Compliance aids have been developed to assist patients better manage their medicines by organising individual doses according to the prescribed dosing schedule throughout the day. While well-sealed dose administration aids (DAAs) such as the WebsterPak are commonly used by community and hospital pharmacists to repackage medicines, it is not known which compliance aids are used by patients in their homes. Many of these aids, such as the dosette box or pill organiser are readily available under a variety of brands, but do not have adequate airtight seals.

Removal of medicines from primary packaging and repacking into a compliance aid invalidates the stability guaranteed by the manufacturer. Only a small number of medicines (e.g. atenolol, paracetamol, frusemide prochlorperazine and clozapine) have been investigated for stability following repacking into DAAs by pharmacists.

Llewelyn et al studied the stability of sodium valproate, which is known to be hygroscopic when repacked into DAAs and stored under various temperature and humidity conditions. The results highlighted that accelerated conditions of temperature and humidity must be taken into account, as well as the fact that different countries (and even within countries) may experience variable temperature, humidity and light conditions. These studies have been performed using well-sealed DAAs commonly used by pharmacies in Australia.

Elmasry et al reported on the quantitative analysis of mebeverine, mesalazine, sulphasalazine and dispersible aspirin stored in a monitored dosage system, highlighting not only that the tablets were stored together, but also the differences in terms of safety and risk between medications repacked under the supervision of a pharmacist and those being repacked into compliance aids by patients.

Low-dose aspirin is prescribed for primary prevention of stroke and acute myocardial infarction in older people. A recent study reported that low-dose aspirin (acetylsalicylic acid [ASA]) was a cost-effective option in primary prevention and that the majority of health systems are more than willing to pay for any additional quality-adjusted life year gained. Tablet splitting or dividing has been an accepted practice for many years as a means of obtaining the prescribed dose of a medication and for cost-saving purposes. The storage of split tablets is not well discussed in the literature and anecdotal evidence suggests that many patients split tablets in advance and then store these in bottles that previously contained the same medication, a different medication or some other substance, or in a

FIGURE ONE: Hydrolysis of aspirin to salicylic acid

Aspirin (ASA) → Salicylic Acid

Water / moisture
compliance aid such as a dosette box. Due to stability concerns, patients are generally advised that if only half a tablet is used, the unused half should be discarded, particularly with medicines that are known to be unstable, when exposed to light and air.

ASA is rapidly hydrolysed to salicylic acid (SA) on exposure to moisture (see Figure One) and the limit of the SA content in dispersible ASA tablets is 3%. Chromatographic methods have been described to determine ASA in pharmaceutical formulations and biological fluids.

Investigators using reverse-phase high-performance liquid chromatography (HPLC) have recommended a short time limit for the determination of ASA between sample preparation and analysis in order to prevent degradation. The lack of exact data on the stability of these samples in an HPLC autosampler prior to analysis is the limitation of these assays. Studies by Kees et al, Gandhimathi et al and Montgomery et al have also been limited by their lack of specificity and data relating to robustness in terms of the stability of samples for HPLC injection. Other limitations include the use of mobile phases, which are complex and not cost effective, and the use of chloroform (environmentally inappropriate solvent) for the extraction of ASA.

Considering the above repacking practices and that ASA is rapidly hydrolysed to SA on exposure to moisture, this study aimed to determine the stability of ASA in dispersible tablets repacked into dosette boxes, a practice often undertaken by patients.

METHOD

High performance liquid chromatography

The Varian ProStar HPLC system consisted of a 240 quaternary solvent delivery module, 210 autosampler and a photodiode array detector. A Pursuit XRs C18 (5µm, 250 x 4.6mm) reverse-phase column (at 40°C) was selected as the stationary phase. The mobile phase was water:methanol:phosphoric acid (1M (35:60:5)) and the detection wavelength was 235nm. An injection volume of 20µL was used with a flow rate of 1mL/min. Data were analysed using Varian Star Chromatography Workstation. The method was validated for accuracy, precision, linearity and range, sensitivity, robustness (solution stability) and specificity.

Storage conditions

The following four storage conditions were investigated: refrigeration (5±3°C); controlled room temperature (25°C; 60% relative humidity [RH]); accelerated (40°C; 75% RH) simulated by a climate chamber conformant to the International Conference on Harmonisation requirements; and ‘in-use’ with natural variations in daylight exposure and internal temperature fluctuations (23–26°C; 45–60% RH).

Dispersible aspirin 300mg tablets (Solprin, Reckitt Benckiser) whole and split (halved along the tablet score line) were removed from the primary (foil) packaging and immediately repacked into dosette boxes and stored for one week at each of the four storage conditions. For the controls, Solprin 300mg tablets in primary (foil) packaging were also stored under the same four conditions. All of the Solprin tablets tested had the same batch numbers and an expiry date of one year from the time of analysis. The stored tablets were tested for drug content (ASA) and the degradation product (SA) at days 0 and 7.

