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Use of fractal dimensions in the study of excipients: application to the characterization of modified lactoses

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Abstract

In this paper, the morphological and surface characteristics of lactose and coated lactose particles are investigated, continuing with the use of SEM descriptors and fractal dimensions to characterize powder particles. The coating materials were different acrylic polymers of the Eudragit® type. The size parameters of lactose and coated lactoses indicated that the particle forms deviated from irregular or acicular forms. Shape factor data of coated substances obtained demonstrated that these particles presented regular contours. This fact signifies that lactose particles without coating treatment present irregular profiles with patent edges implying poor flow properties. The aspect ratio values of coated lactoses were close to unity and smaller than that showed by lactose. It is concluded that the polymer particles are placed on the irregularities of lactose particles, smoothing the roughness of the excipient surface. The fractal dimensions calculated from the slope of Richardson plots were 1.11 for lactose and 1.04, 1.05 and 1.08 for coated lactoses. These results are consistent with the shape parameters and flow properties. Some interesting relationships between SEM descriptors and a number of rheological properties have been found.

Keywords: Lactose; Coated lactose; Size and shape descriptors; Surface geometry; Fractal dimension; Flow properties

1. Introduction

The behaviour of bulk solids is clearly influenced by the shape and surface characteristics of the particles integrating the powder. Several operations in pharmaceutical technology, such as pulverization, screening, granulation and/or drying, are also strongly influenced by the morphological structure of the solids components (Thibert et al., 1988). The effects of morphological particle features on the flow properties of materials, packing of powders and biopharmaceutical characteristics of the formulations elaborated are widely known (Romero and Rhodes, 1991).

In previous investigations (Fernández-Arévalo, 1989; Fernández-Arévalo et al., 1990), we have described the rheological properties of lactose coated with different acrylic resins. Lactose, a common excipient used for oral solid pharmaceutical forms due to low cost and appropriate physicochemical characteristics, has unfavorable

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technological properties defined by its rheology. With this coating process, the rheological properties of these powders were substantially improved.

On the other hand, fractal geometry is a mathematical tool used to describe the surface morphology and the degree of surface irregularity of a particle (Mandelbrot, 1984; Graf, 1991). The fractal concept of Mandelbrot describes the surface of particles in terms of 'fractal surface', with a characteristic parameter referred to as the fractal dimension (D). Fractal analysis relies on the fact that the perimeter of a silhouette edge is dependent on the step length with which we measure it. Thus, the smaller the step length is, the larger is the perimeter measured, since more details of the structure are taken into account. Therefore, the fractal dimension of particle contours is used to characterize the surface roughness. This relationship is given by Mandelbrot's classical expression:

$$L_\delta = k \cdot \delta^{1-D}$$

where D is defined as the fractal dimension, δ denotes the step length and L_δ is the perimeter estimated with step length δ. An ideal fractal structure should produce a linear plot at all resolutions, when $\ln L_\delta$ is plotted against $\ln \delta$. The slope of this straight line is S, where $S = 1 - D$. D is the fractal dimension and represents the degree of irregularity of the particle surface. The more irregular and wiggly a substance is, the greater is the value of D (Farin and Avnir, 1987).

In this study, a scanning electron microscope connected to an image processor was used to obtain, automatically, a wide variety of parameters describing the shape and granulometric characteristics of the powder particles. This method offers numerous advantages over other methods (optical microscopy): automatic and more accurate measurements, saving of great amount of time and yielding more reliable conclusions from the results with a smaller number of observations (Paraira et al., 1994).

Consequently, the main purpose of this work was to describe the morphological characteristics of lactose and coated lactose with 6% of different types of Eudragit® using fractal analysis and to find a correlation between the fractal dimensions (D), shape parameters obtained by scanning electron microscopy and rheological properties, flow and packing properties, of all these products.

