

Forced Degradation Automation

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Abstract

Conditions and Case Study

Conclusion and Future Work

Forced degradation is an important method used in drug development in the pharmaceutical industry. Forced degradation studies are used for multiple purposes, including demonstration of the specificity of separation methods, gaining insight into degradation pathways, and discernment of degradation products in formulations that are related to drug substances versus those that are related to other ingredients of a formulation.

However, FDA guidance for forced degradation is vague with respect to experimental conditions. In order to harmonize the procedures of forced degradation, an automated method for forced degradation was developed, utilizing the CTC LEAP PAL workstation automation system.

The Automated Forced Degradation approach significantly reduces the amount of manual labor used to perform the tests and harmonizes the operational procedures of forced degradation.

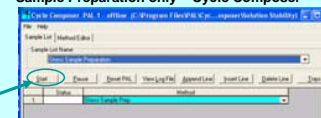
The Automated Forced Degradation system is user-friendly and is intended to be used as a "walk-up system" that is able to prepare forced degradation and linearity samples, perform on-line HPLC analysis as well as generate reports automatically. The details of the system will be discussed along with a number of case studies demonstrating its use.

Automated Forced Degradation Conditions

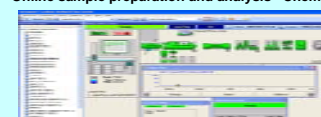
Stress Type	Major Degradation Pathway	Reagents	Co-solvent (if necessary)	API Conc.	Temp.	Sampling Time	Comments
Primary Solution Phase Conditions							
Acid/Base	Hydrolysis	0.01N HCl 0.01N NaOH	Acetonitrile	Analysis concentration*	40° C (increase if needed)	3 hours	Alcohol solvents can facilitate acid/base catalyzed addition of alcohol
Acid/Base	Hydrolysis	0.1N HCl 0.1N NaOH	Acetonitrile	Analysis concentration*	40° C (increase if needed)	24 hours	Alcohol solvents can facilitate acid/base catalyzed addition of alcohol
H ₂ O ₂	Nucleophilic Oxidation	0.3 % H ₂ O ₂ /pH 7 buffer solution	MeOH or EtOH	Analysis concentration*	RM	24 hours	Acetonitrile solvent react with H ₂ O ₂ to form peroxyacetic acid
ASIN	Auto-oxidation	5 mM ASIN in MeOH/H ₂ O (1:1)	See comments	Analysis concentration*	40° C	24 hours	Severe solvent effects currently under investigation
Thermal	Heat	NA	Acetonitrile	Analysis concentration*	100° C	4 hours	

User Friendly "Walk Up System"

Sample Preparation only – Cycle Composer



Online sample preparation and analysis – ChemStation/Altas



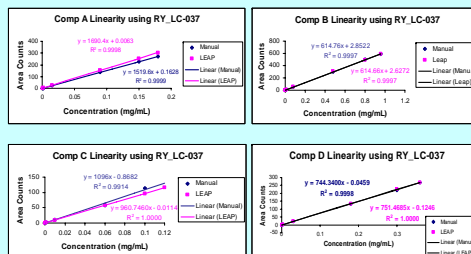
Conclusions

- The LEAP system has been approved and validated for use in performing method validations and forced degradation studies
- Linearity, reproducibility, ease of use, and open access have been demonstrated
- The automated sample preparation, online analysis, and auto report streamline pre- PCC chemical stability screen

How Does the Leap Work?



Establishing Linearity Manual vs. LEAP

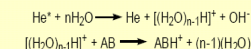


DART for Quick ID of Degradants?

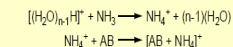
Direct Analysis in Real Time (DART) technology to interface with existing LC/MS



Gas-phase proton transfer reactions



Gas-Phase Chemical Ionization



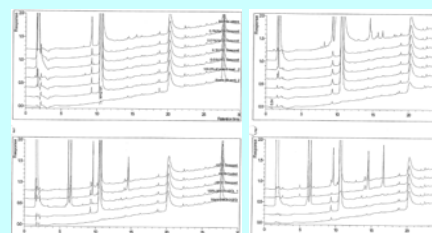
Future Work

- Develop and validate forced degradation workflow for lead Op activities
- Demonstrate the use of the LEAP System as a method development tool for kinetic profiling, on-line MS ID, etc.
- Evaluate and develop low throughput solubility/stability/redispersability combined workflow
- Evaluate low throughput dissolution screen

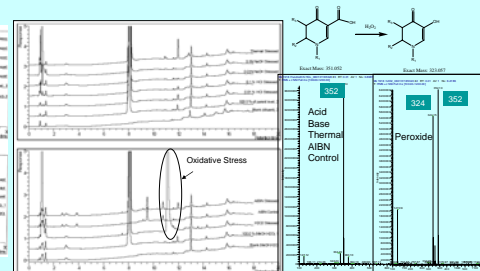
Goals of the Automated System

- User friendly format – a "Walk-Up System"
- Reproducibly and accurately performs method validation and forced degradation
- Automated Report featuring linearity, LOQ, LOD, and degradation profile overlays
- Adaptability of system to changing conditions (solvents, degradation conditions, etc.)

Automated Report Stress Degradation Overlays



Dart Analysis Compound E



Acknowledgements

Merck

- Lou Crocker, Mike Riebe, Alexander Chin
- Zhihong Ge, Chris Welch, Vinni Antonucci, Bing Mao, Abraham Ahmed
- Xiaoyi Gong, Adam Beard, Biba Mirlinda, Naijun Wu
- Allen Templeton, Andrey Peresypkin
- John Delella, JJ Yates, Neil Rissen, Donglan Cai, Doug West, Adam Duckworth

Leap Technologies

- Carlos Perez, Scott Donenfeld, Brian Peat

IonSense

- Brian Musselman