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RESEARCH

Stability Implications of Repackaging Paracetamol Tablets into Dose Administration Aids

Alison Haywood, Martina Mangan, Beverley Glass

ABSTRACT

Background: Despite the widespread use of dose administration aids (DAAs) there is little available data on the stability of drugs during repackaging or storage in these devices.

Aim: To investigate the physicochemical stability of paracetamol tablets repackaged in DAAs.

Method: Physicochemical stability studies were performed on a commonly used paracetamol tablet directly after heat-sealing in a DAA frequently employed in practice, then at ambient (25 ºC; 60% relative humidity) and accelerated (40 ºC; 75% relative humidity) conditions, over a 3-month period. Physical characteristics of the tablets (weight uniformity, physical appearance, thickness, hardness, friability, disintegration, dissolution rates) were evaluated at time = 0, directly after heat-sealing, 1 month and 3 months. Chemical stability was confirmed by high performance liquid chromatography (HPLC). The results were compared to control samples stored in the original packaging at the various environmental conditions studied.

Results: All compendial requirements for physicochemical stability were met for both ambient and accelerated conditions over the 3-month period. Chemical stability of paracetamol content fell within the required range of 95–105% of the labelled amount, for all environmental conditions.

Conclusion: This study provides evidence on the stability of paracetamol tablets in a DAA, to support pharmacists in making sound clinical and operational decisions regarding the repackaging of paracetamol in these devices.

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INTRODUCTION

Stability of a pharmaceutical may be defined as the capability of a particular formulation, in a specific container/closure system, to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications.[1,2] Pharmaceuticals are expected to meet their specifications for identity, purity, quality, and strength throughout their defined storage period at specific storage conditions.

The stability of manufactured dosage forms is routinely confirmed by manufacturers, where stability studies on packaged dosage forms are conducted by means of real-time, long-term tests and accelerated stability tests at specific temperatures and relative humidities representing storage conditions experienced in the distribution chain of the climatic zone(s) of the country or region of the world concerned.[3,4] Although stability of a dosage form is often seen to be the responsibility of the manufacturer, this does not include removal from the original packaging.[5] In electing to repackage a drug into a dose administration aid (DAA) (medication compliance device/unit-dose container), pharmacists must consider the implications of the transfer to a non-manufacturer pack on drug stability. Despite the widespread use of these devices, there is little available data on the stability of the drugs during repackaging or storage in DAAs.

The stability of a pharmaceutical is affected by many factors, such as the stability of the active ingredient(s), potential interaction between active(s) and excipients, manufacturing process, dosage form, packaging system, environmental conditions encountered during transport, storage and use, and length of time between manufacture and usage.[1,3] In addition to the chemical decomposition (hydrolysis, oxidation, isomerisation, polymerisation, photochemical degradation) of the drugs and/or excipients, physical changes to the solid dosage form, such as changes in tablet hardness, friability, disintegration and/or the dissolution rate may lead to both altered physical appearance and/or bioavailability of the drug.

Drug decomposition often does not follow simple reaction processes (kinetics) and with certain drug substances, more than one type of decomposition can occur simultaneously.[6] Additionally, the kinetics of drug decomposition in solid dosage forms is often more complex than in solution.[4,6,7] Any increase in temperature, often encountered in storage, transport or in-use, usually increases the rate of degradation. This situation is further complicated by the many different types of DAAs commercially available with varying degrees of protection against air, light and moisture and the many possible combinations of drugs being packed in a single blister/sachet of a DAA with increased potential for interaction. It is therefore difficult to predict the physicochemical stability of drugs repackaged in DAAs without stability data on the specific drug in the DAA concerned.

DAAs are commonly packed in a controlled room temperature environment (25 ºC; 60% relative humidity — RH) however, they may be subsequently exposed to increased temperature and humidity in-use, especially in rural and remote regions of Australia, hence the need for studies at accelerated conditions (40 ºC; 75% RH). Australia has climatic conditions encompassing the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Zones II, III and IV, where the long-term storage condition of 30 ºC ± 2 ºC/65% RH ± 5% RH (Zones III and IV) has been given as a suitable alternative to 25 ºC ± 2 ºC/60% RH ± 5% RH for Zones I and II.[8] Additionally, paracetamol must be protected from moisture as it contains an amide group which is sensitive to hydrolytic degradation.[6]

This pilot study aimed to investigate the physicochemical stability of paracetamol tablets repackaged in DAAs.

