Stability of Frusemide Tablets Repackaged in Dose Administration Aids

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ABSTRACT

Background: Repackaging tablets into a dose administration aid (DAA) requires that the pharmacist consider the stability of the active pharmaceutical ingredient and the excipients of the drug product. Frusemide is susceptible to photo-degradation and is commonly repackaged into DAAs.

Aim: To evaluate the stability (chemical and physical) of frusemide tablets repackaged into DAAs.

Method: Frusemide tablets repackaged into DAAs were evaluated for physicochemical stability over a period of 8 weeks at a controlled room temperature (25 ± 2°C) and other relevant in-use conditions. In addition, photostability studies were performed according to the International Committee on Harmonisation (ICH) guidelines.

Results: Chemical stability was confirmed for all storage conditions, including the ICH light conditions, with the frusemide content within the British Pharmacopoeial range of 95 to 105%. Although the physical stability was confirmed by all tests (weight uniformity, hardness, friability, disintegration, dissolution), storage in a simulated pharmacy environment after one week and exposure to ICH light conditions resulted in a yellow colouration of the tablets.

Conclusion: Although the chemical and physical stability of frusemide was within acceptable limits during the study, the discoloration of the tablets from light exposure is unacceptable. It is recommended that DAAs are stored protected from light immediately after repackaging with frusemide tablets, and that patients are counselled to store the DAA in a cool dark place.

INTRODUCTION

The shelf-life of a drug product may be affected by the intrinsic stability of the active pharmaceutical ingredient (API) and interactions between the API and the excipients. Shelf-life also depends on the dosage form, packaging, manufacturing process, and environmental conditions during transport, storage and use. Instability can lead to:

- loss of potency due to the degradation of the API;
- accumulation of potentially toxic degradation products causing adverse reactions in patients;
- changes in the physical appearance of a product that may affect patient compliance through loss of confidence in the medication.

In addition to chemical decomposition by hydrolysis, oxidation, isomerisation, polymerisation, or photochemical degradation of the API and/or excipients, physical changes in tablet hardness, friability, disintegration, or dissolution rate may lead to altered physical appearance (discolouration) or bioavailability of the drug product.

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Manufacturers’ packaging is designed to protect drug products from environmental factors encountered during storage, such as light, air (oxygen, carbon dioxide, other gases), and moisture while ensuring limited interactions between the product and the packaging material. However, this does not guarantee the stability of the API and the drug product on removal and repackaging into a dose administration aid (DAA). Although the stability of a dosage form is often seen to be the responsibility of the manufacturer, this does not include removal from the original packaging. In electing to repack a drug product into a DAA, pharmacists must consider the implications of the transfer to a non-manufacturer pack on drug stability. Despite the widespread use of these devices (due to their benefit in terms of health outcomes and cost of health care) there is little available data on the stability of the drug products when repackaged into such devices.

A recent survey of 392 products revealed that, although some information can be obtained from manufacturers, there is still a shortage of short-term stability data for the transfer of drug products into these devices. Frusemide is commonly used in the treatment of hypertension and is thus likely to be a candidate for DAA use. Additionally, frusemide displays intrinsic instability to light, and was therefore chosen as a model compound to determine the effects of light on repackaging drug products into DAAs.

The photolytic degradation of frusemide commonly involves photo-oxidation, photoreduction, photohydrolysis and photodehalogenation (Figure 1). Solid-state, photostability degradation takes place on the surface of the drug product usually leaving the interior of the preparation unaffected. Therefore, drug products, e.g. tablets, exposed to UV/visible light, do not necessarily follow any particular reaction order mode, because the rate of degradation depends on the absorptive and reflective properties of the surface layer, which can change during product degradation (e.g. particle size, crystal modification, colour).

