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RESEARCH PAPER

Influence of the Disintegrant on the Drug Percolation Threshold in Tablets

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ABSTRACT

Previous papers studied ternary tablets containing different concentrations of polyvinylpyrrolidone cross-link (PVP-CL) as disintegrant. The drug percolation threshold, p_{cl}, for these tablets was estimated to fall in the range 0.26–0.31 of total porosity. The aim of the present paper is to study if the presence of the disintegrant agent (PVP-CL) in these tablets, exerts an important effect on the drug percolation threshold obtained. For this purpose, binary tablets containing the same model drug and excipient have been prepared in identical technological conditions. The drug percolation threshold in these matrix tablets has been calculated following the method of Bonny and Leuenberger (5). The results obtained show no significant difference between p_{cl} in the binary matrix tablets and the drug percolation threshold found in the tablets containing the disintegrant agent. This result supposes a stimulus for the application of the principles of percolation theory to a great number of pharmaceutical systems containing disintegrant agents or substances which cause a strong change in its release behavior.

INTRODUCTION

In 1957, Broadbent and Hammersley presented a statistical theory—percolation theory—which was able to explain the behavior of disordered systems (1,2). This theory has been employed to predict the behavior of a large number of mathematical, physical, and chemical systems (3).

Percolation theory was introduced in the pharmaceutical field by Leuenberger et al. (4). This theory is able to provide a characterization of pharmaceutical systems consisting of mixtures of two components distributed at

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random (5–12). A cluster is defined as a group of neighbor-occupied sites in the lattice, and the probability at which a cluster just percolates a system (a tablet in our case) is termed the "percolation threshold" (13).

The mean particle size of the components has an important influence on the percolation thresholds in tablets (10,14). A linear reletionship between the mean drug particle size and the drug percolation threshold, p_{c1}, has been found in a previous study (15). If this relationship is confirmed as generally valid, the percolation threshold can soon become a useful preformulation parameter.

The percolation theory has been developed for binary mixtures. Nevertheless, drug delivery systems usually contain more than two components. Therefore, in previous works (16,17), ternary tablets containing different concentrations of KCl as hydrophilic water-soluble model drug, Eudragit® RS-PM as hydrophobic water-insoluble excipient, and polyvinylpyrrolidone cross-link (PVP-CL) as disintegrant (hydrophilic but water insoluble), were compressed and studied.

The release study of these tablets showed a change in the studied release parameter (dissolution efficiency, E_d). This change was attributed to the obtention of an infinite cluster of KCl in the studied tablets. So, the drug percolation threshold for these ternary tablets was estimated to be in the range 0.26–0.31 of total porosity (17).

The aim of the present paper is to study the effect that the presence of the disintegrant agent (PVP-CL) exerts on the drug percolation threshold obtained in these tablets. For this purpose, binary tablets containing the same model drug (KCl) as well as the same hydrophobic, matrix-forming excipient (Eudragit RS-PM) have been prepared in technological conditions identical to those used for the ternary tablets. Therefore, the same compression pressure used for the ternary tablets (420 MPa) was employed. So, very similar and low porosities (1.9–2.9%) were obtained. Furthermore, as in the case of ternary tablets, different weights of the prepared mixtures were compressed in order to obtain tablets of similar volume (0.39 cm^3) for the 8 formulations tested.

Due to the fact that the binary tablets composed by KCl and Eudragit RS-PM are inert matrices, the drug percolation threshold, p_{c1}, in these tablets can be calculated following the method of Bonny and Leuenberger (5). This method is based on the calculation of the β property (see Materials and Methods section). This property depends linearly on p_{c1} in inert matrices which are bicoherent systems, i.e., which contain both drug and excipient infinite clusters, simultaneously. At present this method is the most useful one for the determination of the drug percolation threshold in pharmaceutical tablets, and has been widely used for this purpose (6,10,12,15,16).

MATERIALS AND METHODS

Potassium chloride (Siegfried, CH-Zofingen) was used as a model drug. Binary mixtures of KCl with Eudragit RS-PM (Röhm Pharma, D-Weiterstadt) have been prepared using a Turbula mixer (type T2C), with pre-5 min of mixing time. Both products were previously sieved (Retsch, type Vibro) and the 90–180 μm granulometric fraction was selected. Different amounts of the mixtures were weighed (Mettler type PM-460) and compressed in a Zwick 1478 universal testing instrument with a compression force of 40 kN (421 MPa).

Calculations were made in order to obtain approximately the same volume (0.39 cm^3) for all the tablets. The composition (w/w) of the binary formulations studied is shown in Table 1. The diameter and height of the tablets were measured in 10 replicates (Pel, type export). The mean and the standard error (SE) for these measurements were calculated. These mean values were used to calculate the tablet volume and its theoretical porosity.

The dissolution studies were carried out in the USP XXII apparatus (HETO, Model MA 6 VS) using the rotating disk method so that only one surface of the tablet was exposed to the dissolution medium (water at 37° ± 0.5°C). The rotational speed was kept constant at 50 rpm. The KCl released was calculated by a conductometric method as described in previous papers (10,12,15).

