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Repackaged sodium valproate tablets – Meeting quality and adherence to ensure seizure control

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ABSTRACT

Purpose: Sodium valproate, which is commonly repacked to assist with adherence to ensure seizure control, is hygroscopic and therefore sensitive to moisture. The aim of this study was thus to determine the stability implications of removing the enteric coated tablets from their original packaging and repackaging into a Dose Administration Aid (DAA) with storage under various environmental conditions.
Methods: Physicochemical stability of enteric coated sodium valproate tablets repackaged into a DAA and stored at controlled room temperature, accelerated and refrigerated conditions was evaluated for 28 days. A validated high performance liquid chromatography method was used for the quantitation of the drug content.
Results: Although the chemical stability (sodium valproate between 95 and 105% of labelled content) was maintained for 28 days for all storage conditions, for those tablets stored under accelerated conditions the integrity of the enteric coat was compromised after only 8 days.
Conclusions: Repackaging of enteric coated sodium valproate should be undertaken with caution and be informed by storage climate. This is particularly relevant for those patients living in hot, humid environments where they should be advised to store their DAA in a refrigerator.
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1. Introduction

Epilepsy is a chronic condition with effective seizure control reliant on adherence to a daily dosage regimen [7,11,22]. This presents a challenge for both patients and health care professionals with non adherence increasing the public health burden associated with both hospital admissions and costs [10,19].

Dose Administration Aids (DAAs), also known as Multi-compartment Compliance Aids (MCCA or MCA) or monitored dosage systems (MDS), are designed to assist patients in managing their medicines by organising individual doses according to the prescribed dosing schedule throughout the day [17,34]. Examples of these devices include Nomad [28], Venalink [32], WebsterPak [33], EasyBLIST [8], and MedicoPak [21]. In addition to DAAs provided by pharmacies, repackaging companies supply repackaged medicines in strip type packaging for distribution to pharmacies and/or patients include Thrifty White Pharmacy [29], APHS (Australian Pharmaceutical Healthcare Systems) [2], and MPS (Medication Packaging Systems Australia) [23].

Medicines are expected to meet their specification for identity, purity, quality and strength throughout their defined storage period. Stability of a medicine is confirmed by the manufacturer for the duration of the shelf-life of the product, provided that the medicine remains in the original packaging and is stored under specific conditions. Although DAAs might assist in managing medicine regimens, repackaging, which requires removal from the original packaging, invalidates the manufacturers stability guarantee. Generally manufacturers tend to discourage repackaging of medication as there is little supporting stability data available [6]. Very few studies have been reported in the literature on the stability of medicines repackaged in DAAs [3,13,14,16,18,24,25].

This is particularly important for the antiepileptic drug, sodium valproate, which is known to be unstable in the presence of moisture due to its hygroscopic nature. Sodium valproate is available as an oral liquid, injectable product and a tablet [1], with some tablets containing an enteric coat, which reduces the gastrointestinal symptoms associated with this active ingredient [20].

Some drug substances are particularly sensitive to the effects of moisture. Exposure to these conditions during storage in a DAA,

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particularly in hot, humid environments with elevated relative humidity (RH), may result in the chemical or physical stability being compromised. Guidelines [26,27,31] generally advise against repackaging hygroscopic medicines into DAAs.

In recent times, anecdotal evidence has suggested that the integrity of sodium valproate tablets repackaged in DAAs has been compromised. Thus the primary aim of this study was to investigate the stability of enteric coated sodium valproate tablets repackaged in DAAs and stored under ambient and accelerated environmental conditions, with a view to providing patients advice regarding appropriate storage of their medicine.

