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Differential surface properties of commercial crystalline telmisartan samples

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ABSTRACT

The aim of the present study was to investigate differences in surface chemistry of commercially available telmisartan (TMS) samples in Indian market and to correlate them to the surface molecular environment. Comprehensive characterization of material properties of four TMS samples from different sources showed that all samples exhibited same polymorphic form, but different particle shape, particle size distribution, surface energetics and surface chemistry. Wettability and surface free energy were determined using sessile drop contact angle technique. TMS samples exhibited significant variations in their wetting behavior. The role of crystal shape, particle size distribution, surface energetics and surface chemistry in controlling TMS powder wettability was collectively explored by contact angle experiments. Evaluation of work of adhesion (W_a), immersion (W_i) and spreading (W_s) indicated that samples had differential wetting behavior. The surface chemistry was elucidated by X-ray photoelectron spectroscopy (XPS). The surface polarity index was determined by XPS and expressed as (oxygen + nitrogen)-to-(carbon) atomic concentration ratio. It was found to be different for all four TMS samples. Crystal morphology of TMS polymorph A was predicted using Bravais–Friedel Donnay–Harker (BFDH) method. Molecular lipophilic surface potential (MLSP) data for TMS showed the varied surface lipophilic environment throughout the molecule. Hence it can be concluded that the differential abundance of surface elements play an important role in controlling the biopharmaceutical performance of TMS powder samples.

1. Introduction

Active pharmaceutical ingredients (APIs) are frequently delivered to the patient in suitable dosage forms. Solids provide a convenient, compact and generally stable format to store an API or a drug product. Understanding and controlling the solid-state properties of APIs is therefore an important aspect of the drug development process (Singhal and Curatolo, 2004; Sun, 2008). APIs can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals, and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability, purification, stability and other behavioral performance of the drug (Huang and Tong, 2004).

The solid state properties of solids can be categorized as bulk properties (such as solubility, compactibility, and elasticity) and surface properties (such as interfacial tension, wettability, adhesion, and cohesion). Among these, surface level properties are influenced by surface chemistry and energetics. Many processes of pharmaceutical importance initiate at the surface, and can be critically affected by surface behavior. Such processes include crystal nucleation and growth, powder dispersion in liquids, fracture mechanics, powder flow, powder compaction and the coating of solids (Shekunov and York, 2000; Van Eerdenbrugh et al., 2008). For situations where powder dispersion of drugs in water or water penetration into solid compacts is required, a lack of wetting due to unfavorable surface energetics leads to significant difficulty in disintegration and/or dissolution (Blagden et al., 2007). Thus, surface interactions can be expected to relate to the ease of production (for example, mixing, granulation, tabletting, etc.), the stability (given that solid state chemical interactions and reactions will be through surface contact) and the ultimate biological fate (e.g. dissolution rate of solid dosage forms or the distribution of particles in human body) (Blagden et al., 2007; Ho et al., 2009). Hence the study of surface properties of APIs can be expected to provide data that will at worst explain batch to batch variability and at best provide control for approaches such as process analytical technology (PAT).

Particle wetting is one of the most important surface properties which is primarily governed by powder surface energetics (Buckton et al., 1988; Zografi and Tam, 1976). Several reports are available in literature that accounts the differential surface energetics and wetting behavior of different crystalline and amorphous phases of drugs (Heng et al., 2006a, 2006b, 2006c; Puri et al., 2010). The variations in the macroscopic surface behavior can be attributed to differential solid surface chemistry. The emergence of surface disorder in crystalline materials can substantially alter their surface behavior significantly and may sometimes lead to erratic biopharmaceutical performance (Blagden et al., 2007). For the

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amorphous solids, wettability and their interaction strength with aqueous media are important characteristics to be studied as they can influence the supersaturation levels achieved during the dissolution process and its physical stability (Puri et al., 2010).

Recently, it has been observed that, variations in surface properties of similar solid state forms could also affect the biopharmaceutical and pharmacokinetic performance of the API (Agrawal et al., 2004). Therefore, in addition to optimal solid form characterization, evaluation of such variations has gained a significant importance in pharmaceutical industry.

In the current manuscript, we present a case of telmisartan (TMS) whose polymorphic form A samples were procured from different pharmaceutical API manufacturers of India and evaluated for their differential surface properties. We characterized solid state and surface properties of TMS samples and despite being formed of same polymorph, the samples exhibited significant differences in their surface properties. This study is expected to highlight the importance of surface characterization of API and to emphasize the role of surface properties in bringing substantial changes in the samples whose molecular level properties are similar.

TMS is an angiotensin II receptor blocker and is used as an antihypertensive agent. It belongs to biopharmaceutics classification system (BCS) class II and has an aqueous solubility of 0.075 mg/ml. TMS has an absolute bioavailability of 44% (Kausalya et al., 2011). The theoretical biopharmaceutical parameters were calculated for TMS using its highest dose of 80 mg, particle size of 100 μm (i.e., unmicronized), effective permeability (P_{eff}) of 2×10^{-4} cm/s and small intestinal transit time (T_{si}) of 199 min (Amidon et al., 1995). TMS showed a dose number (D_0) of 4.1, which was greater than the favorable value of 1 (Kasim et al., 2004), a dissolution time (T_{disso}) of 529 min leading to dissolution number (D_n) of 0.375 and an absorbable dose (D_{abs}) of 149 mg. These values indicate the dissolution rate limited oral bioavailability of TMS (Rinaki et al., 2004). TMS is available in crystalline form A in the market and there are several manufacturers of TMS form A in the Indian market.

