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Evaluation of microwave oven heating for prediction of drug–excipient compatibilities and accelerated stability studies

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ABSTRACT

Microwave ovens have been used extensively in organic synthesis in order to accelerate reaction rates. Here, a set up comprising a microwave oven combined with silicon carbide (SiC) plates for the controlled microwave heating of model formulations has been applied in order to investigate, if a microwave oven is applicable for accelerated drug stability testing. Chemical interactions were investigated in three selected model formulations of drug and excipients regarding the formation of ester and amide reaction products. In the accelerated stability studies, a design of experiments (DoE) approach was applied in order to be able to rank excipients regarding reactivity: Study A: cetirizine with PEG 400, sorbitol, glycerol and propylene glycol. Study B: 6-aminocaproic acid with citrate, acetate, tartrate and gluconate. Study C: atenolol with citric, tartaric, malic, glutaric, and sorbic acid. The model formulations were representative for oral solutions (co-solvents), parenteral solutions (buffer species) and solid dosage forms (organic acids applicable for solubility enhancement). The DoE studies showed overall that the same impurities were generated by microwave oven heating leading to temperatures between 150 °C and 180 °C as compared to accelerated stability studies performed at 40 °C and 80 °C using a conventional oven. Ranking of the reactivity of the excipients could be made in the DoE studies performed at 150–180 °C, which was representative for the ranking obtained after storage at 40 °C and 80 °C. It was possible to reduce the time needed for drug–excipient compatibility testing of the three model formulations from weeks to less than an hour in the three case studies. The microwave oven is therefore considered to be an interesting alternative to conventional thermal techniques for the investigation of drug–excipient interactions during preformulation.

1. Introduction

The study of the compatibility between an active pharmaceutical ingredient (API) and potential excipients for a drug formulation, named drug–excipient compatibility study, is important in the development of the drug product with the best stability profile (Crowley and Martini, 2001; Di and Kerns, 2009). Conventionally, the studies have comprised mixing the API with one or more potential excipients and submitting these mixtures to accelerated storage conditions with the subsequent analysis by a chromatographic technique, primarily HPLC coupled to UV (Elder, 2007; Qiu, 2006; Wu et al., 2011). However, stability studies are time-consuming, and could be a hindrance for submission of the drug file to regulatory authorities. It would therefore be advantageous, if the reaction rates for the degradation of API and formation of impurities could be accelerated in order to save time. The possibility of identifying the optimal excipient for a given formulation within minutes instead of waiting hours, days, or even months could be intriguing and may have a positive impact on the time spend during drug development.

Defining the quality target product profile containing acceptable purity, stability and drug release is one of the fundamental principles of Quality by Design (QbD) applied in formulation development of a drug product (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2009). A part of QbD constitutes the use of design of experiments (DoE), which is a statistical experimental design, where several factors at a time can be investigated using a limited number of experiments (10–20 experiments) (Eriksson et al., 2008). However, it is critical to define all the factors having an impact on drug stability from initial studies; otherwise, one may overlook important factors making the conclusions drawn from the DoE

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study erroneous. Different designs exist in DoE depending on the objective of the study. Screening designs are mainly applied to identify the most important factors out of many, whereas optimization designs are used for existing products or procedures in order to optimise the settings of the already identified significant factors (Eriksson et al., 2008). The simplest statistical designs are based on input factors containing only two levels, but since drug–excipient compatibility studies frequently comprise the evaluation of more than two potential excipients that may interact in a non-linear fashion, it may be a bit more challenging to generate a good experimental design with relatively few runs.

The utilization of microwaves for reaction rate enhancements in organic synthesis, first described by Gedye et al. (Gedye et al., 1986) and Giguere and Majetich (Giguere et al., 1986), has gained increasing interest over the last decades, which is reflected by the growing number of publications concerning microwave-assisted organic synthesis (Lidström et al., 2001). Microwaves are electromagnetic waves, typically with a frequency of 2.45 GHz. The electric field of the microwaves applies a force, changing in direction, to molecules, which start to rotate. The friction between the rotating molecules creates di-electric heating, the primary mode of heating in a microwave oven (Galema, 1997). Some controversy has existed regarding a specific microwave effect being the cause of the observed increase in reaction rates, but the application of more precise and reliable temperature measurements of the samples has excluded such an effect (Jahngen et al., 1990; Kappe, 2013; Raner et al., 1993). As temperature gradients were observed in the microwave oven for reactions performed with different solvents, reaction plates made of silicon carbide (SiC) were introduced. Silicon carbide is a strongly microwave absorbing material, which is chemically inert and can be used at very high temperatures (melting point 2700 °C) (Damm and Kappe, 2009b). Use of the SiC plate means that heating mainly occurs via conduction and not by di-electric heating effects, and it has been shown that solvents known to possess different microwave heating characteristics are heated with the same rate (Obermayer et al., 2009).