2. Material and methods

Physicochemical studies were performed on 200 mg enteric coated (EC) tablets (Epilim EC200, Sanofi-Aventis) repackaged in a DAA (WebsterPak®). The DAAs were stored at controlled room temperature (25 ± 2 °C), accelerated (40 ± 2 °C; 75 ± 1.5% RH) and refrigerated (5 ± 3 °C) conditions, as per ICH guidelines [15], for 28 days. The results were compared to control samples immediately removed from the manufacturer's original packaging. All samples were chosen at random from the respective packaging (DAA and control) and had a remaining shelf-life of at least one year at the time of sampling. Physical characteristics of the tablets, including weight uniformity, physical appearance, thickness, hardness, friability, disintegration and dissolution rates, were evaluated according to British Pharmacopoeia (BP) compendial requirements [5] and chemical stability was confirmed by high performance liquid chromatography (HPLC). Percentage relative standard deviations were determined for representation of accuracy in the measurement. IBM SPSS Statistics (version 21) was used for ANOVA analysis to determine the level of significance ($p < 0.05$) of results obtained.

2.1. Physical stability

Physical tests were performed on the tablets according to compendial requirements [5,30]. Appearance was determined organoleptically by comparison to the original samples. Tablet weight uniformity was determined using an AND HM-200 analytical balance. Tablet hardness and thickness was determined using a VK 200 tester. Tablet friability was determined using a Vankel (VK) dual drum friabilator. A maximum loss of weight that is not greater than 1% is considered to be acceptable.

Disintegration was determined using a VK 100 disintegration tester as per a modified method for delayed-release tablets described in the USP [30]. Six tablets from each storage condition were exposed initially to simulated gastric fluid (pH 1.2) at 37 ± 0.5 °C for 1 h, with subsequent exposure in simulated intestinal fluid prepared without pancreatin (pH 6.8) under the same conditions. The standard is met if no disintegration occurs in the simulated gastric fluids and complete disintegration occurs in the simulated intestinal fluids for all tablets.

Dissolution tests were performed according to the BP method (method B) described for a delayed-release solid dosage forms on a BP Apparatus II (paddle apparatus) (VK 7000) maintained at 37 ± 0.5 °C. Tablets were initially exposed to an acidic environment (0.1 M hydrochloric acid at pH 1.2) for 2 h at 50 rpm, removed and then placed in a buffer solution (phosphate buffer at pH 6.8) for 45 min at 100 rpm. Samples of the dissolution fluids were taken after the acidic-stage and at the end of the buffer-stage and analysed using the HPLC method described below.

2.2. Chemical stability

A Varian Prostar system consisting of a 210 solvent delivery module, 410 autosampler and a 325 ultraviolet detector was used to quantify sodium valproate. A Waters μBondapak C18 (4.6 × 250 mm) reverse-phase column (maintained at 30 °C) was selected as the stationary phase. The mobile phase consisted of potassium dihydrogen orthophosphate and acetonitrile (40:60) adjusted to pH 3.0 with orthophosphoric acid (Univar, Australia). A detection wavelength of 220 nm was used. An injection volume of 50 μL was used with a flow rate of 1 mL/min. Data were analysed using Varian Star Chromatography Workstation (version 6.41). A calibration curve for sodium valproate was constructed from 20 to 500 μg/mL ($r^2 = 0.999$). Standards were prepared in phosphate buffer at pH 6.8 and subsequently acidified (0.1 M hydrochloric acid at pH 1.2). Tablets were not crushed for sampling purposes to avoid the sampling error associated with the tablet coating. Triplicate whole tablets were placed in 100 mL phosphate buffer, sonicated for 10 min, and diluted appropriately in buffer to prepare a solution containing approximately 0.1 mg/mL sodium valproate. A 5.0 mL sample was then acidified using 0.12 mL 5 M HCl and filtered through a 0.45 μm filter (Millipore) prior to analysis.

2.3. Statistical methods

The Kruskal–Wallis statistical analysis test was used to analyse the results of the dissolution testing after storage under the different conditions. Findings were subsequently subjected to post hoc comparisons using Dunn's test. For all cases the level of significance was 0.05.

