The data were obtained at time intervals varying from 1 to 60 s, depending on previous experiences with each batch. The top and bottom electrodes are made from stainless steel, the bottom one consisting of a 0.5-mm-square mesh. The top and bottom electrodes are considerably larger than the matrices (60-mm diameter). A standard filter paper was placed on top and bottom of the sample to guarantee the water availability as well as uniform contact with the electrode and the imbibing material. The constant contact between the matrices, filters, and electrodes was assured by a compressing spring. The wetting material, polyurethane, allows water transport to the sample, popular garden green used to prepare flower adornments. Three supporting columns that are conveniently insulated hold the structure together. A water detector is incorporated to provide a starting point or zero time.

Table I. Composition of the Assayed Tablets, KCl Percentages, Size Fraction Selected by Sieving, Equivalent Volume Diameter Found Using Laser Diffraction, and Drug/Excipient Size Ratio

		KCl (μm)		Eudragit RS-PM (μm)		
Range [KCl] %	Batch	Sieving fraction	Volume diameter	Sieving fraction	Volume diameter	Size ratio KCl/Eu
20–60	E	050–100	85	100–150	125	0.68
20–60	L	100–150	144	100–150	125	1.15
20–70	D	150–200	211	050–100	72	2.93
20–70	F	150–200	211	100–150	125	1.69
30–80	C	150–200	211	150–200	211	1.00
30–80	B	150–200	211	200–250	268	0.79
20–80	A	150–200	211	250–300	288	0.73
20–60	K	250–300	302	100–150	125	2.42
20–60	M	300–350	345	100–150	125	2.76

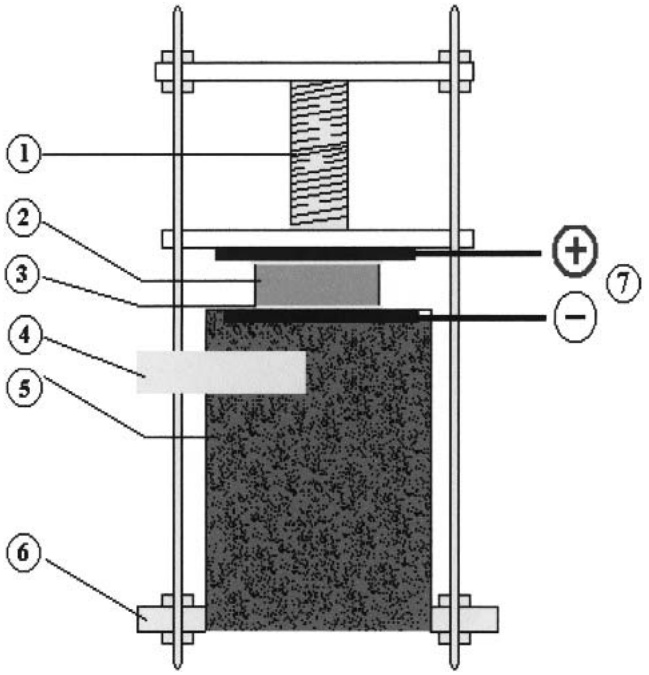

Fig. 1. Representation of the apparatus used for the conductivimetric evaluation of the consolidated matrices. Where: ①, compressing spring; ②, sample; ③, filter paper; ④, water detector; ⑤, wetting material; ⑥, solid structure, ⑦ electrodes connected to the resistor bridge.

RESULTS AND DISCUSSION

Previous papers (11,12) have reported that changes in the drug percolation threshold are due to the drug/excipient particle size ratio. In the current paper, 20 batches of tablets have been prepared using 9 different drug/excipient particle size ratios (ranging from 0.68 to 2.93). Table I summarizes the composition of the studied batches.

