Forced Degradation Studies for Glycopyrrolate, Formoterol & Budesonide By UPLC

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Abstract: Forced degradation studies include the degradation of new drug substance and drug product at conditions more severe than accelerated conditions. These studies illustrate the chemical stability of the molecule which further facilitates the development of stable formulation with suitable storage conditions. ICH guidelines demonstrate certain degradation conditions like light, oxidation, dry heat, acidic, basic, hydrolysis etc.

Keywords: Degradation; Drug substance; Stability; Safety; Testing; ICH guidelines, FDA

1. INTRODUCTION

To determine the interaction among multi-drugs, the dose-response surface provides a comprehensive description on dose effects. For estimating the high dimensional dose-response surface, experimental designs are required that provide selected concentrations or dose-levels of combinations, which allow exploration of the dose-effect surface with high accuracy at reasonable sample sizes. Recently, we developed a novel method to screen the large number of combinations and identify the functional structure of the dose-response relationship by using the dose-response data of single drugs and pathway/network knowledge [1].

Forced degradation studies provide the approach to analyse the stability of drug samples in pharmaceutical industries. Drug product safety and efficacy is affected by the chemical stability of the molecule. Stability of molecule information provides the data for selecting proper formulation, package, proper storage conditions and shelf life. These data also play a significant role which is required in the regulatory documentation. Before filling registration dossier it is obligatory to execute stability studies of new drug molecules [2-3].
Chemical stability of pharmaceutical molecules is a matter of great concern as it affects the safety and efficacy of the drug product. The FDA and ICH guidances state the requirement of stability testing data to understand how the quality of a drug substance and drug product changes with time under the influence of various environmental factors. Knowledge of the stability of molecule helps in selecting proper formulation and package as well as providing proper storage conditions and shelf life, which is essential for regulatory documentation. Forced degradation is a process that involves degradation of drug products and drug substances at conditions more severe than accelerated conditions and thus generates degradation products that can be studied to determine the stability of the molecule. The ICH guideline states that stress testing is intended to identify the likely degradation products which further helps in determination of the intrinsic stability of the molecule and establishing degradation pathways, and to validate the stability indicating procedures used [4]. But these guidelines are very general in conduct of forced degradation and do not provide details about the practical approach towards stress testing. Although forced degradation studies are a regulatory requirement and scientific necessity during drug development, it is not considered as a requirement for formal stability program.

The pharmacological properties of budesonide, glycopyrronium and formoterol are well established [5-6]. This section primarily focuses on the pharmacological properties of budesonide/glycopyrronium/formoterol, an FDC of two bronchodilators with different mechanisms of action and a glucocorticosteroid, formulated using a co-suspension delivery technology [7-8]. Budesonide is a potent glucocorticosteroid with a rapid onset of action and demonstrates dose-dependent anti-inflammatory action in the airways.

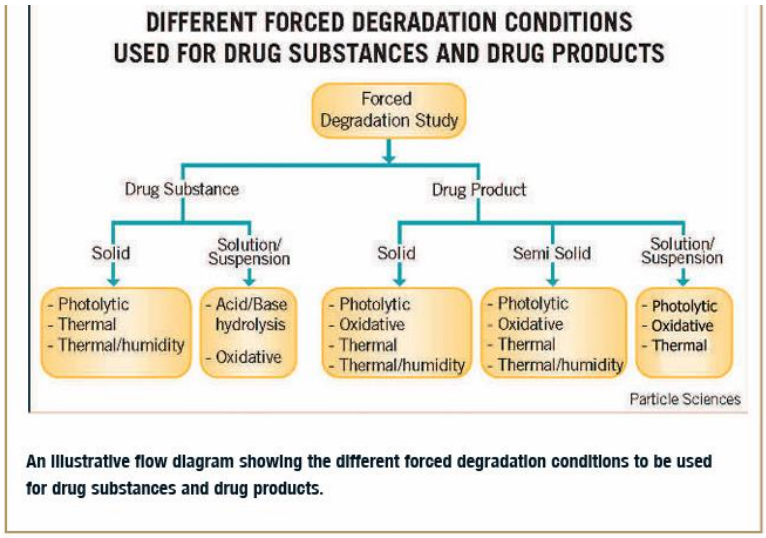
Budesonide/glycopyrronium/formoterol delivered by a pressurized metered-dose Aerosphere inhaler is formulated using a co-suspension delivery technology, which creates a uniform suspension of drug crystals and porous phospholipid particles, thereby enabling simultaneous delivery of multiple drugs from one inhaler

[9]. This delivery technology offers excellent dose uniformity and stability, and minimizes the potential for formulation-related drug–drug interactions in combination therapies [9]