3. Results

3.1. Physical stability

No changes to tablet appearance were seen for those tablets stored repackaged under refrigerated and controlled room temperature conditions for 28 days. However, for those tablets stored under accelerated conditions of temperature and humidity, rupturing of the tablet coat was observed after 8 days (Fig. 1). No further physical tests were able to be performed on tablets stored at accelerated conditions for a period greater than 8 days. The enteric coat is designed to remain intact until the tablet reaches the small intestine to avoid the gastrointestinal symptoms associated with sodium valproate.

A slight increase in tablet weight and thickness was observed for those tablets stored repackaged under accelerated conditions (Fig. 2). The BP compendial requirements for friability of uncoated tablets were met under all storage conditions, with a weight loss of less than 1% for all tablets.

When compared to control samples, tablet hardness decreased by 9.1% for those tablets stored at controlled room temperature for 28 days, and 33.4% for those stored under refrigerated conditions

Fig. 1. Visible rupturing of enteric coating after storage at 40 °C; 75% RH for eight days.

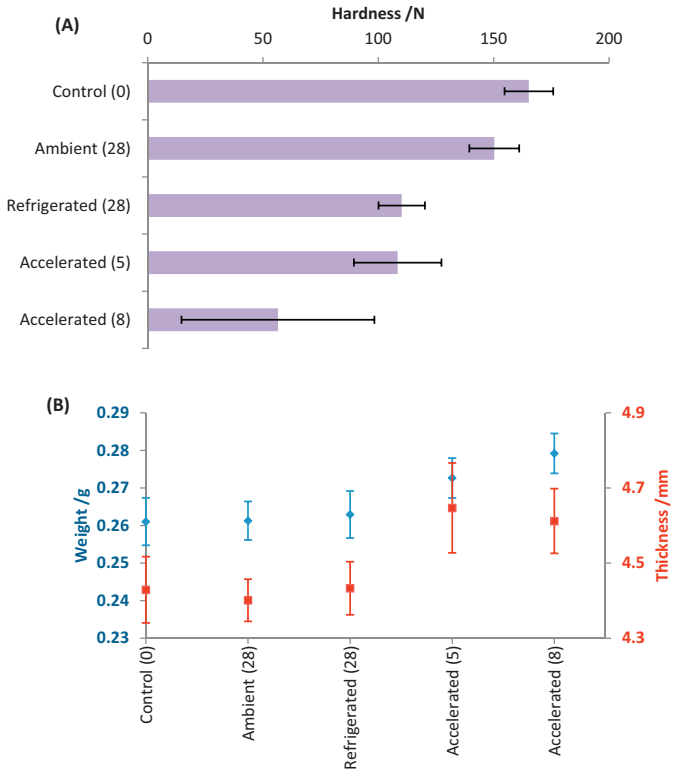

Fig. 2. Effect of exposure to various storage conditions on (A) tablet hardness and (B) weight and thickness. Number in parentheses = days of test. Weight ($n = 20$), hardness ($n = 10$), thickness ($n = 10$); mean ± 2SD.

(Fig. 2). After five days of storage at accelerated conditions tablets showed a 34.4% decrease in hardness, which a 62.0% decrease after 8 days. In the previous study [18], tablets stored repackaged under accelerated conditions were too soft to be tested appropriately after 3 days. The enteric coat may therefore provide slightly improved resistance to elevated conditions of humidity and temperature. It should also be noted that the relative humidity in the refrigerator was monitored using a data logger (Tinytag Plus), which recorded temperature and humidity at 5-min intervals throughout the specified time period, and found to vary greatly with an average RH of 68.4%. The increased exposure to humidity in the refrigerator may explain the decrease in tablet hardness.

The USP compendial requirements for disintegration are met if no disintegration occurs in the simulated gastric fluid, with subsequent complete disintegration occurring in the simulated intestinal fluid. The requirements were met for all storage conditions except for those stored under accelerated conditions for eight days, where disintegration of tablets began in the simulated gastric fluid.

