Evaluation of In-Use Stability of Anticoagulant Drug Products: Warfarin Sodium

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ABSTRACT: The objective of the study was to evaluate the stability of warfarin products during use by patients or caregivers. For evaluation, three commercial products manufactured by different processes were selected and placed at 30°C/75%RH to simulate in use condition. Samples were withdrawn up to 12 weeks and analyzed for the physicochemical changes. Scanning electron microscopy demonstrated increasing holes and craters in the tablets over the timeframe. Near-infrared chemical imaging and powder X-ray powder diffraction corroborated the change arising from conversion of crystalline to amorphous forms of the drug. Hardness and disintegration time of the tablets were found to increase progressively. With increasing time, moisture contents of the products were found to increase and consequent decrease in isopropyl alcohol content of the product. Dissolution of the tablets in media at pH 4.5 demonstrated discrimination between crystalline and amorphous drug products. Overall, percent drug dissolved in each product at 30 min was found to decrease with increasing exposure time. Dissolution of drug decreased from 54% to 38% and 82% to 54% for the two products while the third product maintained consistently high level of dissolution. These results suggest that the drug product quality attributes can change during use. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:4232–4240, 2015

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INTRODUCTION

Stability of a drug is a critical quality attribute throughout product development cycle. It starts with preclinical assessment of developability of candidate molecules, evaluation during formulation development, and clinical testing for NDA, and continues till post marketing surveillance.[1] Irrespective of phases of the development cycle, an overall objective of stability evaluation during different phases is to ensure the integrity of a molecule until it is administered for a certain therapeutic performance. Alteration of the integrity can arise from physicochemical properties of drug and excipients, manufacturing processes, container closure systems, storage conditions, and packaging materials properties.[2] Therefore, a systematic stability study at predetermined time points during preclinical and clinical studies assists in enhancing insight about the molecules. Stress testing at an early stage of development provides a wealth of information about the drug molecules, which includes the type of stress causing drug degradation and its specific degradants(s), and degradation pathways.[1] These inputs help in developing stability indicating analytical methods for evaluation of the integrity of the product. At the late stage of a drug development, when the drug is formulated into suitable dosage forms for clinical testing and marketing, data from accelerated stability study of the drug product assures, to some degree, product quality during drug distribution chain system and storage.[3]

Continued integrity or quality of drug product, particularly those dispensed in multidose container or bulk pharmacy packaging, during actual patient or caregiver use (in-use) is critical in eliciting expected treatment outcome. Expectation of continued integrity of the product may not be fulfilled after the packaging integrity of the container is breached for withdrawing the first dosage unit.[4] For example, if the drug is susceptible to oxidation, repeated opening and closing of the container during in-use may modulate the quality of the product resulting in differences in treatment benefit at the beginning and successive doses of the product. The environmental factors such as temperature, light, humidity can also affect the product on successive drawing of the unit dosage during the remaining course of treatment. The degree of impact by these factors depends on the type of dosage forms, nature of excipients used, frequency and duration of exposure during repeated opening and closing of bottle, number of dosage units withdrawn each time to pick a dose and their contacts with patients' or caregivers' bare hands. Therefore, stability of drug or drug product under controlled and in-use condition provides a holistic understanding of the integrity of drug molecule at the time of its use. The implication of a poorly understood molecule may lead to catastrophic failure of the product either at late stage of product development[5] or post marketing approval. Loss of the integrity of the drug molecule at any stage may alter their physicochemical properties and therefore impact clinical outcome. If chemically degraded to toxic product, it may harm the patients instead of benefitting them.[6]

Warfarin sodium, an anticoagulant drug, has been widely used to treat various cardiovascular conditions and prevent clotting after medical intervention.[7] International normalized

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ratio (INR), which represents the effectiveness of the anticoagulant, is frequently monitored for patients on warfarin therapy. Being a narrow therapeutic index drug, the INR value for the patient is maintained between 2 and 3. The drug exists in two solid states: amorphous and crystalline.[8] Commercially available products are manufactured using crystalline warfarin sodium an active pharmaceutical ingredient. Crystalline warfarin sodium is a clathrate molecule containing isopropyl alcohol (IPA) as a guest molecule in the crystal lattice.[9] Furthermore, it has been demonstrated that it loses crystallinity at high humidity at which water replaces IPA[10] thereby loosing crystalline structure. With the available information regarding warfarin sodium, it is important to evaluate the stability of its drug products during use and how in-use handling of the product affects the quality.

