International Journal of Pharmaceutics, 96 (1993) 175–181

IJP 03211

Percolation theory: application to the study of the release behaviour from inert matrix systems

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(Received 4 January 1993)
(Accepted 2 February 1993)

Key words: Percolation theory; Cluster; Percolation threshold; Inert matrix; Controlled release

Summary

In the present paper, release profiles obtained from matrix tablets prepared with Eudragit® RS-KCl and a usual eccentric machine were studied. The results were in agreement with previously reported release studies for compacts prepared using a hydraulic press. The most outstanding aspect is the study of the influence of the particle size of drug and excipient on the release behaviour of the matrices, and its evaluation on the basis of percolation theory. The influence of soluble drug loading has also been studied. This new theory has been shown to be a useful tool to explain the release profiles from inert matrix compressed tablets.

Introduction

Modelling of controlled release of a water-soluble drug from matrix systems has been widely investigated. The increased use of drug delivery formulations based on porous or 'channelled' polymeric materials has led to re-evaluation of the existing models, including the Higuchi model, which can be referred to as 'classical theories' (Salomon and Doelker, 1980).

On the other hand, Gurny et al. (1982) described the existence of zero-order release periods using ethylcellulose inert matrix tablets. The presence of these periods was attributed to the saturation of drug into the water filled pores of the matrix. Under these conditions, the dissolution rate becomes slower than the rate of diffusion and determines the release kinetics of the process.

More recently, Potter et al. (1992) observed that drug and excipient particle sizes, as well as the drug loading of tablets, exert a great influence on the release behaviour. Furthermore, these factors have a considerable effect on the time of onset and duration of the zero-order release period.

In all these investigations, the results obtained were interpreted using the above-mentioned classical theories.

Percolation theory, based on the formation of clusters and on the existence of site or bond percolation phenomena, was proposed by Leuen-

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berger et al. (1987, 1990), Leuenberger and Leu (1992), Holman and Leuenberger (1988) and Bonny and Leuenberger (1991) to explain the release process. The probability at which a cluster just percolates a system (a tablet in this case) is termed the percolation threshold. These authors explain the changes in dissolution kinetics of a matrix controlled release system over the whole range of drug loadings and derive a model for readily estimating the values of the percolation thresholds for the diffusion behaviour.

Continuing with our research into this subject (Rabasco et al., 1992), the aims of this work were as follows: firstly, to confirm whether data obtained using potassium chloride-ethylcellulose compacts with a hydraulic press (Gurny et al., 1982; Potter et al., 1992) can be extrapolated to those obtained from potassium chloride-Eudragit® RS tablets prepared on a usual eccentric machine. Secondly, to apply percolation theory in order to determine whether it is useful to explain the release profiles from inert matrices and to compare the proposed interpretations with both percolation theory and the classical theories.

Materials and Methods

Potassium chloride (Acofarma, Tarrasa, Barcelona, Spain) was used as a model water-soluble drug. It was incorporated at different drug contents (Table 1) to ensure that it was present above its solubility in the aqueous pores of the matrix. As matrix-forming material, Eudragit® RS PM (Industrias Sintéticas Curtex, Barcelona, Spain) was used. It is a hydrophobic, non-swelling acrylic polymer. Both compounds were sieved (Retsch, tipo Vibro).

TABLE 1

Tablet formulations

Lot	KCl particle size (μm)	Excipient part. size (μm)	KCl (% w/w)	Excipient (% w/w)
1	125–250	125–250	50	50
2	250–350	125–250	50	50
3	125–250	250–350	50	50
4	250–350	250–350	50	50
5	125–250	125–250	40	60
6	125–250	125–250	60	40
7	125–250	125–250	80	20

The different mixtures were compressed on an eccentric machine (Bonals A-300) without any further excipients. Cylindrical tablets with a weight of 600 mg and a diameter of 10 mm were prepared at the maximum compression force accepted by our formulations.

Dissolution studies were carried out in the USP XXII apparatus (Turu Grau, model D-6) using the rotating disc method so that only one surface of the tablet (0.79 cm^2) was exposed to the dissolution medium (deaerated water at 37 ± 0.5°C). The rotational speed was kept constant at 50 rpm. Release of KCl was detected by the increase in conductance of the dissolution medium using a Crison micro CM-2201 digital conductivity-meter linked to a chart recorder and an IBM-compatible personal computer. The system provides one conductivity datum per s.

