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Full Length Article

Study of polymorphism using patterned self-assembled monolayers approach on metal substrates

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ABSTRACT

Polymorphism is a molecule's ability to possess altered physical crystalline structures and has become an active interest in pharmaceuticals due to its ability to influence a drug's physical and chemical properties. Crystal stability and solubility are crucial in determining a drug's pharmacokinetics and pharmacodynamics. Changes in these properties due to polymorphisms have contributed to recalls and modifications in industrial production. For this study, the effects of surface interactions with pharmaceuticals were examined through surface modification methodology using organic phosphonic and sulfonic acid self-assembled monolayers (SAMs) developed on a nickel or zinc oxide metal substrate. Drugs analyzed included carbamazepine, cimetidine, tolfenamic acid, and flufenamic acid. All drugs were thermodynamically applied to the reformed surface to aid in recrystallization. It was hypothesized and confirmed that intermolecular bonds, especially hydrogen bonds between the SAMs and pharmaceutical drugs, were the force that assisted in polymorph development. The study was successful in revealing multiple forms for each drug, including their commercial form and at least one additional form using micro FT-IR, Raman spectroscopy, and PXRD. Visual comparisons of crystal polymorphisms were performed with IR microscopy.

1. Introduction

Solid-state chemistry defines polymorphism as the capacity for molecules to develop multiple organizations of their crystalline lattice (Fig. 1) [1,2]. The effects of polymorphism generate different physical and chemical properties, including color, solubility, bioavailability, and kinetics[3]. The variation in drug properties due to polymorphs could cause pharmacokinetic and pharmacodynamic changes, which are studied within medicinal chemistry. Pharmacokinetics is summarized by the absorption, distribution, metabolism, and excretion of the drug. Pharmacodynamics reveals the intensity of the response between the drug and the body's active site, which is reliant upon intermolecular bonds [4]. According to the Food and Drug Administration (FDA), the most stable and bioavailable form is often used for formulation of a drug. Investigation into polymorphisms has prompted drug recalls, such as Ritonavir (1998) [5], Rotigotine (2003) [6], and Avalide (2010) [7].

Past methods of reproducing polymorphs include: solvent-base screening [8–10], seeded melt crystallization [11,12], solid-state transformation [13], and limited surface interaction studies [14–16]. Self-assembled monolayers (SAMs) have been previously used to initiate heterogeneous nucleation and growth from solution and to control crystallization processes [16–20]. Crystallization and nucleation have been achieved using ngold [18,19] and silanes on silicon surfaces [17,21]. These systems have shown to form a surface that acts as a template for oriented and patterned nucleation [17]. Here, the surface modification method presented a reformed surface for the drug to interact with using nickel oxide (NiO) and zinc oxide (ZnO) metals as the substrate and organic acids as the SAMs using phosphonic and sulfonic acids as presented in Fig. 2. The organic acids resemble the molecular structure of common surfactants used to improve kinetics through solvent interaction

Abbreviations: SAMs, Self-Assembled Monolayers; NiO, nickel oxide; ZnO, zinc oxide; NSAID, Non-Steroidal Anti-Inflammatory drug; CBZ, Carbamazepine; CIM, Cimetidine; TFA, Tolfenamic Acid; FFA, Flufenamic Acid; DRIFT-IR, Diffuse Reflectance Infrared Fourier Transform Spectroscopy; PXRD, Powder X-Ray Diffraction; Micro-FT-IR, Microscopic Fourier Transform Infrared Spectroscopy; THF, Tetrahydrofuran; HDSA, Hexadecanesulfonic acid; ODPA, Octadecylphosphonic acid; COOH-PA, 16-phosphonohexadecanoic acid; Di-PA, (12-phosphonododecyl) phosphonic acid; HU-PA, 11-hydroxyundecylphosphonic acid; U-PA, 10-undecynylphosphonic acid.

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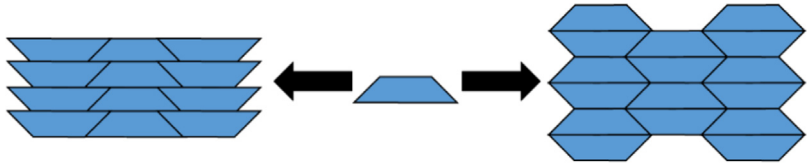

Fig. 1. Diagram of intermolecular change from neighboring unit cells illustrating the basis for the construction of polymorphic crystalline lattices.