The obtained tablets were measured and weighed. Release profiles were obtained following the experimental conditions described in the previous section. As an example, the obtained release profiles for tablets containing 211 μm KCl and 72 μm Eudragit RS-PM are shown in Fig. 2. As it can be observed in this figure, a change in the release profiles appears around 50% w/w KCl content. According to the percolation theory, the drug percolation threshold, that is, the volume fraction at which the drug starts to form an infinite cluster that percolates the whole tablet, must be close to the total porosity of this batch of tablets.

The drug percolation thresholds (p_{c1}) have been calculated with the standard method (7), as described in the "Materials and Methods" section. The critical porosity (ε_c) that corresponds to the drug percolation threshold (p_{c1}) was estimated as the intersection with the abscissa when β is plotted vs. the total porosity, ε. According to this standard method, proposed by Leuenberger and Bonny (7), only the β values situated in the linear zone above the drug percolation threshold, p_{c1}, and below the excipient percolation threshold, p_{c2}, are used in calculating ε_c.

Figure 3 shows the obtained drug percolation thresholds as a function of the mean drug/excipient particle size ratio for all batches. As in previous studies (11,12), a linear relationship can be appreciated between these two parameters. An increase in the drug particle size produces an increase in the drug percolation threshold. For the excipient particle size, the contrary effect could be observed, that is, the larger the excipient particle size, the lower the drug percolation threshold. This relationship has been explained in terms of the effectiveness of each component to percolate the system (11,12). These results confirm the previously reported relationship as well as the accuracy in the estimation of the percolation thresholds in the present paper.

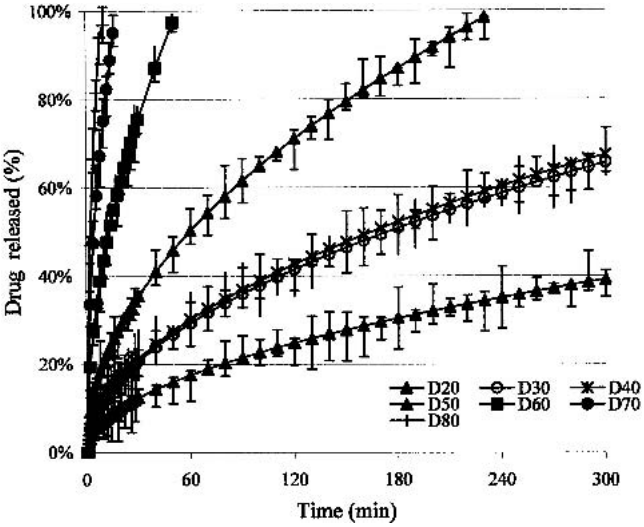

Fig. 2. Dissolution profile for batch D (211μm KCl and 72μm Eudragit RS-PM).

Once the batches have been characterized and their percolation thresholds estimated, the tablets were subjected to the proposed wet conductivimetric technique employing the apparatus developed for this purpose, described in the previous section.

Three types of conductivity profiles, were observed (we have denoted them as profiles ①, ②, and ③). They varied

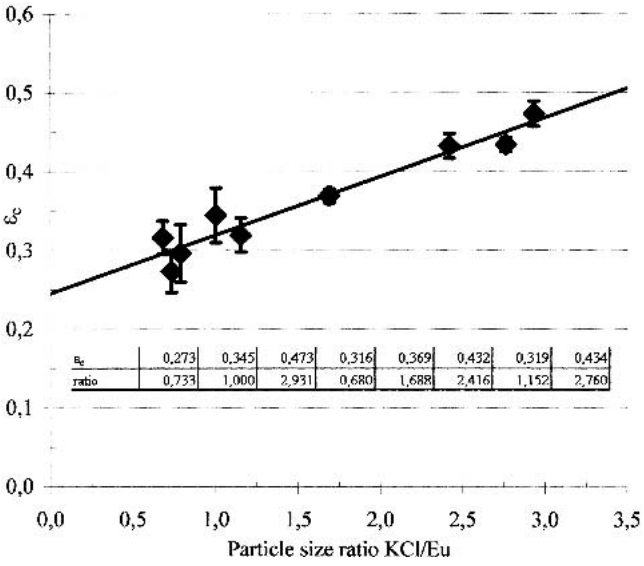

Fig. 3. Variation of the estimated percolation threshold found with the standard method, ε_{csd}, (±SD) plotted against the drug/excipient particle size ratio (KCl/Eudragit RS-PM).

mainly on the value and speed of reaching C_{max} and the behavior obtained after this point.