The BP method B test for dissolution requires that each tablet should release no more than 10% of active ingredient in the acidic environment over a period of 2 h, after which and no less than 80% must be released after 45 min in buffer solution. The requirements were met for all tablets (Table 1). Dissolution studies were not performed on those tablets stored at accelerated conditions for 8 days since they did not pass the disintegration test.

Table 1
Effect of exposure to various storage conditions on the dissolution of sodium valproate tablets repackaged in DAAs.

Storage conditions	% Dissolved (acid conditions)	% Dissolved (buffer)
Time = 0	None	103.4 ± 2.6
28 days (25 °C; 60% RH)	None	102.3 ± 2.3
28 days (5 ± 3 °C)	None	91.7 ± 3.8
5 days (40 °C; 75% RH)	1.3 ± 0.2	97.6 ± 3.7

Values are expressed as mean ± 95% CI ($n = 6$).

The Kruskal–Wallis statistical analysis was performed on the above results of the percentage of sodium valproate that was dissolved after 45 min in buffer. This was done in order to compare the dissolution behaviour of the control tablets and the tablets after storage in refrigerated, ambient or accelerated conditions using the null hypothesis that there is no difference in dissolution behaviour between the four conditions. After ranking the results and performing the analysis, the Hcalc value was calculated to be 63.9. Since there were four treatment groups, each consisting of six observations with a significance level of 0.05, the Hcrit value was seen to be 7.815. As the value for Hcrit is smaller than that of Hcalc the null hypothesis can be accepted in that there is no significant difference between the dissolution behaviour of the control tablets and that of the tablets after storage in the three various conditions. Post hoc analysis using Dunn's Test was also performed comparing the dissolution behaviour of the control tablets with the behaviour of the tablets after storage in the three conditions separately. A standard error of 4.08 was calculated and values for Qcalc and Qcrit were determined. It was found that none of three conditions differed in dissolution behaviour in comparison to the control tablets since in each case the value of Qcalc was found to be less than the value found for Qcrit allowing the null hypotheses of no differences in behaviour to be accepted. This illustrates that there is little variability of the tablets tested in terms of their dissolution profiles supporting the fact that repackaging is safe for tablets stored in the various conditions tested for the time periods specified.

3.2. Chemical stability

The retention time for sodium valproate was 6.8 min. Linearity was confirmed over the concentration range used ($r^2 = 0.999$). Concentrations of sodium valproate in the samples were determined from respective peak areas in relation to constructed standard curves and then converted to a percentage of the initial sodium valproate concentration. The results showed that the sodium valproate content was within the range (95–105% of labelled amount) specified in the BP monograph [4] under all storage conditions.

4. Discussion

This study has shown that it is acceptable to repackage enteric coated sodium valproate tablets for up to 28 days under either refrigerated (5 ± 3 °C) or controlled room temperature (25 ± 2 °C) conditions. However, storage under accelerated conditions of humidity and temperature is not advised, with the enteric coat of the tablet rupturing after 8 days.

These findings concur with a recent study reporting on the chemical and physical stability of 100 mg immediate-release sodium valproate tablets repackaged into DAAs (WebsterPak®), stored under accelerated (40 °C; 75% RH), room temperature (25 °C; 60% RH) and refrigerated (2–8 °C) conditions [18]. It was found that although the sodium valproate drug content remained within the acceptable range of 95–105% for all conditions (chemically stable) unacceptable weight variation and variable dissolution profiles resulted during the 56-day storage period. In fact, after seven days under accelerated conditions, tablets only attained 60% dissolution after 45 min, failing the BP compendial test which requires that no less than 80% of stated drug amount be dissolved after 45 min. Tablets became unusable after ten days with implied variability in terms of bioavailability and consequences for the patients' level of seizure control. Fig. 3 highlights the effect of humidity on the physical stability of the tablets, particularly for those stored under accelerated conditions.

