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Multifractal and mechanical analysis of amorphous solid dispersions

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ABSTRACT

The formulation of lipophilic and hydrophobic compounds is a challenge for the pharmaceutical industry and it requires the development of complex formulations. Our first aim was to investigate hot-melt extrudate microstructures by means of multifractal analysis using scanning electron microscopy imaging. Since the microstructure can affect solid dosage form performance such as mechanical properties, a second objective was to study the influence of the type of adsorbent and of the presence of an amorphous compound on extrudate hardness. β-Carotene (BC) was chosen as poorly water-soluble model compound. Formulations containing a polymer, a lipid and two different silica based inorganic carriers were produced by hot-melt extrusion. Based on scanning electron microscopy/energy dispersive X-ray spectroscopy, the obtained images were analyzed using multifractal formalism. The breaking force of the strands was assessed by a three point bending test. Multifractal analysis and three point bending results showed that the nature of interparticle interactions in the inorganic carrier as well as the presence of amorphous BC had an influence on the microstructure and thus on the mechanical performance. The use of multifractal analysis and the study of the mechanical properties were complementary to better characterize and understand complex formulations obtained by hot-melt extrusion.

1. Introduction

More than 40% of newly developed chemical entities are poorly water-soluble, which often implies erratic absorption and a reduced oral bioavailability (O'Driscoll and Griffin, 2008). Some compounds exhibit limited water solubility because of solvation limitation as they are highly lipophilic, while other drugs are hydrophobic based on comparatively high crystal energy (Bergström et al., 2007). Particularly challenging are drugs that combine both lipophilicity and hydrophobicity, which requires special formulation strategies. One of the most successful oral formulation approaches of poorly-water soluble drugs is the solid dispersion (SD) technique (Serajuddin, 1999). It corresponds to the dispersion of an active compound in a solid matrix that is generally composed of a polymer and excipients. The most preferred type is here the amorphous SD, where the drug is dispersed either in an amorphous state or at a molecular level in an amorphous carrier. Among the additives that can be used, lipid excipients can be a key for the formulation of lipophilic compounds. Lipid excipients have been introduced in amorphous SD formulations by Serajuddin (1999) in the 1990′s to overcome limitations encountered in systems using polymeric carriers only. Indeed, lipids can prevent drug recrystallization in the matrix and can be of further biopharmaceutical benefit. Such additives can increase drug solubilization upon aqueous dispersion and may circumvent precipitation, while another mechanism is an optional enhancement of membrane permeability (Kuentz, 2012; O'Driscoll and Griffin, 2008). Moreover, lipids have a low physiological toxicity, offer a wide range of physico-chemical properties and are inexpensive (Reitz and Kleinebudde, 2007).

In this study, β-carotene (BC), also known as provitamin A, was selected as model compound that is lipophilic as well as hydrophobic. In a previous work, we already demonstrated that a specific combination of a polymer, a solid lipid and an inorganic adsorbent provided an amorphous SD of low-dose BC by hot-melt extrusion (HME) (Adler et al., 2016a). The key to success of this formulation strategy was the creation of designed lipid microdomains (DLM). This DLM delivery system is a molecularly

Abbreviations: BC, β-carotene; BSI, breaking strength index; DLM, designed lipid microdomain; DSC, differential scanning calorimetry; EDS, electron dispersive X-ray spectroscopy; HME, hot-melt extrusion; HPLC, high-performance liquid chromatography; PVPVA, polyvinylpyrrolidone-vinylacetate; SD, solid dispersion; SEM, scanning electron microscopy; Si, silicon; T_g, glass transition temperature; XRPD, X-ray powder diffraction.