A typical example of profile ① is provided in Fig. 4. Two distinct phases can be appreciated before a maximum in conductivity (C_{max}) is reached. The initial imbibing phase, characterized by the first regression line, starting at $t = t_i$ (contact time or initial time) and a second phase, which we called saturation phase, that starts at t_s, and finds a maximum of conductivity (C_{max}) at a time t_{max}. The initial phase commences when the first conductive channel between both sides is established. During this phase, this channel is being saturated of water. When the first channel is saturated ($t = t_s$), a progressive invasion and subsequent saturation of other channels of smaller diameter takes place. This fact leads to a rapid rise in conductivity until t_{max}. The decrease after C_{max}, indicates the extraction of the solute toward the reservoir. This type of profile reveals a rapid capillary penetration and suggests not only the existence of a capillary network of large size but also the presence of homogeneity in the pore size.

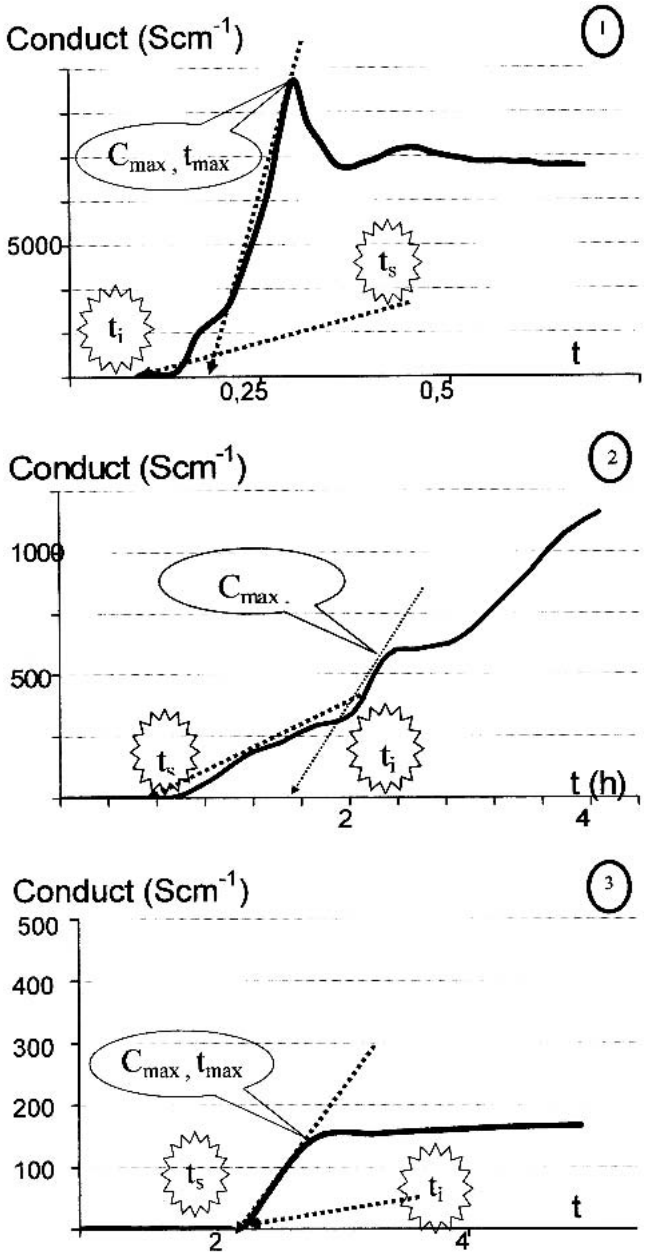

Fig. 4. Conductivity profiles ①, ②, and ③. The best fit regression lines for the different phases are also shown, as well as the characteristic points of the profile: t_i, contact time; t_s, saturation time; C_{max}, maximum conductivity value; t_{max}, time at which the maximum conductivity value was obtained.

