Stability of Extemporaneously Compounded Clobazam 1mg/mL Suspension

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INTRODUCTION

Clobazam is a 1,5-benzodiazepine which has potent anticonvulsant properties, in addition to its anxiolytic characteristics. Due to these properties, clobazam is used as an adjunctive treatment for refractory generalized epilepsy. Clobazam is only available in Canada as 10 mg tablets. Given that no commercial oral liquid is currently available in Canada, an extemporaneous oral liquid formulation is required for administration to children and other patients for which tablets cannot be taken. An oral suspension should satisfy the following ideal criteria: be acceptable to patients, easily compounded using a commercially available suspending vehicle, stable for an adequate amount of time, and be of sufficient concentration to avoid administration of large volumes.

The stability of a simplified clobazam suspension has not been previously published. Pharmacists require good stability data in order to compound suspensions along with having confidence in the expiry of the suspension. Therefore, a stability study on a clobazam suspension was required.

OBJECTIVES

The objective of this study was to evaluate the stability of clobazam 1 mg/mL suspensions stored in amber glass bottles, amber plastic PET and amber plastic PVC bottles at both 23 C (RT) or 4 C and plastic oral syringes at 23 C (RT) only.

The concentration of clobazam in bottles (23ºC and 4ºC) and syringes (23ºC) was evaluated during storage at each temperature using a validated stability indicating liquid chromatographic method using UV detection.

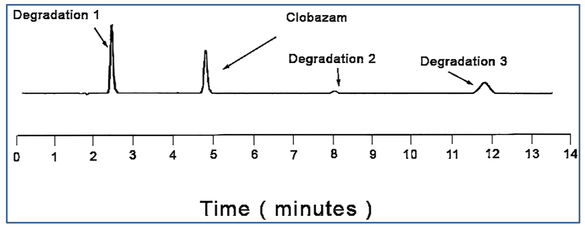

Figure 1. The chromatogram represents 0.05mg/mL clobazam with 16.5% of the initial concentration remaining after incubated with NaOH at a pH of 11.4 for 62 minutes at 95 C. Three degradation products are observed which eluted at 2.3, 8 and 11.8 minutes, well separated from clobazam which eluted at 4.6 minutes.

METHODS

Liquid Chromatographic Method

The liquid chromatographic system consisted of a Supelcosil ABZ plus C18 column and 50% acetonitrile and 50% aqueous 0.05 mmol/L phosphoric acid as the mobile phase with a flow rate of 1 mL/min and UV detection at 226 nm.

Assay Validation

Following development of the chromatographic system capable of separating clobazam from its degradation products (Figure 1), the accuracy and reproducibility of standard curves was then tested over 5 days. During the study, within-day and between day errors of reproducibility were assessed by the coefficients of variation and the standard deviation of regression for the standards, quality control (QC) samples and suspension samples .

Stability Study: Bottles and Syringes at 23 C and 4 C

On study day 0, three separate 300mL batches of clobazam 1mg/mL suspensions were prepared with Oral Mix (Medisca) and clobazam 10mg tablets (Apotex). Each 300 mL batch was divided into 6x50mL and placed in 100mL size amber glass, amber PET and amber PVC bottles (allows airspace) for a total of 18 bottles. Half of the bottles were stored at room temperature (23° C, exposed to ambient light), the other half were refrigerated (4° C). One separate 100 mL batch was also compounded and 1.5mL were drawn into 3 mL oral syringes (30 syringes total) which were stored at room temperature (23° C). Samples from bottles were analyzed by HPLC in duplicate on days 0, 2, 7, 14, 21, 28, 42, 56, 72, and 91 and samples from syringes on days 0, 2, 7, 21, 42 and 91.

Data Reduction and Statistical Analysis

Analysis of variance was used to test differences in concentration on different study days, at different temperatures and in different bottle containers. The 5% level was used as the a priori cut-off for significance. Clobazam concentrations were considered “acceptable” or “within acceptable limits” if the lower limit of the 95% confidence limit of concentration remaining was greater than 90% of the initial (day 0) concentration.

