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Review

Fractal analysis as a complementary approach to predict the stability of drug delivery nano systems in aqueous and biological media: A regulatory proposal or a dream?

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ABSTRACT

The morphology of drug nanocarriers correlates with their functionality, which is mainly shuttled on their surface where most of the interactions and interfacial phenomena occur. The quantification of their morphological fingerprint requires an analytical tool that should be established based on experimental data and can be correlated with their stability. The morphological quantification picture of the advanced Drug Delivery nano Systems (aDDnSs) could be achieved via fractal analysis and by introducing a novel proposed parameter, defined as ω_D. This parameter is based on mathematical limits determined experimentally and on already existing theories on the colloidal fractal aggregation process which can correlate the morphological characteristics of aDDnSs with their physicochemical stability in aqueous and biological media. This review article proposes the fractal analysis and the ω_D as an analytical tool and prediction parameter, respectively, which are able to promote an attractive and alternative path for studying drug delivery nanocarriers. Moreover, these approaches could facilitate the scale up process of pharmaceutical industry, and could shed more light in the quantification of drug delivery nanosystems.

Contents

1. Introduction

In recent years, a considerable amount of knowledge in science and technology has been accumulated in the international data bases. The life and the material sciences are being closer than in the past, since advanced research defines that the physicochemical behavior (i.e., interfacial phenomena) of synthetic systems are considered to be very close to the functionality of those biological systems occurring in the nature. However, the efforts to translate and to project the results of science and technology and to mimic the natural occurring behavior is a difficult task, while their applicability for producing regulatory guidelines is considered to

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; DLCA, diffusion limited cluster aggregation; RLCA, reaction limited cluster aggregation; aDDnSs, advanced Drug Delivery nano Systems; ADME, absorption, biodistribution, metabolism and excretion.

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be an international debate between regulatory authorities, scientific community and pharmaceutical industries.

Pharmaceutical nanotechnology is a promising multidisciplinary scientific field that covers issues from molecular biology and biochemistry, colloid science, and nanomedicine (Hamley, 2003; Hughes, 2005; Nayak and Lyon, 2005; Whitesides and Grzybowski, 2007; Cerofini et al., 2008; Marcato and Durán, 2008; Bonacucina et al., 2009; Ravichandron, 2009; Whitesides and Lipomi, 2009; Mishra et al., 2010; Souza et al., 2010; Crommelin and Florence, 2013). Drug delivery is considered as an emerged scientific and technological platform for producing innovative drugs and giving priority to the pharmaceutical technology and mainly to pharmaceutical nanotechnology (Rowland et al., 2012). One of the promising categories in drug delivery nanocarriers are liposomes (Bangham et al., 1965; Gregoriadis et al., 1974). Nanocarriers produced by combining liposomes and polymers, are considered as new classes of soft-matter DDnSs and classified as advanced Drug Delivery nano Systems (aDDnSs) (Papagiannaros et al., 2005; Gardikis et al., 2010a,b, 2011; Kontogiannopoulos et al., 2012; Pippa et al., 2013a,b,c,d,e, 2014a; Demetzos and Pippa, 2014). The approach that we have to follow in order to develop appropriate protocols for the production of aDDnSs is mainly based on arguments that have to address the question: can we set up synthetic systems that are able to mimic living cells' behavior in terms of their functionality, following the biosynthetic evolution occur in Nature? It is of interest to clarify that the functionality in living organisms is mainly related to the cooperativity between the biomaterials as well as on their thermodynamic and physicochemical characteristics. It should also be considered that the design and the development processes of a drug nanocarrier requires careful selection of appropriate biomaterials, adequately contributing to aDDnSs effectiveness. However, the bio-inspired approach for designing effective aDDnSs seems to be a real challenge, not only for the scientific and technological point of view, but also for regulatory purposes. The quantification of their morphological characteristics requires an analytical concept and fractal analytical approach, which is proposed in this article. In our point of view, much work should be done in this field in order to establish a batch-to-batch traceability in the scale-up process in the pharmaceutical industry, in order to be able to claim the quality, effectiveness and safety of the pharmaceutical products. Finally, it is a challenge for scaling up biotechnological and even biosimilar products based on their morphological characteristics and on their functionality by avoiding side effects that are highly influenced by their immunogenicity and can be correlated with their physicochemical instability.

