RESEARCH

# Stability of Frusemide Tablets Repackaged in Dose Administration Aids

**Luke Bowen, Martina Mangan, Alison Haywood, Beverley Glass**


## 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 photodegradation 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 ºC) 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 discolouration 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.


**J Pharm Pract Res 2007; 37: 178-81.**

## 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.[1,2] Instability can lead to:

- loss of potency due to the degradation of the API;[2]
- accumulation of potentially toxic degradation products causing adverse reactions in patients;[3] and
- changes in the physical appearance of a product that may affect patient compliance through loss of confidence in the medication.[2]

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 repackage 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.[4-7] 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.[7]

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.[8]

The photolytic degradation of frusemide commonly involves photo-oxidation, photoreduction, photohydrolysis and photodehalogenation (Figure 1).[9-12] Solid-state, photochemical 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).[9]

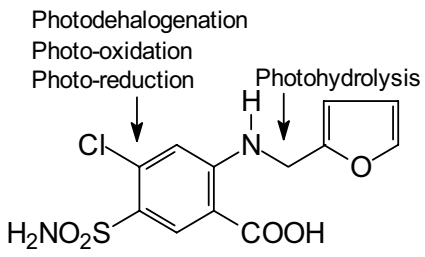


**Figure 1. Chemical structure of frusemide and sites of photo-degradation**

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.[10] 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.[11,12] Interconversion of the polymorphs can occur during changes in temperature and storage at high humidity.[11] This interconversion in solid-state preparations during storage can therefore adversely affect the therapeutic efficacy of that product.

## METHOD

Physicochemical studies were performed on frusemide 40 mg tablets (Uremide) stored at controlled room temperature and two simulated in-use conditions, in a DAA (Webster-pak) frequently used in practice, over a period of 8 weeks.[13,14] Physical characteristics of the tablets such as weight uniformity, physical appearance, thickness, hardness, friability, disintegration and dissolution rates were monitored and chemical stability was confirmed by high performance liquid chromatography (HPLC). Photostability studies were performed as per the International Committee on Harmonisation (ICH) guidelines and the amount of frusemide quantitated by the validated HPLC method.[15] All samples were chosen at random and had a remaining shelf-life of at least two years at the time of sampling. Percentage relative standard deviation and standard error of the mean were determined for representation of accuracy in 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.

### Storage Conditions

Considering the shortage of short-term stability data for the transfer of drug products to DAAs, storage conditions were chosen to simulate in-use conditions encountered *in situ* during storage in pharmacies (i.e. from time of repackaging to dispensing of medication) and in patients' homes, over a period usually encountered in practice (8 weeks).[13] The storage locations were:

- control: protected from light at controlled room temperature (25 ±2 ºC; 60 ±5% relative humidity);
- home: blister-side up in a bathroom exposed to a standard 60 watt tungsten bulb and indoor indirect daylight (i.e. window-filtered sunlight); and
- pharmacy: blister-side up on a bench top exposed to fluorescent lighting and indoor indirect daylight. Relative humidity and air temperature were recorded using Tiny-tag plus data loggers.

### Chemical Stability

A number of HPLC assay methods have been developed to quantify frusemide and its degradation products.[16-21] 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.[22] 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 µbondapak (5 µmol, 250 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 ($r^2 = 0.999$). 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 40 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.

### Photostability

DAAs were placed blister-side up in the Hereaus Suntest CPS+ (ATLAS) and exposed to the visible wavelength 400 to 800 nm at 1.2 million lux hours and the UV wavelength 300 to 400 nm at 200 watt hours/$m^2$ as per the ICH guidelines.[15] Protected samples (wrapped in aluminium foil) were used as dark controls to evaluate the contribution of any thermally induced change. Triplicate samples were prepared by accurately weighing and finely crushing 15 tablets for the test conditions. The amount of frusemide was quantitated as per the HPLC method described.

### Physical Stability

Physical tests were performed following methodology recently described by Haywood et al.[13] Appearance was determined organoleptically by comparison to the original samples. Tablet weight uniformity was determined using an AND HM-200 analytical balance. Tablet friability was determined using a Vankel (VK) dual drum friabilator. Tablet hardness and thickness was determined using a VK 200 tester. Disintegration was determined using a VK 35-1300 disintegration tester. A disc was added to each tube and purified water (Millipore ELIX10) (37 ±0.5 ºC) was used as the medium. These physical tests were performed in triplicate. Dissolution tests were performed in duplicate on a BP Apparatus II (paddle apparatus) (VK 7000) operating at 50 rpm, using a phosphate buffer (pH 5.8) (BDH Merck) dissolution media (900 mL) maintained at 37 ±0.5 ºC. Samples were filtered through a 0.45 µm filter (Millipore) and the filtrate diluted 1:4 with dissolution medium and assayed on a Cary 100 UV/VIS spectrophotometer at 270 nm.