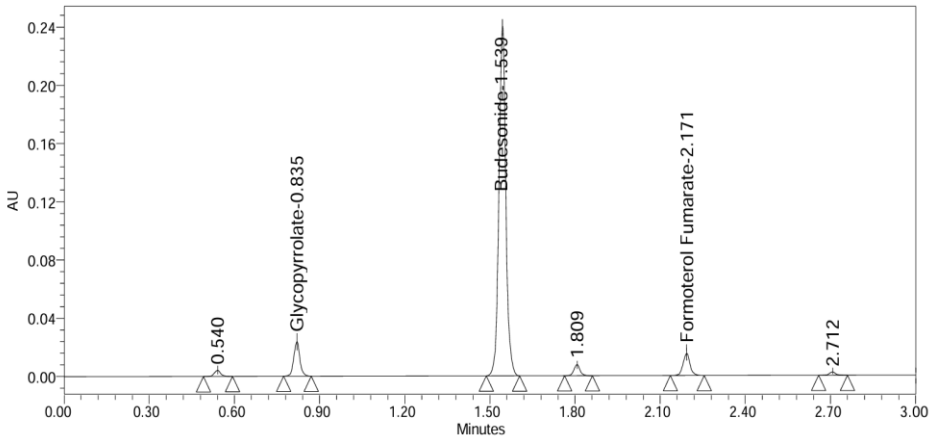
2. RESULTS AND DISCUSS

FORCED DEGRADATION STUDIES:

1. Acid Degradation:
Procedure:
Accurately weigh 241 mg of Glycopyrrolate, Budesonide and Formoterol fumarate sample and transferred into a 10ml volumetric flask and add 1ml of 1N HCl. Leave it for 15 min. After 15 min add 1ml of 1N NaOH to neutralize the solution and diluted to volume with diluent and mixed.
The above solution is injected into UPLC system.
2. Alkali Degradation:
Procedure:
Accurately weigh 241 mg of Glycopyrrolate, Budesonide and Formoterol fumarate sample and transferred into a 10ml volumetric flask and add 1ml of 1N NaOH. Leave it for 15 min. After 15 min add 1ml of 1N HCl to neutralize the solution and diluted to volume with diluent and mixed.
The above solution is injected into UPLC system.
3. Peroxide Degradation:
Procedure:
Accurately weigh 241 mg of Glycopyrrolate, Budesonide and Formoterol fumarate sample and transferred into a 10ml volumetric flask and add 1ml of 10% H_2O_2. Leave it for 15 min. After 15 min diluted to volume with diluent and mixed.
The above solution is injected into UPLC system.
4. Reduction Degradation:
Procedure:
Accurately weigh 241 mg of Glycopyrrolate, Budesonide and Formoterol fumarate sample and transferred into a 10ml volumetric flask and add 1ml of 10% Sodium bi sulphite solution. Leave it for 15 min. After 15 min diluted to volume with diluent and mixed.
The above solution is injected into UPLC system.
5. Thermal Degradation:
Procedure:
200 mg of Glycopyrrolate, Budesonide and Formoterol fumarate standard was exposed at 105°C for 6 hrs and the exposed standard was analysed. 40mg of Budesonide, 5mg of Glycopyrrolate and 12mg of Formoterol fumarate was transferred into 10ml volumetric flask and make up to the mark.
The above solution is injected into UPLC system.
6. Photolytic Degradation:
Procedure:
500mg of sample was placed in photo stability chamber for 3 hrs and the exposed sample was analysed. 241 mg of sample was transferred into 10ml volumetric flask and make up to the mark.
The above solution is injected into UPLC system.
7. Hydrolysis Degradation:
Accurately weigh 241 mg of Glycopyrrolate, Budesonide and Formoterol fumarate sample and transferred into a 10ml volumetric flask and add 3ml of HPLC water. Leave it for 15 min. After 15 min diluted to volume with diluent and mixed.
The above solution is injected into UPLC system.

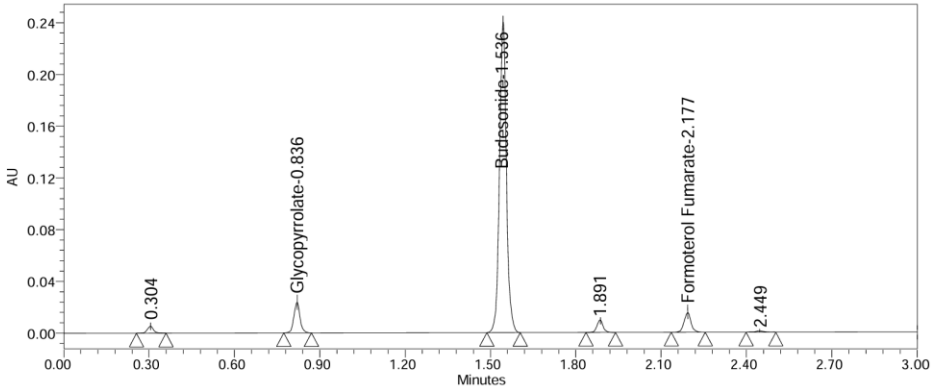


An illustrative flow diagram showing the different forced degradation conditions to be used for drug substances and drug products.