According to our search of the bibliography, only a few applications of fractal geometry to the study of excipients have been found (Bergeron et al., 1986; Thibert et al., 1988; Cartilier and Tawashi, 1993). For this reason, we consider it particularly interesting to characterize solid drugs based on the analysis of individual particles and quantifying the particle shape due to the need of the pharmaceutical industry to find methods for the rapid characterization and validation of solid drugs, especially when high-speed automated production chains are used (Bergeron et al., 1986; Ramadan and Tawashi, 1991). Recently, our research group has successfully applied fractal analysis to characterization of the particle morphology of diclofenac hydroxyethylpyrrolidine (Fernández-Hervás et al., 1994).

2. Experimental

2.1. Materials

The following were obtained from the indicated sources. Core material: lactose (Acofarma, Tarrasa, Barcelona, Spain); suspension medium: alcohol 96° (PQS, Sevilla, Spain) and purified water; coating material: acrylic polymers type Eudragit® E 12.5%, L 12.5% and S 12.5% (Curtex, Industrias Sintéticas S.A., L'Hospitalet, Barcelona, Spain) to prepare the coated substances (lactose E, L and S).

The coating process and the rheological tests assayed have been previously reported (Fernández-Arévalo et al., 1990).

2.2. Image processing system

The shape and size of salt particles were examined using a scanning electron microscope (Philips, XL30). A very thin coat of carbon was applied to each sample, which was examined at different magnifications and some micrographs were taken of each sample. Size and shape parameters of the solids was determined using an

Table 1
Parameters obtained by using SEM contour analysis and fractal analysis techniques

Technique	Characteristic	Parameter	Symbol
SEM	size	maximum diameter	D_{max}
contour		minimum diameter	D_{min}
analysis		area	A
		perimeter	P
		equivalent circle diameter	ECD
	shape	shape factor	S
		maximum horizontal distance	X_{max}
		maximum vertical distance	Y_{max}
		aspect ratio	a
		projection X	Proj X
		projection Y	Proj Y
Fractal	surface	fractal dimension	D
analysis	geometry		

image analysis system connected to the microscope mentioned above. They are obtained, automatically, using a special computer program. This experimental method has been previously reported (Fernández-Hervás et al., 1994).

Table 1 lists the information obtained in terms of size (maximum and minimum diameters, area, perimeter and equivalent circle diameter) and shape parameters (shape factor, maximum horizontal distance, maximum vertical distance, aspect ratio, projection in the horizontal direction and projection in the vertical direction) that describe the micromorphology of isolated particles.

2.3. Equivalent circle diameter (ECD)

This parameter is the diameter of the circle that has an area equal to that of the particle.

$$ECD = 2 \cdot \sqrt{(\text{area}/\pi)}$$

2.4. Shape factor

This factor provides information about the elongation of the particle. For a circular particle,