Fig. 3. Sodium valproate tablets after 21 days of storage at accelerated (left), refrigerated (middle) and controlled room temperature (right) conditions.

Drug release and bioavailability is affected by a tablet's dissolution profile, a component of physical stability. Carbamazepine, another well-established drug used to treat epilepsy, has a history of irregular drug performance and clinical failures, with several reports showing high dissolution variability in carbamazepine tablets on the market world-wide and even among carbamazepine tablets of the same brand [12]. In 1990, the Food and Drug Administration (FDA) reported that carbamazepine tablets can lose one third of their effectiveness if exposed to moisture due to tablet hardening, poor dissolution and poor absorption in the body [27]. It is therefore important to consider the effects that inappropriate storage can have on medicine stability and ultimately seizure control in patients.

5. Conclusion

Daily antiepileptic drug therapy medication is the foundation of epilepsy treatment [11]. DAAs have the potential to improve adherence, especially when combined with additional adherence aids, such as the use of an alarm reminder (clock, mobile phone, reminder aids), personal reminder (member of household, carer or friend/neighbour), or calendar on the fridge to mark off when medicine has been taken, or simplifying complex drug regimens.

Although there are few data [9] on the stability and therefore the efficacy and safety of medicines during packing and storage, this study provides new evidence on the stability of enteric coated sodium valproate when repackaged in DAAs. It is important however, that DAAs are stored in a cool, dry place protected from light, for example inside lockable cabinets or medicines trolleys. Monitoring the integrity of DAAs throughout the usage period is recommended, since DAAs may be subjected to a reasonable amount of handling and accidental rupture of the blister seals may occur, allowing tablets to be exposed to increased levels of humidity.

These research findings highlighting the storage of DAAs in the refrigerator for those patients living in hot and humid climates is significant as it provides the first evidence that this is a safe option. Health care professionals can play an important role in advising patients, carers and other members of the health care team on the stability of medicines and the importance of packaging, storing and using medicines correctly.

Conflict of interest

The authors report no conflict of interest.

