COMPOUNDING AN ORAL LIQUID FORMULATION OF DIAZEPAM ALCOHOL-FREE

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BACKGROUND AND IMPORTANCE

The shortage of drugs is a common international problem. Pharmaceutical compounding is a viable alternative, being especially relevant in pediatrics. An example of such a situation is the oral liquid formulation of diazepam, indicated for epilepsy and seizures. However, only formulations that use ethanol as a cosolvent are described in the scientific bibliographies. This excipient is not recommended in pediatrics, with children´s age-dependent proposed limits by EMA/FDA/WHO.

AIM AND OBJECTIVES

Development of an oral liquid formulation of diazepam ethanol-free.

MATERIALS AND METHODS

A compounding vehicle, B9 National Compounding Formulary, formulated with the suspending agent Avicel RC581 polymer was used to prepare Diazepam 0.4 mg/ml oral suspension. Tablets and bulk material were used as drug sources. An alternative vehicle, with a suspending agent Vivapur, was also tested. The stability of the drug was verified throughout 90 days in different temperature storage conditions (ambient and refrigerated) using the in-house HPLC method employing the UltiMate 3000 HPLC (Thermo Fisher Scientific, USA). The particle size was measured using Mastersizer 300 (Malvern Panalytical, UK). Organoleptic characteristics were also tested.

Image 1. UltiMate 3000 HPLC (Thermo Fisher Scientific, USA): stability tests
Image 2. Mastersizer 300 (Malvern Panalytical, UK): particle sizes tests

RESULTS

After 7 days more than 10% of drug loss was observed for the ambient storage preparations, both tablets and bulk, and for the refrigerated bulk preparation (Figure 1 and 2). The tablets refrigerated formulation maintained more than the 90% of the drug content until the 60-day mark. No significative changes were observed in the particle size after 60 days in all the samples (Figure 3). The organoleptic characteristics (smell, taste and texture) remained unchanged in all the preparations until the third month.

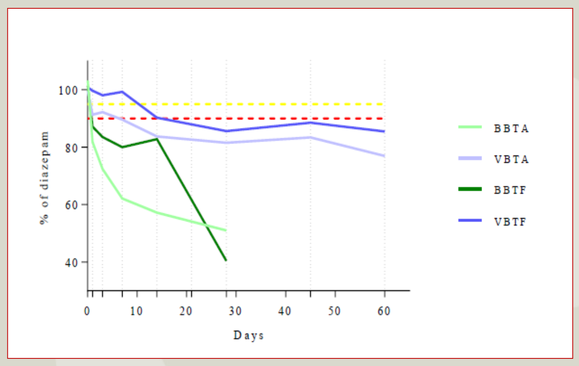

Figure 1: The four preparation´s concentration of bulk material (B) diazepam and lactose as excipient with Vivapur (V) and Avicel (B), stored at ambient temperature (TA) and fridge temperature (TF) - 95% (yellow line) and 90% (red line) were the limits that define.

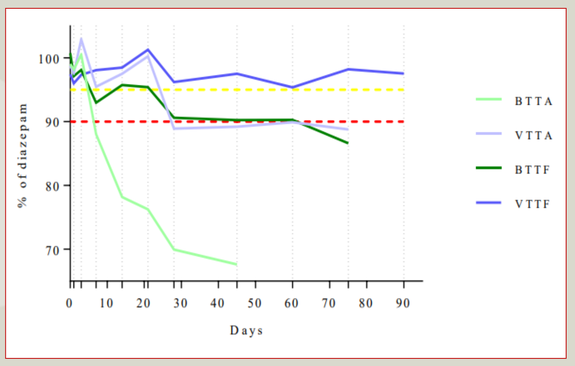

Figure 2: The four preparation´s concentration of tablets (T) with Vivapur (V) and Avicel (B), stored at ambient temperature (TA) and fridge temperature (TF) - 95% (yellow line) and 90% (red line) were the limits that define.

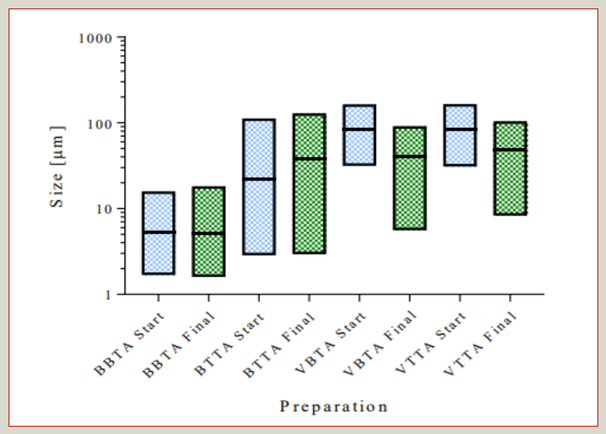

Figure 3: Differences between the starting measurements on the particles and the final ones after two months and a half. Each horizontal black line represents a Dx value (10, 50 and 90 respectively bottom, middle and top) and tells how many particles are below that result.

CONCLUSIONS AND RELEVANCE

A stable alcohol-free diazepam suspension was achieved. The tablets produced a more stable formulation than the bulk source, especially when stored at a lower temperature. This formulation can solve the problem of shortcoming, allowing the appropriate administration of pediatric treatments. Still allows further compliance with the recommended composition limits of ethanol, excluding this excipient from its composition.

References and/or acknowledgements:
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