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A Forced Degradation Study: Overview of Stress – Testing Program

Fidelta d.o.o. introduces a generic approach for conducting stress testing on drug substances and drug products. The established strategy is evaluated and verified according to the regulatory guidance documents (ICH guidelines, FDA Guidance for Industry, FDA Reviewer Guidance, European Pharmacopoeia, etc.), with emphasis on what should be considered during early development as well as for late-clinical phases and for registration application dossiers. Stress testing of the drug substance can help identify the likely degradation products, which examination can be useful in establishing degradation pathways, the intrinsic stability of the molecule and validate the stability-indicating potential of analytical method used. This results could be helpful by generation of more stable formulations and can be used for development of manufacturing processes or to select proper packaging and conditions for long-term storage.

Forced Degradation Study Design

Stability-stress testing will be performed in different pH environment, in the presence of oxygen and ID65 light and at elevated levels of temperatures and humidity, in a solid form and / or in solution.

Hydrolysis	Mechanism	Conditions
0.1 N HCl	acid-catalyzed	start, 1d & 3d at 60°C
0.1 N NaOH	base-catalyzed	start, 1d & 3d at 60°C
H_2O	-	start, 1d & 3d at 60°C
pH 2 / 20% HP-β-CD	HP-β-CD protect for hydrolysis or kinetically accelerate	start, 1d & 3d at 60°C
pH 4 / 20% HP-β-CD		start, 1d & 3d at 60°C
pH 6 / 20% HP-β-CD		start, 1d & 3d at 60°C
pH 8 / 20% HP-β-CD		start, 1d & 3d at 60°C
pH 10 / 20% HP-β-CD		start, 1d & 3d at 60°C
pH3 / 30% HP-β-CD / PEG400 (8:2)		start, 1d & 3d at 60°C
0.5% Methyl cellulose		start, 1d & 3d at 60°C

Oxidation	Mechanism	Conditions
0.3% H_2O_2 in H_2O/MeOH (9:1)	ionic mechanism, N- or S-oxidation	start, 1d at RT
5mM ACVA* in H_2O/MeOH (95:5)	radical oxidation (ROO·) (autoxidation)	start, 1d & 2d at 40°C
0.5mM Cu(II) and Fe(III) in H_2O	single electron transfer - oxidation	start, 1d & 3d at 40°C
PEG 400	radical induced oxidation (ROO·)	start, 1d & 3d at 60°C

* 4,4'-Azobis-cyanovaleric acid - alternatively another azo-compound (R-N=N-R') can be used, e.g. 1mg/ml of AAPH in CH_3CN at 40°C

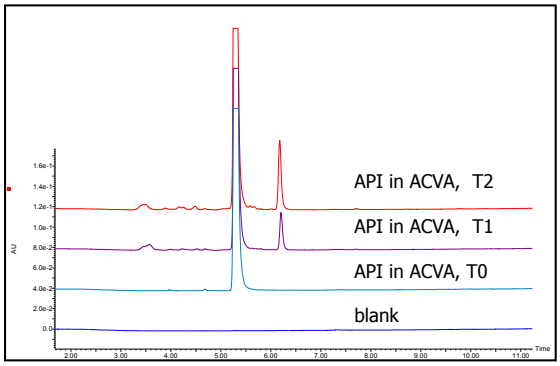
The observed degradation is classified into three categories: minor degradation of the main compound lead to degradation not more than 1 area%, moderate degradation of the main compound lead to degradation between 1 – 10 area% and significant degradation with more than 10 area% degradation of the main compound.

Testing of samples will be performed at defined sampling points using specific developed stability-indicative analytical method. All degradation products and impurities ≥ 0.1 area% will be considered in summarized overview of results.

Light	Mechanism	Conditions
H_2O + control	photo-induced oxidation and photolysis	8h at 700W/m² (ICH)*/ 1h at 300W/m²**
PEG 400 + control		8h at 700W/m² (ICH)*/ 1h at 300W/m²**
0.5% Methyl cellulose + control		8h at 700W/m² (ICH)*/ 1h at 300W/m²**
20% HP-β-CD + control		8h at 700W/m² (ICH)*/ 1h at 300W/m²**
Solid + control		8h at 700W/m² (ICH)*/ 1h at 300W/m²**

* corresponds to ICH light
** corresponds to daylight exposure behind window glass during 8h

Heat	Mechanism	Conditions
solid	-	start, 7d at various temperatures
Heat/Humidity	**Mechanism**	**Conditions**
solid	-	start, 7d at various temperatures and various relative humidities



Isolation and identification of degradation products by means of NMR spectroscopy, high resolution mass spectrometry (HRMS) and multiple stage mass spectrometry (MS^n) can be performed at request.

Conclusion

Forced degradation is one of the biggest challenges of early method development; critical and selective leading of the study and understanding of mechanisms will be greatly rewarded in the efficiency of your further drug substance or drug product development.

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