ELSEVIER

International Journal of Pharmaceutics 130 (1995) 115–119

international journal of pharmaceutics

Fractal and reactive dimension in inert matrix systems

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Received 26 June 1995; revised 16 October 1995; accepted 23 October 1995

Abstract

The aim of this work is to use the fractal geometry to explain the behaviour of inert matrix systems during the release process. First, the Menger sponge with a fractal dimension of 2.727 was chosen as a model of pore-system to characterize the porous body generated by leaching tablets containing a water-insoluble polymer (Eudragit® RS 100) and a model water-soluble drug (ClNa). The fractal dimension, D, of inert matrix systems is calculated by mercury porosimetry. A direct relation between the value of D and the particle size of binary systems has been established. Second, the reactive dimension parameter is considered to determine the effective surface during the release test. The comparison between D and D_R has allowed to illustrate that the release process is governed by two phenomena: roughening and trapping.

Keywords: Fractal geometry; Fractal dimension; Reactive dimension; Inert matrix systems

1. Introduction

Fractal geometry (Mandelbrot, 1984) has emerged recently as an analytical tool which is suitable for the description of complex structures, such as those which are found in most porous objects. The basic approach of fractal analysis is the following: it is possible to describe quantitatively the complex geometry of an object if this object is symmetric to transformations of scale. By this one means that the same type of geometry features are seen either at different magnifications or by probes of various sizes; or more generally, a power law scaling relation characterizes one or more of the properties of an object or a process:

$$\text{property} \propto \text{scale}^D$$

where D is the fractal dimension of the surface for which the property is relevant. So, relevant examples for 'property' are the shape of the pore size distribution curve, the surface area or the rate of an heterogeneous reaction (Farin and Avnir, 1988). The scale or yardstick would be pore diameter, cross sectional area of an adsorbent, or particle size. The exponent D indicates how sensitive the property of a system is to change in scale.

Mandelbrot's original definition of a pure fractal object suggests that a fractal is a shape made

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SSDI 0378-5173(95)04366-*H*

of parts similar to the whole in some way (self-similar). In general, fractals are disordered systems whose disorder can be described in terms of non-integer dimension (Pfeifer and Obert, 1989). This fact suggests that the system with classical dimensions, 1, 2, 3 are degenerated and that this degeneracy is defined in non-integral dimension.

The pore system can be considered as an ideal fractal only when the geometry, i.e., the pore size distribution is similar for all magnifications. In this case the internal surface of the pores tends to infinity, whereas the volume of the material is finite (Usteri et al., 1990). The Menger sponge represents an ideal fractal with a dimension, $D = 2.727$ (Mandelbrot, 1984). This pore structure is generated from an initial cube by taking out (coring) the middle thirds, where 'third' is a linear measure, 1/3 of an edge length. The resulting inside construct, that is, the pore structure of the original cube, is depicted in Fig. 1(A). It consists of 6 cubic shoe boxes of total inside area $6 \cdot 4 \cdot (1/3)^2 = 8/3$. Fig. 1(B) shows the object obtained after four iterations, Menger sponge. Continuing 'forever' would yield a construct with infinite inside surface area and zero mass (Rothschild, 1991).

The Menger sponge is generated by continual and successive coring operations, interior and connected surface area is created to such a degree, with even more of the same features on an even smaller scale, that surface nearly fills the volume of the body.

The count of replica of area $(1/3)^{2k}$ and side length $r_k = (1/3)^k$ that are needed to cover the total inside area of the kth construction requires a number of $N(r_k) = \text{const.}\ r_k^{-D}$, where D is given by log 20/log 3.

The parameter D reflects the morphology of the particle surface and pores structure but its surface need not coincide with the reactive surface which participates actively in the dissolution process (Farin and Avnir, 1987). Analogously, the course of a reaction or process in an outcome of a complex interplay between details of the reaction medium and the surface active of the material. The fractal geometry describes the surface which participates actively in a process through the parameter reactive dimension, D_R.

The method generally used to determine D_R is based on the Wenzel law (Kopelman, 1989). We found that $v \propto R^{DR-3}$, where v is the reaction rate, indeed describes the activity of many heterogeneous reactions such as reactive dissolution, changes in surface chemical composition and thermal decompositions. The relationship between D and D_R is dictated by various effects such as the screening effect that an outer region of a porous particle has on inner regions, trapping of molecules in micropores, changes in morphology during the course of a reaction, and chemical selectivity (Farin and Avnir, 1987, 1988).

