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Using the Percolation Theory to Explain the Release Behavior from Inert Matrix Systems

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ABSTRACT

A novel analysis of drug release process from binary matrix systems has been realized and a study of the initial stage of the process has been carried out. A fast and easy technique has allowed the acquisition of one experimental datum per second. Release data have been analyzed by means of a detailed statistical study. The dissolution profiles were studied applying different kinetic models (zero order, logarithmic, and Higuchi equation). In all the cases studied, a starting process of zero or first order, indicative of a surface-dependent mechanism, has been found. Then, a parameter, named as critical time of kinetic change (t_c), has enabled the authors to establish the instant at which a diffusion release mechanism, according to Higuchi equation, is consolidated. From this time until the end of the process, release mechanism of matrices was shown to be diffusion controlled. The influence of the drug loading and the particle size over the release properties of tablets has also been investigated and it has been evaluated on the basis of percolation theory. The results show a major significance of particle size over the initial drug release and a decrease of its influence along the time. On the other hand, the drug loading variable shows an important influence over the release properties along the whole process.

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INTRODUCTION

There are several reviews in the literature concerning drug delivery systems from matrix systems (1–4). However, no studies about the onset of the release process have been found. Nevertheless, this subject may be interesting to explain diverse phenomena such as the penetration of the dosage form by the dissolution medium, the diffusional release mechanism, or the initial lag time. The present study has been undertaken in order to acquire new information that allows to control, from the initial stages, the relation between the formulation of a medicament and the active substance release.

In recent years, percolation theory (5), based on the formation of clusters and on the existence of site or bond percolation phenomena, is a new mathematical tool that allows for explanation of the release process (6–8). The probability at which a cluster just percolates a system is termed percolation threshold. Leuenberger et al. (7) explain the changes in dissolution kinetics of a matrix-controlled release system and other technological properties of dosage forms according to this theory.

In previous papers (9–12) we have applied the concepts of percolation theory and percolation thresholds to the study of the release behavior from inert matrix systems. The aims of this work are as follows: first, to propose a new analysis of release data obtained from binary matrix systems in order to provide a more complete knowledge of the release process; second, to study the influence of two formulation factors, drug loading and particle size, over the initial stage of the drug release process, as well as its evolution along the time. In addition, percolation theory has been used to provide an explanation for behavior of these matrix systems.

MATERIALS AND METHODS

Sodium chloride (Acofarma, Tarrasa, Barcelona, Spain) was used as a model water-soluble drug and Eudragit® RS 100 (Industrias Sintéticas Curtex, Barcelona, Spain) was chosen as a matrix-forming material. Both compounds were crushed and sieved (Retsch, type Vibro) and the granulometric fractions of 50–100, 100–150, 150–200, 200–250, and 250–300 μm were selected. The sodium chloride load in the tablets varied from 20% to 80% (w/w). Binary mixtures of sodium chloride and Eudragit® RS 100 were prepared in a V blender for 10 minutes. The different mixtures were compressed on an eccentric machine (Bonals A-300) without any further excipients. Tablets with a weight of 250 mg and a diameter of 9 mm were prepared at the maximum compression force accepted by our formulations.

Dissolution studies were carried out by the USP XXII paddle method (Turu Grau, model D-6). A total of 700 mL of purified water at 37 ± 0.5 °C was employed as dissolution medium. The rotational speed was kept constant at 50 rpm. Release of sodium chloride was detected by an increase in conductance of the dissolution medium, using a digital conductivity-meter (Crison, model micro CM-2201) linked to a chart recorder and an IBM-compatible personal computer. The system provides one conductivity datum per second. For each batch, the drug release from three tablets was measured until complete release under sink conditions.