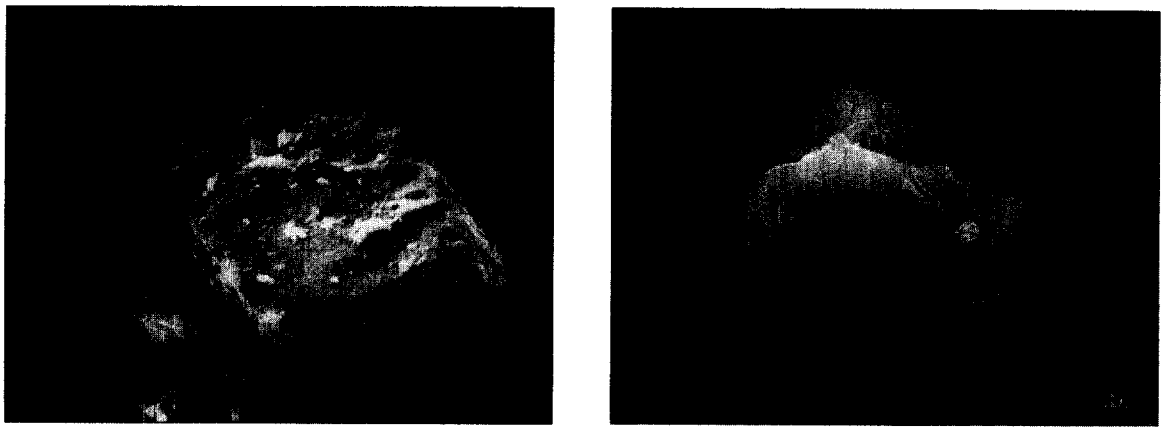

Fig. 1. Scanning electron micrographs of: (a) lactose; (b) modified lactose with Eudragit® E.

Table 2
Size parameters and shape descriptors of particles of the indicated products (mean values, standard deviations and standard errors; $n = 20$)

Parameters	Lactose			Lactose E			Lactose L			Lactose S		
	Mean	SD	e	Mean	SD	e	Mean	SD	e	Mean	SD	e
A (μm^2)	22609.44	11660.04	2606.36	16785.00	7257.3	1622.79	83588.75	42804.25	9571.31	49562.01	16225.20	3628.07
P (μm)	983.06	214.69	48.01	982.35	221.64	49.56	1046.38	358.73	80.21	935.2	159.20	35.60
ECD (μm)	221.28	58.02	12.97	247.92	52.89	11.82	249.81	65.81	14.71	247.72	42.78	9.57
D_{max} (μm)	306.38	70.03	15.66	333.15	66.60	14.88	335.27	100.75	22.53	320.78	61.00	13.64
D_{min} (μm)	210.64	60.77	13.59	234.33	64.77	14.49	231.56	65.97	14.75	231.43	42.11	9.42
X_{Max} (μm)	243.05	73.98	16.54	269.46	77.97	17.43	252.21	74.18	16.59	248.15	64.52	14.43
Y_{Max} (μm)	227.84	80.39	17.97	257.52	62.1	13.89	262.09	94.81	21.20	266.25	48.66	10.88
a	1.14	0.34	0.07	1.09	1.17	0.27	1.03	0.20	0.04	0.95	0.28	0.06
Proj X (μm)	263.09	73.54	16.44	285.00	80.22	17.94	276.34	85.03	19.01	269.29	70.22	15.70
Proj Y (μm)	254.79	72.89	16.30	275.82	65.28	14.61	289.41	99.11	22.16	280.34	51.70	11.56
S	0.52	0.19	0.04	0.64	0.38	0.09	0.61	0.09	0.02	0.69	0.06	0.01

the shape factor is 1; for all other particles, the shape factor is smaller than 1.

$$\text{shape factor} = 4\pi\left[\text{area}/(\text{perimeter})^2\right]$$

2.5. Maximum horizontal and vertical distances

These refer to the maximum horizontal and vertical distances between two points on the boundary of the particle on horizontal and vertical lines, respectively.

2.6. Aspect ratio

The aspect ratio is the ratio of the horizontal maximum and the vertical maximum distance of the particle. For a round or a square particle, the aspect ratio is unity. For those elongated in the X-direction the ratio is larger than one. Particles elongated in the Y-direction have an aspect ratio smaller than unity.

2.7. Projections in the horizontal and vertical direction

These are the maximum distances (the range) of all boundary points projected onto the X- and Y-axes, respectively.

2.8. Fractal analysis

The fractal dimension of a particle was calculated from the slope of the Richardson plot (ln of perimeter length vs ln of step length) as indicated above (Thibert et al., 1988; Ramadan and Tawashi, 1991).

