European Journal of Pharmaceutical Sciences 48 (2013) 502–513

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Development of a new sodium diclofenac certified reference material using the mass balance approach and ^{1}H qNMR to determine the certified property value

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ARTICLE INFO

Article history:
Received 8 July 2012
Received in revised form 8 November 2012
Accepted 13 November 2012
Available online 6 December 2012

Keywords:
Sodium diclofenac
Active pharmaceutical ingredients (API)
Certified reference materials (CRM)
Metrological traceability
Analytical quality control

ABSTRACT

Certified reference materials (CRMs) are essential tools to guarantee the metrological traceability of measurement results to the International System of Units (SI), which means the accuracy and comparability of results over time and space. In the pharmaceutical area, only a few CRMs are available and the use of (non-certified) reference materials is a much more common practice. In this paper, the studies on a new candidate CRM of sodium diclofenac based on the ISO Guides 34:2009 and 35:2005 are described. The project steps included characterization, homogeneity test, stability studies, and uncertainties estimation. In the characterization, the mass fractions of organic, inorganic, and volatile impurities were determined, and the results were cross-checked by independent reference methods or interlaboratorial study. The API mass fraction was calculated by mass balance and cross-checked by quantitative proton nuclear magnetic resonance (^{1}H qNMR). The paper also presents a Monte Carlo simulation to estimate the measurement uncertainty as an approach to validate the GUM results in ^{1}H qNMR. The homogeneity between batch units was verified, and the candidate CRM stability under transport and storage conditions was evaluated in short- and long-term stability studies. The CRM certified property value and corresponding expanded uncertainty, obtained from the combined standard uncertainty multiplied by the coverage factor ($k = 2$), for a confidence level of 95%, was (999.76 + 0.10) mg g^{-1}.

1. Introduction

In 2008, the National Institute for Metrology, Quality, and Technology (Inmetro, Brazil) started a pioneering project to develop certified reference materials (CRMs) of active pharmaceutical ingredients (API). The main motivation for this project was the small number of API CRMs available on the market: At that time, only dextromethorphan hydrobromide from the United States Pharmacopeial Convention (USP) was available (United States Pharmacopeial Convention, 2012). Although the USP produces more than 2500 (non-certified) reference materials (RMs), until today only three more CRMs have been offered in the market, namely, theophylline, phenytoin, and carbamazepine. Other institutions that recognized the importance of API CRMs are the National Metrology Institute of Japan (NMIJ) (17β-estradiol CRM for clinical chemistry) (NMIJ, 2012), the National Metrology Institute of China (NIM) (paclitaxel CRM) (Liu and Yang, 2010), and another Chinese research group (CRM of anthraquinone in the herbal medicine Rhei) (Yang et al., 2010). Inmetro produced CRMs of captopril and metronidazole (Nogueira et al., 2011a, 2011b, 2012) and has recently concluded certification studies for the sodium diclofenac CRM.

By definition, a reference material (RM) is a material sufficiently homogeneous and stable regarding one or more specified properties that has been established as fit for its intended use in a measurement process (ISO Guide 30, 1992). A certified reference material (CRM) is a reference material characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides the value of the specified property, the associated uncertainty, and a statement of metrological traceability (ISO Guide 30, 1992). In practical terms, the certificate for a CRM states the certified property value and the measurement uncertainty, and can ensure metrological traceability of results, which is not true when an RM is used.

The metrological traceability of measurement results to the International System of Units (SI) aims at ensuring that measurement results are accurate, reliable, and comparable over time and space. By definition, the metrological traceability is the property of a measurement result in which the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty (JCGM, 2012), which

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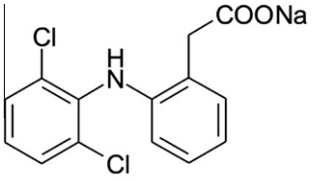
http://dx.doi.org/10.1016/j.ejps.2012.11.005



Sodium diclofenac

Fig. 1. Chemical structure of sodium diclofenac.

means that traceability and uncertainty are intimately linked (Eurachem/Citac, 2000). Laboratories accredited under ISO/IEC 17025:2005 are required to prove the metrological traceability of their measurement results (ISO/IEC 17025, 2005).

The SI is formed by seven basic units, namely, meter (m), kilogram (kg), second (s), Ampere (A), Kelvin (K), candela (cd), and mole (mol), and the metrological traceability chain is easily observed for some of them. The kilogram, for instance, is the only unit that still exists as a materialized standard, kept at BIPM, France. From this standard, prototypes are calibrated and sent to several national metrology institutes (NMIs) under specific storage conditions, where the prototypes can be used to calibrate working standards from research institutes and industrial laboratories. This creates a metrological traceability chain, in which the uncertainties of the calibrated standards increase the farther they are from the original standard. The tendency in all fields is to substitute materialized standards (such as the kilogram) with physical concepts, which is already a reality, for instance, in the case of meter.

