Stability of Extemporaneously Compounded Temozolomide 10mg/mL Oral Suspension

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INTRODUCTION

Temozolomide is an antineoplastic drug used to treat a variety of cancers. Color changes and crystal formation have been observed in previously published stability studies on temozolomide suspensions. Furthermore, stability data in various containers such as glass, PET and polypropylene oral syringes are lacking.

Pharmacists require acceptable stability data in order to compound suspensions and to have confidence in the expiry assigned.

OBJECTIVES

The objective of this study was to evaluate the stability of 3 different temozolomide 10 mg/mL suspensions stored in amber glass, amber plastic PET bottles and plastic oral syringes at both 23 C (RT) or 4 C using Oral Mix SF (sugar free) vehicle.

The concentration of temozolomide in bottles and syringes was evaluated during storage at each temperature using a validated stability-indicating liquid chromatographic method using UV detection.

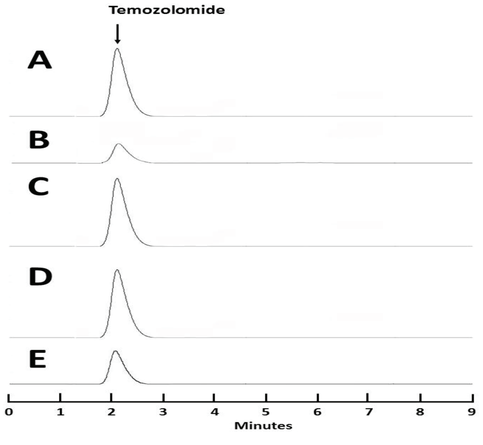

Figure 1. Chromatograms of Temozolomide
Chromatogram A represents 0.5 mg/mL of temozolomide at time zero prior to incubation with heat. Chromatogram B represents temozolomide sample after 240 minutes of incubation at 40ºC when 20.4% of initial temozolomide remains. Chromatogram C represents a sample in Oral Mix SF stored in a PET bottle at 4ºC on day zero. Chromatogram D represents a sample in Oral Mix SF after 56 days storage at 4ºC when 93.89% remained. Chromatogram E shows temozolomide in Oral Mix SF after storage at 25ºC for 56 days when approximately 32.6% remains. Degradation products were not visually evident in any chromatogram during the accelerated or stability study.

METHODS

Liquid Chromatographic Method

The liquid chromatographic system consisted of a Supelcosil ABZ (Supelco, Toronto) C18 column with 30% acetonitrile and 70% 0.05M phosphoric acid with 0.01 M sodium lauryl sulfate as the mobile phase with a flow rate of 1 mL/min and UV detection at 330 nm.

Assay Validation

Following development of the chromatographic system capable of separating temozolomide 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 batches of 3 different formulations of temozolomide 10 mg/mL suspensions were prepared. All formulations were prepared using temozolomide 100 mg tablets (Merck) and Oral Mix SF (Medisca). Formulation #1 also contained povidone K30. Formulation #2 contained povidone K30 and citric acid. Formulation #3 contained no additives. All formulations were stored, protected from light, in 3 different container types (glass, PET bottles and plastic oral syringes). Half the samples of each container type were stored at 25ºC, the other half at 4ºC. On study days 0,5,8,14,21,28,35,42,56 physical stability was assessed and the temozolomide concentration was determined from samples drawn from each container type and storage. Results are reported in Table 1 and 2.

Data Reduction and Statistical Analysis

Analysis of variance was used to test differences in concentration on different study days, at different temperatures, in different bottle containers and with different formulations. The 5% level was used as the a priori cut-off for significance. The most appropriate BUD is assigned by using the fastest degradation rate, with 95% CI, while never exceeding the study duration. This is determined by the intersection of the lower limit of the 95% confidence interval (CI) of the observed degradation rate and the time to achieve 90% of the initial concentration <T-90(95%)>.

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RESULTS

Table 1. Studies of Temozolomide at 4ºC reported as Percent remaining relative to Concentration on Day 0