RESULTS AND DISCUSSION

Study of the Initial Stage

In order to evaluate the initial stage, time intervals from 2 to 2 seconds during the 2 initial minutes, and from 10 to 10 seconds until the end of the study, have been considered. The experimental data obtained during the first 2 minutes have been evaluated according to three kinetic models (zero order, Higuchi equation, and first order). Correlation coefficients and release constants obtained are shown in Table 1. A great similarity between the correlation coefficients corresponding to the three kinetic models is observed. These results indicate that this parameter is not useful to evaluate the drug release mechanism during the first phase of the process.

To resolve this problem, a different evaluation of the release data is provided (9,13,14). Thus, consecutive linear regressions of the amounts of sodium chloride released as a function of time have been realized by increasing progressively the number of data evaluated. The F Snedecor parameter, obtained from the analysis of variance of the studied regressions, has been selected in order to determine the best fit to a specific kinetic model. The results have been defined by means of the highest F Snedecor value. The representation of this parameter versus time, for each of the three studied kinetic models, has enabled the authors to estimate the cutoffs between the obtained profiles as well as to deduce the exact time in which a change in the kinetic type happens. From these cutoffs a parameter, named critical time of kinetic change, t_c, has been defined.

As examples, in Figures 1 and 2 it can be observed that before this time, t_c, the drug is released following a surface-dependent mechanism (zero order and first

Table 1

Evaluation of Dissolution Parameters

Granulometric Fractions	Drug Loading (%)	n	$Q = kt + a$		$Q = k't^{1/2} + a$		$Q = ae^{-k''t}$	
			k	r	k'	r	k''	r
50–100 μm	20	131	0.0089	0.9687	0.9484	0.9993	0.0002	0.9818
	30	120	0.0115	0.9680	1.0447	0.9992	0.0002	0.9811
	40	116	0.0133	0.9872	1.1737	0.9984	0.0003	0.9787
	50	100	0.0394	0.9555	2.0496	0.9971	0.0011	0.9839
	60	99	0.0428	0.9628	2.0885	0.9974	0.0010	0.9636
	70	98	0.0477	0.9665	2.1808	0.9979	0.0013	0.9567
	80	97	0.0521	0.9655	2.2400	0.9985	0.0013	0.9504
100–150 μm	20	116	0.0160	0.9564	1.2762	0.9978	0.0004	0.9982
	30	114	0.0155	0.9594	1.2541	0.9990	0.0004	0.9950
	40	111	0.0173	0.9504	1.3294	0.9976	0.0005	0.9954
	50	105	0.0264	0.9369	1.7476	0.9950	0.0012	0.9827
	60	103	0.0371	0.9201	1.9633	0.9900	0.0018	0.9870
	70	98	0.0559	0.9098	2.6800	0.9848	0.0018	0.9870
	80	94	0.0907	0.9456	3.3651	0.9953	0.0026	0.9959
150–200 μm	20	116	0.0108	0.6979	1.0588	0.8381	0.0002	0.7491
	30	121	0.0098	0.9651	1.0666	0.9834	0.0002	0.9950
	40	122	0.0113	0.9258	1.0919	0.9846	0.0004	0.9898
	50	117	0.0134	0.9439	1.1418	0.9918	0.0004	0.9724
	60	110	0.0194	0.8804	1.5105	0.9707	0.0007	0.9876
	70	96	0.0700	0.8762	3.0322	0.9714	0.0025	0.9907
	80	91	0.1106	0.9507	3.7468	0.9953	0.0040	0.9860
200–250 μm	20	120	0.0133	0.9579	1.1805	0.9957	0.0004	0.9971
	30	115	0.0157	0.9451	1.3093	0.9922	0.0012	0.9846
	40	109	0.0229	0.8577	1.7541	0.9776	0.0009	0.9664
	50	107	0.0254	0.8777	1.8018	0.9656	0.0008	0.9682
	60	100	0.0434	0.9067	2.3345	0.9786	0.0017	0.9817
	70	94	0.0939	0.9839	3.4164	0.9926	0.0031	0.9912
	80	92	0.0989	0.9696	3.4097	0.9957	0.0028	0.9898
250–300 μm	20	130	0.0081	0.9549	0.8540	0.9970	0.0002	0.9949
	30	116	0.0144	0.9017	1.2647	0.9793	0.0004	0.9693
	40	114	0.0162	0.8009	1.4368	0.9956	0.0005	0.9917
	50	102	0.0495	0.9360	2.3258	0.9926	0.0011	0.9884
	60	98	0.0338	0.7893	2.2104	0.9189	0.0026	0.9920
	70	96	0.0762	0.8964	2.3677	0.9733	0.0027	0.9872
	80	90	0.1205	0.9960	4.0845	0.9717	0.0034	0.9650