Results and Discussion

Effect of potassium chloride and Eudragit® RS particle size on drug release

In order to determine the onset and the end of the zero-order release periods, we have taken into account the linear regression coefficients (r_{xy} must be above 0.999) and the dispersion of the

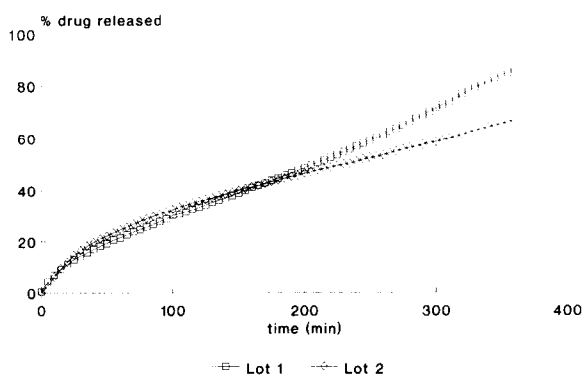

Fig. 1. Percentage of drug released vs time for tablets prepared with different KCl particle sizes and small excipient particle size.

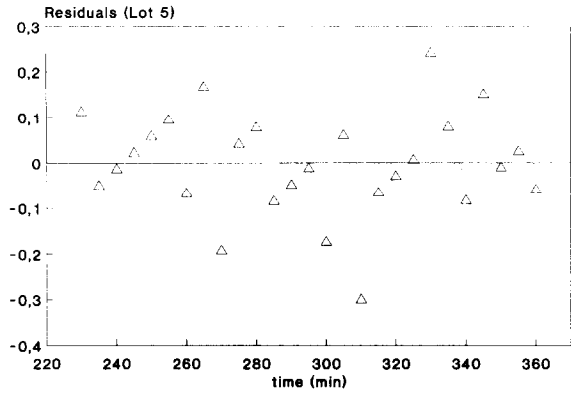

Fig. 2. Residuals obtained from the linear regression between percentual released amount of drug and time for lot 5, from 235 to 360 min.

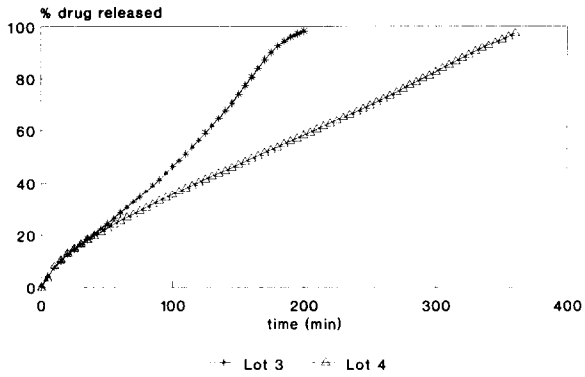

Fig. 3. Percentage of drug released vs time for tablets prepared with different KCl particle sizes and large excipient particle size.

residuals (see Fig. 2). In all the considered periods, the best fit corresponds to zero-order kinetics.

The release profiles corresponding to lots 1–2 are shown in Fig. 1. In Fig. 1, the influence of KCl particle size in tablets made with excipient having a smaller particle size is depicted. Lot 2 contains KCl particles of greater size than lot 1, and shows a linear release profile over an extended period of time (130 min). The end of this zero-order period is determined by the termination of the release studies (360 min). At this point, the tablets were not completely exhausted of drug.

As can be seen in Fig. 1, lot 2 shows a lower zero-order release rate constant than that of lot 1. Furthermore, the time period required to attain zero-order kinetics for this group of tablets was longer than for the first lot, as can be appreciated from the data presented in Table 2.

TABLE 2

Zero-order release parameters

Lot	Onset (min)	End (min)	Rate (% min^{-1})	n	r
1	190	360	0.2378	35	0.9990
2	230	360	0.1310	27	0.9994
3	70	360	0.4855	35	0.9992
4	180	130	0.2470	37	0.9998
5	235	360	0.0720	26	0.9991
6	5	120	0.5622	24	0.9999
7	2	50	2.0345	10	0.9995

Fig. 3 (lots 3–4) shows similar results in comparison with Fig. 1, in relation to the effect of KCl particle size and considering the largest Eudragit® RS particle size. The inclusion of the larger size fraction of KCl (lot 4) also yielded a more extensive zero-order period and a lower zero-order release rate than lot 3.

Fig. 4 (lots 1–4) indicates that the inclusion of the larger size fraction of Eudragit® RS results in an overall increase in drug release rate. This influence is greater with lower particle size of the soluble substance.