Standard and sample solutions

Standard solutions of ASA (2–30µg/mL) and SA (2–10µg/mL) were prepared. For each assay (in triplicate), 20 tablets were selected at random, removed from the primary packaging and finely crushed using a mortar and pestle. A sample equivalent to 300mg of aspirin was then transferred to a 50mL volumetric flask and extracted with a solution of methanol:formic acid (98:2). Extracted tablet samples were sonicated for three minutes each and filtered through 0.2µm syringe filter. Further dilution with mobile phase resulted in a solution containing approximately 15µg/mL aspirin. All samples were protected from light during extraction and stored in amber vials and analysed using the stability-indicated HPLC method.

RESULTS

High performance liquid chromatography

Several extraction media (eg, acetonitrile, methanol, ethanol, mobile phase) were evaluated to achieve the best extraction recovery of ASA. Single tablets (in triplicate) were dissolved in each extractant, filtered, diluted with mobile phase and analysed immediately. The ASA per cent recovery for the extractants was: acetonitrile (80%), methanol (99%), ethanol (95%) and mobile phase (water:methanol:phosphoric acid 35:60:5) (95%). Methanol produced the best extraction recovery, and the addition of formic acid 2% improved the peak shape. The method proved to be valid for accuracy, precision, linearity (correlation coefficients greater than 0.9999 for both ASA and SA) and sensitivity.

Robustness (solution stability)

Due to the susceptibility of ASA to hydrolysis, sample solutions may degrade during the extraction process or sample preparation for HPLC analysis. This may be attributed to the water containing...
mobile phase and that the sample was maintained in the HPLC autosampler prior to analysis. Therefore, an assessment was made of the stability of the sample solutions prepared in the following manner. A tablet was extracted, diluted and maintained in the HPLC autosampler under laboratory conditions (25 ± 2ºC), it was then repeatedly analysed by HPLC over an eight-hour period. Extracted tablet sample solutions on the HPLC autosampler when subjected to repeat sampling after five hours showed a 2% decrease in concentration of the analyte, ASA. These results informed all analyses, where samples were always extracted, diluted and analysed within the five-hour time period and usually within two hours to ensure stability of the analyte.

**Specificity**
As per International Conference on Harmonisation guidelines, forced degradation studies were performed on tablet samples under the stress conditions of light, heat, humidity, acid/base hydrolysis and oxidation. The conditions used in this study were designed to avoid complete, but achieve no less than 5% degradation of the active pharmaceutical ingredient, ASA.

Other than SA, no major degradation products were observed, when ASA was subjected to acid/base, oxidative and photolytic stress. A summary of the amount of ASA remaining after exposure to various stress conditions of light, heat, humidity, acid/base hydrolysis and oxidation is presented in Table One. Peak purity test results confirmed that the ASA peak was homogeneous and pure in all the analysed stress samples, confirming that the ASA was unaffected by the presence of the degradant SA or tablet excipients.

**Storage conditions**
Aspirin is rapidly hydrolysed to SA on exposure to moisture...
for the ASA and SA content across the four storage conditions.

With regards to the physical attributes, the aspirin tablets removed from the original packaging exhibited signs of physical degradation within seven days of being repacked into dosette boxes and stored at accelerated conditions (see Figure Two). The tablets swelled, became soft, disintegrated easily and developed a pink discoloration.

**DISCUSSION**

A simple and cost-effective HPLC method was developed to quantitate ASA in dispersible aspirin tablets that is accurate, precise, sensitive and specific. The extraction method using methanol resulted in an extraction recovery of 99% and was superior to other solvents. In addition, methanol presented an environmentally safe option compared to chloroform used by Montgomery et al.

Our study also presents important information on the robustness of the HPLC method, which ensures the stability of ASA in the samples prior to analysis. This stability-indicating method can therefore be used to determine ASA in dispersible aspirin tablets repacked into dosette boxes.

Although our results concur with Elmasry et al in terms of the aspirin content when stored under standard conditions, these authors did not specify the exact temperature conditions, conduct the stability study under accelerated conditions, or monitor the amount of the degradant, SA. However, they highlighted the risk associated with patients using dosette boxes to manage medicines and their work presents a valuable insight into the implications of storing different medicines together in a compliance aid.

These results are also in agreement with the findings of a study highlighting that discoloration in aspirin tablets was due to exposure to high humidity. Dispersible tablets are listed as an example of solid dosage forms that should not be repacked into compliance aids, according to guidelines, such as the Professional Practice Standards and Dose Administration Aids Service.

In conclusion, while the ASA content of the dispersible aspirin tablets remained within specifications at room temperature, there were changes in the physical appearance under accelerated storage conditions.

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Some key references are listed at the end of this article and a full list of references are provided in the original publication.

**ERRATUM**

The Clinical Pharmacy continuing professional development article published in the AJP’s December 2012 issue identified the wrong authors. It should have noted that article was authored by Christopher Freeman BPharm, DradDipClinPharm; W Neil Cottrell BScPharm(Hons), MScPharm, PhD; Greg Kyle BPharm, M Clin Pharm, PhD; Ian D Williams MBBS, FRACGP; Lisa Nissen BPharm, PhD. The error resulted from not replacing the authors of the previous clinical pharmacy CPD article published in October 2012. The AJP apologises unreservedly to the authors and readers for this error.