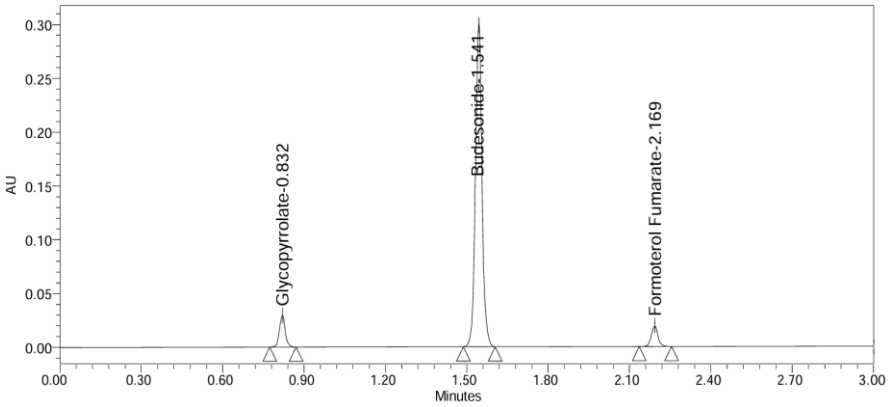
Peak Results

	Sample Name	Name	Area	USP Tailing	USP Plate Count	USP Resolution
1	Acid deg		19779	1.24	7042	
2	Acid deg	Glycopyrrolate	154254	1.08	6543	2.79
3	Acid deg	Budesonide	2425247	1.17	18561	6.86
4	Acid deg		339781	1.03	10617	2.31
5	Acid deg	Formoterol Fumarate	73164	0.94	5458	3.19
6	Acid deg		10099	0.87	9236	3.94



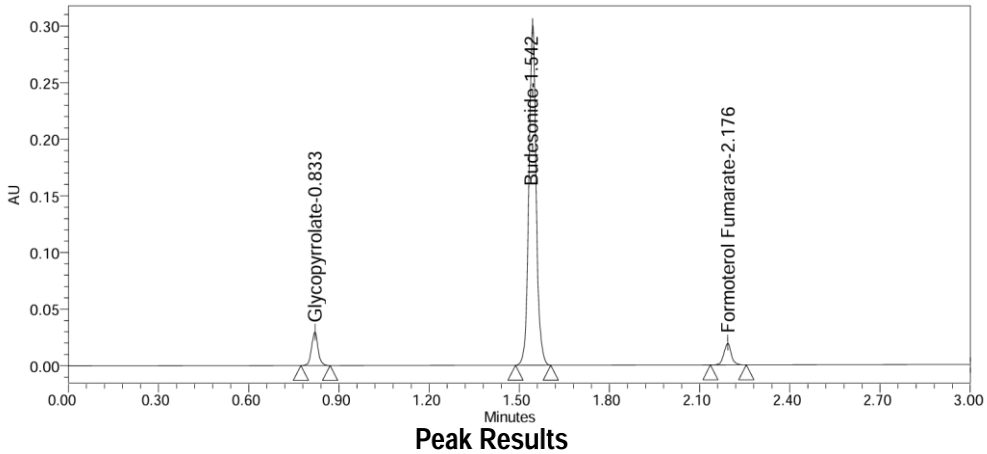
Peak Results

	Sample Name	Name	Area	USP Tailing	USP Plate Count	USP Resolution
1	Alkali deg		21671	1.20	5619	
2	Alkali deg	Glycopyrrolate	152361	1.09	6525	4.96
3	Alkali deg	Budesonide	2401963	1.10	18537	6.82
4	Alkali deg		363068	1.01	15164	3.12
5	Alkali deg	Formoterol Fumarate	74288	0.97	5440	2.77
6	Alkali deg		8964	1.05	12965	2.48