The data obtained in our study are consistent with those reported by Potter et al. (1992) using KCl and ethylcellulose as raw materials in compacts (800 mg, 12 mm diameter) prepared by compression at 140 MPa with a 2 s dwell time. This long dwell time was employed by the latter

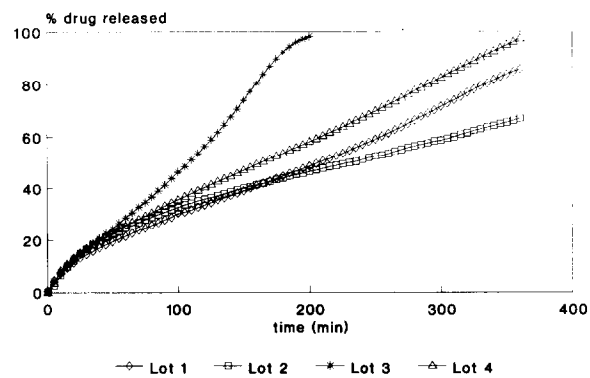

Fig. 4. Release profiles for lots 1–4.

authors to ensure the consistent deformation of the viscoelastic ethylcellulose. In our case, similar results were obtained by employing a direct compression process in an eccentric machine over formulations containing Eudragit® RS as matrix forming insoluble excipient. The only difference is related to the lower release rate constant found in our compressed tablets. This situation can be due to differences in the dimensions between their compacts and our tablets, originating from the greater surface area exposed to the dissolution medium in the compacts prepared by Potter et al. (1992). Therefore, we have found that the behaviour of the release profiles is similar to that reported by Potter et al. (1992).

Classical theories attribute the increase in the release rate achieved by using the smaller particle size of the soluble drug to the faster dissolution rate of this powder fraction. On the other hand, the use of more insoluble excipient particle size results in an increased porosity and a possible decrease in tortuosity exhibited by these matrices (Potter et al., 1992). The principal drawback of these classical theories is related to the use of the tortuosity, i.e., a theoretical parameter, and hence, it cannot be experimentally determined.

On the basis of percolation theory, this kinetic release behaviour can be explained. The use of smaller particle sizes will result in the easier formation of an infinite cluster of this substance. So, the tablets prepared with the insoluble excipient of smaller particle size will contain a more consistent insoluble infinite cluster, which will determine a slow release rate of the soluble drug. As shown in Figs 1 and 3, this is in agreement with the data obtained from both our tablets and the compacts made by Potter et al. (1992).

In the same manner, the use of the smaller particle size of soluble drug (KCl) will produce a more extended infinite cluster of this substance. From a general viewpoint, this would induce a rapid rate of drug release from these matrices. Nevertheless, during the initial stage, for matrices containing drug particles completely coated by excipient particles, different behaviour can be expected. In this type of matrices, the surface area of drug exposed to the medium at each moment can be considered to be the sum of all the sections corresponding to the pores where the drug is being dissolved.

In Fig. 5, a scheme of the sections corresponding to two different matrix systems is represented. In both cases, the surface exposed to the medium is similar when the particles placed on the tablet surface or in the finite clusters connected to this surface are being dissolved.

In matrices containing KCl with the largest particle size (case I), pores with greatest sectional areas should be found. Consequently, solvent access and the diffusion process are facilitated. In

