Progress in Materials Science 82 (2016) 39–82

Contents lists available at ScienceDirect

Progress in Materials Science

journal homepage: www.elsevier.com/locate/pmatsci

Drug self-assembly: A phenomenon at the nanometer scale with major impact in the structure–biological properties relationship and the treatment of disease

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ARTICLE INFO

Article history:
Received 10 February 2016
Received in revised form 13 March 2016
Accepted 16 March 2016
Available online 17 March 2016

Keywords:
Pharmaceutical Materials Science (PMS)
Drug research and development
Hydrophobic and amphiphilic drugs
Drug self-aggregation
Structure–biological performance relationship
Nanotechnology

ABSTRACT

Under water-rich conditions, small amphiphilic and hydrophobic drug molecules self-assemble into supramolecular nanostructures. Thus, substantial modifications in their interaction with cellular structures and the ability to reach intracellular targets could happen. Additionally, drug aggregates could be more toxic than the non-aggregated counterparts, or vice versa. Moreover, since self-aggregation reduces the number of effective "monomeric" molecules that interact with the target, the drug potency could be underestimated. In other cases, the activity could be ascribed to the non-aggregated molecule while it stems from its aggregates. Thus, drug self-assembly could mislead from drug throughput screening assays to advanced preclinical and clinical trials. Finally, aggregates could serve as crystallization nuclei. The impact

Abbreviations: BBB, blood brain barrier; CAC, critical aggregation concentration; CD, cyclodextrin; CMC, critical micellar concentration; ^{13}C NMR, carbon nuclear magnetic resonance; CNS, central nervous system; CP, cloud point; DLS, dynamic light scattering; DLVO, Derjaguin–Landau–Verwey–Overbeek model; DMSO, dimethyl sulfoxide; EPR, enhanced permeation and retention; ESR, electron spin resonance; GIT, gastrointestinal tract; ^{1}H NMR, proton nuclear magnetic resonance; Log*P*, octanol-water partition coefficient; Mβ-CD, methyl-β-CD; ME, microemulsion; NCE, new chemical entity; NE, nanoemulsion; NNRTI, non-nucleoside reverse transcriptase inhibitor; NTA, Nanoparticle Tracking Analysis; O/W, oil-in-water; PBS, phosphate buffer saline; PEG, poly(ethylene glycol); Pc, phthalocyanine; PD, pharmacodynamics; PDT, photodynamic therapy; PEO-PPO, poly (ethylene oxide)-*b*-poly(propylene oxide) block copolymer; PK, pharmacokinetic; PR&D, pharmaceutical research and development; Py, porphyrin; ROS, reactive oxygen species; SAXS, small angle X-rays diffraction; SLS, static light scattering; TCA, tricyclic antidepressant; TeCA, tetracyclic antidepressant; TEM, transmission electron microscopy; THF, tetrahydrofuran; TM-AFM, Tapping-Mode Atomic Force Microscopy; TSC, thiosemicarbazone; W/O, water-in-oil.

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http://dx.doi.org/10.1016/j.pmatsci.2016.03.004

that this phenomenon has on the biological performance of active compounds, the inconsistent and often controversial nature of the published data and the need for recommendations/guidelines as preamble of more harmonized research protocols to characterize drug self-aggregation were main motivations for this review. First, the key molecular and environmental parameters governing drug self-aggregation, the main drug families for which this phenomenon and the methods used for its characterization are described. Then, promising nanotechnology platforms investigated to prevent/control it towards a more efficient drug development process are briefly discussed.

Contents

1. Introduction

1.1. The challenge of drug development

New drug development is a long and tortuous process characterized by high attrition rates [1,2]. Only one out of 10,000 new chemical entities (NCEs) reaches the market after approximately 15 years of research [3]. The Tufts Center for the Study of Drug Development recently estimated that the aver-