In previous papers, (Fernández-Hervás et al., 1994; Holgado et al., 1995) we had used the fractal geometry in the characterization of solid drugs. The aim of this work is to offer an extension of the concept of fractal and reactive dimension applied to the behaviour of inert matrix systems during the release test. In addition, from a review of the literature, no applications of the reactive dimension parameter, to dosage form has been found.

2. Materials and methods

2.1. Materials

Sodium chloride (Acofarma, Tarrasa, Barcelona, Spain) was used as a model water-soluble drug and Eudragit® RS 100 (Industrias Sintéticas Curtex, Barcelona, Spain) has been chosen as the material forming matrices.

2.2. Elaboration of tablets

Both compounds were sieved (Retsch, type Vibro) and the granulometric fractions which comprised between 50–100, 100–150, 150–200, 200–250 and 250–300 μm, were selected. The sodium chloride load in the tablets was 50% (w/w). Binary mixtures of sodium chloride and Eudragit® RS 100 were prepared in a V blender during 10 min. The mixtures were compressed on a 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.

2.3. Dissolution tests

Dissolution studies were carried out using the USP XXIII paddle method (Turu Grau, model D-6). 700 ml of purified water at 37 ± 0.5°C was employed as the dissolution medium. The rotational speed was kept constant at 50 rpm. Release of sodium chloride was detected by the 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.

2.4. Fractal analysis

After dissolution testing, the tablets were air-dried at room temperature. The determination of the pore radio and specific cumulative surface area was performed by mercury porosimetry (Fison Instruments, mod-400). The maximum applied intrusion pressure was of 4000 bars. The fractal dimension was calculated from the slope of the Richardson plot (ln of specific cumulative surface area vs ln of pore radio).

To calculate the reactive dimension, each batch was subjected to a dissolution assay. Once the release profiles had been obtained, the amodelistic parameter cession efficiency (EC) was then calculated. The reactive dimension was obtained from the slope of the plot of ln EC vs ln size particle.

3. Results and discussion

Preliminary studies have revealed that in lots of tablets with a charge of 50% w/w both components of the matrix system form infinite network (Fernández-Hervás, 1994). Plotting the accumulative specific surface vs pore radio of a tablet on a double logarithmic diagram, we get a straight line (Fig. 2). The fractal dimensions are calculated from the slope of Richardson plot as show in Table 1, it can be observed that D, acquired a non-integer value different the topological dimension 3. It is possible to affirm that progressive release of sodium chloride generates a porous network. After dissolution tests a porous body is formed and this system presents fractal nature.

The fractal dimension of the leached tablets ranges between 2.50 and 2.36 depending on the particle size of sodium chloride. So, the influence of the drug particle in the structure of the pore system is evident and this phenomenon has been reflected in the values of D. A direct relation between D and the particle size has been found (Fig. 3).

On the other hand, the fractal geometry describes the surface which participates actively in a reaction through the parameter reactive dimension, D_R. In order to visualize the relationship between D and the release process, the parameter D_R is determined. As indicated above, to calculate D_R different granulometric fractions were selected (Fig. 4). In matrix systems elaborated the active component corresponds to the soluble particle. During the release process the particles of sodium chloride are progressively dissolved, thus the amount of particles in the matrix tablet decreases. This phenomenon is reflected in a decrease in the reactive dimension data with time (Table 2). Consequently, D_R was calculated at predetermined time periods. In relation to these results, it is possible to affirm that at the initial process the higher value of D_R is indicative of a higher surface reactive exposed to the dissolution medium. During the test, the release of the drug produces a decrease in the active surface and the value of D_R also decreases.

