# Stability of Paracetamol Tablets Repackaged in Dose Administration Aids for *prn* Use: Implications for Practice

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## ABSTRACT

**Background:** Paracetamol tablets are often repackaged into dose administration aids (DAAs) for *prn* use. Pharmacists have limited information regarding the long-term stability of *prn* medicines stored in DAAs for extended periods due to infrequent dosing. According to current guidelines, in the absence of specific data, medicines should not be stored in a DAA for longer than 8 weeks.

**Aim:** To determine the physicochemical stability of paracetamol tablets repackaged into DAAs and stored for 12 months.

**Method:** Paracetamol (Panamax) tablets were removed from primary packaging, repackaged into DAAs (Multi Dose Webster-pak) and stored under ambient (25 ºC; 60% relative humidity) and accelerated (40 ºC; 75% relative humidity) conditions for 12 months. Physical characteristics of the tablets, such as appearance, weight uniformity, thickness, hardness, friability, disintegration and dissolution rates were evaluated at baseline, 3, 6 and 12 months. Chemical stability was confirmed by high performance liquid chromatography.

**Results:** All compendial requirements for physical stability were met for tablets stored under ambient and accelerated conditions over the 12-month period. Chemical stability was confirmed, with paracetamol content in the tablets within the British Pharmacopoeial range of 95% to 105% of the labelled amount.

**Conclusion:** This study provides data on the stability of paracetamol tablets repackaged into DAAs and stored under ambient and accelerated conditions for 12 months. Pharmacists will be able to make risk–benefit assessments and recommend a 12-month expiry on paracetamol *prn* DAAs.

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## INTRODUCTION

Paracetamol is a valuable first-line drug for relieving mild to moderate pain and has been successfully combined with opioids for the management of severe pain.[1-3]

Dose administration aids (DAAs) are used to manage medications for patients in their homes and for residents in aged care and other facilities. The level and type of care often determines which medicines are repacked and the type of DAAs used. High-care facilities and most patients in the community administer when necessary (*pro re nata [prn]*) medicines from the primary packaging, while regular non-*prn* medicines are often packed in DAAs. Low-care facilities, where registered or enrolled nurses are not always available to administer medications, utilise repackaged *prn* medicines, as per the *Guidelines for Medication Supply to Residential Aged Care Facilities* (RACFs).[4] In such facilities, paracetamol is one of the most commonly repackaged *prn* medicines, with two paracetamol tablets packed into each blister of a *prn* DAA.

Although previous Australian Government guidelines proposed that medications for RACFs not be stored in DAAs for longer than 6 weeks, the current dose administration aids service guidelines for pharmacists recommend that, in the absence of specific data, medicines should not be stored in a DAA for longer than 8 weeks.[5,6] It is also recommended that the quantity packed for *prn* medicines should not exceed the quantity that reasonably could be expected to be required over 8 weeks.[6] Pharmacists have been challenged to balance these guidelines in their risk assessment for safe medication supply to RACFs. The infrequent dosing of *prn* medicines makes it difficult to predict a suitable quantity to repackage. These conflicts must be balanced with respect for the autonomy and rights of consumers as per the *Code of Ethics for Pharmacists*.[7]

Removal of a medicine from primary packaging and repackaging into a compliance aid invalidates the stability guarantee of the manufacturer. Despite this, only a limited number of medicines have been investigated for stability following repackaging into compliance aids, namely aspirin, atenolol, clozapine, frusemide, paracetamol, prochlorperazine and sodium valproate.[8-14] However, the stability of these repackaged medicines has not been investigated for a 12-month period.

Paracetamol subsidised under the Australian Pharmaceutical Benefits Scheme is supplied in quantities of 100 or 300 for patients with chronic arthropathies.[15] For patients with an infrequent need for paracetamol, this may necessitate disposal and replacement of large quantities of paracetamol every 8 weeks, or considering previous research on the stability of paracetamol, every 3 months.[12] Frequent replacement of *prn* DAA packs that may contain viable medications places additional cost on the patient, and extra workload and cost on the RACF and pharmacy.

Haywood et al.[12] have reported on the physicochemical stability of paracetamol tablets repackaged into DAAs and stored for 3 months. Therefore, we aimed to determine the physicochemical stability of paracetamol tablets repackaged into DAAs and stored for 12 months.