Table 3
Flow and packing parameters of the indicated products (mean values, standard deviations and standard errors; $n = 10$)

Parameters	Lactose			Lactose E			Lactose L			Lactose S		
	Mean	SD	e	Mean	SD	e	Mean	SD	e	Mean	SD	e
Flow rate (g/s)	19.57	0.98	0.31	23.33	1.44	0.45	24.88	2.32	0.73	23.61	1.47	0.46
Angle of repose (°)	41.04	0.65	0.20	29.74	0.89	0.28	31.55	0.94	0.30	33.21	0.27	0.09
Bulk density (g/cm^3)	0.64	0.01	0.01	0.62	0.002	0.001	0.63	0.003	0.001	0.61	0.002	0.001
Tapped density (g/cm^3)	0.94	0.004	0.001	0.69	0.004	0.001	0.70	0.002	0.001	0.66	0.002	0.001
Haussner index	1.46	0.04	0.01	1.13	0.03	0.01	1.11	0.01	0.002	1.10	0.04	0.01
Percentage of compressibility	31.48	1.71	0.54	10.10	0.30	0.10	10.07	0.63	0.20	8.94	0.37	0.12

3. Results and discussion

3.1. Morphological analysis of lactose. Rheological properties

As an example, Fig. 1 shows the SEM micrographs illustrating the shape and surface of lactose (Fig. 1a) and modified lactose with Eudragit® E (Fig. 1b).

To determine the size and shape characteristics and fractal dimension of lactose and coated lactose, the 150–400 μm sieve fraction was used. The assays were carried out employing 20 isolated particles.

The size characteristics and shape descriptors of the samples are specified in Table 2. Table 3 lists the flow properties of the products showing that all rheological properties of the coated excipients have been improved by using the coating technique.

In relation with size parameters, no great differences between lactose and coated lactoses are evident. This fact is reflected in the same relation maintained by the parameters D_{max} and D_{min}: 1.45, 1.42, 1.45 and 1.39 for lactose, lactose E, lactose L and lactose S, respectively. These are the most representative parameters of the physical reality of the particles (Paraira et al., 1994), the values obtained indicating a deviation from irregular or acicular forms of particles.

Considering the shape parameters, it is interesting to emphasize the shape factor (S) and aspect ratio (a) data obtained for coated substances. The shape factor parameter is used to measure object complexity, namely, contour complexity (Ramadan and Tawashi, 1991). The S data obtained yielded similar values and smaller than unity, suggesting that the particles of coated products, although not being completely circular particles, have regular contours. On the other hand, the values of this parameter for coated products are larger than that reached by lactose and more pronounced differences are observed. This circumstance signifies that lactose particles without coating treatment would present irregular profiles with patent edges implying poor flow properties (see Table 3).

On the other hand, the aspect ratio values of the coated samples are close to unity and less than that shown by lactose, indicating the rounding of lactose particle edges by the application of the polymer coating. The small particles of Eudragit® are placed on the irregularities and interstices of lactose particles, smoothing the roughness of the excipient surface. This situation is consistent with the rheology parameters obtained for these products (see Table 3).

Therefore, it can be concluded that the application of the coating process on lactose particles modifies the particle surface by depositing the Eudragit® particles on hollows and irregularities of the excipient surface (see Fig. 1). This phenomenon has been demonstrated by the values of the shape parameters obtained from SEM image analysis.

3.2. Fractal contour analysis

The fractal dimensions calculated from the slope of Richardson plots were 1.11, 1.04, 1.05 and 1.08 for lactose, lactose E, L and S, respectively (see Fig. 2). Table 4 shows the regression values obtained for Richardson plots of lactose and the modified lactoses. To calculate the fractal dimension of the surface (D_s), the approximation proposed by Farin and Avnir (1992) is used.