k = release constant ($mg \cdot s^{-1}$); k' = release constant ($mg \cdot s^{-1/2}$); k'' = release constant (s^{-1}); r = correlation coefficient.

order). After that, the drug is released by a diffusion process. Initially, the fitting to a zero-order process implies a constant surface exposed to the dissolution medium. Nevertheless, it has been shown (15) that this statement is questionable, although the results obtained in dissolution tests are in accordance with the previous assumption. The particles of soluble component on the tablet surface are directly exposed to the dissolution medium and released according to a first-order mechanism.

After the dissolution process some pores are generated in the system because of the release of sodium chloride particles. The progressive formation of pores and their connection favor the generation of channels that allows the release of the remaining sodium chloride by a diffusion process. The exact time in which the

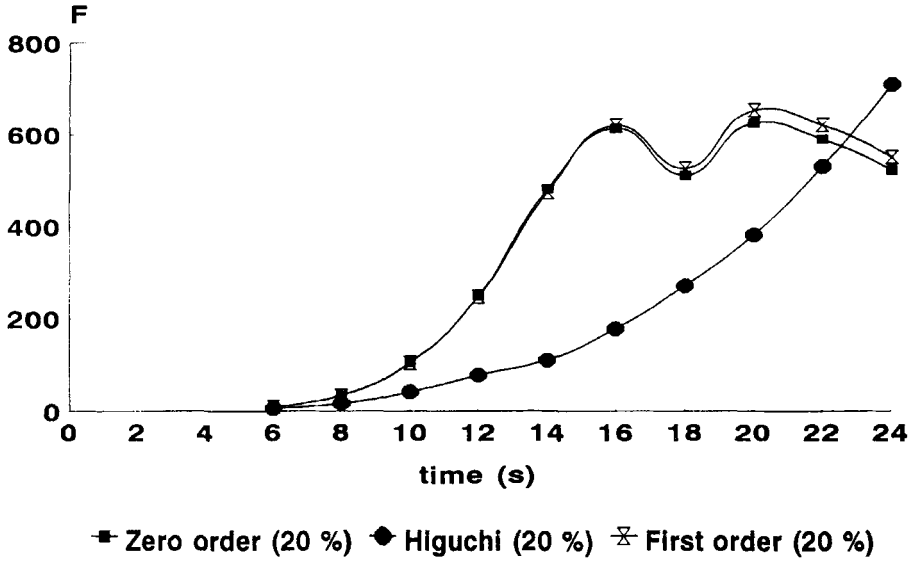

Figure 1. Evolution of *F* Snedecor versus time. Granulometric fraction (50–100 μm).

release mechanism fits to Higuchi equation, t_c, changes as a function of tablet drug loading and the particle size of the soluble component (Table 2).

The results obtained to the ANOVA realized over the release data (Table 3) have shown that the release process during the initial phase is significantly influenced by the two studied variables.

In relation to the influence of drug loading, as an example, the release profiles corresponding to lots elaborated with the granulometric fractions comprised between 250 and 300 μm are shown in Figure 3. In all lots considered, a direct relationship between the percentage of active substance and the release rate is evident: the higher the drug amount in the tablet, the higher the drug amount that is accessible to the medium.