## METHOD

Physicochemical stability studies were performed at baseline, 3, 6 and 12 months on 8 paracetamol tablets (Panamax, Sanofi-Aventis) with 2 years to expiry, repackaged into DAAs (Multi Dose Webster-pak). The DAAs were stored at ambient (25 ± 1 ºC; 60 ± 1.5% RH) and accelerated (40 ± 1 ºC; 75 ± 1.5% RH) conditions in a dark climate chamber as per the International Conference on Harmonisation guidelines.[16] Percentage relative

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standard deviation and standard error of the mean were determined to represent accuracy in the measurement. Statistical Package for the Social Sciences (version 18) was used for ANOVA analysis to determine the level of significance ($p < 0.05$) of results obtained.

**Physical Stability**

Appearance was evaluated organoleptically in comparison to the original samples. Tablet weight uniformity was measured using an AND HM-200 analytical scale (Ph Eur method 2.9.5).[17] Tablet friability was determined using a VK dual drum friabilator (Ph Eur method 2.9.7).[17] Tablet hardness and thickness was assessed using a VK 200 tablet hardness tester (Ph Eur method 2.9.8).[17] Disintegration was determined using a VK 35-1300 disintegration tester with purified water (Millipore Elix10) (37 ± 0.5 ºC) as the medium (Ph Eur method 2.9.1).[17] Dissolution tests were performed (Ph Eur method 2.9.3) on a British Pharmacopoeia (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 withdrawn at 2, 4, 10, 20 and 25 minutes and filtered through a 0.45 µm filter (Millipore). The filtrate was diluted 1:100 with NaOH (0.1 M) (Sigma Aldrich) and assayed for paracetamol content using a Cary 100 UV-Vis spectrophotometer at 257 nm according to the test for dissolution for paracetamol tablets.[18] All physical tests used are described in the study by Haywood et al.[12]

**Chemical Stability**

The high performance liquid chromatography (HPLC) method described in the US Pharmacopoeia (USP) was used to quantify paracetamol in the presence of its degradants and tablet excipients.[19] The HPLC system (Varian ProStar) consisted of a 240 solvent delivery module, 210 autosampler and a 330 photodiode array detector. A Waters µbondapack C18 (10 µm, 250 x 4.6 mm) reverse-phase column and a mobile phase consisting of methanol and water (1:3) with a flow rate of 1.5 ± 0.1 mL/min and injection volume of 10 µL was used with a detection wavelength of 243 nm. A calibration curve for paracetamol was constructed for concentrations from 5 to 25 µg/mL ($r^2 = 0.999$). Twenty tablets were ground to a fine powder and triplicate samples containing 100 ± 5 mg paracetamol were weighed, diluted with mobile phase and filtered through a 0.45 µm filter (Millipore) prior to analysis.

## RESULTS

**Physical Stability**

No organoleptic changes were observed in any of the samples over the 12-month period under ambient or accelerated conditions. There was no significant change ($p > 0.05$) in the BP compendial requirements for tablet weight uniformity, hardness or thickness, demonstrating that moisture sorption or desorption had not occurred. All tablets disintegrated in less than 4 minutes, with no trends of increased or decreased disintegration time. No significant difference ($p > 0.05$) was seen in the dissolution profiles of the tablets stored under all conditions, with the dissolved paracetamol remaining above 80% after 25 minutes for all tablets. The quality of the repackaged paracetamol tablets was confirmed regarding their disintegration, hardness, weight uniformity, friability, and dissolution rate over 12 months, including for the accelerated storage conditions encountered in various regions of Australia. Results for the physical stability including disintegration, friability and hardness are shown in Table 1, with dissolution profiles shown in Figure 1.

**Table 1. Physical stability of paracetamol tablets stored in dose administration aids under accelerated conditions (40 ºC; 75% relative humidity) for 12 months**

| Storage time (month) | Hardness (N)* | Friability (% loss)† | Disintegration time (s)‡ |
|---|---|---|---|
| 0 | 161.7 ± 12.9 | 0.20 | 158 |
| 3 | 168.1 ± 7.6 | 0.19 | 181 |
| 6 | 163.8 ± 16.6 | 0.20 | 191 |
| 12 | 162 ± 12.9 | 0.43 | 127 |

*Values are expressed as mean ± SD (n = 20). †Values are expressed as mean (n = 20). ‡Values are expressed as mean (n = 6).

