



Technology Review Series

Forced Degradation Studies

Forced degradation studies are a necessary part of developing an API into a viable drug products. To accomplish this , four main degradation mechanisms heat, hydrolytic, oxidative [O2] and photolytic degradation need to be investigated.

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There are several key questions to answer during early phase drug development. Questions needing answers include:

- What is the chemical stability of the API?
- What physical form should be selected for development?
- Which salt form should be used?
- What are the chemical degradation pathways of the API?
- Do the major degradation products match the metabolites of the API?
- Which formulation should be selected?
- What are appropriate storage conditions for the API and formulations?

Forced degradation plays an important role in answering these questions and determining the ability to develop a drug.

The initial purpose of forced degradation studies is to investigate stability-related properties of an API and to develop an understanding of the degradation products and pathways. These studies should also be used to evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values. Forced degradation studies are also used to provide degraded samples for the development of stability-indicating analytical methods for the API. The information developed from a forced degradation study can also be utilized in several other areas of development, including analytical methods development, formulation development and storage conditions, manufacturing-processing, safety-toxicological, identification of possible genotoxic degradants, identification of potential metabolites and API design/discovery.

Forced degradation studies are most beneficial if done early in the drug development process. The reasoning for this is that these studies yield predictive information on the nature of the degradants which are valuable when assessing the appropriate synthesis routes, API salt selection and formulation development. These early studies can

help provide information needed for the following:

- In development of stability-indicating analytical methods.
- As a predictive tool to help understand degradation pathways and stability-related issues.
- To predict API stability before real-time stability data is available.

Through the use of these early development degradation studies the focus should be the garnering of as much information as possible about the chemistry of the API. To accomplish this, forced degradation studies are done on both the solid state and aqueous solution or suspension forms of the API. Furthermore, the use of analysis at multiple time points allows for approximation of rates of degradation and such testing at early time points can provide a distinction between primary and secondary degradation products. This approach allows for better degradation pathway determination

Forced degradation studies should be repeated as needed through out the drug development process. For example, when there are changes in API impurity profile, API salt or polymorph form. When carried out in late development such studies are referred to as confirmatory studies. Confirmatory studies are quantitative in nature.. Full mass accountability of the API, its impurities and degradation products are generated from these late stage studies. Furthermore, based upon the outcome of these studies, if necessary, new or orthogonal methods may need to be developed to account for all observed degradation. Also, confirmatory studies for API are done after finalization of the synthetic route and form of the API. Such studies are typically done in Phase III with one of the registration batches of the API. For drug products, confirmatory studies are done when final formulation(s) and packaging are chosen. After the confirmatory studies are completed, a report on

degradation products and pathways is generated and included in or used to support NDA filings.

The following are general conditions that should be employed when conducting forced degradation studies:

Solid State

- Heat
- Heat/humidity
- Light

Solution and/or Suspension

- Hydrolysis at various pHs
- Unbuffered HCl, NaOH, water
- Buffer solutions (used to determine if pH adjustment needed to attain maximum stability)
- Oxidative stress testing
- H₂O₂ (to mimic possible presence of peroxides in excipients)
- Metal ions (to mimic possible exposure during manufacture)
- Radical initiators (to mimic autoxidation)
- Light

The general approach for carrying out the testing of samples generated from forced degradation is through the use of HPLC (LC) with either a UV or PDA detector. In most instances the initial starting method will be some generic LC method with an appropriate column to effectuate separation. Over time, this method will be refined or modified so that complete separation of the API and its degradants are achieved.

Once a satisfactory LC method has been developed the process of identifying the structure of degradants can begin. This involves transferring the method for use with LC-MS. LC-MS is powerful analytical tool specifically capable of providing structural elucidation.

By using LC-MS, and where needed LC-NMR, information on the structure of each impurity and degradation product of an API can thus be developed. This information, along with a fundamental understanding of the API's chemistry provides the means for understanding the API's degradation pathways. In addition, the elucidation and identification of these structures allows investigating whether the degradation products are known compounds that have been previously

characterized or whether they are potential carcinogens or genotoxins

Having identified the degradation products the results of the forced degradation can be formalized. This formalization must include both the degradation conditions used and the proposed structures of the degradation products observed for those conditions. A proposed mechanism of degradation that identifies potential degradation products and pathways can thus be understood. Armed with this, a stable formulation with proper packaging and/or storage conditions can thus be developed.

About the authors

James Menoutis is the CEO of Quantex Laboratories. He has over 30 years experience as an analytical chemist, group leader, researcher, manager and technology executive. His experience includes toxicology, clinical chemistry, methods development and analysis of pharmaceuticals and botanicals, analysis and methods development for the analysis of clinical pharmaceuticals, pesticide residue analyses, occupational health and analytical toxicological. He has an extensive analytical background in mass spectrometry which includes, GC-MS, LC-MS and HRGC-HRMS. His research interests include the development of GC-MS and LC-MS methods for the identification and measurement of impurities and degradants including those that are carcinogenic and genotoxic. He holds certification as a Certified Professional Chemist and as a Certified Professional Chemical Engineer from The National Certification Commission in Chemistry and Chemical Engineering and is a Fellow of the American Institute of Chemists. He is a member of a number of professional and scientific societies, and serves as Vice President of the New Jersey Institute of Chemists and is a member of the Life Sciences Advisory Board of the New Jersey Technology Council.

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