Accelerated Stability Studies by High Performance Liquid Chromatography

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2012 Sigma Aldrich® Summer Intern Program

Cerilliant® Analytical Reference Standards
a SIGMA-ALDRICH® company

Abstract

The purpose of this study was to perform accelerated stability studies to predict the shelf lives of 21 Cerilliant products and compare the results to available real time stability information. From the rates of degradation, an Arrhenius plot was constructed for each product to yield the rate of degradation at the control temperature and the energy of activation for thermolytic degradation. Thermolytic degradation was assumed to be the only decomposition pathway.

Experimental Design

Twenty two ampules of each product were placed in different storage conditions for a total of 28 days. All products are ampuled solution standards, flame-sealed under argon.

22 Total Ampules	5 Time points (in days)
2 @ Freezer (control)	T=0
5 @ Refrigerator, Room Temperature, 40°C, 60°C	T=3, 7, 14, 21, 28

At each timepoint, one ampule was transferred from each storage condition to the freezer. After 28 days timepoint, all samples were analyzed for purity by HPLC.

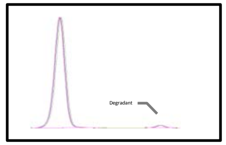
Left: Samples of D-069 pulled from the 60°C storage condition. From left to right: sample after 3, 7,14, 28 days. The darkened color and precipitate are due to degradation.

Right: HPLC was used for the analysis of samples. Stability indicating HPLC methods were developed for the analyses.

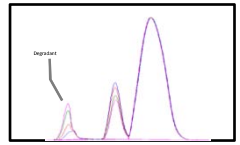
Products tested for the Study

Oxazepam	O-902	(-)-Δ^9-THC	T-005	7-Aminoclonazepam	A-916
Oxazepam glucuronide	O-023	Propofol	P-076	Noroxycodone HCl	N-011
Norbuprenorphine	N-059	Cocaine-N-Oxide	C-119	Tacrolimus	T-049
Morphine-6B-D-glucuronide	M-096	Benzoylecgonine	B-004	Butylone HCl	B-045
Vitamine B1 (Thiamine HCl)	V-014	Propoxyphene	P-011	Rufinamide	R-015
Mycophenolic Acid	M-106	Desmethylolanzapine	D-069	Green Tea Catechin mix	G-016
Thyroid	T-075	Dopamine	D-081	25-Hydroxyvitamin D3	H-083

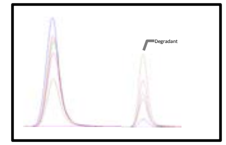
Degradation Effects on Selected Products



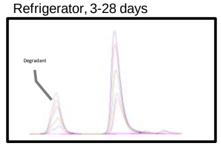
Morphine-6B-D-glucuronide (M-096)
Refrigerator, 3-28 days



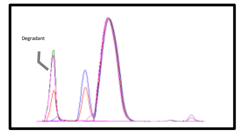
Cocaine N-oxide (C-119)
Room Temperature, 3-28 days



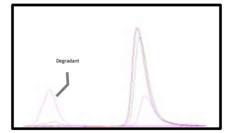
Oxazepam (O-902)
40 degrees, 3-28 days



Vitamin B1 (V-014)
60 degrees, 3-28 days



Cocaine N-oxide (C-119)
All Storage Conditions, 28 days



Vitamin B1 (V-014)
All Storage Conditions, 28 days

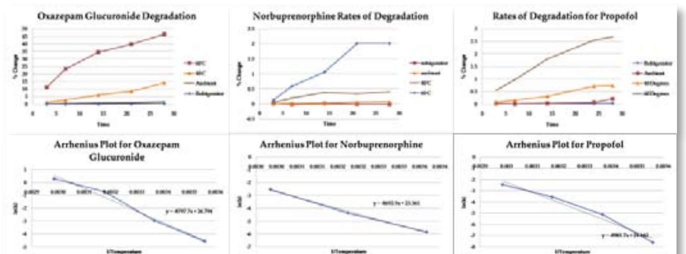
These select chromatogram portions show the amount of degradation over time and with increasing temperature.

Treatment of Data

The change in % area value vs. time was plotted for each temperature. The change in % area was defined as the absolute difference between the freezer sample's % area and the % area of other samples. Microsoft Excel was used to plot this change over time for each storage condition and determine a linear trend line. The slope (k) of this trend line gives the rate of degradation at a given temperature. A plot of ln(k) vs. 1/T was also created for each product using the slopes from each storage condition and was used to determine the shelf-lives reported. The slope of this line was also used to determine the activation energy for thermolytic degradation using the Arrhenius relationship k=Ae^(-Ea/RT) where k= degree of rate constant , A=pre-exponential factor, Ea=Activation energy , R=universal gas constant and T=temperature in Kelvin.

Degradation and Arrhenius Plots

Selected examples of degradation analysis are shown below.



Results

Name of Product	Rates of Degradation (%/day) Refrigerator	Room Temperature	40°C	60°C	Predicted Shelf Life (years)	Expiry Date Assigned from Real Time Study (years)	Energy of Activation (kcal/mol)
Oxazepam	0.0133	0.1723	1.8971	1.2927	2.8	4	16.7632
Oxazepam glucuronide	0.0104	0.0513	0.5	1.328	5.9	5	17.4714
Norbuprenorphine	-0.0005	0.0029	0.0127	0.0803	197.3	5	17.2632
Morphine-6β-D-glucuronide	0.0022	0.0027	0.0117	-0.0046	96.6	3	8.6436
Mycophenolic Acid	0.0092	0.3215	0.4663	0.2516	0.9	On Retest	10.7088
(-)-Δ^9-THC	0.0039	0.0049	0.017	0.0931	16.9	5	14.059
Cocaine N-oxide	0.0212	0.2974	0.1442	0.0516	28.7	On Retest	11.1625
Propofol	0.0005	0.006	0.0287	0.0865	193.3	On Retest	17.6779
Benzoylecgonine	0.0019	0.0148	0.0931	0.7222	63.1	5	20.4051

The data for products not included in this section had not been analyzed at the time of this poster's submission.

Discussion

This study was conducted under the assumption that all of the compounds followed the Arrhenius relationship .The compounds were assumed to have the same degradation mechanism at all temperatures and that the rate of the degradation stayed constant for each temperature condition.[1] The storage conditions were chosen so that % change outside the range of analytical variation would be observed in the samples. Most of the shelf lives estimated from the Arrhenius plots agree with real time data. Real time data is only collected on products for up to five years and the experimental data predicts shelf lives that go beyond 5 years. In example s of oxazepam and morphine-6β-D-glucuronide results did not match the real time studies. The degradation rates for these compounds were non-linear at one or more temperatures and the Arrhenius plots could not accurately predict a shelf-life.

Conclusion

An accelerated stability study was performed on 21 selected Cerilliant products. The products were stressed in a variety of temperature conditions and the predicted shelf-lives were compared to the available real time stability data. This method of predictive stress degradation can be used on new Cerilliant products to estimate a shelf-life before real time data is available. Cerilliant introduces ~100 new products a year and accelerated stability studies could provide customers with critical long term storage information.

Bibliography 1. Pharmaceutical Stress Testing: Predicting Drug Degradation ; Baertschi, S. W., Ed.; Drugs and the Pharmaceutical Sciences volume 153; Informa Healthcare: New York New York, 2007.

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