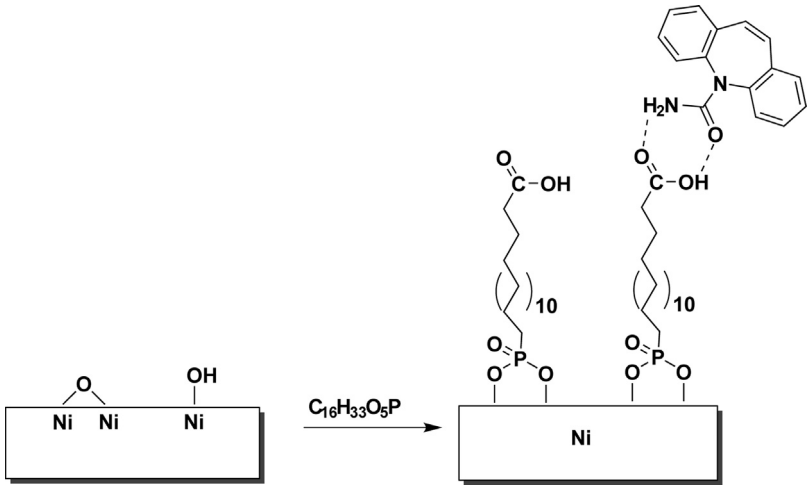

Fig. 2. Addition of COOH-PA SAM on NiO metal substrate and interaction with CBZ. Orientation of SAMs is consistent between NiO and ZnO metal substrates.

with hydrophilic head groups [22,23]. Metal selection was based on their reactivity by forming an overall uniform adsorbed layer. The interface was formed by the organic acid SAMs to provide a functionalized surface on the metal substrate for drug interactions through hydrogen-bonding and other interactions [24–27].

Once the surface was constructed, the drugs were placed in contact with the SAM for recrystallization. The phosphonic and sulfonic acids and active pharmaceuticals analyzed [carbamazepine (CBZ), cimetidine (CIM), tolfenamic acid (TFA), and flufenamic acid (FFA)] were selected because each had the capacity to form strong intermolecular bonds as indicated by their structures (Fig. 3). Intermolecular forces, mainly hydrogen bonds, are hypothesized as a driving force in polymorphism development and are of particular interest [22,28]. The product drug samples were analyzed using Diffuse Reflectance Infrared Fourier Transform Spectroscopy (DRIFT-IR), Microscopic Fourier Transform Infrared Spectroscopy (Micro-FT-IR), Powder X-ray Diffraction (PXRD), and Raman Spectroscopy.

Carbamazepine ($C_{15}H_{12}N_2O$), brand name Tegretol®, is an anti-convulsant drug for epileptic seizure treatment with four known polymorphisms. It can also be prescribed for trigeminal neuralgia and manic episodes in order to reduce electrical activity within neurons [29,30]. Cimetidine ($C_{10}H_{16}N_6S$), brand name Tagamet®, is classified as an anti-histamine drug used for the treatment of ulcers and common heartburn symptoms by decreasing stomach acid production. Cimetidine prevents retrograde flow of stomach acid, which would normally cause injury to one's esophagus [10,31]. Tolfenamic acid ($C_{14}H_{12}ClNO_2$), or Clotam®, has five known polymorphs and is a Non-Steroidal Anti-Inflammatory Drug (NSAID) used for pain relief of migraine headaches [32,33]. Lastly, flufenamic acid ($C_{14}H_{10}F_3NO_2$), another NSAID drug applied topically to relieve joint pain, is one of the current leading polymorphic compounds with eight known forms [14,34].

2. Experimental section

2.1. Preparation of metal substrates

Sheets of ZnO metal foil (Alfa Aesar, 0.25 mm thick, 99.98%) and NiO metal foil (Alfa Aesar, 0.25 mm thick, 99.5%) were cleaned 5 times with 120–1200 grit sandpaper, increasing levels of fineness with each cleaning to remove carbon coating. Foil was then cut into 1 × 1 cm tiles. The tiles were cleaned in ultrasonic baths of acetone for 25 min, methanol for 25 min, and tetrahydrofuran (THF) for 30 min. Clean tiles were dried in an oven at 80 °C overnight. Before SAM modification, tiles were again cleaned in a THF ultrasonic bath for 25 min and allowed to air dry.

2.2. Preparation of HDSA

Hexadecanesulfonic acid, sodium salt (Sigma-Aldrich, 98%) was placed in an acidification reaction overnight using 6 M hydrochloric acid to convert the salt to the desired acid, Hexadecanesulfonic acid (HDSA), required for SAM preparation. Success of the reaction and lack of contamination was analyzed using ^{1}H nuclear magnetic resonance.

2.3. SAMs modification

ZnO tiles were modified with 1 mM octadecylphosphonic acid (ODPA; Strem Chemicals, Inc., 97%), 16-phosphonohexadecanoic acid (COOH-PA, Sigma-Aldrich, 97%), or HDSA solutions prepared in THF. NiO substrates were modified using the same acids and also (12-phosphonododecyl) phosphonic acid (Di-PA; Aldrich, 97%), 11-hydroxyundecylphosphonic acid (HU-PA; Aldrich, 95%), or 10-undecynylphosphonic acid (U-PA; SiKÉMIA, 95%). Prepared solutions were placed in an ultrasonic bath for 15 min and poured over dried metal substrates and then left to dry in air. To ensure proper acid layer formation, DRIFT-IR was collected after the sub-