METHOD

Physicochemical stability studies were performed on a commonly used paracetamol tablet (Panamax, Sanofi-

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Synthelabo) at controlled room temperature (25 ± 1 ºC; 60 ± 1.5% RH) and accelerated (40 ± 1 ºC; 75 ± 1.5% RH) conditions, as per ICH guidelines, in a ICH-compliant climatic chamber (Binder KBF 720), and directly after heat-sealing in a Multi Dose Websterpak DAA, over a 3-month period.[9] Physical characteristics of the tablets (weight uniformity, physical appearance, thickness, hardness, friability, disintegration, dissolution rates) were evaluated according to British Pharmacopoeia (BP) requirements (detailed below), at the following intervals: time = 0, directly after heat-sealing, 1 month and 3 months. Chemical stability was confirmed by high performance liquid chromatography (HPLC). The results were compared to control samples stored in the manufacturer's original packaging at the various environmental conditions studied. All samples had a remaining shelf-life of at least two years at the time of sampling. Tablets were chosen at random from the respective packagings (DAA or control) for the physicochemical stability tests described below.

Physical Stability

Appearance was determined organoleptically in comparison to the original samples. Tablet weight uniformity was determined on 20 tablets using an AND HM-200 analytical balance in accordance with *Ph. Eur. method 2.9.5*.[10] Tablet friability was determined on 20 tablets using a VanKel dual drum friabilator in accordance with *Ph. Eur. method 2.9.7*.[11] Tablet hardness and thickness was determined on 20 tablets using a VanKel VK200 tester using the standard testing protocol in accordance with *Ph. Eur. method 2.9.8*.[12] Disintegration was determined on 6 tablets using a Vankel 35-1300 disintegration tester in accordance with *Ph. Eur. method 2.9.1*, using Apparatus A.[13] A disc was added to each tube and purified water (Millipore Elix10 electrodeionisation system) (37 ± 0.5 ºC) was the medium. Dissolution tests were performed as per *Ph. Eur. method 2.9.3*, on a BP Apparatus II (paddle) (VanKel VK7000) operating at 50 rpm, using a phosphate buffer (pH 5.8) (BDH Merck) dissolution media (900 mL) maintained at 37 ± 0.5 ºC.[14] Samples were taken 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 on a Cary 100 UV/VIS spectrophotometer at 257 nm as per the test for dissolution described in the specific monograph for Paracetamol Tablets in the BP.[15]

Chemical Stability

A stability-indicating HPLC method was used to quantify paracetamol in the presence of its degradants and formulation excipients.[16] The Varian ProStar system consisted of a 240 solvent delivery module, 210 autosampler and a 330 photodiode array detector. The stationary phase was a Varian C18 (5 µm, 150 x 4.60 mm) reverse-phase column. An acetic acid (0.05 M): acetonitrile (Sigma Aldrich) (85:15) mobile phase and a detection wavelength of 243 nm was used. The weakly acidic mobile phase reduced the tendency for the phenol group in paracetamol (pKa 9.5) to ionise.[16,17] The flow rate was 1 ± 0.1 mL/min and the injection volume, 25 µL. A calibration curve for paracetamol was constructed from 5.0 to 25.0 µg/mL ($r^2 = 0.999$). Triplicate samples containing 125 ± 10 mg paracetamol were prepared from a portion of powder prepared from ten ground tablets. The powder was mixed and diluted appropriately with acetic acid (0.05 M) and filtered through a 0.45 µm filter (Millipore) prior to analysis.[16]

Data Analysis

Percentage relative standard deviations were determined for representation of accuracy in the measurement. Statistical Package for the Social Sciences (version 12) was used for ANOVA analysis to determine the level of significance ($p < 0.05$) of results obtained.

RESULTS

The effect of various storage conditions on the physicochemical parameters of the paracetamol tablets under various conditions in the DAA and original packaging (control) are shown in Table 1. Dissolution rate profiles of the paracetamol tablets stored under various storage conditions in the DAA and original packaging (control) are shown in Figure 1.

