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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.

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.