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Review

On the ubiquitous presence of fractals and fractal concepts in pharmaceutical sciences: A review

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ABSTRACT

Fractals have been very successful in quantifying nature's geometrical complexity, and have captured the imagination of scientific community. The development of fractal dimension and its applications have produced significant results across a wide variety of biomedical applications. This review deals with the application of fractals in pharmaceutical sciences and attempts to account the most important developments in the fields of pharmaceutical technology, especially of advanced Drug Delivery nano Systems and of biopharmaceutics and pharmacokinetics. Additionally, fractal kinetics, which has been applied to enzyme kinetics, drug metabolism and absorption, pharmacokinetics and pharmacodynamics are presented. This review also considers the potential benefits of using fractal analysis along with considerations of nonlinearity, scaling, and chaos as calibration tools to obtain information and more realistic description on different parts of pharmaceutical sciences. As a conclusion, the purpose of the present work is to highlight the presence of fractal geometry in almost all fields of pharmaceutical research.

Contents

Abbreviations: FBS, fetal bovine serum; PBS, phosphate buffer saline; DPPC, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; DPPG, 1,2-dipalmitoyl-*sn*-glycero-3-phospho-(1'-*rac*-glycerol); DODAP, 1,2-dioleoyl-3-dimethylammonium-propane; DLA, Diffusion Limited Aggregation; RLCA, Reaction Limited Cluster Aggregation; MLCRSs, Modulatory Liposomal Controlled Released Systems; aDDnSs, advanced Drug Delivery nano Systems; ADME, absorption, biodistribution, metabolism and excertion; PK, pharmacokinetics; PD, pharmacodynamics.

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1. Introduction

The structural complexity of most objects found in nature cannot be completely described by the Euclidean geometry. The irregularity in shape, of common objects and materials with rough surfaces, as well as the cells of living organisms are considered as natural tracks that need further studies and holographic approaches in order to really disclose and understand their multi-functionality. Structure often possesses invariance under changes of the scale of magnification, which can be captured well by the fractal geometry. Fractal geometry is an extension of the conventional Euclidean geometry that allows the measures to change in a non-integer or fractional way when the unit of measurement changes. This characteristic can be described by assigning a fractional number – a fractal dimension – to the dimension of the object. Fractal analysis has proven to be a useful tool in quantifying the structure of a wide range of both idealized and naturally occurring objects, extending from pure and applied mathematics, physics and chemistry, to biology and medicine. Mandelbrot was the first to model this irregularity mathematically. In various fields of research, e.g. physics, chemistry and physiology, scientists are increasingly finding that the nonlinear phenomena control the processes; physical or physiological heterogeneity are everywhere while heterogeneous conditions prevail in numerous physical, physiological, biophysical and biochemical processes. Today's science shows that the real word is mostly nonlinear and, therefore, the techniques of nonlinear dynamics are required to analyze the nonlinear phenomena. In parallel, structural and functional heterogeneities can be described and understood with the concept of fractals. In essence, fractals are complex geometric patterns, however, they are used more often than many people are aware of. Fractals are being used in applications from image compression to movement of particles in physics to biological analysis. Until the development of fractal dimension, scientists were only capable of observing the nonlinear dynamical character of the natural structures and processes. Nowadays, they have mathematical tools, which describe, explain and prove the chaotic properties of nature, such as the weather. Computers became an integral part of this scientific revolution, allowing simulations with nonlinear dynamical systems and visualizing the results over time; scientists were able to watch the chaotic evolution of a naturally-occurring phenomenon on a computer's screen. Historically, mathematical 'strange' structures existed before fractals. They were characterized as 'pathological' since they did not fit the patterns of Euclid Exotic shapes, irregular geometrical objects and extraordinary figures emerged, revealing a world where mathematical objects (graphic representations of algorithmic processes) implied the real world. The late Benoit Mandelbrot was the first mathematician to shape this new area into an individual self-standing theory, which instantly became the most popular of all. He introduced the neologism *fractal* to unite all these strange objects under one term. "I coined *fractal* from the Latin adjective *fractus*. The corresponding Latin verb *frangere* means 'to break'; to create irregular fragments. It is therefore sensible and how appropriate for our needs- that, in addition to 'fragmented' (as in *fraction* or *refraction*), *fractus* should also mean "irregular", both meanings being preserved in "*fragment*".

Pharmaceutical *Nano*technology and Pharmacokinetics are important elements in pharmaceutical sciences that could act complementary in order to develop innovative drugs. The inspired approach of Mandelbrot to disclose the geometric reality in nature's objects and the appropriate procedures resulted in new approaches in the science and technology of drug delivery. The fractal approach can be characterized as the driving force to explore new paths for developing bio-inspired drug delivery systems (i.e. liposomes, dendrimers, polymerosomes, etc.), which are fractal objects (Table 1) that can be able to deliver pharmacomolecules to the specific sites of the organism. The design characteristics of nanotechnological formulations were recently outlined by fractal geometry, while biological systems are nowadays comprehensively understood as described by the fractal approach (Table 1). Additionally, fractal kinetics has been applied to enzyme kinetics, drug metabolism and absorption, pharmacokinetics and pharmacodynamics. The concepts delineated above are quoted in Table 1. The theory of nonlinear dynamical systems (chaos theory), which deals with deterministic systems that exhibit a complicated, apparently random-looking behavior, has formed an interdisciplinary area of research and has affected almost every field of science in the last 30 years. This is referred to as *chaotic* behavior, a specific subtype of nonlinear dynamics, which is the science dealing with the analysis of dynamical systems.

Table 1
Fractals and fractal concepts in pharmaceutical sciences.

Origin	Examples
Geometry	Arterial, venular networks Dendrimers, liposomes, chimeric systems Pharmaceutical Systems
Structure (conceived)	Volume of distribution Liver
Kinetics in fractal or in disordered systems	Time-dependent kinetics Fractional Kinetics
Dynamics	Attractor of heart dynamics Attractor of secretion of hormones

This review article deals with the potential benefits of using fractal analysis along with considerations of nonlinearity, scaling, and chaos as tools to obtain information and more realistic explanations on different parts of pharmaceutical sciences.

2. Fractals

Fractal geometry has become something of a buzzword since its inception by Mandelbrot (1982). Its popularity rests in the promise of a deeper understanding of complex, chaotic and disordered systems, which have resisted conventional geometrical attempts to model them. In Fig. 1, classic examples of fractals are presented; Cantor's set, Koch's snowflake and Sierpinski triangle. As it applies to the characterization of fine particles, the essentially useful feature of fractal geometry is the recognition of dilatational symmetry or scale invariance, as a measure to characterize structures and morphologies. The expression which embodies the basic concept of the fractal structure of aggregates is very simple:

$$M \sim R^{d_f} \tag{1}$$

where M is the mass of particles, R is a linear measure of size and d_f is the mass fractal dimension, which is a measure of the scaling. This expression can be used to communicate a couple of different concepts: M can represent the mass and R the radius of a particular aggregate such that a collection of aggregates of different sizes collectively display fractal scaling; or on a scale much smaller than an individual aggregate R can represent an imaginary spherical boundary centered on one primary particle and M then means the amount of mass contained within that sphere. The constant of proportionality will be different but the fractal scaling in the two cases is the same (Chu and Liu, 2000; Bushell et al., 2002; Kamiya and Takahashi, 2007; Link et al., 2011).

Since the bulk of the literature on this subject is concerned with the structure of aggregates formed from monodisperse spherical particles, the distinction between mass and number is rarely made.