In those matrices where the water movement is hindered by inherent factors (profile ②), the initial imbibing phase is long-lasting, and the ratio between saturation phase and imbibing phase is smaller (Fig. 4). As it can be appreciated, in these profiles C_{max} is a relative maximum. After this point, the conductivity remains approximately constant for a short time period and then it continues to rise. Only after a long period of time a drop in conductivity is observed, nevertheless the magnitude of this fall is clearly lower than the experienced after C_{max} in profile ①.

The conductivity profile ② is generally observed near the percolation threshold. This behavior can be attributed to the heterogeneity of the distribution of accessible pores in the samples situated close to the drug percolation threshold. As it is well-known (13), the incipient infinite cluster shows a fractal structure with frequent bottlenecks. Therefore, in these matrices the saturation phase before C_{max} actually corresponds to the saturation of the zones easily accessible from the first conductive channel of the matrix. The slow invasion and saturation of the other zones of the matrix implies the pass of water through the bottlenecks that results in a slow increase in conductivity after C_{max}.

The last type of conductivity profile (profile ③), also illustrated in Fig. 4, is characterized mainly by the low value of conductivity reached (below 500 Scm^{-1}). This profile is obtained from matrices well below the percolation threshold. In these profiles, t_i is close to the base or noise. The heterogeneity is so high and the connectivity so low that the conductivimetric evaluation is very difficult and time consuming. The low conductivity reached is attributable to the absence of a network of drug and/or pores spanning the matrix.

Once the patterns of the wet conductivity profiles have been discussed, the second objective of this work was to define some measurable parameters that can be obtained from these profiles and to investigate if they can be used to estimate the drug percolation threshold. For this purpose, the behavior of these parameters with respect to the drug percolation threshold has been studied.

The following parameters have been used: maximum conductivity value, C_{max}, and time corresponding to this value, t_{max}, initial time or contact time, t_i, and saturation time, t_s. The obtained results have been plotted vs. the distance to the dissolution percolation threshold (an example is shown in Fig. 5 for t_{max}). As it was previously mentioned, the dissolution percolation thresholds used as reference have been estimated in this work employing the standard method (7).

As Fig. 5 shows, when t_{max} is plotted as a function of the distance to the dissolution percolation threshold, a clear change can be observed. According to the fundamental equation of Percolation Theory, if this parameter behaves as a critical property, we can expect that

$$t_{max} \propto k \cdot (\varepsilon - \varepsilon_c)^q \qquad (3)$$

where k is a constant, $(\varepsilon - \varepsilon_c)$ is the distance to the drug percolation threshold, and q is a critical exponent.