Recently, a rotor equipped with 4 SiC plates, each containing up to 20HPLC or GC vials has been introduced for microwave ovens. The set up can accommodate temperatures of up to 200 °C and pressures up to 20 bar (Damm and Kappe, 2009a). This opens up for the possibility of investigating reactions at high temperatures in standard HPLC vials, which can be transferred directly to an HPLC instrument with the use of minimal sample quantities and generation of impurities in a shorter amount of time. Despite the considerable effort placed in the investigation of microwave ovens for organic synthesis, only scattered examples exist in the literature, where a microwave oven has been used for accelerated stability studies (Madhavi et al., 2008; Prekodavac et al., 2011; Sonawane and Gide, 2011). These studies only comprise one API each, which has been subjected to microwave-assisted forced degradation such as acid or alkali catalysed degradation. Prekodavac et al. used a SiC plate set up in a microwave oven to study the degradation of indomethacin at different conditions (Prekodavac et al., 2011). However, literature examples do not exist, where the microwave oven has been applied for evaluation of drug–excipient compatibility.

The objective of this study was therefore to investigate, if the time for formation of impurities due to reaction between active pharmaceutical ingredient and excipients can be reduced by the use of microwave oven heating as compared to accelerated stability studies performed at 40 °C and 80 °C in conventional ovens and if the identity of the formed impurities are predictive for the impurities formed at normal storage. A DoE screening design was applied for the studies in the microwave oven in order to identify the factors having a significant impact on the stability of the model formulations and to be able to rank the investigated excipients according to their reactivity. Three case studies were selected after a literature survey in order to evaluate the potential use of the microwave oven: Study A: the anti-histamine cetirizine in combination with co-solvents used for oral formulations: PEG 400, sorbitol, glycerol and propylene glycol (United States Pharmacopoeia-National Formulary, 2014). Study B: the anti-fibrinolytic agent 6-aminocaproic acid in combination with buffers used for parenteral formulations: citrate, acetate, tartrate or gluconate buffer (Akers, 2002). Study C: the beta-blocking agent atenolol in combination with organic acids normally used for increasing the solubility of poorly soluble APIs (Andronis et al., 2001), citric acid, tartaric acid, malic acid, glutaric acid and sorbic acid.

2. Materials and methods

2.1. Materials

Cetirizine dihydrochloride, atenolol, polyethylene glycol 400 (PEG 400), sorbitol, gluconic acid, anhydrous citric acid and glutaric acid were purchased from Sigma–Aldrich Chemie (Steinheim, Germany). Tartaric acid, malic acid, sorbic acid and propylene glycol were obtained from VWR (Copenhagen, Denmark). Glycerol, 6-aminocaproic acid, citric acid monohydrate, formic acid, sodium acetate, concentrated hydrochloric acid, methanol and acetonitrile were obtained from Merck (Darmstadt, Germany). All solvents for HPLC-UV and HPLC-MS analysis were of MS-grade and purchased from VWR (Copenhagen, Denmark). Deionized water was used throughout the studies.

2.2. Instrumentation

A Synthos 3000 microwave oven (Anton Paar GmbH, Graz, Austria) installed with a 4 × 20 MGC rotor capable of holding up to four silicon carbide reaction blocks was used for the studies in the microwave oven. The SiC plates contain bore holes, suitable for 1.5 ml HPLC vials. The closures for the HPLC vials used during heating in the microwave oven were coated with PTFE silicone septa (VWR, Copenhagen, Denmark). Temperature was controlled in the Synthos 3000 by IR temperature measurements every 20 s during a run.

A Memmert universal oven UNE 200 (Memmert GmbH, Schwabach, Germany) was used for storage of the control samples at 40 °C and 80 °C. The oven was pre-heated to the temperature set-point and had a temperature variability of ±0.5 °C.

HPLC-UV analyses were carried out using an Agilent Technology 1200 series HPLC system (Agilent Technologies, Waldbron, Germany) equipped with a G1379B on-line degasser, a G1312B binary pump, a G1316B column oven, a G1367C HiP-ALS-SL auto sampler and a G1315C photodiode array detector.

Mass spectrometry detection was performed using a Thermo LCQ Deca XP Plus ion trap MS, which was operated with electro spray ionisation in the positive mode with the following parameters: Study A: capillary voltage 4000 V, drying gas flow 16 l/min, drying gas temperature 270 °C, vapourize temperature 150 °C. The scan range was from 200 to 1000 amu. Study B: capillary voltage 5000 V, drying gas flow 70 l/min, drying gas temperature 350 °C, vapourize temperature 150 °C. Study C: capillary voltage 5000 V, drying gas flow 35 l/min, drying gas temperature 275 °C, vapourize temperature 150 °C. The scan range for study B and C was from 200 to 800 amu.