MATERIALS AND METHODS

Materials

Three commercial products (A, B, and C) of 5 mg warfarin sodium were purchased from a local pharmacy. These products were selected based on differences in manufacturing process. Products A, B, and C were manufactured using dry granulation, direct compression, and wet granulation, respectively. Primary reference standard of Warfarin was procured from the United States Pharmacopeia (Rockville, Maryland). USP grade of sodium acetate trihydrate and ACS grade n-propanol were obtained from JT Baker (Center Valley, Pennsylvania). Phosphorous pentoxide was purchased from Sigma–Aldrich (St. Louis, Missouri). ACS certified grade of glacial acetic acid, sodium hydroxide, methanol (HPLC grade), and isopropanol alcohol (HPLC grade) were acquired from Fisher Scientific (Pittsburg, Pennsylvania). Cannula full flow 10 μm PVDF filters were obtained from Agilent (Santa Clara, California), automated 0.45 μm PVDF filters were bought from Millipore (Billerica, Massachusetts), and 0.45 μm PVDF syringe filters were purchased from Fisher Scientific. Distilled water (18 MΩ) was collected from an in-house facility (Millipore Milli-Q Gradient A-10 water purification system).

Methods

Stability Study

Warfarin is a unique drug that transforms and become glue at around 70%RH. Normal stability studies are performed at 25°C/60%RH and accelerated studies are performed at 40°C/75%RH. Intermediate studies are performed at 30°C/65%RH. As this humidity does not go up to 70%RH, an internal United States Food and Drug Administration advisory group recommended 30°C/75%RH to account for certain bathroom conditions in which some patients might be storing these tablets. The stability study was performed on three commercial 5 mg strength warfarin sodium products (A, B, and C) kept in pharmacy vials at 30°C/75%RH for 12 weeks. In order to simulate the in-use condition, all tablets in pharmacy vials were placed in the palm of a bare hand for 10 s then replaced back to their dispensing containers. This in-use condition was repeated five days a week for the entire period of the study. All the physical and chemical parameters of the tablets were evaluated at time 0, 1, 2, 4, 6, 8, and 12 weeks.

Scanning Electron Microscopy

Surface morphology of the crystalline or amorphous warfarin sodium in the products was determined by scanning electron microscopy (SEM; JSM-6390 LV; JEOL, Tokyo, Japan). Samples were sputter coated with gold using sputter coater (Desk V; Denton Vacuum, Moorestown New Jersey) under high vacuum (70 mTorr) and high voltage of 30 mV. Morphology was captured at a working distance of 15 mm and at an accelerated voltage of 5 KV.

Near-Infrared Chemical Imaging

Near-infrared chemical imaging (NIR-CI) of the 5 mg warfarin sodium commercial products were acquired by a Sapphire imaging system using SapphireGo software (Malvern, Worcestershire, UK). The instrument employs a focal-plane array detector for the detection of the filtered diffused light from the sample and produces 320 × 256 pixel images. Manufacturer standard procedures were followed before capturing images. In the NIR range starting from 1800 to 2200 nm, the obtained data at an increment of 10 nm and eight scans were co-added to produce an average spectrum. The collected data were then analyzed by ISys chemical imaging software (Malvern). Before analyzing the data, the collected reflectance data were converted to absorbance, truncated and normalized by mean centering and scaling to unit variance by spectrum. A library of the crystalline and amorphous warfarin sodium was created, and PLS2 (partial least squares 2) fitting was employed to obtain PLS concentration scores and images.

X-Ray Powder Diffraction

X-ray powder diffraction (XRPD) patterns for amorphous and crystalline forms of warfarin sodium, excipients (lactose monohydrate and anhydrous), products A, B, and C were collected at each stability time point using a Bruker D8 Advance with DaVinci design (Bruker AXS, Madison, Wisconsin) using Cu Kα radiation ($\lambda = 1.5405$ Å) at a voltage of 40 KV and a current of 40 mA. The system is equipped with the LYNXEYE scintillation detector. Powder sample equivalent to 500 mg were used for data collection. Weighed powder was placed on the sample holder, pressed using zero diffraction plate and scanned over 2θ range of 4°–30° with a step size of 0.00915° at 1 s per step (3000 total steps). Samples were rotated at 15°/min during measurements to get average diffractogram of the sample. The XRPD data collection and data analyses were achieved through Diffract.Suite (V2.2).

Hardness

The crushing strength of the tablets was measured using Pharma Test PTB 111E hardness tester (Pharma Test Apparatebae AG, Hainburg, Germany). Tablets were placed between the plates and a constant force with increasing rate of 20 N/s was applied until the tablet breaks. Six tablets were tested and their mean value in kilopond (Kp) was reported.

Disintegration Time

Disintegration time of the tablet was determined by USP disintegration instrument (Globe Pharma USA; Electrolab-Disintegration Tester (USP) DE-2L; New Brunswick, New Jersey). The instrument consists of a basket rack assembly with a 1-L capacity beaker as described in the USP. The beaker was