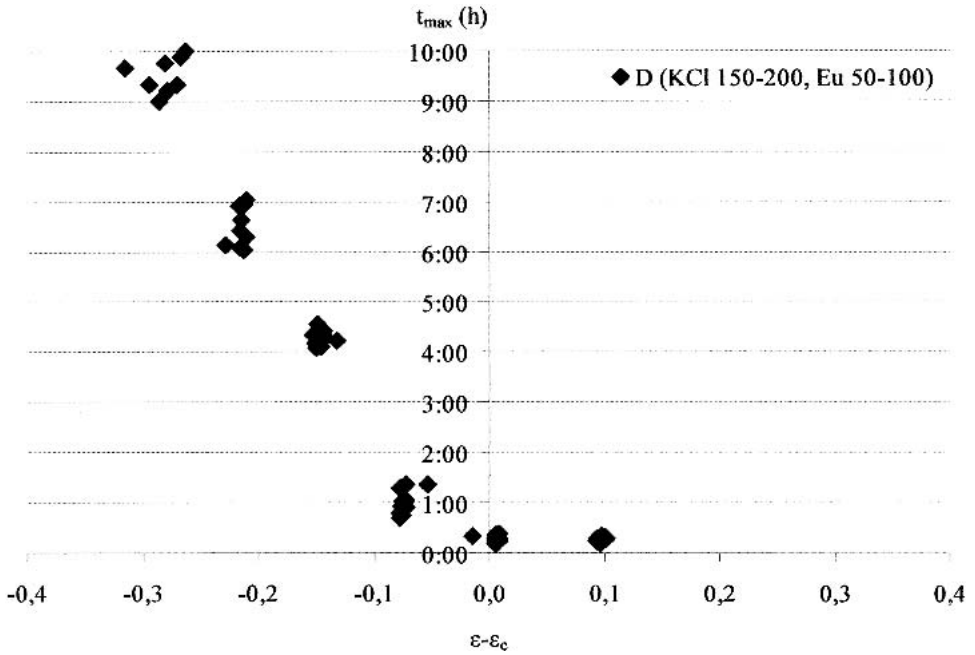

Fig. 5. Plot of the time to the maximum conductivity, t_{max}, against the distance to the dissolution percolation threshold, for batch D (211μm KCl and 72μm Eudragit RS-PM).

A linear regression has been performed for the t_{max} values obtained for each batch, as a function of the distance to the dissolution threshold. Only the data of the batches situated below this threshold have been used in the regressions. The obtained results for the different batches are detailed in Table II. The linear regression has been used as a rough approximation, as the calculation of the exact exponent shows several difficulties, such as the fact that the range of validity of the data that can be used to estimate the exponent is unknown. Theoretically, this range depends on the value of the percolation threshold ($p_c \pm 0.1\ p_c$), therefore, the exponent can not be determined until the percolation threshold, p_c, is estimated. A second difficulty is the high influence that the value of each parameter exerts on the other one in a simultaneous determination of the threshold and the exponent. A third difficulty in practice is the fact that the exponent is very influenced by the points far away from the percolation threshold. Nevertheless, these points provide less information about the position of the threshold, being more influenced by other factors. Taking these considerations into account, we think that the linear approximation can be an excellent tool to have a fast estimation of the percolation threshold using the proposed method until new studies provide theoretical values for the critical exponents corresponding to the studied properties.

Analogous calculations have been performed for the rest

Table II. Statistical Parameters for the Estimation of the Percolation Threshold Using the Time to Maximum Conductivity, t_{max}, and the Initial Time, t_i

Parameter	Batch	F	Prob	n	R^2	m	c	$\epsilon_c - \epsilon_{csd}$
t_{max}	C	72	7.49E-09	27	0.733	−108,053	0.005	0.00
	D	1549	6.51E-41	55	0.966	−151,452	−0.085	−0.05
	E	162	4.68E-07	11	0.941	−195,873	−0.032	−0.01
	F	437	7.77E-20	33	0.932	−183,535	−0.020	−0.01
	K	100	1.97E-09	23	0.818	−84,720	−0.001	0.00
	L	1050	1.85E-11	12	0.990	−185,940	0.001	0.00
	M	163	4.39E-11	22	0.886	−169,665	−0.078	−0.04
t_i	A	14	1.55E-03	20	0.804	−48,187	0.009	0.02
	C	86	1.37E-09	27	0.767	−41,073	0.004	0.01
	D	362	2.35E-25	55	0.870	−13,048	0.003	0.02
	E	42	6.95E-05	12	0.789	−22,371	0.012	0.05
	F	44	1.89E-07	33	0.858	−17,775	0.008	0.04
	K	78	1.71E-08	23	0.777	−9777	0.004	0.03
	L	28	3.32E-04	12	0.714	−21,684	0.017	0.07
	M	146	1.22E-10	22	0.873	−21,898	0.000	0.00

The distance to the percolation threshold found with the standard method, taken as a reference, is also shown. F, Snedecor ratio; Prob, probability; R^2, squared correlation coefficient; m, slope; c, constant term; ϵ_c-ϵ_{csd}, distance from the percolation threshold found with the standard method, ϵ_{csd}.