The drug percolation threshold, p_{c1}, has been calculated following the method of Bonny and Leuenberger (5). This drug percolation threshold corresponds to a critical porosity, ε_c, where the pore network, i.e., the initial pores added to the pores filled up by the drug, begins to percolate the whole matrix.

As indicated in the previous section, this method is based on the calculation of the tablet property β. This property is defined as follows:

$$\beta = \frac{b}{\sqrt{2 \cdot A - \varepsilon \cdot C_s}}$$

b being the slope of the Higuchi plot; A, the concentration of the dispersed drug in the tablet; and C_s, the solubility of the drug in the permeating fluid.

Table 1

Weight, Volume, and Theoretical Initial Porosity of the Studied Ternary Tablets

KCl (% w/w)	Weight (mg)	Volume (ml) ± *SE* (n = 10)	Theoretical ε_0 (%) ± *SE* (n = 10)
100	752	0.3886 ± 5.75E-4	2.2 ± 0.14
80	641	0.3914 ± 5.84E-4	2.9 ± 0.14
70	597	0.3907 ± 7.82E-4	2.7 ± 0.14
60	559	0.3897 ± 1.09E-3	2.6 ± 0.28
40	495	0.3894 ± 6.67E-4	2.4 ± 0.17
30	468	0.3886 ± 8.22E-4	2.2 ± 0.21
20	444	0.3872 ± 1.05E-3	1.9 ± 0.27
10	422	0.3889 ± 8.60E-4	2.3 ± 0.22

Above the drug percolation threshold, p_{c1}, and below the excipient percolation threshold, p_{c2}, the b property behaves as:

$$\beta = - C \cdot \varepsilon_c + C \cdot \varepsilon$$

where C represents a constant, ε is the matrix porosity due to the initial tablet porosity and to the drug content after leaching, and ε_c denotes the drug percolation threshold expressed as critical porosity. Plotting β versus ε, the drug percolation threshold can be readily calculated as the point of intersection with the abscissa.

RESULTS AND DISCUSSION

The presence of a disintegrant as PVP-CL at different concentrations exerts a significant influence on the release profile of a tablet. This influence is shown in Fig. 1, where the release profiles of tablets containing 40% w/w of KCl and different amounts of Eudragit RS-PM and PVP-CL are plotted. It may be observed that there is an important difference between the tablets prepared without disintegrant and the rest of the formulations which contain different amounts of this substance. The aim of this work is to study if the presence of this substance exerts an important influence on the value of the drug percolation threshold, i.e., the concentration at which the drug starts to percolate the tablet.

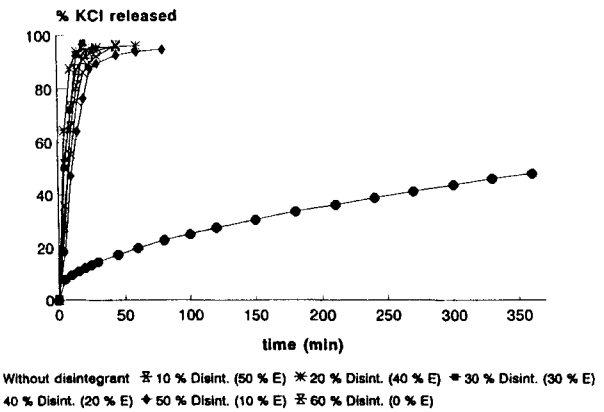

Figure 1.

A previous study (16,17) was conducted on ternary tablets containing KCl as model drug, Eudragit RS-PM as hydrophobic water-insoluble excipient, and polyvinylpyrrolidone cross-link (PVP-CL) as disintegrant (hydrophilic but water insoluble). In this previous study (16,17) using the dissolution efficiency (E_d) values, the drug percolation threshold was estimated in the range 26–31% v/v of total porosity. In the present work, binary KCl/Eudragit RS-PM tablets have been prepared without the disintegrant agent. The drug percolation threshold, p_{c1}, has been calculated in order to study the influence of the disintegrant on p_{c1}.

As indicated in the Introduction section, the binary tablets have been prepared in the same experimental conditions as the ternary tablets previously studied (17). Therefore, different amounts of the mixtures were compressed (see Table 1) in order to obtain approximately the same tablet volume (0.39 cm^3). Furthermore, a high pressure (421 MPa) has been employed in order to obtain tablets with low initial porosities. The height and diameter of these tablets were measured in 10 replicates and their theoretical porosities were found to range between 1.9% and 2.9% (see Table 1). The release profiles of the prepared binary tablets are shown in Fig. 2.

