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Research Paper

Surface modification of acetaminophen particles by atomic layer deposition

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ABSTRACT

Active pharmaceutical ingredients (APIs) are predominantly organic solid powders. Due to their bulk properties many APIs require processing to improve pharmaceutical formulation and manufacturing in the preparation for various drug dosage forms. Improved powder flow and protection of the APIs are often anticipated characteristics in pharmaceutical manufacturing. In this work, we have modified acetaminophen particles with atomic layer deposition (ALD) by conformal nanometer scale coatings in a one-step coating process. According to the results, ALD, utilizing common chemistries for Al_2O_3, TiO_2 and ZnO, is shown to be a promising coating method for solid pharmaceutical powders. Acetaminophen does not undergo degradation during the ALD coating process and maintains its stable polymorphic structure. Acetaminophen with nanometer scale ALD coatings shows slowed drug release. ALD TiO_2 coated acetaminophen particles show cytocompatibility whereas those coated with thicker ZnO coatings exhibit the most cytotoxicity among the ALD materials under study when assessed *in vitro* by their effect on intestinal Caco-2 cells.

1. Introduction

Primary drug particles in powder form which comprise active pharmaceutical ingredients (APIs) are typically solid organic particles. Drug powders are used to create enteral drug dosage forms (such as tablets, capsules, pellets and granules), inhalation powders, parenteral injectable preparations, topical transdermal patches and emulsions, as well as ophthalmic systems such as contact lenses and eye drops. Pharmaceutical manufacturing can benefit from improved surface characteristics of powders that optimize drug loading efficiency and improve powder processability (Ghoroi et al., 2013; Shi and Sun, 2011; Vanhoorne et al., 2014; Ehlers et al., 2009; Sauer et al., 2013; Jallo et al., 2015; Beach et al., 2010). Quite often there is a need to stabilize the desired solid state of the API. These can be amorphous or hydrate states, which make the pharmaceutical processing hard to perform unless the drug powders are coated (Airaksinen et al., 2005; Han and Suryanarayanan, 1999; Matsuo and Matsuoka, 2007; Wu et al., 2011). The

Abbreviations: ALD, atomic layer deposition; API, active pharmaceutical ingredient; ATP, adenosine triphosphate; ATR–FTIR, attenuated total reflectance Fourier transmittance infrared; DCF-DA, dichlorofluorescin diacetate; DEZ, diethylzinc; DMEM, Dulbecco's modified Eagle's medium; DSC, Differential scanning calorimetry; EDTA-PBS, ethylenediamine tetraacetic acid- phosphate buffered saline; FIB-SEM, focused ion bean scanning electron microscope; HBSS, Hank's balanced salt solution; HIFBS, heat inactivated fetal bovine serum; HPLC, high performance liquid chromatography; ICP-MS, inductively coupled mass spectrometry; PBS, phosphate buffered saline; PLGA, poly (lactid-co-glycolic acid); ROS, reactive oxygen species; SD, standard deviation; SEM-EDS, scanning electron microscope with energy dispersive X-ray spectroscopy; TGA, thermogravimetric analysis; TiCl4, titanium tetrachloride; TMA, trimethylaluminum; TNF-α, tumor necrosis factor alpha; TTIP, titanium(IV)isopropoxide; XRPD, X-ray powder diffraction; Wt, weight.

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coating may also provide chemical stabilization for the pharmaceutical (Wu et al., 2011) or control of the drug release (Chen et al., 2006). There are many biological interfaces, such as between nanoparticles and carbon nanotubes and APIs, where control of the surface characteristics of pharmaceutical powders can improve their therapeutic response and bioavailability (Terracciano et al., 2015; Taylor et al., 2014; Schäfer et al., 2013; Chow et al., 2007).

Usually, drug particles in powder form are in the size range of 1–200 μm. Current drug development pursuing improved bioavailability of drug materials is based on the production of nanocrystals and this has reduced the drug particle size to 200–800 nm (Peltonen and Hirvonen, 2014; Sarnes et al., 2013). The most frequently used coating technique on drug powders today is spraying of atomized coating liquid into a fluidized powder bed (Behzadi et al., 2008). The atomization is usually obtained with high pressure air, electrostatics or ultra sound. Coating of small particles can be difficult, because the size of the individual coating liquid droplets is usually over 30 μm (Ehlers et al., 2009; Werner et al., 2007). Spray-drying, a widely used operation in pharmaceutical manufacturing, is also used for particle encapsulation (Vanhoorne et al., 2014; Chow et al., 2007; Vehring, 2008; Dobry et al., 2009), in an attempt to overcome poor tabletability of pharmaceutical crystals (Shi and Sun, 2011; Vanhoorne et al., 2014), or to mask the undesired taste of the API (Shi and Sun, 2011). Spray drying is used to produce solid dispersions, which have already been investigated for some time for increasing the drug release rate and bioavailability of poorly water-soluble drugs, as well for controlling the drug release rate (Dobry et al., 2009; Giri et al., 2012; Huang and Dai, 2014). Dry-particle coating is an alternative method to spray drying where the addition of excipient particles is done by blending them with the API particles. Dry particle coating is favourable, for example, for moisture sensitive drugs since it does not involve the use of aqueous solvents. The removal of solvents from the final formulation is energy-consuming and complicates the process (Sauer et al., 2013; Jallo and Dave, 2015; Beach et al., 2010; Hoashi et al., 2013).