Table III. Difference Between the Percolation Thresholds Found Using the Conductivity Parameters and the Obtained Using the Standard Method ($\epsilon_c - \epsilon_{csd}$)

	Percolation threshold (ϵ_c)			Deviation from the percolation threshold ($\epsilon_c - \epsilon_{csd}$)				
Batch	Standard method (ϵ_{csd})	t_i	t_{max}	C_{max}	t_{max}	t_i	t_s	t_e
E	0.637	0.377	0.316	3.0%	–1.4%	4.7%	3.8%	2.5%
L	0.306			4.0%			3.1%	–0.5%
D	0.416	0.447	0.376	–0.2%	–4.9%	2.2%	–3.2%	–5.6%
F	0.385	0.398	0.353	5.5%	–0.9%	3.6%	7.6%	3.3%
C	0.337	0.342	0.338	2.9%	0.4%	0.8%	0.3%	
B	0.303			2.7%				–1.0%
A	0.312	0.344	0.344	3.1%	1.5%	1.5%	3.3%	3.1%
K	0.423	0.450	0.416	5.1%	–0.1%	3.3%	1.4%	0.6%
M	0.429	0.415	0.376	3.2%	–4.0%	–0.1%	–1.4%	–2.2%
Mean deviation of the method				3.3%	–1.2%	2.3%	1.9%	0.0%
SD				0.02	0.02	0.02	0.03	0.03

The Mean Values and SD are also shown for each parameter.

of the parameters obtained C_{max}, t_i, t_s, and the difference $t_s - t_i$, from the conductivity profiles. The results obtained for the initial time t_i, are also included in Table II.

Using this simple linear approximation and the values of the selected parameters, the drug percolation threshold can be easily estimated. Table III shows the deviation in the estimation of the percolation threshold by linear regression of the values of the parameters studied, ε_c, with respect to the percolation thresholds estimated with the standard method, ε_{csd}. The deviation of C_{max} is understandably larger, 3%, due mainly to the magnitudes involved and to the fact that the resistor bridge used makes the apparatus less sensible to such high values.

In order to estimate the drug percolation threshold (ε_c), we propose t_{max} as an easily measurable parameter showing a linear behavior in the neighborhood of the drug percolation threshold. As Table III shows, there is an excellent agreement with the percolation thresholds estimated employing the standard method (ε_{csd}). Nevertheless, if a fast measurement is needed, the initial time, t_i, provides very accurate results and can be measured in approximately 1 h.

The obtained result may have important consequences in the pharmaceutical dosage form design. Additional studies are needed to know the applicability of the findings presented to different formulations. Nevertheless, if this behavior is general, the characterization of matrices through conductivity analysis can provide important information about the behavior of these systems and can result in a faster method for the estimation of the percolation threshold. It must be born in mind that one of the main handicaps for the estimation of the drug percolation threshold at the moment is that the standard method is time-consuming.

The presented findings support the use of the drug percolation threshold as a preformulation parameter that can improve the quality of pharmaceutical dosage form design.

CONCLUSIONS

A new apparatus has been developed for the study of the conductivity behavior of tablets during imbibition. The wet invasive conductivimetric technique presented in this paper provides valuable information that can lead to the classification of the matrices into one of the three different categories, depending on its position with respect to the drug percolation threshold.

Furthermore, a new method for the estimation of the drug percolation threshold has been developed, based on experimentally measurable parameters obtained from the conductivity profiles. The proposed method has the advantage of being approximately 10 times faster than the previously used method.

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