On the other hand, it has been observed (Table 2) that the drug release mechanism changes as a function of this variable (9,13–14). This kinetic release behavior can be explained on the basis of percolation theory. Thus, for low drug loadings, small t_c values have been

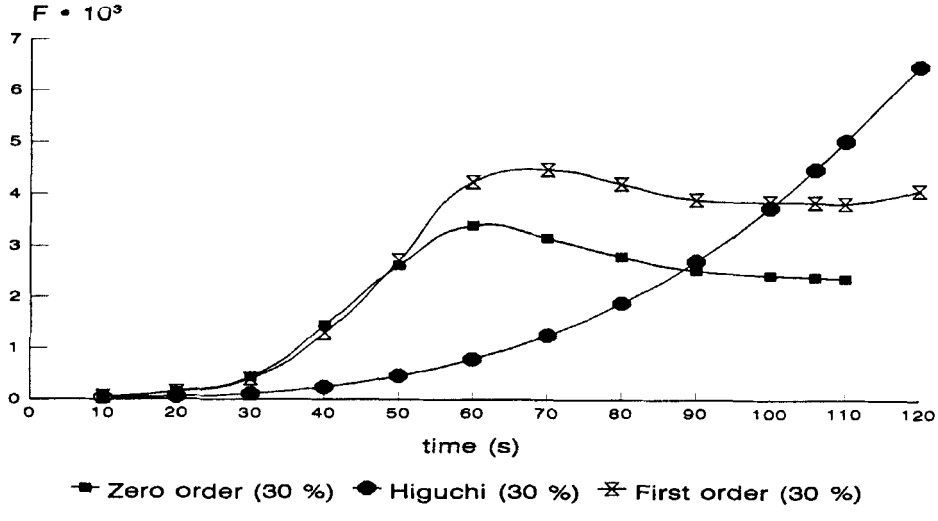

Figure 2. Evolution of *F* Snedecor versus time. Granulometric fraction (200–250 μm).

Table 2

Values of Critical Time of Kinetic Change for the Lots Indicated

Granulometric fractions	Drug content (%)	t_c (s)
50–100 μm	20	23
	30	100
	33	97
	35	95
	40	92
	50	88
	60	72
	70	138
	80	—
100–150 μm	20	40
	30	90
	33	115
	35	117
	40	118
	50	120
	60	130
	70	180
	80	—
150–200 μm	20	60
	30	110
	33	150
	35	185
	40	180
	50	160
	60	140
	70	170
	80	—
200–250 μm	20	88
	30	100
	33	125
	35	145
	40	210
	50	150
	60	140
	70	170
	80	—
250–300 μm	20	112
	30	200
	33	230
	35	250
	40	280
	50	270
	60	—
	70	—
	80	—

found. These tablets show a lower drug amount in surface and the release of this drug by a surface-dependent mechanism lasts a very short time. Consequently, a quick change from first order to Higuchi kinetic happens. Therefore, part of the drug is encapsulated by the Eudragit® RS 100 particles, remaining as isolated networks inside the matrix tablet. When sodium chloride content is increased, t_c values are also higher. However, for drug loadings between 40% and 60% w/w, the change from first order to Higuchi kinetic occurs in a shorter time again, and t_c decreases. This sudden change in t_c value has been related to the presence of the first percolation threshold (16). For these drug/polymer ratios, both components, sodium chloride and polymer, span the tablet in the three dimensions, forming a continuous network of channels that produce the release of drug by a diffusion process.

Finally, matrix tablets prepared with higher drug loading and lower percentage of polymer expose a major surface of drug to the medium and the release of drug by a surface-dependent mechanism lasts more time and, so, the critical time of kinetic change occurs later. The values of t_c increase again (Table 2).

In relation to the effects of the particle size on the release process, we generally found an inverse relationship between both variables (Figures 4–6). The smaller the granulometric fraction, the smaller the release rate. Differences are clearly observed when the lots are assembled in function of the drug loading. Figure 4 shows the release profiles corresponding to tablets with 20% w/w drug loading. The negligible differences observed are due to the very low amount of drug in the tablet and the fast dissolution of sodium chloride. These circumstances mask the influence of the studied variable over the release process. Moreover, as indicated above, in matrix tablets containing a higher amount of inert polymer, a part of the drug is encapsulated by the polymer, remaining as isolated networks inside the tablet.

