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Research Paper

Stability of sodium valproate tablets repackaged into dose administration aids

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Abstract

Objectives Since sodium valproate, a commonly used antiepileptic drug, has been reported to be unstable in the presence of moisture, our objective was to investigate the effect of repackaging into dose administration aids.

Methods Sodium valproate 100 mg immediate-release tablets were repackaged and stored for 56 days at accelerated conditions (40°C/75% relative humidity), room temperature (25°C) and under refrigeration (2–8°C). Samples were analysed at 3, 7, 10, 14, 21, 35, 49 and 56 days to determine chemical stability using high-performance liquid chromatography, while physical testing included assessment of weight changes and dissolution behaviour.

Key findings The results revealed that the sodium valproate content in the tablets remained within the acceptable range of 90–110% under all storage conditions for 56 days. Physical stability, however, was not maintained, with a total weight gain of 12.36% under accelerated conditions over the 56 days. Samples stored under all conditions showed variable dissolution compared to the controls, with the amount of sodium valproate in solution following 45 min of dissolution testing below 75% for half of all the intervals determined.

Conclusions Repackaging sodium valproate tablets into dose administration aids results in unacceptable weight variation and changes in the dissolution profiles.

Keywords dose administration aids; physicochemical stability; repackaging; sodium valproate

Introduction

Dose administration aids (DAAs) have been used to facilitate medication administration to patients for over 30 years. Although originally utilized mainly in hospital and other high-care settings, the current focus on independent living for the elderly, coupled with an ageing population, has seen the popularity of DAAs in the community increase.[1] Furthermore, the wider application of DAAs has been strengthened by various government initiatives worldwide to facilitate the use of these devices. In particular, both the UK and Australia provide funding for the provision of compliance aids to subsets of the population thought to benefit from the use of these devices.[2]

As the removal of a medication from its primary packaging and its repacking into a DAA invalidates the stability guarantee of the manufacturer, it is the responsibility of the pharmacist to make an informed judgement as to the appropriateness and safety of this process. Drug manufacturers, on the whole, tend to discourage repackaging of medications as there is little supporting stability data available.[3] Indeed, only a small number of medications have been investigated for stability following repackaging into DAAs (atenolol,[4] paracetamol,[5] frusemide[6] and prochloroperazine[7]; see Glass *et al.* for a review[2]). Pharmacists thus rely largely on individual drug storage recommendations, available national guidelines for repackaging (e.g. in Australia, the UK and USA[8–10]), and their basic understanding of inherent drug stability to make recommendations as to whether repackaging is appropriate.

DAAs are neither air-tight nor moisture-impermeable and thus environmental elements such as light, humidity and temperature may adversely impact on the stability of drugs repackaged into these devices. Many countries experience a variable climate, and while a medication may be appropriate for repackaging in, for example, a temperate region such as London or Los Angeles, repackaging that same medication in tropical or desert regions

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may be completely inappropriate due to increased heat, humidity and light conditions. Pharmacists also need to consider the potential impact on the patient if the repackaged medication degrades following repackaging, and must answer the following two questions: (1) Is the degradation of active drug substance likely to result in a sub-therapeutic or toxic effect? (2) What is the likely impact of drug failure/drug toxicity on the patient?

Valproic acid, discovered to have antiepileptic properties in the early 1960s, has been licensed for use in parts of Europe since 1967, and in the USA since 1983.[11] It is available in several salt forms, including valproate semi-sodium and sodium valproate. Sodium valproate is reported to be chemically stable in acid and base, in the presence of light and under conditions of extreme temperature.[12] It is, however, expected to exhibit instability in the presence of moisture due to its hygroscopic and deliquescent nature. This raises a question as to whether it is appropriate to repackage this medication, particularly in humid environments, as alterations in physical stability in terms of tablet hardness and the dissolution profile are likely to impact on its bioavailability.

Sodium valproate is therefore an ideal drug candidate for investigation of its stability when stored in DAAs, as its potential to exhibit environmentally-induced physical changes may affect bioavailability *in vivo*, with resulting therapeutic failure and potentially serious implications for the patient. Thus this study aims to investigate the stability of sodium valproate once repackaged into DAAs. As this medication is available worldwide, different storage conditions will be investigated to determine if and under what environmental conditions repackaging and subsequent storage of sodium valproate can be recommended.