The maximum drug loading has been used in particle engineering to distinguish between particle coating and particle encapsulation. Coated drug particles have a core-shell structure and the maximum drug loading of the coated particles is usually above 50 wt-%, preferably above 90 wt-% (Chow et al., 2007). In order to increase the drug loading of conventional encapsulation methods, Singh et al. used pulsed laser deposition to create nanoscale ultra-thin films of poly(lactid-co-glycolic acid) (PLGA) on antiasthmatic budesonide particles. They did not report the film thickness on particles due to an inability to perform thickness estimation, resulting from the non-uniform nature of the particle surfaces (Singh et al., 2002). A modified spray drying method, which can be used both for drug particle synthesis and particle coating by physical vapour deposition, has been developed and studied for synthesizing drug particles (Eerikäinen et al., 2003), for coating salbutamol sulfate particles with L-leucine (Raula et al., 2008), for encapsulating indomethacin nanocrystals in mannitol microparticles with an L-leucine coating (Laaksonen et al., 2011), and for combining budesonide and salbutamol in microparticles coated with L-leucine (Raula et al., 2013; Vartiainen et al., 2016). In this method, APIs, binders and coating material are dissolved in water to form a precursor solution which is used in an aerosol process. The atomized solution mixed with nitrogen gas forms an aerosol which is introduced to a heated laminar flow reactor. In the reactor the solvent will be evaporated forming particles from the solute which will undergo further deposition by the evaporated coating substance (L-leucine) in the gas phase.

State-of-the-art drug processing requires well defined and controlled surface modification techniques. Novel drug delivery systems (Terracciano et al., 2015) are needed for the stabilization of acetaminophen nanocrystals in aqueous medium (Das et al., 2013), targeted drug delivery based on metal cation attachment to active pharmaceutical ligand forming coordination compounds (Ledeti et al., 2013), and biomedical imaging and molecular diagnostics (Park et al., 2010).

Because of the inhomogeneous nature of the surfaces and irregular shape of drug powder particles, current coating techniques usually fail to achieve smooth conformal coatings around particles, despite the rather large size of the original particle (>100 μm in diameter). At present, there is a real need to obtain thin conformal coatings for small API particles. Novel ways to protect, modify and functionalize drug particles potentially provide remarkable improvements in the development and usage of pharmaceuticals.

Atomic Layer Deposition (ALD) is a surface controlled, self-limiting layer-by-layer method for depositing thin films onto solid supports from the gaseous phase of the precursors. ALD is widely considered as a superior method for coating three-dimensional and porous substrates, and has gained an important and established role in the semiconductor industry and its development (George, 2010; Miikkulainen et al., 2013; Hyde et al., 2007; Johnson et al., 2014; Knez et al., 2006a,2006b; Kääriäinen et al., 2013). The two most important advantages of ALD are excellent conformality and film thickness control at the sub-nanometer level. Each atomic layer formed in the sequential process is a result of saturated surface controlled chemical reactions. Commonly, in the growth of binary compounds, such as metal oxides, a reaction cycle consists of two reaction steps. In one step the metal compound precursor is allowed to react with the surface and become chemically bonded to it. In the next step the metal reacts with the oxygen precursor. Between the steps a purge is applied to remove any excess of precursor and the reaction by-products. This reaction cycle is repeated as many times as necessary to achieve the desired film thickness. The precursors form stoichiometric films with large area uniformity and conformality even on complex surfaces with deformities. Layer-by-layer growth allows one to change the material composition abruptly after each step (George, 2010; Miikkulainen et al., 2013). ALD producing conformal nanometer scale films is a well demonstrated method on various particles with different size and composition (Ferguson et al., 2000, 2004a, 2004b; Hakim et al., 2005; McCormick et al., 2007; King et al., 2008, 2012; Nevalainen et al., 2009; Longrie et al., 2014). Furthermore, ALD on powder substrates is scalable for manufacturing. Early development of ALD on particles utilized fluidized bed batch reactors which are well-established technologies in the pharmaceutical industry. The latest development in particle ALD has focused on continuous processing of particles following the trends in industrial powder processing (Van Ommen, 2010). It is suggested that pharmaceutical manufacturing can benefit from capabilities of ALD. Potential applications can be *e.g.* particle surface functionalization, stabilization of APIs, and improved bulk properties such as better powder flowability.

In this work, we have studied ALD on solid pharmaceutical particles by depositing conformal nanometer scale metal oxide films on particles of the drug acetaminophen. Acetaminophen is a widely used analgesic and antipyretic drug agent. In order to show the proof-of-concept for the application of ALD on API we have investigated the physicochemical characteristics after ALD coating, the drug dissolution, and cytotoxicity of ALD oxide coated acetaminophen.

2. Material and methods

2.1. Atomic layer deposition (ALD) on acetaminophen particles

ALD on acetaminophen particles was carried out in a rotary ALD reactor as described by McCormick et al., 2007; shown in Fig. 1,