Table 1. Effect of storage conditions on the physicochemical parameters of paracetamol tablets

Storage conditions		Hardness (Newtons)*	Friability (% loss)†	Disintegration time (s)
t = 0		146.4 ± 10.0	0.12	193
t after heat-sealing		147.8 ± 9.6	0.17	199
25 ºC 60% RH (1 month)	DAA	113.6 ± 8.4	0.06	178
25 ºC 60% RH (1 month)	C	126.9 ± 9.0	0.04	175
25 ºC 60% RH (3 months)	DAA	144.1 ± 9.6	0.12	177
25 ºC 60% RH (3 months)	C	149.2 ± 13.1	0.17	178
40 ºC 75% RH (1 month)	DAA	154.0 ± 10.9	0.12	234
40 ºC 75% RH (1 month)	C	154.4 ± 13.0	0.15	233
40 ºC 75% RH (3 months)	DAA	153.0 ± 10.0	0.12	243
40 ºC 75% RH (3 months)	C	158.5 ± 4.4	0.09	261

RH = relative humidity; DAA = dose administration aid;
C = control
*expressed as mean SD (n = 20); †expressed as mean (n = 20)

Physical Stability

No organoleptic changes were observed for any of the samples or controls stored under the environmental conditions over the 3-month period. The BP compendial requirements for weight uniformity, friability, hardness, disintegration and dissolution were met for the samples (tablets stored in DAA) and controls (tablets stored in original packaging), stored under ambient and accelerated conditions, over the 3-month period, as follows:

- Weight uniformity. Not more than two of the individual masses, of 20 units taken at random, deviated from the average mass by more than 5% (i.e. for an uncoated tablet of greater than 250 mg average mass) and none deviated by more than twice that percentage.[10]
- Friability: A maximum loss of 1% of the mass of the tablets tested is considered to be acceptable. For tablets weighing up to 0.65 g each, a sample of 20 tablets is taken.[11]
- Hardness: Tablets are oriented in the same way with respect to the direction of application of the force, and results are in newtons (N) as the mean, minimum and maximum values of the forces measured.[12]

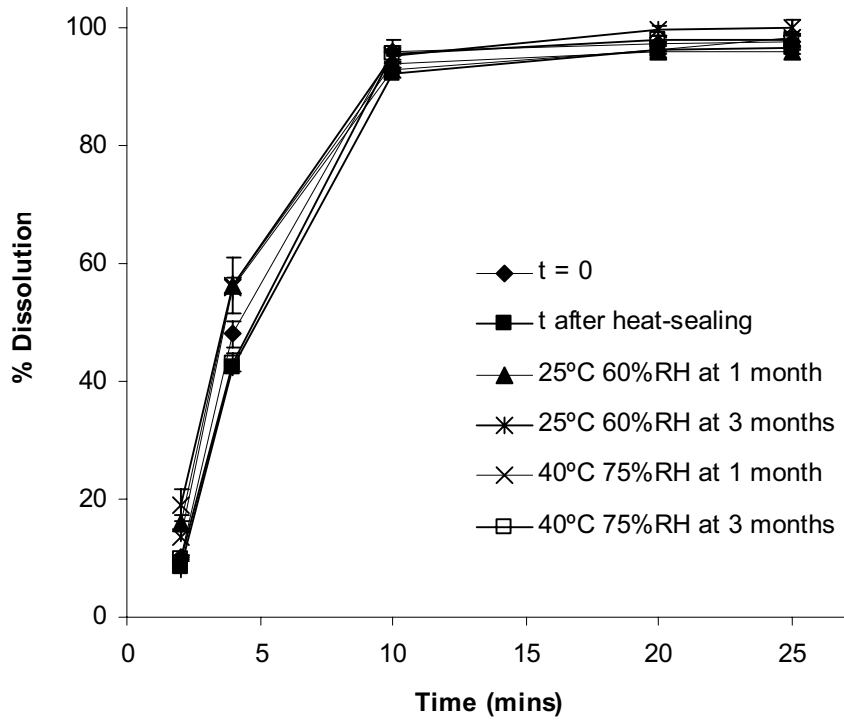

Figure 1. Dissolution rate profiles of paracetamol tablets stored under various environmental conditions (values expressed as mean ± SD, n = 6).