Materials and Methods

Materials

Sodium valproate 100 mg immediate-release tablets (Epilim; Sanofi-Aventis Australia Pty Ltd; batches BH206, 223 and 236) were obtained from commercial sources. Repackaging materials, including polyethylene blisters and foil backings, were obtained from a single manufacturer. The high-performance liquid chromatography (HPLC) mobile phase, consisting of potassium dihydrogen orthophosphate (Univar, Australia) and 190-grade acetonitrile (Unichrom, Australia), was adjusted to pH 3.0 with orthophosphoric acid (Univar, Australia), and was used as a solvent for preparation of standard and test samples for assay and in quality controls. Standard solutions were prepared from valproic acid sodium salt powder (Sigma Chemicals, Australia). Dissolution fluid used was simulated gastric fluid (pH 1.2),[13] prepared without pepsin enzyme. Double-filtered, purified water (Millipore) was used throughout the study.

Repackaging and storage

Sodium valproate tablets were removed from their protective primary packaging and immediately resealed within a DAA using a domestic iron, at the medium temperature setting with no steam. Care was taken to avoid unnecessary contact with the tablets and to minimise their exposure to moisture. Immediately following repackaging, each DAA was stored under its prescribed conditions until testing was undertaken.

Three storage conditions were utilised: (1) in an ICH-compliant humidity–temperature cabinet (Binder KBF-ICH 720; Binder Germany) at accelerated conditions (45 ± 2°C/ 75 ± 5% relative humidity (RH)),[14] (2) in a conventional refrigerator (5 ± 3°C), and (3) in an incubator (Thermoline TRI-140, Thermoline Scientific, Australia) set at 25 ± 2°C. Temperature and humidity conditions within in the storage chambers were monitored for the duration of the study (Tinytag Plus: -40/85°C and Tinytag Plus: 0/100% RH, Gemini Data Loggers, UK).

A sample of sodium valproate tablets tested for drug content, cumulative weight gain and dissolution behaviour immediately after being removed from the manufacturer's primary packaging at day 0 and at day 56 served as controls. Following repackaging, tablets maintained under each storage condition were tested for drug content, cumulative weight gain and dissolution behaviour at days 3, 7, 10, 14, 21, 35, 49 and 56.

High-performance liquid chromatography method

Chemical content of the sodium valproate tablets was analysed using a validated reverse-phase HPLC method, coupled to a UV detector set to 220 nm. The HPLC system consisted of a quaternary pump system (Varian, model 240), autosampler (Varian, model 410) and photodiode array PDA detector (Varian, model 330). A reverse-phase column (Waters, C-18 column: μ-bondapak 4.6 × 250 mm) was used in the HPLC analysis. The mobile phase flow rate was set to 1 ml/min and the injection volume was 50 μl. Analyses were conducted at ambient laboratory temperature (24.5 ± 1.5°C). The methods utilised in this study were validated in accordance with the EU validation of analytical procedures.[15] Validation parameters of specificity, linearity, accuracy, precision and robustness were confirmed for this method. Range was established as 80–380 μg/ml, detection limit as 1.4 μg/ml and quantitation limit as 56 μg/ml.

Chemical stability: sodium valproate assay

Because of the hygroscopic nature of sodium valproate, a method for chemical assay was developed and validated. A tablet sample expected to contain 1000 mg of sodium valproate was made up to 50 ml with mobile phase, sonicated for 20 min to ensure dissolution and then further diluted with mobile phase, to achieve a final concentration expected to contain 0.1 mg/ml sodium valproate. A sample of 1.5 ml of the resultant solution was then filtered through a 0.45 μm filter (Millex HV, Millipore Corporation, Ireland) and analysed in duplicate for sodium valproate content using the validated HPLC method.

Purity analysis was performed on assay results for control tablets and tablets from each storage condition after 56 days of storage. A photodiode array detector was used to generate a purity parameter (PuP), calculated for three spectra across the compound peak, indicative of the homogeneity of a given peak, to confirm the chemical purity and thus the specificity of the method.

Physical stability: weight change

Due to the hygroscopicity of the sodium valproate, it was impractical to remove tablets from the packaging to be reweighed at each testing day. Thus, the weight of a single DAA containing eight tablets was measured at each testing time for each storage condition.

Physical stability: dissolution studies

Significant 'coning' of drug at the base of the vessel occurred when utilising dissolution apparatus II (rotating paddle) as specified in the *British Pharmacopoeia*,[16] even when paddle speed was increased to 100 rev/min. Using this method, less than 100% dissolution was achieved even after 2 h of testing. A switch to dissolution apparatus I (rotating basket) at 100 rev/min successfully eliminated the 'coning', and provided consistent dissolution results with fresh sodium valproate tablets.