In chemistry, however, metrological traceability to the mol is not a trivial task, and may be ensured by combining several tools, including the following: (i) calibrating measuring systems, e.g., analytical balances (Bich, 2009; Silva and Camões, 2010), (ii) using certified reference materials (CRMs) for calibrating equipment (Silva and Camões, 2010; Sega et al., 2009; Priel et al., 2009), (iii) validating analytical methods, and (iv) using primary measurement methods (Sega et al., 2009). Primary reference measurement procedures are used to obtain a measurement result without relation to a measurement standard for a quantity of the same kind (JCGM, 2012), and potential measurement methods pointed out by the Consultative Committee for Amount of Substance (CCQM) include gravimetry, coulometry, titrimetry, isotopic dilution mass spectrometry (IDMS), and the determination of freezing point depression (ISO Guide 35, 2006).

When developing CRMs, primary reference methods play an important role, since the ISO Guide 35:2006 (ISO Guide 35, 2006) states in paragraph 9.3 that the certified property values of reference materials should be determined by (a) measuring with a single primary method, (b) measuring with two or more independent reference methods, (c) measuring with a network of laboratories using one or more methods of demonstrable accuracy, or (d) using a method-specific approach giving only method-specific assessed property values, using a network of laboratories.

The main goal of the present work was to develop and certify a new sodium diclofenac CRM (Fig. 1). This CRM is intended to be used in conducting quality control assays, method development and validation, for assigning traceable property values (and corresponding uncertainties) to non-certified reference materials, and to guarantee the metrological traceability, accuracy, and comparability of the measurement results.

2. Materials and methods

The certification steps included characterizing the material, which consisted of determining the mass fractions of organic impurities with HPLC–DAD, of inorganic impurities with ICP-MS, and of volatile impurities with loss on drying. Then the certified property value (API mass fraction) was calculated with the mass balance. The mass fraction of the organic impurities was cross-checked with a different reference method (HPLC–DAD using different columns and pH values), the mass fraction of the inorganic impurities was cross-checked with an inter-laboratory study, and the certified property value obtained with the mass balance was cross-checked with quantitative proton nuclear magnetic resonance (^{1}H qNMR). The measurement uncertainty was estimated for each result.

2.1. Instrumentation

For organic impurities analysis, a high performance liquid chromatography (HPLC) system from Shimadzu (Kyoto, Japan), consisting of a LC-20AT quaternary pump, a DGU-20A$_3$/DGU-20A$_5$ on-line degasser, a SIL-20A/20AC auto-sampler, a SPD-20A photodiode array detector, and a CBM-20A/20A interface, was used. Lab Solution software was used for data processing.

The inorganic impurity analysis was carried out with ICP-MS using an Elan DRC II system from Perkin Elmer (Shelton, CT, USA) with a Meinhard cyclonic spray chamber and nebulizer (Golden, CO, USA), after sample digestion in a Multiwave 300 microwave digestion system from Anton-Paar GmbH (Graz, Austria).

Total volatile content was estimated with loss on drying, using a digital oven 400 from Nova Ética (São Paulo, Brazil). The water mass fraction was determined using a Karl Fischer coulometer (831 model) from Metrohm AG (Bleiche West, Switzerland) equipped with a generator electrode without a diaphragm, a current generator electrode (400 mA), and a platinum indicator electrode (10 μA), connected to an oven sample processor (774 model, Metrohm), a stirrer (728 model, Metrohm), and a controller (774 SC model, Metrohm). The residual solvents were analyzed in a Focus gas chromatograph equipped with a flame ionization detector (GC-FID) and a Triplus headspace injector from Thermo Scientific (Waltham, MA, USA). The results were processed using Chromquest 5.0 software.

Quantitative nuclear magnetic resonance (^{1}H qNMR) measurements were recorded on a VNMRSYS-500 spectrometer from Varian (Palo Alto, CA, USA), operating at 11.7 T. The 90° pulse length was optimized, and T_1 was determined with the inversion-recovery sequence. A relaxation delay of five times the greater measured T_1 was used in the subsequent experiments, to ensure that most nuclei had relaxed completely. For data processing and integration, MestReNova software version 6.0.2 from Mestrelab Research (Santiago de Compostela, Spain) was used. Phase correction was performed manually for each sample, and baseline correction was applied over the entire spectral range.

All sample solutions were gravimetrically prepared using analytical balances (Shimadzu), model AUW 220D, with a resolution of 0.01 mg.

2.2. Samples and reagents

The sodium diclofenac candidate CRM was placed in amber glass flasks. The flasks were then closed with rubber stoppers and aluminum seals (500 units, nominal mass 500 mg) and used for the certification studies. All tests were carried out using the candidate CRM in its final packaging form as intended for dispatch to customers.

For the HPLC–DAD comparative studies, the sodium diclofenac USP reference standard (batch H0B150, 100.0%, previous drying at 105 °C for 3 h) and the diclofenac-related compound A USP reference standard (1-(2,6-dichlorophenyl)-1,3-dihydro-2H-indol-2-one, batch IOD 337) were used. The reagents were HPLC-grade