2. Morphological characterization of aDDnSs

Fractal geometry is a tool to describe systems and physical phenomena, like aggregation in nanoworld (Lattuada et al., 2001, 2003a,b; Sabín et al., 2007a,b; Roldán-Vargas et al., 2008, 2009; Pippa et al., 2012a,b,c). Additionally, fractal analysis is used to determine the morphology of colloidal nanostructures other than liposomes, such as dendrimers and polymeric nanoparticles (Ogasawara et al., 2000; Metulio et al., 2004; Sotiriou et al., 2007; Kim et al., 2008; Jasmine and Prasad, 2010; Al-Jamal et al., 2005; Marcos et al., 2007; Obrzut et al., 2013). By combining biomaterials like lipids, phospholipids, polymers, dendrimers etc., the concept of bio-inspired aDDnSs can be achieved based on the functionality as occurring in living cells and by the phase transition behavior of biomaterials, as the thermodynamic/physicochemical balance demands (Pippa et al., 2014a).

Nanotechnology could play a key role on the accuracy of morphological characteristics of nanoscaled materials produced nanostructures, overcoming the physical metrological limitations (Wagner et al., 2006; Caruthers et al., 2007).

According to Vamvakas et al., there is not so far a specific regulation framework in European Union regarding the use of nanoscaled products and the active regulatory mechanism in this matter based on the Article 1.2 (b) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Off. J. Eur. Union 28.11.2001 as amended, consolidated version: 05/10/2009) (Tomalia, 2009; Vamvakas et al., 2011).

2.1. Fractal analysis of aDDnSs

Fractal analysis has recently been used to describe the morphology of liposomes and liposomal aggregates (examples are given in the Supplementary material) (Kontogiannopoulos et al., 2012; Kanniah et al., 2012; Karalis et al., 2001; Karalis and Macheras, 2002; Lattuada et al., 2001, 2003a,b; Lin and Zhang, 2013; Losa and Nonnenmacher, 1996; Marcos et al., 2007). Furthermore, fractal analysis has been considered as a complementary analytical method to evaluate the size distribution of nanoparticles (Kanniah et al., 2012). Table 1 presents fractal dimensions of liposomal nanoparticles as well as their aggregation kinetics equations. Our previous works were related to the physicochemical characterization (size, polydispersity, ζ-potential) of conventional charged and uncharged liposomes, as well as chimeric liposomal carriers, the determination of their fractal dimension (mass fractal (d_f) and surface fractal (d_s)), in an aqueous (HPLC grade water and phosphate buffer saline – PBS) and in a biological (fetal bovine serum – FBS) media have been recently published (Pippa et al., 2012b,c, 2013a,b,c,d). The aggregation kinetic equations of unstable liposomal dispersions are presented in Table 1.

According to recent literature, the high value fractal dimension of the clusters or aggregates generated by very small nanoparticles could be explained by thermal restructuring (Fernández-Nieves et al., 2001; González et al., 2002; Wu et al., 2013). On the other hand, no clear explanation can be given for the small fractal dimensions of the clusters made of large particles. Some authors have pointed out that as the energy minimum increased in depth, the resultant clusters or aggregates pass from a very compact structure to a typical diffusion-limited cluster aggregation (DLCA) fractal dimension values (Fernández-Nieves et al., 2001; González et al., 2002; Wu et al., 2013). In addition, the kinetics of growth changed from those observed in reaction-limited cluster aggregation (RLCA) to DLCA. This phenomenology can be explained within the framework of a reversible growth model, arising from the fact that aggregation takes place in an energy minimum of restricted depth. A cluster- and/or aggregate-restructuring model are further developed to simulate the topological evolution of structured mixed materials due to change of colloidal conditions. The obtained results indicate that the cluster fractal dimension changed as sintering proceeds for small clusters or aggregates, in contrast to results for clusters with constant fractal dimension values (Fernández-Nieves et al., 2001; González et al., 2002; Wu et al., 2013).

For example, the morphological characteristics between conventional liposomes (high fractal dimension values) and chimeric liposomes (generally lower fractal dimension values than the conventional liposomes) are different as indicated by d_f values (Pippa et al., 2013a,b,c,d). The components used for producing chimeric liposomes i.e., lipids and polymers have different self-assembly properties (molecular weights, hydrophilic/hydrophobic ratio, self-assembly properties and biocompatibility/biodegradability characteristics). These differences are crucial concerning the liposomal surface roughness and curvature.