Figure 1. Chemical structure of frusemide and sites of photo-degradation

Solid-state frusemide preparations are also susceptible to physical instability, including moisture sorption and desorption, and polymorphic transformations. A study on the storage of frusemide tablets at elevated humidity has shown a significant increase in water content with a subsequent decrease in tablet hardness and disintegration time. Frusemide can exist as a number of different polymorphs each displaying different physicochemical characteristics. In studies conducted on the polymorphs of frusemide it was found that some of these forms are more photostable and display improved dissolution and disintegration profiles than others. Interconversion of the polymorphs can occur during changes in temperature and storage at high humidity. This interconversion in solid-state preparations during storage can therefore adversely affect the therapeutic efficacy of that product.
Triplicate samples were prepared by accurately weighing and wrapped in aluminium foil. They were used as dark controls to consist of a 240 solvent delivery module, 410 autosampler from 15 to 50 °C, 20 µL column. A methanol:acetic acid (1%) (Sigma Aldrich) (65:35) mixture was chosen to simulate in-use conditions encountered in situ. Considering the shortage of short-term stability data for the measurement, statistical Package for the Social Sciences was used for ANOVA analysis to determine the level of significance (p < 0.05) of results obtained.

Method

Chemical Stability

A number of HPLC assay methods have been developed to quantify frusemide and its degradation products. An assay, adapted from these studies, was developed to provide accurate, reproducible and specific quantitation of frusemide in the presence of its possible degradation products. The Varian Prostar system consisted of a 240 solvent delivery module, 410 autosampler and a 330 photodiode array detector. The stationary phase was a C18 (150 x 4.60 mm) reverse-phase column. A methanol:acetic acid (1%) (Sigma Aldrich) (65:35) mobile phase (pH 3.67) and detection wavelength of 270 nm was used. The flow rate was 1 ±0.1 mL/min and the injection volume, 20 µL. A calibration curve for frusemide was constructed from 15 to 50 µg/mL (r² = 0.999). Triplicate samples were prepared by accurately weighing and finely crushing 15 tablets for each of the storage conditions. The powder was mixed and diluted appropriately with mobile phase to prepare a solution containing approximately 10 µg/mL frusemide, which was then filtered through a 0.45 µm filter (Millipore) prior to analysis. Amber glass cuvettes were used and all samples were prepared and transferred in flasks wrapped in foil.

Results

Results therefore show that the frusemide content was within the range (95 to 105% of labelled amount) specified in the BP monograph for Frusemide Tablets under all storage conditions over a period of 8 weeks. The compendial requirements were thus met for all storage conditions.

Physical Stability

The average weight at each sampling period, under all storage conditions, showed no trends in weight loss or gain, demonstrating no significant moisture sorption or desorption.
A slight decrease in tablet hardness was noted after one week of storage under ‘control conditions’. However, all tablets disintegrated in less than 30 seconds, with no discernable trends of increased or decreased disintegration time after an initial slight decrease after one week of storage under all conditions. No significant difference was seen in the disintegration profiles of the tablets stored under all storage conditions, with the API in solution remaining above 80% after 45 minutes for all tablets. The quality of frusemide tablets was confirmed regarding their disintegration, hardness, weight uniformity, friability, and dissolution rate over a period of 8 weeks (Table 1).

In conclusion, because of the discolouration of frusemide tablets after one week, DAAs should be protected from light in the pharmacy and in patients’ homes. This can be achieved by placing the DAA into a light-protecting sleeve (e.g. foil, cardboard) and/or stored protected from light. A recent study made further practical recommendations for patients that include:13

- careful removal of tablets to prevent accidental rupture of adjacent blisters, thus exposing tablets to air and moisture;
- monitoring DAA integrity throughout the in-use period; and
- consideration of an appropriate location to store the DAA to avoid unnecessary exposure to light, heat and humidity.

In conclusion, because of the discolouration of frusemide tablets after one week, DAAs should be protected from light immediately after repackaging and patients should be advised to store DAAs in a cool dark place. The results of this study provide further evidence to support pharmacists in making positive decisions regarding the repackaging of medicines in these devices.

Competing interests: None declared.

References