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Cross-sectional analysis of impregnated excipient particles by energy dispersive X-ray spectroscopy

Plamen I. Grigorov, Benjamin J. Glasser, Fernando J. Muzzio *

Department of Chemical and Biochemical Engineering, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, United States

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ABSTRACT

Impregnation of active pharmaceutical ingredients (APIs) onto porous excipients has numerous benefits for solid dosage formulations. Previous work has successfully demonstrated the manufacturing of pharmaceuticals using fluidized bed (FB) impregnation of APIs onto porous carriers and discussed its advantages (such as easy to implement, improvement of blend uniformity and dissolution kinetics, and stabilization of amorphous APIs). This study aims to develop methods for analysis of the spatial distribution of the impregnated API inside the porous excipient. An understanding of the spatial distribution of the API can be important if one wants to achieve high drug loadings. In addition, the spatial distribution of the API can impact its dissolution rate. The impregnation profile is analyzed using energy dispersive X-ray spectroscopy (EDS). Two formulations are investigated using Fenofibrate and Acetaminophen (model APIs), impregnated onto Neusilin (porous excipient). Several methods are presented for particle embedding and cutting in order to produce cross-sections for analysis. Embedding with carbon-based resins/adhesives produces cross-sections with high quality but the resins contaminate the sample with carbon and reduce the detection of trace elements. Manually cutting particles immobilized on carbon tape or inorganic-based adhesives produces cross-sections with a higher degree of roughness but improves the detection of trace elements and reduces/eliminates carbon contamination in the sample, allowing for API detection by its carbon footprint. EDS analytical results showed that for both Fenofibrate and Acetaminophen formulations examined in this work, the API profile is highly uniform (detected by both carbon and characteristic trace elements).

1. Introduction

Impregnation is a process by which a solute is incorporated inside a porous matrix. This process is widely used in heterogeneous catalyst preparation [1,2]. There are many advantages in placing catalytic moieties inside porous carriers: increasing total surface area available for reaction, improving overall reactivity, catalyst stabilization and reducing cost to name a few. In recent years impregnation has gained popularity in pharmaceutical applications. An increasing amount of academic research has been focused on the preparation of solid dosage formulation using impregnation [3–6]. There are several advantages of placing an active pharmaceutical ingredient (API) into a porous carrier to produce a dosage form: cost reduction, improvements to API uniformity, improvements to API release profile and improved blend flowability.

In order to incorporate an impregnant inside a porous solid matrix, that impregnant has to be in a liquid form - either in a form of a solution, a very fine suspension or in a molten state [7–9]. The two most common methods used for impregnation in catalyst preparation are dry impregnation and wet impregnation [1]. During dry impregnation, solution transport is achieved through capillary action, which is triggered when the solution meets the dry support. On the alternative, the solute transport during wet impregnation is only through diffusion as the porous support is initially wetted with pure solvent. Dry impregnation methods could vary depending on the fluid used to solubilize the impregnant. Supercritical CO_2 impregnation is another method for placing a solute into a porous support [10,11]. Impregnation methods also vary in the way the solution and the solid carrier are brought into contact. Impregnation can be achieved in many types of equipment designed to handle solids: blenders, granulators and dryers [12]. One particular method for impregnation that our group has been studying for pharmaceutical use (preparation of solid dosage drug formulations) and that has shown several advantages over more common manufacturing methods is fluidized bed (FB) impregnation [3,4].

The final impregnation profile of the solute inside the porous particle can have an impact on the desired performance of the catalyst [13]. There are several types of profiles that can be achieved during impregnation: uniform, egg-shell, egg-white or egg-yolk. Research in the field has shown that these profiles can be affected by the processing conditions (impregnation and drying temperatures), the nature of the solute, the carrier and their interaction [14–16]. In the case of pharmaceutical

* Corresponding author at: Rutgers University, Department of Chemical and Biochemical Engineering, 98 Brett Road, Piscataway, NJ 08854, United States.

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impregnated formulations, the API profile type could affect its release from the porous excipient, its long-term stability and overall the formulation efficacy. Obtaining a cross-section for analysis is not generally a simple task. Heterogeneous catalysts are typically made of large cylindrical (or spherical) carries, several millimeters in size. Cutting such large carrier particles and exposing their cross-section area is usually not a problem. However, pharmaceutical excipients that are suited for impregnation normally are small spherical particles (up to 300–400 μm in diameter), which are much more difficult to handle and cut. Such particles need to be immobilized in place or embedded into a solid matrix before cutting. Popular materials for embedding solid particles are resins - liquid organic substances, which after polymerization provide a solid matrix with an excellent optical property [17,18].

The impregnation profile inside porous particles can be studied by numerous analytical techniques, once the cross-section of the particle is obtained and exposed for analysis. Available analytical methods today span the whole spectrum of electromagnetic radiation. The main categories include: radio-waves (NMR microscopy), microwaves (EPR microscopy), infrared light (IR microscopy), visible and ultraviolet light (photography, light microscopy, UV–vis microscopy), infrared through ultraviolet light (Raman microscopy, fluorescent microscopy) and X-rays (X-ray microscopy, X-ray computed tomography) with many other subcategories [19,20]. The choice of analytical tool depends on the information (qualitative or quantitative) and detail (sample size and spatial resolution) that are needed. During the pre-digital age, impregnation profiles in catalysts were investigated using autoradiography [21] or photography [22–25]. Other optical methods involved directly measuring the impregnation profiles using a microdensitometer [26] or a digital camera [27,28]. In all cases, optical analyses required a very good contrast between the impregnated and the non-impregnated regions and relatively large particles (several millimeters in diameter).