Between 30% and 60% (w/w) drug loadings (Figure 5), it can be observed that, in general, an increase in particle size implies an increase in release rates. This situation is explained by the dimensions of the pores generated after the dissolution of the particles connected to the tablet surface. These pores are replicas of the sodium chloride particles. Consequently, for tablets elaborated with the smallest particles the penetration of the medium inside the tablet as well as the release of dissolved drug is slower. When formulations with 70% (w/w) of sodium chloride are studied (Figure 6), higher differences between the profiles are observed. The drug is released according to the size of the pores formed

Table 3

Dissolution Efficiency—Multifactorial Analysis

Source	D.F.	Sum of Squares	Mean of Squares	*F*	Prob.
A	6	777.865	129.644	310.644	<0.0001
B	4	570.979	142.745	341.554	<0.0001
AB	24	934.738	38.9474	93.1918	<0.0001
Residual	70	29.2549	0.4179		
Total	104	2312.84			

A = drug loading; B = particle size.

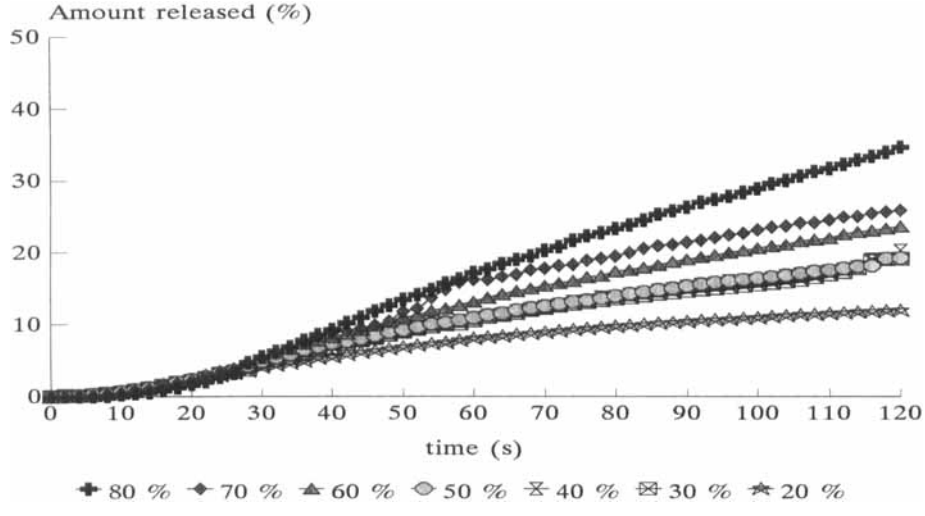

Figure 3. Release profiles of lots elaborated with the granulometric fraction 250–300 μm during the initial stage (120 s).