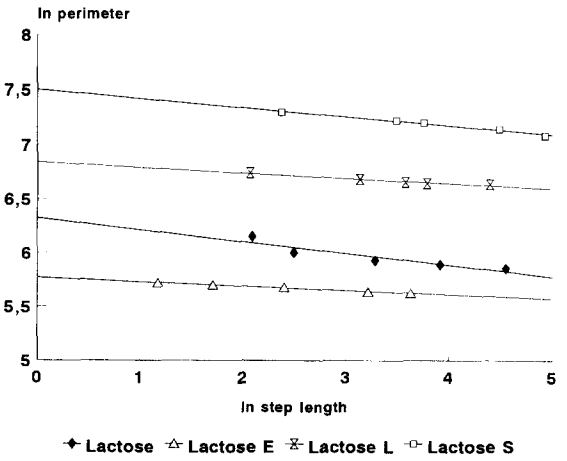

Fig. 2. Richardson plot of lactose and modified lactoses.

Table 4
Regression values obtained for Richardson plots (standard errors in parentheses)

Product	n	Slope	Constant term	r_{xy}	F	P
Lactose	5	−0.1099 (0.025)	6.324 (0.051)	0.9284	18.725	0.0228
Lactose E	5	−0.0398 (0.002)	5.769 (0.004)	0.9956	339.793	0.0003
Lactose L	5	−0.0497 (0.007)	6.842 (0.012)	0.9719	51.074	0.0056
Lactose S	5	−0.0817 (0.006)	7.500 (0.012)	0.9919	183.956	0.0009

In this case, $D_s = D_1 + 1$ and then D_s would yield values of 2.11, 2.04, 2.05 and 2.08. The degree of irregularity is now given by D_s, the results obtained for coated samples indicating small rugged and smooth particles, as D_s is situated between 2 and 3. In relation to this concept, Farin and Avnir (1989) report that $D_s \approx 2$ refers to the classical assumption of smooth and flat areas of the particles.

All these results are in agreement with the shape parameters and flow properties indicated above. Some interesting relationships have been found between some of these parameters tested. As an example, Fig. 3 shows the direct and inverse relationships found between fractal dimension (D) and angle of repose and flow rate, respectively.

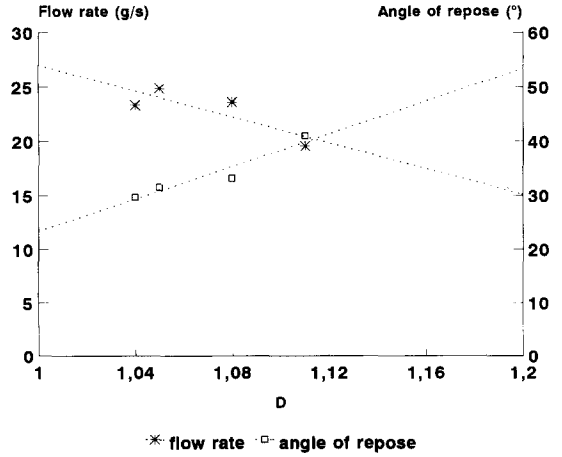

Fig. 3. Relationships between D, flow rate and angle of repose.

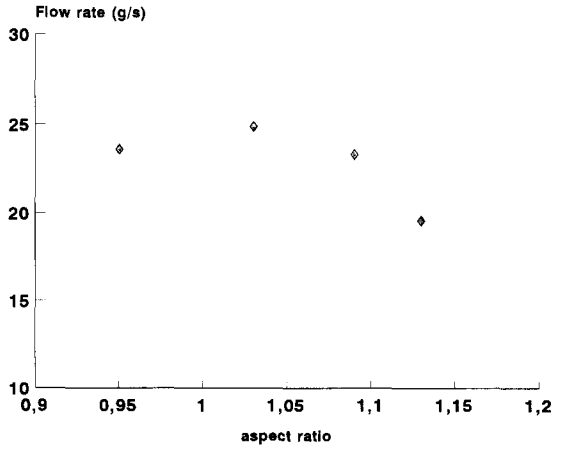

Fig. 4. Relationship between aspect ratio and flow rate.