Impregnation profiles in large enough pellets can also be analyzed using UV–vis micro-spectroscopy. This technique can be used to gain information on the spatial distribution of the catalyst [29], knowledge of its chemical structure [30] and changes during catalyst preparation [28]. The reported resolution of the method starts at 100 μm and can potentially go down to 1–3 μm [31]. Chemical imaging techniques could also be used to map dynamic processes. Infrared spectroscopy has proven advantageous in studying dynamic adsorption processes inside supported catalysts [32,33]. Very often, multiple analytical techniques are used simultaneously in order to significantly amplify the knowledge that could be obtained during the analysis. One such combination is atomic-force microscopy (AFM) coupled with IR spectroscopy. This approach combines the unique spatial resolution capabilities of AFM with the chemical analysis capabilities of IR spectroscopy, making it possible to capture IR spectra at the nanoscale [34,35]. Raman imaging techniques can also be very powerful when characterizing impregnation profiles in catalysts during the impregnation or drying stages [36–38]. The technique has become very popular in drug product development and characterization [39]. Its applications have been proven very useful in determining API's content uniformity in various pharmaceutical formulations [40]. The ability of Raman spectroscopy to differentiate crystal forms of the same API makes it a powerful tool in determining the spatial distribution of polymorphs [41,42]. It can be also used to determine how processing conditions (for example drying) influence the API distribution in the individual particles of the final formulation [43]. Similar to UV–vis, Raman spectroscopy can be coupled with AFM to further increase its spatial resolution [44]. Computed X-ray tomography (known as CAT scan in medicine) is a powerful imaging technique used to analyze the internal microstructure of an object. It has been applied successfully to the analysis of the internal structure and porosity of various powder agglomerates and granules [45–47]. The technique can be also used to study dynamic processes, such as die compaction and mixing [48].

Nuclear magnetic resonance (NMR) spectroscopy is an analytical method routinely used by chemists for determining the physical and chemical properties of atoms or molecules. NMR spectroscopy relies on the excitation of nuclei possessing a non-zero spin and makes it a great tool for qualitative (identification) or quantitative analyses. One very powerful variation of NMR spectroscopy is MRI (magnetic resonance imaging), where the magnetic field is intentionally made inhomogeneous and dependent on spatial coordinates (as opposed to NMR where the magnetic field is highly homogeneous). This allows MRI to produce 2D or 3D images of objects along with information about their chemical compositions. Besides its wide-spread use as a diagnostic tool in modern medicine and other biomedical applications, MRI is getting attention as a powerful imaging technique in various engineering fields [49,50]. In supported catalyst preparation, MRI has proven to be a powerful technique for imaging the spatial metal distribution during the impregnation and drying stages [51,52]. The technique can also be used to provide data in operating model reactors (internal structure, mass/heat transport, chemical conversion) [53,54]. MRI has also found use in pharmaceutical applications for monitoring drug release [55–57]. Another imaging technique similar to MRI is electron paramagnetic resonance (EPR) imaging. Materials under study must have unpaired electrons in order to be detected (metal complexes, organic radicals). Successful applications of this imaging technique include studies of diffusion processes in pharmaceutical drug delivery systems [58,59].

Arguably, the most powerful imaging technique today is electron microscopy (EM), which is capable of achieving high magnifications to submicron levels and below [60]. The original form of EM, called transmission electron microscopy (TEM), relies on the transmission of electrons through the sample in order to create an image. The technique requires a very high accelerating voltage (>100 keV) and a very thin sample (<200 nm) in order to achieve effective transmission [61]. TEM and its modification, STEM (scanning transmission electron microscopy), are the most powerful electron microscopy techniques, which can easily achieve nanometer and atomic level magnifications [62]. Scanning electron microscopy (SEM) is the other main form of EM, which relies on detecting emitted electrons from the sample's surface. It is not as powerful as TEM/STEM, but still capable of achieving magnifications to micron and submicron levels. The advantage of SEM is that it does not require thin specimens and such high accelerating voltages (typically <30 keV) as TEM.

Combining an electron microscope with a detector for characteristic X-rays, gives rise to energy-dispersive X-ray spectroscopy (EDS), another very powerful analytical method for quantitative and qualitative surface analysis. Generated X-rays inside the SEM are characteristic for each atom in the periodic table (excluding He and H) and their detection by EDS allows for measuring the elemental composition of the sample. What makes EDS particularly useful is that the amount of emitted X-rays from each element is directly proportional to its concentration (mass or atomic fraction) in the sample. In order to construct the spatial distribution of elements, early EDS systems had to analyze the cross-section of the sample at different points and then plot signal intensity vs. distance [63,64]. Further improvements in the EDS technology and increase in computational and storage power of computers has led to the development of a process known as X-ray mapping, where data about elemental composition and concentration can be used to construct an elemental map. This allows one to visualize the spatial distribution of all detected elements on the sample's surface [65,66]. EDS systems can be coupled with both types of electron microscopes, resulting in elemental maps with submicron (SEM/EDS) and nanoscale resolutions (TEM/EDS, STEM/EDS) [67–71].

In previous work, we introduced a method for API impregnation in a fluidized bed, describing the many advantages it presents to pharmaceutical formulations [3]. In subsequent work we further investigated the advantages that API impregnation can provide for improving dissolution kinetics of poorly-soluble drugs [4]. As already pointed out, there have been a lot of research directed towards studying of impregnation