Dissolution studies were carried out using two 100 mg tablets in 500 ml of dissolution medium at 37 ± 0.5°C and 100 rev/min. This concentration allowed accurate quantification of sodium valproate in solution using the developed and validated HPLC method. Experiments were run in duplicate: 5 ml samples were withdrawn and replaced with fresh dissolution medium every 15 min for a total of 2 h. Samples were immediately filtered through a 0.45 μm membrane filter and then analysed for sodium valproate content using the HPLC method.

Statistical methods

Statistical analysis of the change in dissolution of sodium valproate tablets following storage under different conditions of temperature and humidity over time was performed using the Kruskal–Wallis test at each sampling time. All significant cases were subject to post-hoc comparisons of the control to each storage condition, performed using Dunn's test. A significance level of $P < 0.05$ denoted significance in all cases.

Results

Chemical stability: sodium valproate assay

No significant loss of sodium valproate was demonstrated following storage for 56 days under any of the investigated storage conditions, with all assays returning values within the acceptable range of 90–110% (Table 1).[16] This was confirmed by purity analysis, which demonstrated homogeneity of the peak for sodium valproate in the tablets from each of the three storage conditions at 56 days (Table 1). The PuP mean, standard deviation, similarity (sim) and dissimilarity (diss) values were within accepted limits of standard deviation (SD) ± 0.5 nm,[17] sim: 1.000–0.998; dis: 0.000–0.060. Each of the peaks did not significantly differ from the sodium valproate standard (Table 1), nor did they differ significantly from each other (SD = 0.062).

Physical stability: weight change

The hygroscopicity of sodium valproate was demonstrated by fluctuation in tablet weight under all storage conditions. Weight gain occurred as a result of absorption of moisture in all tablet samples (Figure 1), with the most significant change evidenced by tablets stored under accelerated storage conditions. These tablets gained weight linearly ($y = 0.4027x + 0.0283$; $R^2 = 0.999$) over the first 14 days of storage. This weight gain plateaued towards the end of the storage period, with a total weight gain of 12.36% over the 56-day storage period.

The initial reduction in weight of tablets stored at both 2–8 and 25°C may be explained by moisture uptake of sodium valproate on brief exposure to ambient conditions after removal from their primary packaging prior to repacking. This additional water content would thus have been included

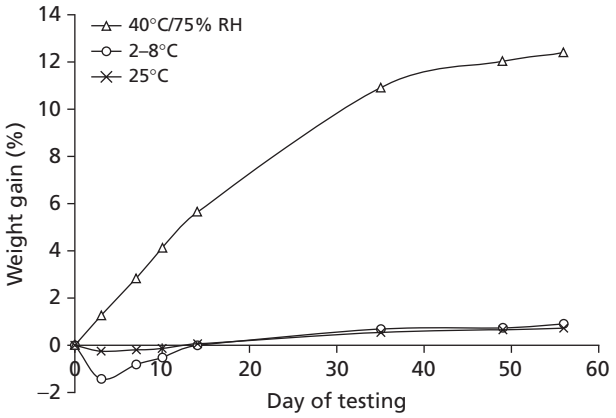

Figure 1 Percentage weight gain over time for repackaged sodium valproate tablets. Repackaged sodium valproate tablets were stored at 40°C/75% relative humidity (RH), 2–8°C or 25°C for 56 days.

Table 1 Measures of chemical stability for sodium valproate standard and repackaged sodium valproate tablets stored under three different experimental conditions

Treatment	Rt	PuP (mean ± SD)	Similarity	Dissimilarity	Sodium valproate content (mg; mean ± SD)
Sodium valproate standard	6.787	213.97	–	–	95 ± 0.58
Sodium valproate tablets (repackaged)					
40°C/75% RH	6.920	213.90 ± 0.07	0.999	0.006	100 ± 0.46
2–8°C	6.840	213.89 ± 0.08	0.999	0.008	100 ± 0.53
25°C	6.893	213.88 ± 0.09	0.999	0.008	90 ± 0.46

Comparison with standard sodium valproate of retention times (Rt), mean and standard deviation (SD) for purity parameters (PuP), similarity and dissimilarity values, and mean and SD of sodium valproate content for repackaged tablets stored at 40°C/75% relative humidity (RH), 2–8°C or 25°C for 56 days.

when the initial weight of the tablets was measured following repackaging. Once placed into their experimental storage conditions, the tablets would be expected to re-equilibrate their water content with their immediate environmental surroundings, the humidity of which was lower than that experienced initially in the laboratory. Although this process would normally occur relatively rapidly, a lag time is involved due to the drier air having to first penetrate the DAA. The gradual weight increase may be attributable to penetration of moisture into the centre of the tablet, where it would remain and accumulate at a faster rate than it would be lost due to the protective excipient matrix.

