RESEARCH ARTICLE

Photostability of Crystalline Versus Amorphous Nifedipine and Nimodipine

DRIEKUS GROOFF,[1] FARZAANA FRANCIS,[1] MELGARDT M. DE VILLIERS,[2] ERNST FERG[1]

[1]Department of Chemistry, Nelson Mandela Metropolitan University, Port Elizabeth 6031, South Africa

[2]School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53705

Received 24 January 2013; revised 12 March 2013; accepted 13 March 2013

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23533

ABSTRACT: True solid-state photostability of the drugs nifedipine and nimodipine was investigated during exposure to UV–visible radiation. Photostability was studied on a small scale as thin films of approximately 1 mg drug, which contained either amorphous or re-crystallised stable phases. High-performance liquid chromatography analysis revealed a greater rate and extent of decomposition for the amorphous phases. Photoexposed amorphous nifedipine exhibited approximately 1.8-fold larger first-order decomposition rate constant (k) relative to its crystalline phase. The increase in k was more significant for photoexposed amorphous nimodipine at approximately sixfold relative to its crystalline phase. Photodecomposition in scaled-up samples of the stable crystalline phases for both drugs was monitored with X-ray diffraction in Bragg–Brentano geometry. The similarities in the calculated photodecomposition extents to results from small scale validated the specificity of the X-ray analysis technique to the photodecomposition region. The considerably faster decomposition rates in small-scale studies were attributed to a maximised surface area (A) for quantity (m_0) of exposed drug. Kinetic interpretations of true solid-state stability should consider the sample solid dimensions in terms of the direct exposed A and m_0 in the photodecomposition region, that is, outer layers in solid. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: photodegradation; polymorphism; amorphous; solid-state stability; kinetics; pharmaceuticals; X-ray powder diffractometry; chemical stability; nifedipine; nimodipine

INTRODUCTION

The monitoring of the photostabilities of active pharmaceutical ingredients is an important matter for the pharmaceutical industry as light-induced chemical degradation, with the associated loss of therapeutic efficacy, results in a limited shelf life of the final pharmaceutical product. Other undesirable effects may include increased phototoxicity as a result of adverse photochemical reactions.[1] The International Conference of Harmonization Harmonized Tripartite Guideline considers photostability testing as integral to the stress evaluation of new drug substances and products.[2]

Photodegradation of light-sensitive pharmaceuticals can be attributed to their high absorptivity for radiation in the UV to/or visible range of wavelengths. A review by Bhalekar et al.[3] discussed the factors influencing photodegradation rate in the solid and solution states of pharmaceutical dosage forms. However, there is still a poor understanding of solid-state photodegradation. This can be attributed to a number of variables associated with factors such as particle size, drug content and dosage form properties such as tablet geometry and tablet preparation. In addition, changes in the solid-state forms of a drug (crystalline or amorphous) should also be considered while determining the solid-state photodegradation of drug solids. For example, because polymorphs differ in terms of their arrangement or packing of molecules in the crystal lattice, it is expected to manifest in differences of their physical and chemical stabilities. Especially, amorphous drugs have higher free energy, greater free volume and molecular mobility relative to their crystal forms and increased chemical instability.[4,5]

Correspondence to: Driekus Grooff (Telephone: +27-41-5041219; Fax: +27-41-5042236; E-mail: dgrooff@nmmu.ac.za)

Journal of Pharmaceutical Sciences
© 2013 Wiley Periodicals, Inc. and the American Pharmacists Association

The 1,4 dihydropyridine group of compounds, used for the treatment of hypertension and cardiovascular disease, are well known for their light sensitivity. The drugs commonly undergo photodegradation to their therapeutically inactive pyridine derivatives.[6–9] Onoue et al.[10] investigated the *in vitro* phototoxicity of several dihydropyridine-type calcium channel antagonists and reported that UVA/B exposure increased their phototoxic potential because of the formation of reactive oxygen species. Photodegradation in the solid-state occurs predominantly as a surface phenomenon. Mention was made of the surface darkening of nifedipine powder and tablets upon exposure to UV and visible light either as a result of daylight or lamp irradiation.[11,12] Photostability reports from the tablet[13] and powder forms[12,13] of nifedipine suggested that a measure of true solid-state stability needed to account for (or eliminate) the effect of particle size and drug content under a controlled constant illuminance. However, the effect of crystal form changes on the photostability of the 1,4 dihydropyridine compounds has not been fully elucidated.