Taking into account that the studied binary tablets are inert matrices, p_{c1} can be calculated following the

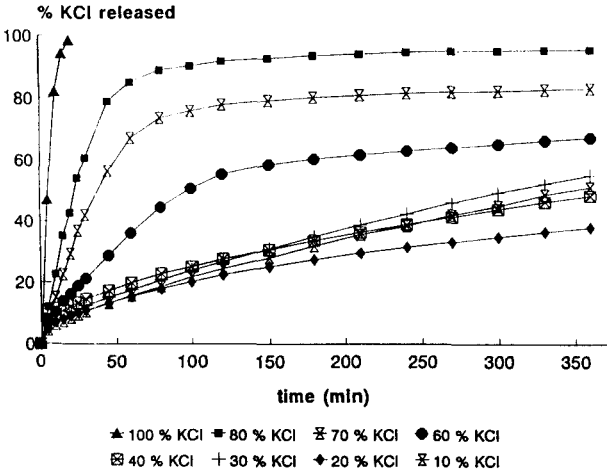

Figure 2.

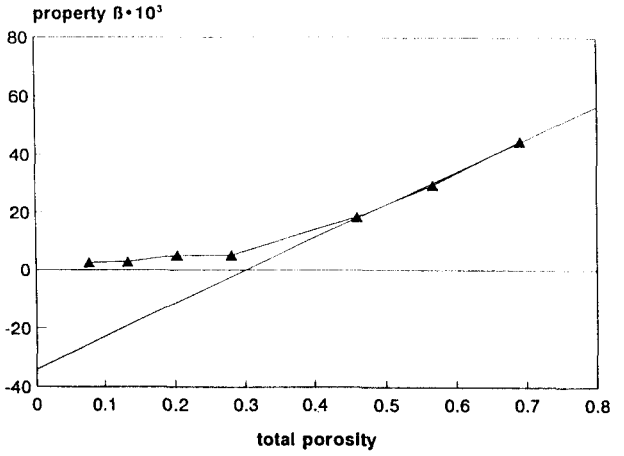

Figure 3.

method of Bonny and Leuenberger (5). This method is, at the moment, the most adequate one for the estimation of the drug percolation threshold in inert matrices. The β property has been calculated according to Eq. (1). Table 2 shows the obtained β values, as well as the parameters involved in their calculations. According to the method of Bonny and Leuenberger, the β property has been plotted as a function of the total porosity of the tablets (see Fig. 3). The drug percolation threshold, p_{c1}, may be estimated from the intercept with the abscissa of the regression line corresponding to the β values of the tablets formulated between the drug percolation threshold, p_{c1}, and the excipient percolation threshold, p_{c2}.

From the release profiles (Fig. 2), it is clear that there is a change in the release behavior between 40% and 60% w/w of KCl loading. On the other hand, none of the studied matrix tablets showed disintegration at any time. This fact indicates the existence of an insoluble excipient infinite cluster, i.e., that these tablets are below the excipient percolation threshold, p_{c2}.

Taking into account these facts, as well as the linear behavior of the β values of the tablets containing 60%, 70%, and 80% of KCl as a function of the total porosity (Fig. 3), it may be assumed that these tablets are situated between p_{c1} and p_{c2}. Therefore, these matrices fulfill the conditions of the method of Bonny and Leuenberger and may be used in order to estimate the drug percolation threshold.

As Fig. 3 shows, the regression line of the β values of the matrices containing 60% to 80% of KCl, gives a value of 30.2 ± 0.76% v/v of total porosity for p_{c1}. This value is included in the drug percolation range (26–31% v/v of total porosity) previously found for the ternary tablets containing PVP-CL as disintegrant. So,

Table 2

β-Property Values and Parameters[a] Involved in Their Calculations

% KCl	ε	$b \pm SE$	r	n	F	Prob.	A	β-10³
80	0.6910	0.07152 ± 4.6E-3	0.9825	9	194.8	<0.0001	1.308	44.48
70	0.5672	0.04010 ± 2.6E-3	0.9838	10	240.4	<0.0001	1.072	29.41
60	0.4607	0.02319 ± 6.8E-4	0.9913	14	682.6	<0.0001	0.865	18.42
40	0.2808	0.00494 ± 5.3E-5	0.9992	17	8809.5	<0.0001	0.507	5.14
30	0.2040	0.00408 ± 1.1E-4	0.9943	18	1379.8	<0.0001	0.361	2.59
20	0.1348	0.00186 ± 1.0E-5	0.9998	17	31163.0	<0.0001	0.229	5.02
10	0.0778	0.00119 ± 3.1E-5	0.9941	20	1510.1	<0.0001	0.108	2.84

[a]ε: total porosity; b: Higuchi constant ($g \cdot s^{-1/2} \cdot cm^{-2}$); r: correlation coefficient; n: number of cases; F: Snedecor ratio; A: concentration of drug dispersed in the tablet ($g \cdot cm^{-3}$); β: tablet property ($g^{1/2} \cdot cm^{-1/2} \cdot s^{-1/2}$)

from the obtained data, it may be concluded that the drug percolation threshold does not undergo an important change due to the presence of the disintegrant.

These facts indicate that the drug percolation threshold behaves as a quite general parameter; i.e., even after adding a disintegrant agent, which causes a very important change in the release profiles of the tablets, the drug percolation threshold shows no significant changes. This result supposes a stimulus for the application of the principles of percolation theory to a great number of pharmaceutical systems containing disintegrant agents, or substances which cause a strong change in its release behavior.

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