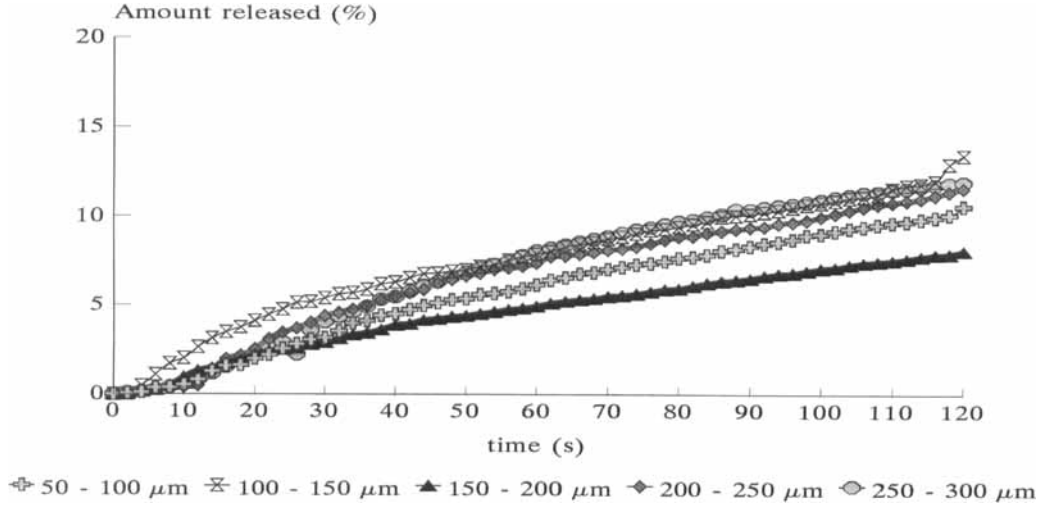

Figure 4. Release profiles of lots elaborated with 20% w/w of drug loading.

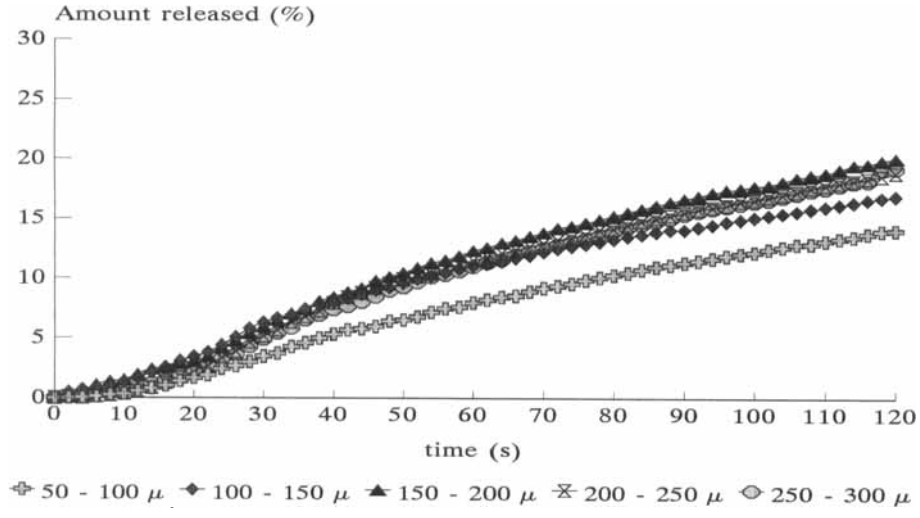

Figure 5. Release profiles of lots elaborated with 50% (w/w) of drug loading.

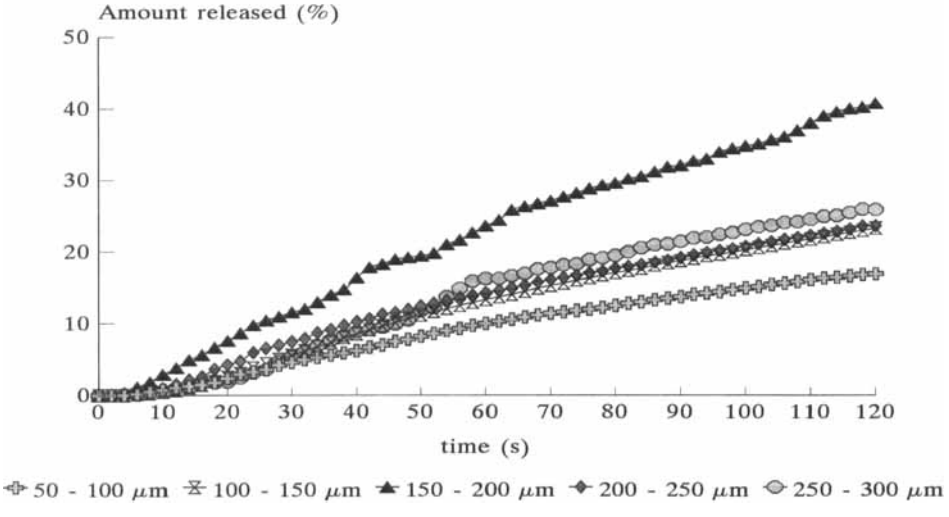

Figure 6. Release profiles of lots elaborated with 70% (w/w) of drug loading.