## RESULTS

### Storage Conditions

The in-use storage conditions over the 8 week period were recorded as follows:

- In-use (a) 'pharmacy conditions' ranged from 22 to 27 ºC, and 33.5 to 78.0% relative humidity; and
- In-use (b) 'home conditions' ranged from 21.5 to 30.5 ºC and 27.5 to 95.5% relative humidity.

### Chemical Stability

Method validation for accuracy, precision, specificity and linearity was carried out as per the ICH guidelines.[23] The retention time for frusemide was 4.8 minutes with peak purity determined through spectral library comparison and peak purity determinations (Varian Prostar Polyview 2000) of the respective samples and standard solutions. The absence of co-eluting degradants and excipients was verified with spectral similarities of > 0.999 (photodiode array detection) for the pure and sample frusemide peaks achieved. Linearity was confirmed over the concentration range used ($r^2 = 0.999$). Concentrations of frusemide in the samples were determined from respective peak areas in relation to constructed standard curves and then converted to a percentage of the initial frusemide concentration. The amount of frusemide per tablet (vs labelled amount) as a function of storage time is shown in Figure 2. The results showed that the frusemide content was within the range (95 to 105% of labelled amount) specified in the BP monograph for Furosemide Tablets under all storage conditions over a period of 8 weeks.[24] The compendial requirements were thus met for all storage conditions.

### Photostability

Irradiation under the ICH conditions resulted in 98% of frusemide remaining, while 101% was reported for the dark controls. The results therefore show that the frusemide content was within the range of 95 to 105% of the labelled amount. This confirms the minimal degradation occurring to be due to light and not heat (Hereaus Suntest CPS+ was maintained at 40 ºC) generated on light exposure. A change in colour to a pale yellow was observed for the samples and not the dark controls.

### 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.

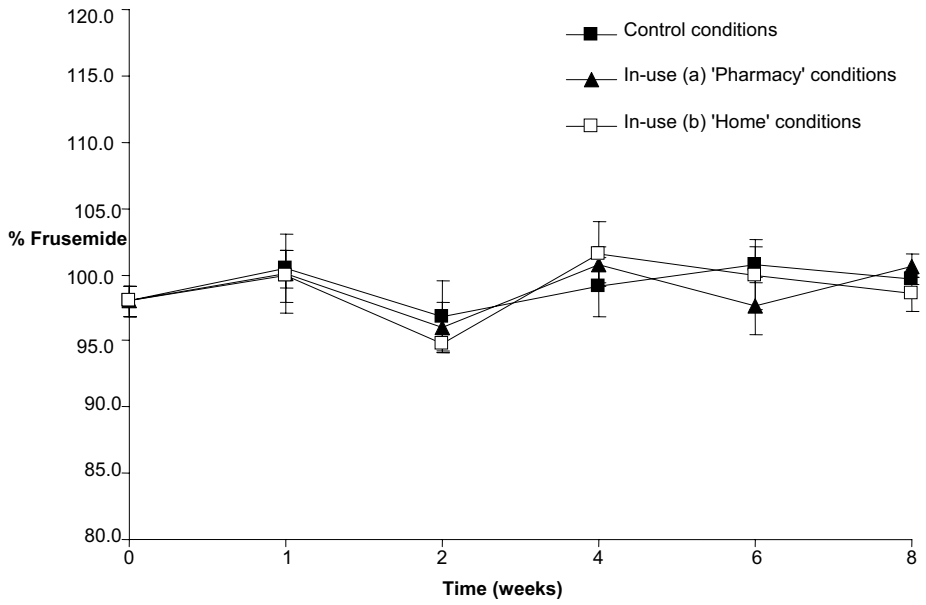


**Figure 2. Chemical stability of frusemide tablets under various storage conditions (values expressed as mean ± SEM, n = 3)**

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 dissolution 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).

**Table 1. Physical stability of frusemide tablets after 8 weeks of storage under various environmental conditions**[13]

| Physical test | Requirement | Storage | Results |
|---|---|---|---|
| Friability | Max loss of 1% of the tablets mass is acceptable | Control<br>In-use (a)<br>In-use (b) | 0.08%<br>0.10%<br>0.10% |
| Disintegration | All tablets disintegrated after 15 min | Control<br>In-use (a)<br>In-use (b) | 19 sec<br>18 sec<br>20 sec |
| Dissolution | Amount of active ingredient in solution after 45 min is not less than 70% of the stated amount | Control<br>In-use (a)<br>In-use (b) | 100.18%<br>94.56%<br>94.48% |

There were noticeable organoleptic changes in the tablets stored under 'pharmacy conditions' with a progressive yellow discolouration over the 8 weeks, starting in week 1. The frusemide tablets stored under 'control conditions' and 'home conditions' did not change from their original, pure white colour.

## DISCUSSION

A recent study examined the stability implications of repackaging paracetamol tablets in a commonly use DAA.[13] The samples in this study were stored under controlled laboratory conditions (long-term and accelerated) according to the ICH Technical Requirements for Registration of Pharmaceutics for Human Use guidelines.[25] The results of the stability study were extrapolated to suggest that paracetamol tablets repackaged into a DAA offering sufficient protection from moisture would remain stable for an in-use period of around 6 weeks (2 weeks for advanced packing and delivery on a 4-week supply).