2. Materials and methods

2.1. Materials

Four commercial samples of telmisartan (TMS), polymorphic form A, produced by API manufacturers based in India, were obtained as gift samples and coded as TMS-1 to 4. All the samples were analytically >99% pure as per the certificate of analysis supplied by manufacturers and were used as received. All the other reagents and solvents used were of analytical grade or HPLC grade. Double distilled water filtered through 0.2 μm membrane filter was used in all the experiments.

2.2. Methods

2.2.1. Differential scanning calorimetry (DSC)

DSC analysis of TMS samples was carried out on DSC (TA instruments Q2000, New Castle, Delaware, USA) equipped with TA Universal Analysis software. The instrument was calibrated for heat flow and temperature with high purity standards of indium and zinc. TMS (3–5 mg) was weighed into a T_{zero} aluminum pan and analyzed at a heating rate of 10 °C/min over a temperature range of 25–300 °C with nitrogen purging (50 ml/min). All the analyses were carried out in triplicates.

2.2.2. Thermogravimetric analysis (TGA)

TGA was performed using Mettler Toledo 851^e TGA/SDTA (Mettler Toledo, Switzerland) operating with Star^e software version Solaris 2.5.1. Drug samples (5–7 mg) were weighed and analyzed under nitrogen purge (20 ml/min) in alumina crucibles at a heating rate of 10 °C/min over a temperature range of 25–300 °C.

2.2.3. Powder X-ray diffraction (PXRD)

PXRD patterns of samples were recorded at room temperature using Bruker's model D8 Advance Diffractometer (Karlsruhe, West Germany) equipped with a 2θ compensating slit, using Cu Kα radiation (1.54 Å) at 40 kV and 40 mA passing through nickel filter with divergence slit (0.5°), antiscattering slit (0.5°) and receiving slit (0.1 mm). Samples were mounted on zero-background sample holder and subjected to a continuous scan over an angular range of 3–40° 2θ at a step size of 0.01° and scan rate of 0.1 s/step. Obtained diffractograms were analyzed with DIFFRAC^{plus} EVA (version 9.0) diffraction software.

2.2.4. Fourier transformed infrared spectroscopy (FTIR)

The infrared spectra were recorded in a FTIR spectrophotometer ((Spectrum One, Perkin-Elmer, Buckinghamshire, U.K.). Potassium bromide (KBr) pellet method was employed and background spectrum was collected under identical conditions. Each spectrum was derived from 16 single averaged scans collected in the region 400–4000 cm^{-1} at a spectral resolution of 2 cm^{-1}, Fourier transformed and rationed against background interferogram. Spectra thus obtained were analyzed using spectrum version 3.02 software.

2.2.5. Optical microscopy

Samples were observed under Leica DMLP polarized microscope (Leica Microsystems Wetzlar GmbH, Wetzlar, Germany) equipped with Linkam LTS 350 hot stage. Photomicrographs were acquired using JVS color video camera and analyzed using Linksys32 software. The powder samples were observed for the diameter (i.e. length along the longest axis of individual particles) of 100 particles under 500× magnification. Cumulative particle size distribution curves were plotted to determine the diameters corresponding to 50% and 90% of cumulative undersize particles, i.e., $d(0.5)$ and $d(0.9)$, respectively.

2.2.6. Scanning electron microscopy (SEM)

TMS samples were examined by SEM (S-3400, Hitachi Ltd., Tokyo, Japan). Sample to be investigated was mounted onto aluminum stage using double sided adhesive tape and sputter coated with a thin layer of gold at 10 Torr vacuum before examination with the help of ion sputter (E-1010, Hitachi Ltd., Tokyo, Japan). The specimens were scanned with an electron beam of acceleration potential of 1.2 kV and the images were collected as secondary electron mode.

2.2.7. Sessile drop contact angle measurement

Contact angle of powder samples were measured by sessile drop method, using Drop shape analyzer instrument (FTA 1000, First Ten Angstrom, Virginia, USA). Pellets were prepared by compacting 150 mg of powder at 800 psi pressure in a hydraulic press (Hydraulic Unit Model 3912, Carver Inc., WI), with a dwell time of 30 s, in 8 mm punch die set (surface area 0.5 cm^2). The porosity of all the prepared pellets was found to be in the range of 25 ± 3%. Analysis of pellets by PXRD and DSC confirmed that no solid-state transition occurred during compaction. Pellets were mounted on glass slide and drop of phosphate buffer (pH 7.5) was dispensed on them. The video was captured by the FTA image analyzer. Contact angle was calculated by the instrument by fitting mathematical expression to the shape of the drop and then calculating the slope of the tangent to the drop at the liquid–solid–vapor interface line. The contact angle made at 0.2 s from the time of contact of drop to the solid surface was taken for comparative assessment