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designed formulation that tailors specific interactions between a solid fatty acid and an inorganic carrier. While the DLM formulation uses lipid in solid form, also liquid excipients could be of interest as direct solubilizer and polymer plasticizer. It was already reported that SD based on polymeric carriers have the tendency to be sticky and an intuitive expectation suggests that addition of a liquid lipid excipient may increase this undesired effect leading to difficulties of handling (Yan et al., 2015). Therefore, the use of inorganic carriers with good oil adsorption capacity and that are already employed for the conversion of liquid to solid dosage forms, can be a key to improve polymeric SD quality (Kutza et al., 2013). The combination of liquid lipid, polymer, and inorganic carrier has already been reported in a previous study (Adler et al., 2016b). The focus was on the influence of processing parameters and type of adsorbents on the microstructure of HME extrudates by introduction of multifractal analysis. Multifractals provide a powerful mathematical model to describe complex structures that cannot be described by the Euclidean geometry. Multifractals correspond to the superposition of homogeneous fractal objects that are characterized by their self-similarity or invariance under scale of magnification (Cheng, 1999; Lopez-Sanchez et al., 2011). Fractal geometry has largely profited from the evolution of image analysis (Dathe et al., 2006; Gómez-Carracedo et al., 2009; Mendoza et al., 2010). Optical microscopy, electron microscopy, atomic force microscopy, or confocal Raman spectroscopy are methods that provide morphological, structural or compositional information (Park et al., 2012). Fractals and multifractals of such imaging methods data are of particular interest for a better understanding of object microstructure, when a link to a mathematical dimension (or a set of dimensions) is possible. Multifractal analysis has been previously used mostly in food applications or in geosciences (Mendoza et al., 2010; Posadas et al., 2001). In the field of pharmaceutics, the single fractal formalism has been applied to numerous applications such as drug dissolution and release (Kosmidis et al., 2003; Pippa et al., 2013; Thibert et al., 1988; Valsami and Macheras, 1995) pharmacokinetics (Dokoumetzidis and Macheras, 2011), pharmacodynamics (Dokoumetzidis et al., 2001), or surface ruggedness of solids (Thibert et al., 1988). The multifractal formalism has been introduced only recently (Adler et al., 2016b). The purpose of the current study is to follow-up on our previous work on HME formulations by comparing microstructural analysis and multifractal analysis with a mechanical property of the extrudates. A first aim is to study microstructures of hot-melt extrudates using a multifractal analysis of scanning electron microscopy (SEM)/energy dispersive X-ray spectroscopy (EDS) images. A polymer and a lipid excipient having solubility parameters close to that of BC were selected, and two types of silica based adsorbents were chosen. The influence of the type of inorganic excipient and of the presence of amorphous BC on the SD microstructure was assessed. Finally, the breaking strength of the extrudates was measured and results were compared to results and insights gained from the microstructural analysis.

2. Materials and methods

2.1. Materials

Polyvinylpyrrolidone-vinylacetate (PVPVA; Kollidon VA 64) was purchased from BASF (Ludwigshafen, Germany). Propylene glycol dicaprylocaprate (Labrafac PG) was kindly donated by Gattefossé (Saint-Priest, France). Granulated form of colloidal silicon dioxide (Aeroperl 300 Pharma) was supplied by Evonik Industries (Hanau, Germany). Syloid XDP 3050 (Syloid XDP) was provided by Grace GmbH & Co. KG (Worms, Germany). Crystalline β-carotene (BC) was provided by DSM Nutritional Products Ltd. (Basel, Switzerland). *N*-hexane (purity 99%), dichloro-methane (purity 99.5%), cyclohexane (purity 99.5%), methanol (purity 99.8%), ethanol (purity 99.5%) and acetonitrile (purity 99.9%) were obtained from Merck (Darmstadt, Germany). Butylated hydroxytoluene (purity 99%), tetrahydrofuran (purity 99.5%), *N*-ethyldiisopropylamine (purity 98%), 2-propanol (purity 98%) and ammonium acetate (purity 98%) were purchased from Sigma–Aldrich (Steinheim, Germany).

2.2. Hot-melt extrusion

Prior to HME, physical mixtures were prepared by weighing and mixing different ratios of PVPVA, Labrafac PG, adsorbent and BC with a spatula. Formulation compositions are presented in Table 1. Premixes were manually fed into the hopper of a Thermo Scientific Haake MiniLab II conical, co-rotating, twin-screw micro-compounder (Thermo Electron, Karlsruhe, Germany). After one minute of mixing time at 160 °C and 150 rpm, the extrudate strand was allowed to exit from a 2 mm diameter die by opening the bypass valve. The extrudates were collected after cooling at ambient temperature. A fraction of the strands was pelletized using a Thermo Scientific Process 11 Variable length pelletizer (Karlsruhe, Germany) for further SEM/EDS analysis. Extrudates strands and pellets were stored in a fridge until analysis.

2.3. Oil loading capacity

To determine the oil adsorbing capacity of the inorganic materials, we adapted a method from the literature (Choudhari et al., 2014). In brief, 1 g of adsorbent was placed in a beaker and oil was added drop wise until a dry free-flowing paste-like mass was obtained.

2.4. BET powder specific surface area

The specific surface area of the two adsorbents was determined by physical adsorption of nitrogen gas using a Micromeritics Gemini V surface area and pore size analyzer (Norcross, USA). Powders were conditioned over night at 105 °C in nitrogen prior to analysis. BET values were calculated by the software Gemini v.2.00 (Table 2).

2.5. Mercury porosimetry

Pore analysis of Aeroperl 300 and Syloid XDP was performed by Quantachrome GMbH & Co. KG (LabSPA, Odelzhausen, Germany). Mercury porosimetry was conducted using a Quantachrome Poremaster 60 GT. The two adsorbents were conditioned at 150 °C for five hours under vacuum prior to analysis. The Washburn equation was used to calculate pore volume and pore size (Table 2).

Table 1
Hot-melt extrusion formulation compositions.

Formulation	Adsorbent	Composition PVPVA/adsorbent/Labrafac PG/BC (%, w/w)
F1[a]	Aeroperl 300	80/10/10/0
F2	Aeroperl 300	75/10/10/5
F3[b]	Syloid XDP	80/10/10/0
F4	Syloid XDP	75/10/10/5
F5	/	95/0/0/5

[a] drug-free reference formulation for F2.
[b] drug-free reference formulation for F4.