This study investigated the true solid-state photostability of two 1,4 dihydropyridine compounds, nifedipine and nimodipine, as model drugs.[10] The influence of polymorphism, in the absence of the particle size effect, was determined by considering the relative photostabilities of the amorphous (prepared from melt supercooling) and the stable crystalline phases (prepared form melt re-crystallisation). Samples on a small (~1 mg prepared as thin films) and larger scale (~100 mg), irradiated under identical conditions, were analysed for remaining drug content with high-performance liquid chromatography (HPLC) and X-ray diffraction (XRD). Kinetic parameters [rate constant (k), times for 10 ($t_{0.1}$) and 50% ($t_{0.5}$) decomposition], estimated from the first-order degradation behaviour, were interpreted in terms of the drug studied (nifedipine vs. nimodipine), the polymorphic form of the drug (amorphous vs. crystalline) and the sample size.

MATERIALS AND METHODS

Materials

Nifedipine was purchased as the stable polymorph [melting point (mp) 171°C–173°C] from Sigma–Aldrich (Aston Manor, Gauteng, South Africa). Nimodipine was purchased from Sigma–Aldrich as the metastable polymorph (modification I, mp 124°C). Sodium chloride (Associated Chemical Enterprises, Johannesburg, Gauteng, South Africa; assay minimum 99.5%) was used for the creation of constant 75% relative humidity (RH) atmosphere inside a dessiccator. HPLC-grade methanol [minimum assay (gas-liquid chromatography), 99.8%] and acetonitrile [purity (gas chromatography) ≥99.9%] were purchased from BDH Chemicals Ltd (Poole, Dorset, UK).

Polymorphs for Photostability Studies

Amorphous and Stable Crystalline Nifedipine Polymorphs with HPLC Analysis Method (Small-Scale Study)

Approximately 1 mg of accurately weighed nifedipine, on a piece of aluminium foil, was melted on a hot plate set at 185°C. The melt was then covered with a glass coverslip which ensured a uniform sample thickness and free from humidity effects that might contribute to crystallisation processes. The amorphous modification was obtained from cooling the melt on a metal surface at ambient temperature. The stable crystalline polymorph for photostability studies was prepared from re-crystallisation of glass-covered amorphous nifedipine (~1 mg) during oven heating at 150°C [oven supplied by BTL (SA) (Pty) Ltd. (Port Elizabeth, Eastern Cape, South Africa), calibrated by LABTRONIC (Port Elizabeth, Eastern Cape, South Africa)] for 30 min. The identities of the polymorphs were confirmed from differential scanning calorimetry [DSC Q100; TA instruments (Randburg, Gauteng, South Africa)] according to characterisation methods reported in an earlier paper.[14]

Amorphous and Stable Crystalline Nifedipine Polymorphs with XRD Analysis Method (Larger Scale Study)

Approximately 100 mg of nifedipine, on a piece of aluminium foil, was melted on a hot plate set at 185°C. The amorphous modification was obtained by cooling of the melt on a metallic surface at ambient temperature. The sample, on aluminium foil, was mounted on a powder XRD sample holder. The stable modification was obtained from melt re-crystallisation of previously prepared amorphous nifedipine (100 mg) in a dessiccator (with 75% RH atmosphere) maintained at 150°C in oven for 30 min. Both the amorphous and stable modifications were covered with an identical glass cover slip to ensure uniform radiation conditions relative to the small-scale study. The coverslip was, however, removed during XRD analysis (Bruker D8 Advance diffractometer; Bruker-AXS, Karlsruhe, Germany). DSC and XRD analyses, according to the methodology reported in an earlier paper,[15] confirmed the polymorphic purity of the prepared modifications.

Amorphous and Stable Crystalline Nimodipine Polymorphs with HPLC Analysis Method (Small-Scale Study)

Approximately 1 mg metastable polymorph was accurately weighed on aluminium foil and then melted on a hot plate set at 140°C. The melt was covered with a glass coverslip before cooling on a metallic

Download English Version:

https://daneshyari.com/en/article/2484984

Download Persian Version:

https://daneshyari.com/article/2484984

Daneshyari.com