Physical stability: dissolution

Compliance with British Pharmacopoeial (BP) standards for dissolution,[16] which requires no less than 75% of stated drug amount in solution after 45 min of testing, varied at different times and storage conditions.

In this study, all repackaged tablets, regardless of storage conditions, demonstrated differences in dissolution compared to that of the control, with the most pronounced differences in dissolution profiles being demonstrated by tablets stored at 40°C/75% RH.

Tablets exposed to 40°C/75% RH only complied with the BP specifications after 14 days of storage. A reduction of dissolution was initially observed (70% on day 3), which further decreased with subsequent testing (60% on day 7, 56% on day 10). Samples from days 7 and 10 eventually attained 75% dissolution (at 60 and 75 min, respectively); however, maximum dissolution of only 85 and 90%, respectively, was achieved for these two samples.

Tablets stored at 2–8 and 25°C showed varied dissolution results, exhibiting problems similar to those demonstrated by tablets stored at 40°C/75% RH, including failure to comply with BP standards, decreased rate of dissolution and failing to achieve 100% dissolution.

Statistical analysis confirmed differences in dissolution compared to control under each storage condition, and also highlighted the fact that the dissolution results were not predictable, with significant reduction in the release of the drug occurring earlier at 25°C than under accelerated conditions. Tablets stored under accelerated conditions (40° C/75% RH) exhibited significantly reduced drug release at $t = 10$ and $t = 49$ days ($P < 0.05$; see Figure 2), as did tablets stored at 2–8°C at $t = 21$ and $t = 49$ days (see Figure 3). Drug release from tablets stored at 25°C was significantly reduced at $t = 3$ days ($P < 0.05$; see Figure 4). Thus, storage of sodium valproate in DAAs, even under refrigeration, can result in variable release of the drug, with the potential to impact on valproate bioavailability.

Discussion

Sodium valproate tablets were found to be chemically stable following repackaging under all storage conditions tested, with the tablets exhibiting no significant loss of drug content for the duration of the study. The most significant result was the physical instability of sodium valproate tablets, as evidenced by changes in tablet weight and dissolution profile.

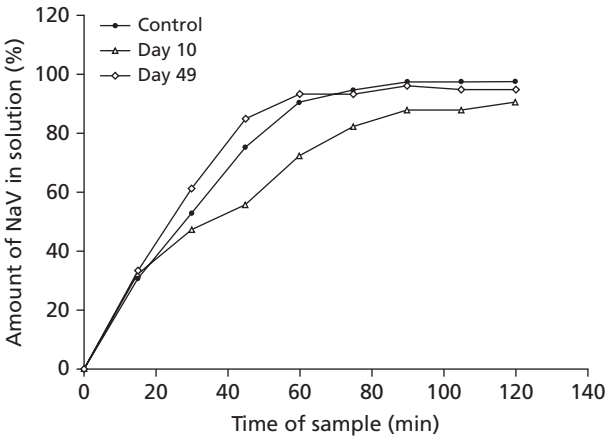

Figure 2 Dissolution profiles of control and repackaged sodium valproate tablets. Dissolution curves are shown for control sodium valproate (NaV) tablets and also for repackaged sodium valproate tablets stored at 40°C/75% relative humidity for 10 and 49 days. Values represent mean ± SD of the percentage of sodium valproate dissolved at each sample time point.

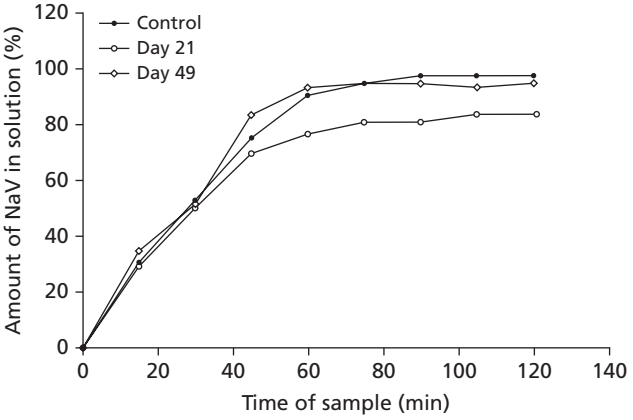

Figure 3 Dissolution profiles of control and repackaged sodium valproate tablets. Dissolution curves are shown for control sodium valproate (NaV) tablets and also for repackaged sodium valproate tablets stored at 2–8°C for 21 and 49 days. Values represent mean ± SD of the percentage of sodium valproate dissolved at each sample time point.