Study Day	Formulation #1			Formulation #2			Formulation #3		
	PET	Glass	Syr	PET	Glass	Syr	PET	Glass	Syr
0	100	100	100	100	100	100	100	100	100
5	99.94	97.84	99.33	98.38	98.09	98.10	98.69	98.24	97.84
8	98.83	97.59	98.27	98.29	98..16	97.84	97.93	97.87	97.42
14	98.69	97.77	98.94	98.44	98.31	98.42	98.12	97.78	97.62
21	100.56	97.40	98.46	97.24	101.22	98.27	100.05	97.94	97.99
28	96.45	96.33	96.81	97.10	96.72	96.55	96.54	97.55	97.13
35	96.26	96.75	96.58	95.35	96.30	96.28	96.53	97.31	96.75
42	96.00	96.37	96.17	95.10	95.86	95.06	95.88	95.56	95.61
56	95.18	95.47	95.61	94.31	94.39	94.49	93.89	94.36	94.97
Slope (%/day)	-0.09	-0.06	-0.08	-0.09	-0.09	-0.09	-0.09	-0.08	-0.07
Intercept	100.19	98.70	99.63	99.39	99.72	99.72	99.71	99.26	98.88
Std regression (Sy.x)	1.05	0.65	0.49	0.49	1.42	0.63	1.03	0.66	0.68
Confidence Interval for slope (%/day)	0.05	0.03	0.022	0.02	0.06	0.03	0.05	0.03	0.03
Fastest slope (%/day; 95% CI)	-0.14	-0.09	-0.10	-0.12	-0.15	-0.12	-0.14	-0.11	-0.10
Upper limit (%/day; 95% CI)	-0.048	-0.008	-0.057	-0.08	-0.02	-0.06	-0.05	-0.05	-0.04
Shortest T-90 (95%CI)(days)	70.36	110.74	98.80	83.64	65.91	85.21	71.08	91.31	99.77

Table 2. Studies of Temozolomide 10 mg/mL Oral Suspensions at 23Cº reported as Percent Remaining relative to Concentration on Day 0

Study Day	Formulation #1			Formulation #2			Formulation #3		
	PET	Glass	Syr	PET	Glass	Syr	PET	Glass	Syr
0	100	100	100	100	100	100	100	100	100
5	93.11	93.58	93.14	92.77	92.12	92.17	92.23	92.22	93.21
8	84.55	84.65	85.37	84.56	84.34	86.63	84.50	84.48	85.27
14	75.29	76.73	75.75	77.35	76.83	76.28	77.47	76.49	75.43
21	66.88	66.45	66.91	65.72	65.64	66.65	66.03	65.28	66.58
28	57.70	57.91	55.95	57.25	56.80	55.83	55.59	55.84	56.04
35	51.19	50.05	50.32	50.97	50.49	48.92	50.76	51.06	47.88
42	44.76	43.76	44.46	44.93	45.42	44.20	43.13	43.94	42.34
56	33.00	36.29	34.06	36.38	36.43	35.46	32.60	32.40	31.65
Slope (%/day)	-1.20	-1.18	-1.21	-1.17	-1.16	-1.20	-1.23	-1.22	-1.26
Intercept	95.34	95.21	95.34	94.89	94.50	95.21	95.38	95.11	95.69
Std regression (Sy.x)	3.84	4.63	4.34	4.57	4.65	4.72	4.01	4.04	4.19
Confidence Interval for slope (%/day)	0.17	0.21	0.19	0.20	0.21	0.21	0.18	0.18	0.19
Fastest slope (%/day; 95% CI)	-1.38	-1.39	-1.40	-1.37	-1.37	-1.41	-1.41	-1.39	-1.45
Upper limit (%/day; 95% CI)	-1.03	-0.98	-1.01	-0.96	-0.95	-0.99	-1.05	-1.04	1.07
Shortest T-90 (95%CI)(in days)	7.27	7.19	7.14	7.28	7.31	7.08	7.12	7.15	6.92

Assay Validation

During the study, the accuracy (% absolute deviation) from the known concentration for standards was 1.38% and QC samples was 1.11%. The error of replicate analysis (CV) within a day averaged 0.29% for the standards and 0.46% for the QC standards and between day variation (CV) averaged 0.77% for the standards and 1.01% 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, averaged 2.56%
Assay validation demonstrated that the method was accurate, reproducible and stability-indicating.

Stability of Temozolomide Suspensions

The shortest T-90 (95%CI) in all container types and formulations was 65 days at 4 C and 6 days (rounded down) at 23 C.

Degradation products were not detected in any samples, although this may be due to the wavelength of detection.

Analysis of variance demonstrated significant changes in concentration due to study day and temperature ($p<0.001$) but not container ($p=0.994$) or formulation ($p=0.967$)

Visual Observations

Temozolomide suspension is white in color but turns to an orange color over time which is more intense in samples at 25ºC. Crystal formation was evident in all formulations studied which increased over time.

CONCLUSION

All 3 oral suspension formulations of 10 mg/mL temozolomide assayed above 93% of the initial concentration for 56 days when stored in any of the 3 types of containers (amber glass, PET, and plastic oral syringes) at 4ºC. At 25ºC, concentrations remained above 92% of initial concentration for only 5 days. The shortest T-90 (95%CI) in all containers at 4ºC is 65 days and 6 days at 25ºC. However, since temozolomide will be exposed to room temperature daily when taken out of the fridge, this could affect potency, depending on duration of storage. Furthermore, crystal growth increased over time in all formulations. For these reasons, it is recommended to assign a much shorter BUD than reported in this study, such as 30 days storage in the refrigerator. The suspension should be dispensed with cooler packs to ensure that it is not exposed to high temperatures while in transit from pharmacy to home. Patients should remove the dose from the bottle and immediately return the suspension to the refrigerator, reducing or eliminating exposure at room temperature.

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