- Disintegration: Uncoated tablets comply with the test for disintegration of tablets and capsules described in *Ph. Eur. method 2.9.1*.[13] The tablets comply with the test if all six have disintegrated after 15 minutes as per *Ph. Eur. monograph 0478*.[18]
- Dissolution: For each of the six tablets tested, the amount of active ingredient in the solution (after 45 minutes) is not less than 70% of the prescribed or stated amount, unless otherwise specified in the monograph, except that if one fails this requirement a further six may be tested individually and all must comply.[14] The content of paracetamol in paracetamol tablets should be 95 to 105% of the stated amount.[15]

Results for the samples at one month at accelerated conditions showed an expected increase in tablet hardness from 146.4 ± 10.0 to 154.0 ± 10.9 N (n = 20), due to the high relative humidity, with a subsequent increase in disintegration time from 193 to 234 seconds (n = 6), whereas controlled room temperature (ambient) conditions revealed a slight decrease in tablet hardness from 146.4 ± 10.0 to 113.6 ± 8.4 N (n = 20) with a corresponding decrease in disintegration time from 193 to 178 seconds (n = 6). These minor physical changes (hardness and disintegration time; $p > 0.05$) had no effect on the dissolution rate profiles of the paracetamol tablets stored under the various conditions (Figure 1). No significant difference ($p > 0.05$) in physical properties between the samples and controls for each storage condition was observed. Therefore, quality of the paracetamol tablets was confirmed regarding their disintegration, hardness, weight uniformity, friability, appearance and dissolution rate over the 1-month period with all results falling within the compendial requirements. Similar results were observed after the 3-month storage period (Table 1). The drug release of the paracetamol tablets was above the BP tolerance limits (not less than 70% drug dissolved within 45 minutes) at both storage conditions over the 3-month storage period.[14,15]

Chemical Stability

The retention time for paracetamol was 3.2 ± 0.1 minutes with peak purity determined through spectral library comparison and peak purity determinations 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 ($r^2 = 0.999$). Concentrations of paracetamol in the samples were determined from respective peak areas in relation to constructed standard curves and then converted to a percentage of the initial paracetamol concentration. The amount of paracetamol per tablet (vs the labelled amount) as a function of storage time is shown in Figure 2. The results showed that the paracetamol content was within the range (95–105% of the labelled amount) specified in the specific monograph for Paracetamol Tablets in the BP for the 3-month storage period at controlled room temperature and accelerated conditions.[15] The compendial requirements were thus met for all of the experimental conditions.[15]

DISCUSSION

The stability studies revealed that the physical properties of the paracetamol tablets were maintained after heat-sealing in the DAA and during storage under controlled room temperature and accelerated conditions over a 3-month period. No significant changes were observed in the physicochemical properties and dissolution-rate profiles of the paracetamol tablets, with all results falling within the BP compendial requirements.

Many different types of DAAs are commercially available, offering varying degrees of protection against air, light and moisture. The DAA used in this study is one frequently employed in practice.

This study suggests that paracetamol tablets repackaged into a DAA, offering sufficient protection against moisture, will remain stable for a reasonable in-use period of approximately six weeks (allowing two weeks

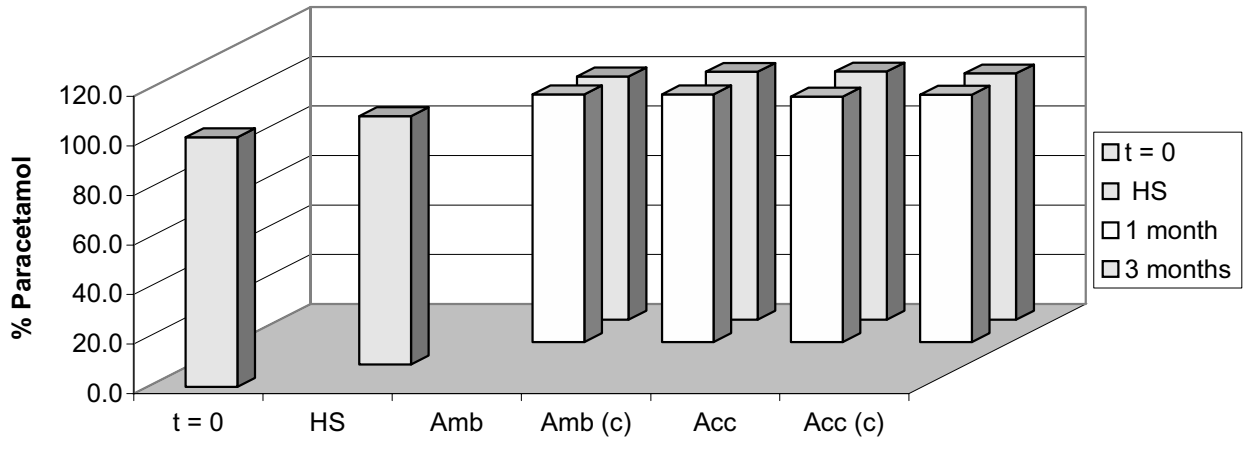

Figure 2. Effect of various storage conditions on the chemical stability of paracetamol tablets (HS = time after heat-sealing; Amb = 25 ºC/60% RH; Amb(c) = 25 ºC/60% RH (control); Acc = 40 ºC/75% RH; Acc(c) = 40 ºC/75% RH (control)).