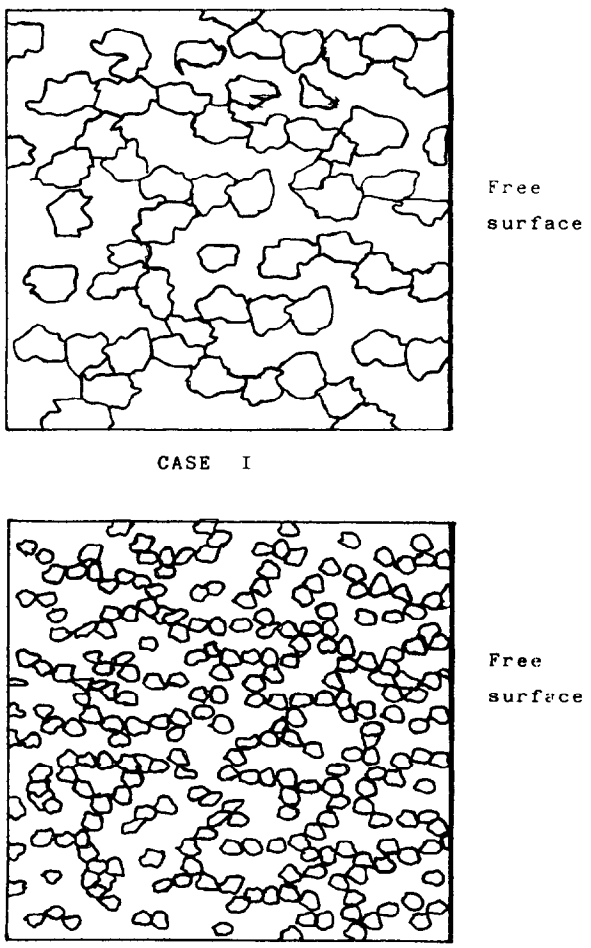

Fig. 5. Schematic section of matrices prepared with two different drug particle sizes. Brittle drug particles are considered to be completely coated by plastic excipient. Initial pores are not represented.

this manner, solvent inside the pores is far from the saturation state, and the situation described by Gurny et al. (1982) does not occur. Because of this, in case I two conclusions can be drawn: (i) the zero-order release profile will not be reached in the first stage; (ii) in the first step, the release rate of drug would be faster in these tablets than those containing KCl of smaller particle size.

On the other hand, in matrices containing KCl of smaller particle size (case II), the reverse of the behaviour during the first stage can be expected; i.e., a slower release rate and a shorter time period to reach zero-order kinetics. These circumstances are due to the fact that pores in these matrices will present a lower sectional area. Hence, saturation conditions in water filling pores should be attained earlier.

In the second stage, for case I, KCl finite clusters connected with the free tablet surface are already exhausted of drug, thus the release rate will decrease. Furthermore, in pores that belong to the infinite cluster, the dissolution of drug continues and the pore length will therefore be increased. Thus, drug concentration into pores begins to reach the saturation conditions needed to attain zero-order release. The zero-order rate constant corresponding to these tablets should be lower than in matrices of case II, since the finite clusters are already exhausted.

The results obtained, corresponding to matrices containing smaller excipient particle sizes (lots 1–2), are consistent with our above explained theory. Data reported by Potter et al. (1992) show that the amount of drug released from compacts prepared with the larger particle size KCl (case I) never surpasses that corresponding to lot 2. Nevertheless, similarly to our experiments, lots containing larger drug particle sizes needed a longer time period to attain zero-order release kinetics.

As shown in Fig. 3, when the larger particle size excipient is used, the amount released from tablets containing the largest drug particles (lot 4) does not greatly exceed that released from lot 3. This can be attributed to the fact that, by using the largest particle size excipient, the above-assumed condition that drug particles are completely coated by excipient particles is not valid. Hence, the smaller KCl particles will always exhibit a higher dissolution rate than the larger drug particles.

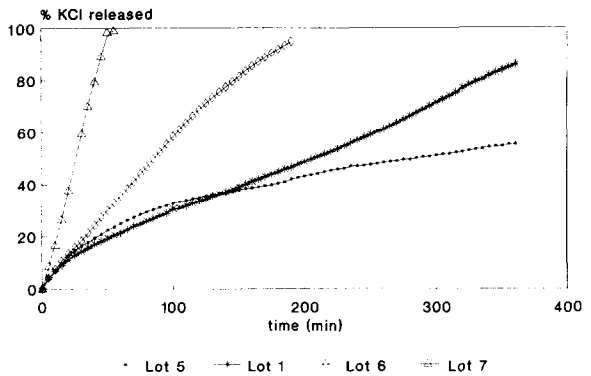

Fig. 6. Percentual drug release profiles for lots 5–7.

Effect of drug loading over release profiles

Figs 6 and 7 show the tablet release profiles expressed as percentual and absolute released amount of drug as a function of time. It is evident that a decrease in KCl concentration in the porous matrix results in a longer time to establish conditions of saturation in the aqueous filled pores. Therefore, the time of onset from zero-order drug release is increased (see Table 2).

Table 2 also shows that the period over which drug is released follows a zero-order kinetic increase at lower initial KCl loading. On the other hand, tablets with the lower initial drug content exhibit a lower percentual zero-order release rate. These results are in agreement with those obtained by Potter et al. (1992) from compacted ethylcellulose matrices.

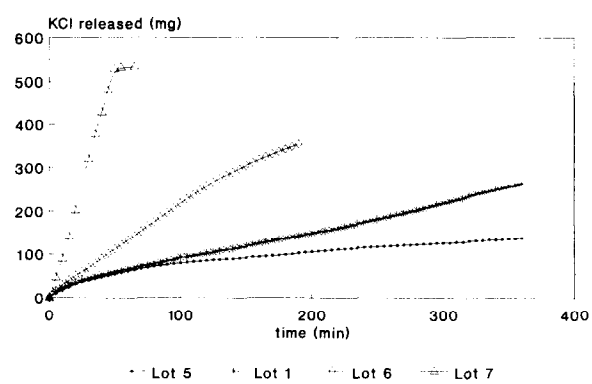

Fig. 7. Amounts of KCl released vs time for lots 5–7.