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References

[1] AMH. Australian Medicines Handbook Online. Adelaide: Australian Medicines Handbook Pty Ltd; 2015.
[2] APHS. Australian Pharmaceutical Healthcare Systems. APHS Packaging; 2015, www.aphspackaging.com.au [accessed 12.02.15].
[3] Bowen L, Mangan M, Haywood A, Glass B. Stability of frusemide tablets repackaged in dose administration aids. J Pharm Pract Res 2007;37:179–81.
[4] British Pharmacopoeia. British Pharmacopoeia Online. Volume III. Formulated preparations: specific monographs. Sodium valproate tablets; 2014.
[5] British Pharmacopoeia. British Pharmacopoeia Online. Volume V. Appendix XII B, XII C, XVII G and XVII H; 2014.
[6] Church C, Smith J. How stable are medicines moved from original packs into compliance aids? Pharm J 2006;276:75–81.
[7] Cramer JA, Glassman M, Rienzi V. The relationship between poor medication compliance and seizures. Epilepsy Behav 2002;3:338–42.
[8] EasyBLIST. EasyBLIST®; 2015, https://www.easyblist.com.au [accessed 12.02.15].
[9] Elliott R. Appropriate use of dose administration aids. Aust Prescr 2014;37:46–50.
[10] Ettinger AB, Manjunath R, Candrilli SD, Davis KL. Prevalence and cost of nonadherence to antiepileptic drugs in elderly patients with epilepsy. Epilepsy Behav 2009;14:324–9.
[11] Faught E. Adherence to antiepilepsy drug therapy. Epilepsy Behav 2012;25:297–302.
[12] Flicker F, Eberle VA, Betz G. Variability in commercial carbamazepine samples—impact on drug release. Int J Pharm 2011;410:99–106.
[13] Glass B, Mangan M, Haywood A. Prochlorperazine tablets repackaged into dose administration aids: can the patient be assured of quality? J Clin Pharm Ther 2009;34:161–9.
[14] Haywood A, Mangan M, Glass B. Stability implications of repackaging paracetamol tablets into dose administration aids. J Pharm Pract Res 2006;36:25–8.
[15] ICH. ICH Harmonised Tripartite Guideline. Stability Testing of New Drug Substances and Products Q1A(R2). ICH Steering Committee; 2003, Available from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1A_R2/Step4/Q1A_R2__Guideline.pdf [07.07.11].
[16] Kockler J, Robertson S, Hope D, Haywood A, Glass BD. Stability of paracetamol tablets repackaged in dose administration aids for prn use: implications for practice. J Pharm Pract Res 2013;43:218–20.
[17] Laufs U, Rettig-Ewen V, Bohm M. Strategies to improve drug adherence. Eur Heart J 2011;32:264–8.
[18] Llewelyn VK, Mangan MF, Glass BD. Stability of sodium valproate tablets repackaged into dose administration aids. J Pharm Pharmacol 2010;62:838–43.
[19] Manjunath R, Davis KL, Candrilli SD, Ettinger AB. Association of antiepileptic drug nonadherence with risk of seizures in adults with epilepsy. Epilepsy Behav 2009;14:372–8.
[20] Martindale. Martindale: the complete drug reference (electronic resource). London: Pharmaceutical Press; 2015.
[21] MedicoPak. MedicoPak®; 2015, http://www.medicopak.com.au [accessed 12.02.15].
[22] Modi AC, Rausch JR, Glauser TA. Patterns of nonadherence to antiepileptic drug therapy in children with newly diagnosed epilepsy. JAMA 2011;305:1669–76.
[23] MPS. MPS (Medication Packaging Systems Australia Pty Ltd); 2015, http://mps-aust.com.au/services/community-daa [accessed 12.02.15].
[24] Mylrea M, Robertson S, Haywood A, Glass BD. Stability of dispersible aspirin tablets repacked into Dosette boxes. J Pharm Pract Res 2012;42:204–7.
[25] Perks S, Robertson S, Haywood A, Glass BD. Clozapine repackaged into Dose Administration Aids: a common practice in Australian hospitals. Int J Pharm Pract 2012;20:4–8.
[26] Pharmaceutical Society of Australia. Pharmaceutical Society of Australia, Dose Administration Aids Service; 2015, http://www.psa.org.au/supporting-practice/professional-practice-standards/dose-administration-aids-service [accessed 12.02.15].
[27] Royal Pharmaceutical Society. Improving patient outcomes through the better use of multi-compartment compliance aids (MCA); 2015, http://www.rpharms.com/unsecure-support-resources/improving-patient-outcomes-through-the-better-use-of-mcas.asp [accessed 12.02.15].
[28] Surgichem. Nomad® Monitored Dosage System; 2015, http://www.surgichem.co.uk/ [accessed 12.02.15].
[29] Thrifty White Pharmacy. HealthyPackRX® by Thrifty White Pharmacy; 2015, http://www.thriftywhite.com/Healthy_Pack_Rx.cfm [accessed 12.02.15].
[30] United States Pharmacopeia. US Pharmacopeia – National Formulary (USP 37-NF 32) Online. <701> Disintegration; 2014.
[31] United States Pharmacopeia. US Pharmacopeia – National Formulary (USP 37-NF 32) Online. <1146> Packaging practice – Repackaging a single solid oral drug product into a unit-dose container; 2014.
[32] Venalink. Venalink®; 2015, http://www.venalink.co.uk [accessed 12.02.15].
[33] Webstercare. Webstercare®; 2015, http://www.webstercare.com.au [accessed 12.02.15].
[34] Zedler BK, Kakad P, Colilla S, Murrelle L, Shah NR. Does packaging with a calendar feature improve adherence to self-administered medication for long-term use? A systematic review. Clin Ther 2011;33:62–73.