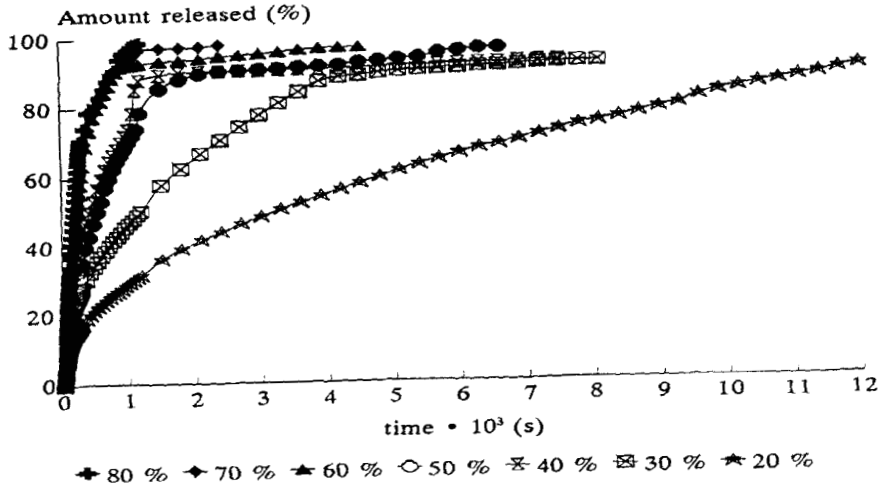

Figure 7. Release profiles of lots elaborated with the granulometic fraction 250–300 μm.

after the dissolution of the particles. Moreover, the high sodium chloride content permits a clear distinction of particle size influence.

Study of the Global Process

The results obtained in a kinetic study of the global release data are compiled in Table 4. In general, the best fit belongs to the Higuchi model. Anyway, the logarithmic equation also shows a good fit of the release data. This fact can be explained since the application of the Higuchi model only is valid until the 80–85% w/w of drug content has been released (17). On the basis of the obtained results, it can be deduced that in the initial stage the release process is governed basically by the drug connected to the surface tablet. Then, the progressive propagation of channels during the process allows the water access into the tablet, and after dissolution the drug is released following a diffusion process.