Classical theories explain the effect of initial drug loading on the duration of the period and on the rate of zero-order release as a reflection of the increase in porosity which will occur as KCl is dissolved (Potter et al., 1992). Percolation theory proposes the existence of three percolating clusters (pores, drug and excipient). Initial drug and excipient clusters can be either finite or span the whole matrix (infinite cluster). The effect of increasing the initial KCl loading of the tablets will be reflected in the formation of a more extensive soluble drug cluster and in a less extensive excipient network. This situation can explain the observed drug release rate, which is faster or slower depending on the drug loading.

With excipient concentrations greater than their percolation threshold, an excipient infinite cluster will be formed. This condition prevents tablet disintegration, although the soluble drug is completely removed by dissolution. Only tablets containing 80% of drug underwent a disintegration process. Therefore, the excipient percolation threshold (denoted as P_{c2}) is situated between 60 and 80% of drug content in this type of matrices. At lower concentrations of KCl, there is a certain drug content (drug percolation threshold, denoted as P_{c1}) below which the drug clusters do not span the whole tablet, remaining as isolated networks. So, part of the drug will be encapsulated by the plastic matrix and release will be incomplete.

On the basis of our experimental data, we believe that all the tablet lots are above the drug percolation threshold (P_{c1}). Data obtained by Potter et al. (1992) suggest the incomplete release from compacts containing low drug loading. This situation can be explained by the fact that the drug percolation threshold is not reached at this low drug concentration. Similar results have been reported by Bonny and Leuenberger (1991) with ethylcellulose inert matrices containing less than 30% soluble drug (caffeine).

In order to confirm this proposed theory, the drug percolation threshold (P_{c1}) was calculated following the method proposed by Bonny and Leuenberger (1991). In the case of a porous matrix, P_{c1} corresponds to a critical porosity, ϵ_c, where the pore network just begins to span the whole matrix. The equations proposed by these authors can be written as:

$$\beta = -C\epsilon_c + C\epsilon$$

where β is a property of the tablet, C represents a constant, ϵ is the matrix porosity due to initial tablet porosity and to drug content after leaching, ϵ_c denotes the critical porosity. β is defined as:

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

where b is the slope of the Higuchi plot, A denotes the concentration of the drug dispersed in the tablet, and C_s is the solubility of the drug in the permeating fluid.

Plotting β vs ϵ, ϵ_c can readily be calculated, giving a slope of C and an intercept of $-C \cdot \epsilon_c$. For the quantitative determination of the lower percolation threshold (P_{c1}) or ϵ_c, the above-men-

TABLE 3

Calculation of the tablet property β

% KCl	ϵ	A	b	r	n	β
40	0.4679	0.5086	7.2660	0.9961	73	8.5344
50	0.5243	0.6772	14.7490	0.9774	73	14.0085
60	0.6036	0.8473	30.7530	0.9842	39	25.9602
80	0.7818	1.2418	75.8306	0.9664	15	52.4054

ϵ, total porosity of matrix; A, concentration of drug dispersed in tablet (g/cm^3); b, slope (g cm^{-2} s$^{-\frac{1}{2}}$); β, tablet property (g$^{\frac{1}{2}}$ cm$^{-\frac{1}{2}}$ s$^{-\frac{1}{2}}$); r, linear regression coefficient; n, number of cases.

Fig. 8. Plot of the tablet property β vs the total porosity ϵ.

tioned equations were used. The results obtained are listed in Table 3.

Fig. 8 shows a plot of β vs ϵ, the point of intersection with the abscissa being ϵ_c. Linear regression analysis yields $\epsilon_c = 0.4180 \pm 0.0097$. This value of the critical porosity corresponds to a KCl content of about 35.5% (w/w). Therefore, these results are in agreement with the above-mentioned theory and confirm that all our prepared tablet lots are above the drug percolation threshold (P_{c1}).

On the basis of these data, the application of percolation theory appears to hold great promise in the study of the release behaviour of controlled release matrices. Further investigations are in progress in order to extend this field.

Acknowledgement

The authors would like to thank Curtex S.A. (L'Hospitalet, Barcelona) for supplying the Eudragit® RS PM and the requested information about this polymer.

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