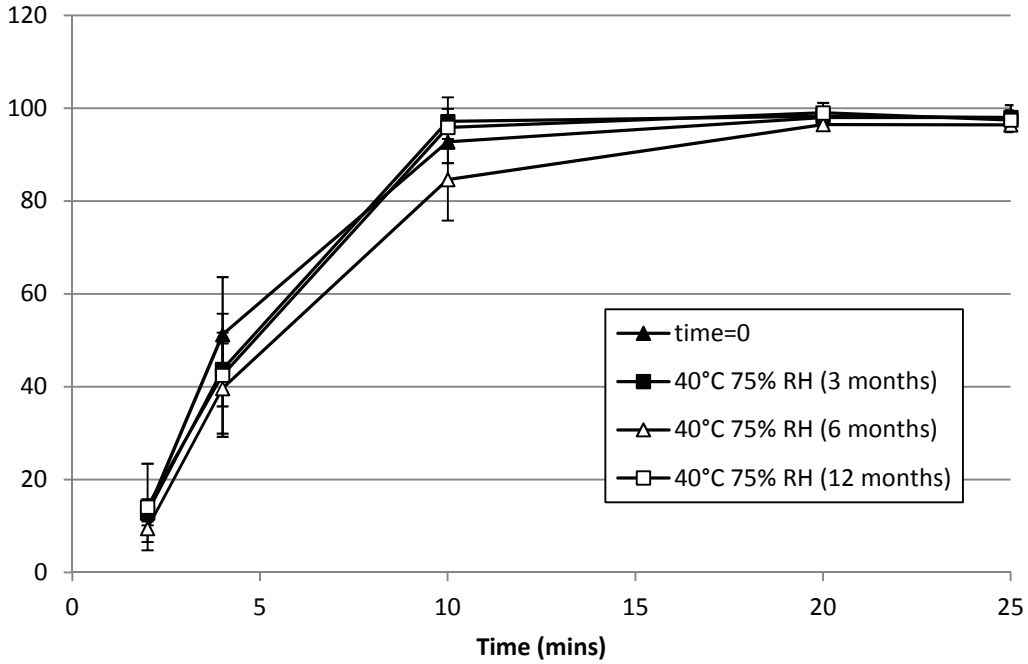


**Figure 1. Dissolution rate profiles of repackaged paracetamol tablets under accelerated conditions (40 ºC; 75% relative humidity) for 12 months (mean + 95% confidence interval; n = 6).**

## Chemical Stability

HPLC method validation for accuracy, precision, specificity and linearity was undertaken as per the International Conference on Harmonisation guidelines.[20] The retention time for paracetamol was 4.3 ± 0.1 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 for the pure and sample paracetamol peaks achieved. Linearity was confirmed over the concentration range used ($r^2 = 0.999$). Paracetamol concentrations in the samples were determined from respective peak areas in relation to constructed standard curves and converted to a percentage of the initial paracetamol concentration. The paracetamol content remained within the BP requirements (95–105% of the labelled amount) over the 12-month storage period, including conditions of elevated heat and humidity (40 ºC; 75% RH), where the percentage of paracetamol was 98.6 ± 0.7% (3 months), 100.1 ± 2.3 (6 months) and 100.2 ± 0.5% (12 months). Chemical stability of paracetamol was confirmed, despite conditions of high humidity and temperature. This is an important finding because of the potential for paracetamol to hydrolyse in the presence of moisture (Figure 2).

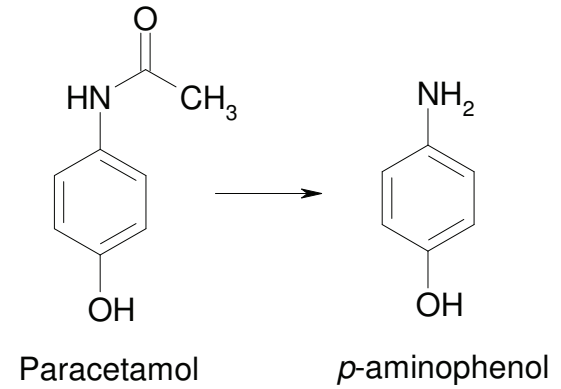


**Figure 2. Hydrolysis of paracetamol**

## DISCUSSION

This study has shown that paracetamol tablets repackaged into a DAA, offering sufficient protection against moisture, will remain stable for up to 12 months, including under accelerated conditions (40 ºC; 75% RH). However, DAAs may be subjected to a reasonable amount of handling and accidental rupture of blister seals may occur, allowing the tablets to be exposed to increased levels of humidity. Since the DAAs in this study were also stored in a dark climate chamber, pharmacists should caution carers to store DAAs away from light as paracetamol is required to be protected from light. This could include storage inside lockable cabinets, medicines trolleys and within medicine storage areas, which aligns with RACF guidelines.[4]

If *prn* packs are being replaced in RACFs more frequently than the medication stability requires, additional costs are borne by the patient, RACF and pharmacy.

In conclusion, this study provides data on the stability of paracetamol tablets repackaged into DAAs and stored under ambient and accelerated conditions for 12 months. Pharmacists will be able to make risk–benefit assessments and recommend a 12-month expiry on paracetamol *prn* DAAs.

**Competing interests:** None declared

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