The primary aim of this study was to investigate the in-use stability implications of repackaging a drug product susceptible to photodegradation into a commonly used DAA over a conventional packaging and in-use period of 8 weeks. Storage conditions were therefore chosen to reflect those typically encountered in patients' homes (home conditions) and in a pharmacy offering a repackaging service (pharmacy conditions).

Although the physical and chemical stability of frusemide was confirmed under all conditions, the tablets stored under 'pharmacy conditions' displayed a progressive yellow discolouration over a period of 8 weeks (starting in week 1). These tablets were exposed to fluorescent lighting which emits more UV light than the standard tungsten bulb encountered in the 'home conditions'. The effect of light was confirmed by the results for the photostability studies conducted according to the ICH guidelines. Although the colour change was noted as having negligible effects on frusemide content (possibly due to it being a surface effect) and physicochemical parameters of the tablets, it should be considered an unacceptable change, since patients are likely to be concerned about a possible compromise in the quality of the medication, and this may have an effect on patient acceptance and hence compliance.

These results indicate that frusemide tablets repackaged into 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.

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Received: 23 January 2007
Revisions requested after external review: 12 June 2007
Revised version received: 17 June 2007
Accepted: 2 July 2007

## *Vale*

**Pamela Elizabeth Nieman**
**16 June 1950—18 July 2007**

Pam Nieman was an extraordinary woman who devoted her life to her family, her profession, community work and her friends. Pam made an enormous contribution to the profession right up until her death on 18 July 2007. Pam was diagnosed with motor neurone disease in November 2006 and, with the absolute and unfailing support of her family and friends, she dealt with the disease with the same determination, dignity and spirit that she applied to all aspects of her life. Pam had a remarkable work ethic and always stood up for what she felt was right. She believed in a fair go for all, and her passionate drive for best practice, social equity and professional progress exemplified her career.

Pam's long and illustrious association with hospital pharmacy began in 1970 when she worked as a student at Peter MacCallum Cancer Institute. In 1971 she completed her traineeship at St Vincent's Hospital and in 1972 moved to The Royal Melbourne Hospital (RMH) to work under the directorship of Neil Naismith. Neil clearly recognised Pam's potential and she became one of the first clinical pharmacists in Victoria. Pam stayed at RMH for over 25 years, where she was valued and respected as a friend and mentor to many pharmacists, technicians and other members of staff.

In 1997 Pam became the Executive Officer of SHPA, the first pharmacist appointed to this role. In 2000, she left SHPA to care for her father, but continued working part-time at the Royal Children's Hospital and then at Monash Medical Centre.

Pam was a member of SHPA for over 35 years where she served on Federal Council as Federal Secretary (1985–1989) and Federal Vice-President (1983–1985, 1989–1993). She also served continuously on the Victorian Branch Committee from 1973 until her death and was an Executive Committee member for over 30 years. Pam believed strongly in continuing education and was an avid conference goer and member of numerous conference organising committees.

Pam represented SHPA on a number of external bodies and served as the hospital representative on the Pharmaceutical Care National Advisory Group and the National Pharmacy Competency Standards Project of the Pharmaceutical Society of Australia (PSA). Pam served as the hospital representative on the Victorian College of Pharmacy's Bachelor of Pharmacy Advisory Committee, and the Graduate Diploma of Hospital Pharmacy Course Re-Accreditation Committee and its Board of Examiners.

In 1984, Pam was appointed to the Pharmacy Board of Victoria, where she worked tirelessly, as Treasurer (1992 and 1993), and President (1993–997). When the old Board was dissolved in 2005, and replaced with a new Board under the *Health Professions Registration Act*, Pam was one of the three members of the previous board who were appointed by the Minister of Health to the new Board. She was elected as its Deputy President, a position she held until her death.

Pam served on the national Association of Pharmacy Registering Authorities, including for three years as its President. She was also Chair of the national Pharmacy Boards' Registration and Education Committee and the New Zealand and Australian Pharmacy Schools Accreditation Committee.

For her enormous contribution to the profession, Pam was awarded two prestigious awards available to SHPA members—Glaxo Medal of Merit (1990) and Fred J Boyd Award (1995). In 1996, Pam was elevated to the status of Fellow [Honoris Causa] by PSA, for her contribution to the whole profession.

Pam also worked hard in the community and over the past five years she worked with a team from local churches in Richmond to provide food for the needy. She was a keen race goer, had a wry sense of humour and enjoyed good food, good wine and good conversation. Pam was generous and considerate and always ready to lend a hand of friendship or support, or to offer condolences or congratulations as the occasion required. This seems to have been the 'Nieman way' and Pam certainly carried on the proud family tradition.

The world will be a poorer place without Pam's unselfish and indefatigable spirit. She will be truly missed but fondly remembered with admiration and respect.