RESULTS

Table 1. Refrigerated (4 C) Studies

Study Day	PVC 1 mg/mL	Glass 1 mg/mL	PET 1 mg/mL
0	100.00	100.00	100.00
2	99.26	98.88	100.57
7	97.63	97.33	97.30
14	97.29	99.21	97.57
21	96.50	97.32	100.29
28	102.17	100.97	102.82
42	100.45	103.65	101.85
56	101.43	98.39	97.33
72	100.59	100.04	99.49
91	97.48	98.31	98.90
Slope (%/ day)	0.009	0.005	-0.005
Intercept	98.96	99.23	99.79
Std regression (Sy.x)	2.045	2.004	1.994
Confidence interval for slope (%/ day)	0.0504	0.0494	0.0491
Fastest slope (%/day; 95% CI)	-0.041	-0.044	-0.054
Upper limit (%/day; 95% CI)	0.059	0.055	0.044
Shortest T-90 (days)	244.41	227.43	183.69
% remaining on day 91 based on fastest degradation rate (95% CI)	96.28	95.99	95.05

Table 2. Room Temperature (23 C) Studies

Study Day	PVC 1 mg/mL	Glass 1 mg/mL	PET 1 mg/mL	Syringe 1 mg/mL
0	100.00	100.00	100.00	100.00
2	99.44	99.06	100.76	102.23
7	98.84	100.31	103.21	102.72
14	98.92	99.26	104.01	
21	97.48	97.89	102.59	99.70
28	99.66	104.03	103.19	
42	101.38	101.52	103.19	102.94
56	98.27	99.91	102.01	
72	96.74	97.41	96.61	
91	97.16	97.57	98.19	96.86
Slope (%/ day)	-0.025	-0.022	-0.045	-0.044
Intercept	99.61	100.42	102.89	101.92
Std regression (Sy.x)	1.270	2.002	2.120	2.004
Confidence interval for slope (%/day)	0.031	0.049	0.052	0.071
Fastest slope (%/day; 95% CI)	-0.056	-0.071	-0.098	-0.115
Upper limit (%/day; 95% CI)	0.007	0.028	0.007	0.028
Shortest T-90 (days)	178.71	140.82	102.48	87.16
% remaining on day 91 based on fastest degradation rate (95% CI)	94.91	93.54	91.12	89.56

Assay Validation

During the study, the accuracy (% absolute deviation) from the known concentration for standards was 1.41% and QC samples was 3.53%. The error of replicate analysis (CV) within a day averaged 1.99% for the standards and 2.44% for the QC standards and between day variation (CV) averaged 1.42% for the standards and 3.27% for the QC standards.

Between day variation for the suspension samples, as measured by the observed standard deviation of regression (Sy.x) for percent remaining, was 1.92% and within a day averaged 2.15%.

Assay validation demonstrated that the method was accurate, reproducible and stability indicating.

Stability of Clobazam Suspensions

The percent remaining based on fastest degradation rate with 95% confidence and an initial concentration of 100%, all bottle types contained not less than 95% at 4 C and not less than 91% at 23 C on day 91. The SD were omitted.

Degradation products were not observed in any samples during the study.

Analysis of variance was unable to detect differences in percent remaining due to temperature (p=0.1709) but significant differences were detected in study days (p<0.001) and container type (p=0.0081).

CONCLUSION

Extemporaneous oral clobazam 1 mg/mL suspensions assayed well above 95% of the initial concentration for 91 days when stored in 3 types of containers (amber glass, PET, and PVC) at 2 different temperatures (23 C and 4 C) and oral syringes at 23 C. However, the best determination with most confidence for assigning an expiry date is based on the percent remaining using the fastest degradation rate with 95% CI . On day 91, PVC and glass bottles (23 C, 4 C) more than 93.54% remained, PET bottles were less stable at 23 C (91.12%) than 4 C (95.05%) and syringes had only 89.56%.

Refrigeration will reduce the degradation rate and minimize bacterial growth. However, since clobazam degradation in bottles, at either 4ºC or 23ºC, results in more than 90% remaining after 91 days of storage with 95% confidence, we recommend a date of 91 days for suspensions stored at either 4ºC or 23ºC in glass, PVC, or PET. Suspensions stored in oral syringes at room temperature should not exceed 87 days.

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