On the other hand, a peculiar relationship has been found between the aspect ratio and flow rate (Fig. 4). It can be seen that aspect ratio values close to unity, indicating regular and round particles, reach maximum flow rate values, thus showing the best flow properties. Therefore, a parameter called the maximum flow rate could be defined on the basis of the shape parameter aspect ratio. In this case, a maximum flow rate of approx. 27 g/s can be found for lactose and modified lactoses.

This circumstance implies that it would be possible to obtain a modified lactose with an aspect ratio value close to unity, and the maximum flow rate of this product would reach a value of 27 g/s. Hence, considering a determined substance and by means of knowing aspect ratio values, the maximum flow rate can be calculated and would reach a constant value for this type of substance. Further studies will be carried out in order to confirm this proposed hypothesis.

Thus, it seems clear that fractal analysis is a useful tool not only for characterizing the irregularity of the surfaces, but also for correlating this fractal parameter with the physical description and flow properties of pharmaceutical solids. The size and shape descriptors obtained above, in combination with the fractal dimension and rheological tests, will provide preformulation assays

with a reliable technique for the appropriate selection of materials and for the detection of undesirable properties related to shape-surface characteristics as it would be possible to predict the flowability characteristics of powder masses.

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References

Bergeron, M., Laurin, P. and Tawashi, R., Effects of particle morphology in selecting pharmaceutical excipients. *Drug Dev. Ind. Pharm.*, 12 (1986) 915–926.

Cartilier, L.H. and Tawashi, R., Effect of particle morphology on the flow and packing properties of lactose. *STP Pharm. Sci.*, 3 (1993) 213–220.

Farin, D. and Avnir, D., Reactive fractal surfaces. *J. Phys. Chem.*, 91 (1987) 5517–5521.

Farin, D. and Avnir, D., The fractal nature of molecule-surface interaction and reactions. In Avnir, D. (Ed.), *The Fractal Approach to Heterogeneous Chemistry. Surface, Colloids, Polymers*, Wiley, Chichester, 1989, p. 273.

Farin, D. and Avnir, D., Use of fractal geometry to determine effects of surface morphology on drug dissolution. *J. Pharm. Sci.*, 81 (1992) 54–57.

Fernández-Arévalo, M., Excipientes modificados: estudio de su reología y su implicación en las características galénicas de comprimidos. Ph.D Thesis, University of Seville (1989).

Fernández-Arévalo, M., Vela, M.T. and Rabasco, A.M., Rheological study of lactose coated with acrylic resins. *Drug Dev. Ind. Pharm.*, 16 (1990) 295–313.

Fernández-Hervás, M.J., Holgado, M.A., Rabasco, A.M. and Fini A., Use of fractal geometry on the characterization of particles morphology. Application to the diclofenac hydroxyethylpirrolidine salt. *Int. J. Pharm.*, 108 (1994) 187–194.

Graf, J.C., The importance of resolution limits to the interpretation of fractal descriptions of fine particles. *Powder Technol.*, 67 (1991) 83–85.

Mandelbrot, B., *Los Objetos Fractales. Forma, Azar y Dimension*, 2nd Edn, Tusquets Editores, Barcelona, 1984, pp. 25–73

Paraira, M., Llovet, X. and Suñé, J.M., Granulometric characterization and study of ibuprofen lysinate by means of an image processor. *Drug Dev. Ind. Pharm.*, 20 (1994) 259–278.

Ramadan, M.A. and Tawashi, R., An automatic system for the classification and identification of microspherical particles using morphological and surface geometry parameters. *STP Pharm. Sci.*, 1 (1991) 242–247.

Romero, A.J. and Rhodes, C.T., Approaches to stereospecific preformulation of ibuprofen. *Drug Dev. Ind. Pharm.*, 17 (1991) 777–792.

Thibert, R., Akbarieh, M. and Tawashi, R., Application of fractal dimension to the study of the surface ruggedness of granular solids and excipients. *J. Pharm. Sci.*, 77 (1988) 724–726.