Table 1
Fractal dimensions (D) of matrices elaborated with different-granulometric fractions after dissolution tests

Granulometric fraction	$D \pm$ S.E
50–100 μm	2.43 ± 0.08
100–150 μm	2.50 ± 0.04
150–200 μm	2.36 ± 0.10
200–250 μm	2.37 ± 0.09
250–300 μm	2.36 ± 0.09

Table 2
D_R values for lots elaborated with 50% (w/w) drug loading

Time (s)	$D_R \pm$ S.E
120	3.24 ± 0.12
300	3.21 ± 0.08
600	3.24 ± 0.07
900	3.19 ± 0.05
1200	3.24 ± 0.05
2400	3.11 ± 0.10
3600	3.06 ± 0.08
4800	3.06 ± 0.08
6000	3.04 ± 0.06
6600	3.03 ± 0.05
7200	3.02 ± 0.05
7800	3.03 ± 0.04
8400	3.02 ± 0.04

On the other hand, at all periods of time, the value of D_R is higher than the value of D. With respect to this relation, $D_R > D$, Farin and Avnir (1987) suggest that the phenomenon can be governed by either roughening or trapping effects. In the first case, the morphology of the surface may change during the dissolution process. In the second, reactive molecules may be trapped in cracks and narrow pores. In our case, two phenomena simultaneously govern the release process. During the test the active surface exposed to the dissolution medium changes due to the release of drug. This behaviour has been reflected in the variable values of D_R obtained (Table 2). It is possible to affirm that the release behaviour of inert matrix systems elaborated can be related to roughening phenomena because the reaction surface offered to the dissolution medium changes in magnitude, D_R, and in morphology.

Simultaneously, along the process, the dissolution medium may be trapped in the pores generated after the release of drug, finding it difficult to exit. In this porous system the reactive medium will have sufficient time to probe the surface irregularity of these traps. According to Farin and Avnir (1987) it can be observed that the surface of this porous network is rougher than the surface.

To investigate the usefulness of D_R to estimate quantitatively the effective surface exposed to the reactive medium, the concept of D_R is applied to different lots elaborated with a charge of 20 and 70% of sodium chloride.

In Table 3 the values of D_R corresponding to the lots elaborated with the minor mixing ratio (20% w/w) are depicted. In this case, it is possible to observe that the values of D_R obtained are very low, it is indicative of the low reactivity of the matrix system studied. In these lots we found by below the first percolation threshold, the sodium chloride forms a finite network, only the particles connected to the surface are dissolved. Therefore, the great amount of inert polymer can cover part of drug, thus the accessibility of the dissolution medium is hampered and the reactivity decreases. In this case, D_R yields quickly to constant values; this fact is indicative of a slow release process.

By the contrary, in lots elaborated with a 70% w/w sodium chloride, D_R acquires an elevated value (Table 4). This fact is due to the great amount of reactive surface exposed to the dissolution medium. It might be expected that the reactivity is favoured and the release process is very fast. Analogously, to the other lots studied, it is possible to observe, in Table 4, that the values of D_R decrease progressively with time.

Table 3
D_R values for lots elaborated with 20% (w/w) drug loading

Time (s)	$D^R \pm$ S.E
120	3.16 ± 0.22
300	3.14 ± 0.84
600	3.09 ± 0.24
900	3.02 ± 0.29
1200	3.14 ± 0.41
2400	3.02 ± 0.01
3600	3.06 ± 0.20
4800	3.03 ± 0.22
6000	3.00 ± 0.20
6600	3.00 ± 0.19
7200	3.01 ± 0.20
7800	3.02 ± 0.21
8400	3.00 ± 0.20
9000	3.01 ± 0.19
9600	3.02 ± 0.17
10 200	3.01 ± 0.16
10 800	3.00 ± 0.17
11 400	3.00 ± 0.16
12 000	3.00 ± 0.16

Table 4
D_R values for lots elaborated with 70% (w/w) drug loading

Time (s)	$D_R \pm$ S.E.
120	3.34 ± 0.28
300	3.42 ± 0.21
600	3.51 ± 0.17
900	3.42 ± 0.14
1200	3.42 ± 0.11
2400	3.26 ± 0.06
3600	3.20 ± 0.05
4800	3.11 ± 0.05
6000	3.08 ± 0.02
6600	3.08 ± 0.09

In view of these results an important conclusion made is that the fractal and reactive dimensions constitute two new tools to characterize a porous body.

Therefore, the reactive dimension allows quantitative knowledge of the active surface exposed in an inert matrix system during the release process. We found that $D_R > D$; this result suggests that two phenomena govern the release process: trapping and roughening.

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