Many dissolution profiles indicated significantly slower, and in some cases incomplete, absorption of sodium valproate.

Slower drug dissolution suggests slowed absorption, potentially resulting in the drug passing through the gastrointestinal tract before the entire dose can be absorbed. Sodium valproate is almost 100% bioavailable,[18,19] thus any change in absorption would be expected to reduce sodium valproate blood levels and could potentially precipitate seizures in epileptic patients. However, slowed dissolution may not result in a sub-therapeutic dose of sodium valproate, as the ingestion of food concurrently with a dose of sodium valproate does not affect the final bioavailability of the drug.[19] Therefore, it is possible that although drug release is retarded due to physical deterioration in some tablets, the

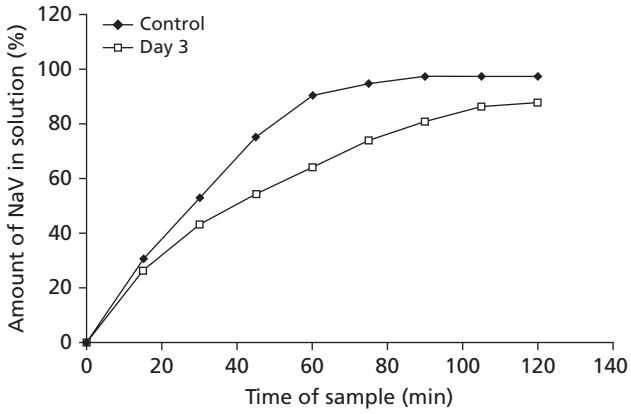

Figure 4 Dissolution profiles of control and repackaged sodium valproate tablets. Dissolution curves are shown for control sodium valproate (NaV) tablets and for repackaged sodium valproate tablets stored at 25°C for 3 days. Values represent mean ± SD of the percentage of sodium valproate dissolved at each sample time point.

patient may still receive the entire dose. However, as sodium valproate is an antiepileptic drug (AED), we must also consider the potential impact of an altered absorption–time profile on therapeutic blood drug levels. There are many documented cases of generic AEDs, including valproate, causing seizures in patients due to slight variations in kinetic time-profiles,[20,21] these problems occurring even though the generic AEDs were confirmed by regulatory bodies to be bioequivalent to their branded counterparts. Whether or not the differences demonstrated in this study do indeed have significant implications for patient health would need to be established with in-vivo studies.

If the dissolution results suggesting less than 100% dissolution do indeed correlate with in-vivo bioavailability, a reduction in patient blood sodium valproate levels would be expected, resulting in a potential loss of seizure control. This exact situation has been documented with both carbamazepine and phenytoin. An epileptic patient reported by Crawford *et al.* took wet carbamazepine tablets and subsequently experienced seizures.[22] This reduced seizure control was attributed to reduced carbamazepine absorption and thus bioavailability, and was demonstrated experimentally when testing of the wet carbamazepine tablets showed a 65% reduction in dissolution. Similarily, Cloyd *et al.* documented phenytoin capsules with a 45% reduction in dissolution, resulting in reduced serum phenytoin levels and seizures in an epileptic patient.[23]

Conclusions

The discussion above highlights the fact that the sodium valproate tablets, although chemically stable following repackaging, are compromised in terms of their physical stability under all storage conditions tested. This is evidenced by the weight gain of the tablets and variation in their dissolution profiles. Statistical analysis confirms reduced drug release during dissolution studies, not only when tablets are stored under accelerated conditions (40°C/75% RH), but also at room temperature (25°C) and under refrigeration (2–8°C). These observed differences, resulting in potential changes in valproate bioavailability, will cause problems in patients due to clinical non-equivalence with sodium valproate tablets that have not been repackaged, resulting in breakthrough seizures.

Since tablets stored in DAAs may be exposed to uncontrolled temperature and humidity during use in patients' homes, based on the results of this study it is inappropriate to repackage sodium valproate tablets into a DAA. Although these findings in no way detract from the value of these devices to facilitate medicines administration and improve patient compliance, they do provide evidence for the pharmacist of potential problems when repackaging drugs susceptible to humidity. This study thus makes a significant contribution to the growing body of evidence of the stability implications of repackaging drugs into DAAs.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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