In order to observe the influence of drug loading and

Table 4

Evaluation of Dissolution Parameters

Granulometric Fractions	Drug Loading (%)	n	$Q = kt + a$		$Q = k't^{1/2} + a$		$Q = ae^{-k''t}$	
			k	r	k'	r	k''	r
50–100 μm	20	131	0.0089	0.9687	0.9484	0.9993	0.0002	0.9818
	30	120	0.0115	0.9680	1.0447	0.9992	0.0002	0.9811
	40	116	0.0133	0.9872	1.1737	0.9984	0.0003	0.9787
	50	100	0.0394	0.9555	2.0496	0.9971	0.0011	0.9839
	60	99	0.0428	0.9628	2.0885	0.9974	0.0010	0.9636
	70	98	0.0477	0.9665	2.1808	0.9979	0.0013	0.9567
	80	97	0.0521	0.9655	2.2400	0.9985	0.0013	0.9504
100–150 μm	20	116	0.0160	0.9564	1.2762	0.9978	0.0004	0.9982
	30	114	0.0155	0.9594	1.2541	0.9990	0.0004	0.9950
	40	111	0.0173	0.9504	1.3294	0.9976	0.0005	0.9954
	50	105	0.0264	0.9369	1.7476	0.9950	0.0012	0.9827
	60	103	0.0371	0.9201	1.9633	0.9900	0.0018	0.9870
	70	98	0.0559	0.9098	2.6800	0.9848	0.0018	0.9870
	80	94	0.0907	0.9456	3.3651	0.9953	0.0026	0.9959
150–200 μm	20	116	0.0108	0.6979	1.0588	0.8381	0.0002	0.7491
	30	121	0.0098	0.9651	1.0666	0.9834	0.0002	0.9950
	40	122	0.0113	0.9258	1.0919	0.9846	0.0004	0.9898
	50	117	0.0134	0.9439	1.1418	0.9918	0.0004	0.9724
	60	110	0.0194	0.8804	1.5105	0.9707	0.0007	0.9876
	70	96	0.0700	0.8762	3.0322	0.9714	0.0025	0.9907
	80	91	0.1106	0.9507	3.7468	0.9953	0.0040	0.9860
200–250 μm	20	120	0.0133	0.9579	1.1805	0.9957	0.0004	0.9971
	30	115	0.0157	0.9451	1.3093	0.9922	0.0012	0.9846
	40	109	0.0229	0.8577	1.7541	0.9776	0.0009	0.9664
	50	107	0.0254	0.8777	1.8018	0.9656	0.0008	0.9682
	60	100	0.0434	0.9067	2.3345	0.9786	0.0017	0.9817
	70	94	0.0939	0.9839	3.4164	0.9926	0.0031	0.9912
	80	92	0.0989	0.9696	3.4097	0.9957	0.0028	0.9898
250–300 μm	20	130	0.0081	0.9549	0.8540	0.9970	0.0002	0.9949
	30	116	0.0144	0.9017	1.2647	0.9793	0.0004	0.9693
	40	114	0.0162	0.8009	1.4368	0.9956	0.0005	0.9917
	50	102	0.0495	0.9360	2.3258	0.9926	0.0011	0.9884
	60	98	0.0338	0.7893	2.2104	0.9189	0.0026	0.9920
	70	96	0.0762	0.8964	2.3677	0.9733	0.0027	0.9872
	80	90	0.1205	0.9960	4.0845	0.9717	0.0034	0.9650

k = release constant ($mg \cdot s^{-1}$); k' = release constant ($mg \cdot s^{-1/2}$); k'' = release constant (s^{-1}); r = correlation coefficient.

Table 5

Dissolution Efficiency—Multifactorial Analysis

Source	D.F.	Sum of Squares	Mean of Squares	*F*	Prob.
A	6	23323.60	3887.270	258.371	<0.0001
B	4	2607.22	651.804	43.3229	<0.0001
AB	24	3140.52	130.855	8.6974	<0.0001
Residual	70	1053.17	150.453		
Total	104	3124.50			

A = drug loading; B = particle size.

particle size over the global release process, a release data ANOVA has been carried out (Table 5). A significant influence of both factors can be observed. Furthermore, an interesting fact has been found: the control of particle size over the global process is not as important as evidenced in the initial phase. However, the drug loading shows a high influence over the release properties along the whole process.

As in the initial phase, a direct relation between drug loading and release rate has been found. For low drug concentrations (20% or 30% w/w sodium chloride) the drug release is incomplete because part of the drug is encapsulated by the matrix substance (7). Tablets elaborated with 80% (w/w) sodium chloride undergo a disintegration process. The percentage of polymer is not suitable to maintain the matrix structure until the end of the release process.

In contrast, a bicoherent system of drug and polymer is formed in the rest of the lots. The dissolution and the release of the soluble component determine the formation of continuous channels that will allow the emptying of the matrix.

CONCLUSION

On the basis of our experimental data we can confirm that the analysis of release provides a more complete knowledge of this process. It supplies information about the release mechanism and allows for an explanation of how the release process is initiated. So this study has proven that the influence of two formulation variables (drug loading and particle size) over the release of drug is different along the process. Furthermore, the percolation concepts explain satisfactorily the results obtained.

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