for advanced packing and delivery on a 4-week supply). However, it is important to note that during use, DAAs may be subjected to a reasonable degree of handling, during which time accidental rupture of nearby blister seals may occur, thereby allowing exposure of the remaining tablets to increased levels of humidity.[19] Pharmacists should always ensure the integrity of the DAA before it leaves the pharmacy and counsel the patient on suitable storage of DAAs in their homes in order to avoid excessive exposure to heat and humidity, and also to be vigilant and monitor that the integrity of the DAA is maintained throughout the dosage period. It is also important to note that this study involved storage at accelerated and ambient conditions of temperature and humidity, inside a dark climatic chamber. Since paracetamol must be protected from light, patients must be advised to store the DAA away from light (e.g. inside a cupboard).[15] The dearth of stability data for the transfer of drugs to DAAs was once again highlighted in a recent article.[20]

The results of this pilot study provide evidence on the stability of paracetamol tablets repackaged in a frequently employed DAA, to support pharmacists in making sound clinical and operational decisions regarding the repackaging of paracetamol in these devices.

Competing interests: None declared.

References

1. Troy DB. Remington: the science and practice of pharmacy. 21st ed. Philadelphia: Lippincott, Williams & Wilkins; 2006. p. 2393.
2. US Pharmacopeia/National Formulary (USP-28/NF-23). Stability considerations in dispensing practice. Rockville: United States Pharmacopeial Convention; 2005.
3. US Pharmacopeia/National Formulary (USP-28/NF-23). Pharmaceutical stability. Rockville: United States Pharmacopeial Convention; 2005.
4. Aulton ME. Pharmaceutics: the science of dosage form design. 2nd ed. Edinburgh: Churchill Livingstone; 2002.
5. Walker R. Stability of medicinal products in compliance devices. Pharm J 1992; 25: 124-6.
6. Florence AT, Attwood D. Physicochemical principles of pharmacy. 3rd ed. Hampshire: Palgrave; 1998.
7. Allen LV, Popovich NG, Ansel HC. Ansel's pharmaceutical dosage forms and drug delivery systems. 8th ed. Philadelphia: Lippincott, Williams & Wilkins; 2005. p. 1-738.
8. ICH:Q1F. Stability data package for registration applications in climatic zones III and IV. ICH Steering Committee; 2003.
9. ICH:Q1A(R2). Stability testing of new drug substances and products (2nd revision). ICH Steering Committee; 2003.
10. British Pharmacopoeia. Appendix XII G: Uniformity of weight (mass). London: British Pharmacopoeia Commission; 2004.
11. British Pharmacopoeia. Appendix XVII G: Friability of uncoated tablets. London: British Pharmacopoeia Commission; 2004.
12. British Pharmacopoeia. Appendix XVII H: Resistance to crushing of tablets. London: British Pharmacopoeia Commission; 2004.
13. British Pharmacopoeia. Appendix XII A: Disintegration test for tablets and capsules. London: British Pharmacopoeia Commission; 2004.
14. British Pharmacopoeia. Appendix XII D: Dissolution test for tablets and capsules. London: British Pharmacopoeia Commission; 2004.
15. British Pharmacopoeia. Specific monograph: paracetamol tablets. London: British Pharmacopoeia Commission; 2004.
16. Watson DG. Pharmaceutical analysis: a textbook for pharmacy students and pharmaceutical chemists. 2nd ed. Edinburgh: Elsevier Churchill Livingstone; 2005. p. 382.
17. O'Neil MJ. The merck index: an encyclopaedia of chemicals, drugs, and biologicals. 13th ed. Whitehouse Station: Merck & Co Inc; 2001.
18. British Pharmacopoeia. General monograph: tablets. London: British Pharmacopoeia Commission; 2004.
19. Saville DJ. Influence of storage on in-vitro release of ibuprofen from sugar coated tablets. Int J Pharm 2001; 224: 39-49.
20. Church C, Smith J. How stable are medicines moved from original packs into compliance aids? Pharm J 2006; 276: 75-81.

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