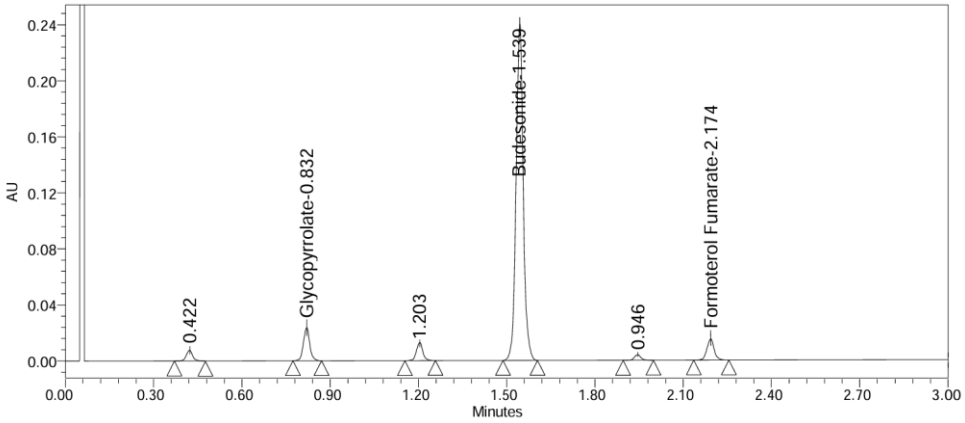
Peak Results

	Sample Name	Name	Area	USP Tailing	USP Plate Count	USP Resolution
1	Control deg	Glycopyrrolate	174038	1.07	6526	
2	Control deg	Budesonide	2765023	1.15	18551	6.81
3	Control deg	Formoterol Fumarate	83263	0.93	5427	5.39



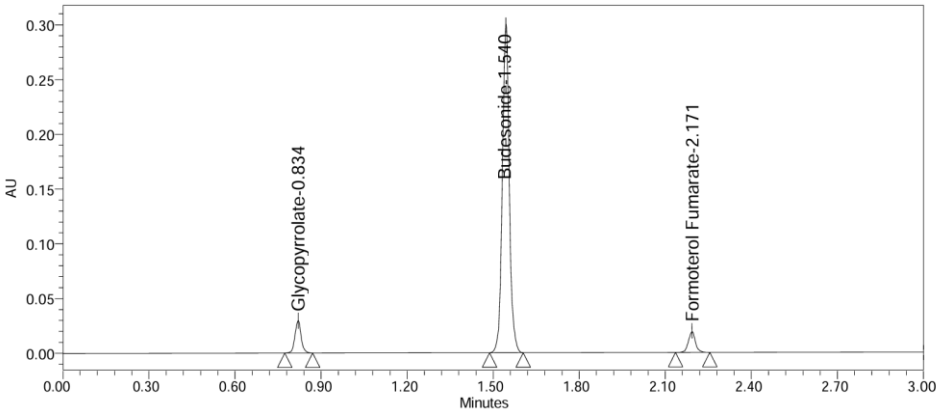
Peak Results

	Sample Name	Name	Area	USP Tailing	USP Plate Count	USP Resolution
1	Hydrolysis deg	Glycopyrrolate	167204	1.02	6542	
2	Hydrolysis deg	Budesonide	2671504	1.16	18531	6.85
3	Hydrolysis deg	Formoterol Fumarate	81551	0.93	5429	5.31



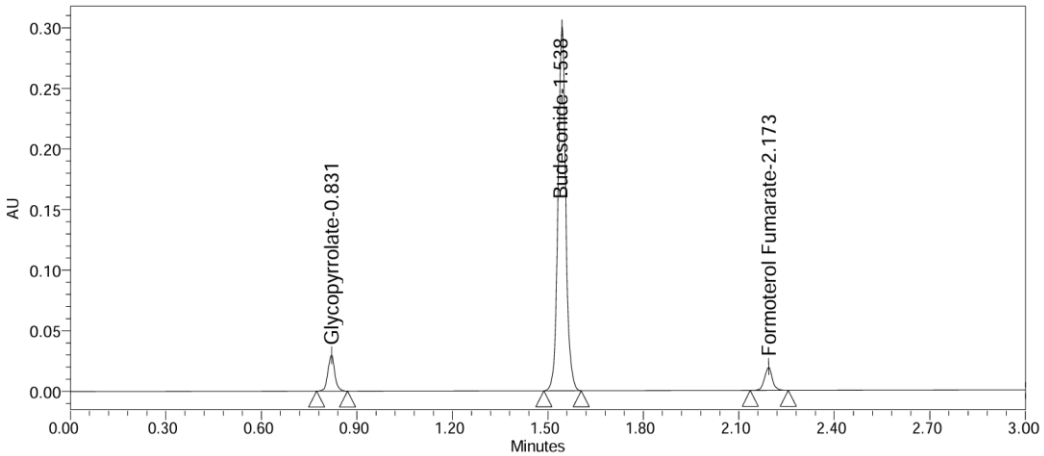
Peak Results

	Sample Name	Name	Area	USP Tailing	USP Plate Count	USP Resolution
1	Peroxide deg		24281	1.15	4237	
2	Peroxide deg	Glycopyrrolate	149750	1.06	6565	3.61
3	Peroxide deg		415527	1.00	8986	3.65
4	Peroxide deg	Budesonide	2349490	1.13	18521	3.31
5	Peroxide deg		11123	0.91	9033	3.52
6	Peroxide deg	Formoterol Fumarate	72137	0.99	5453	2.73



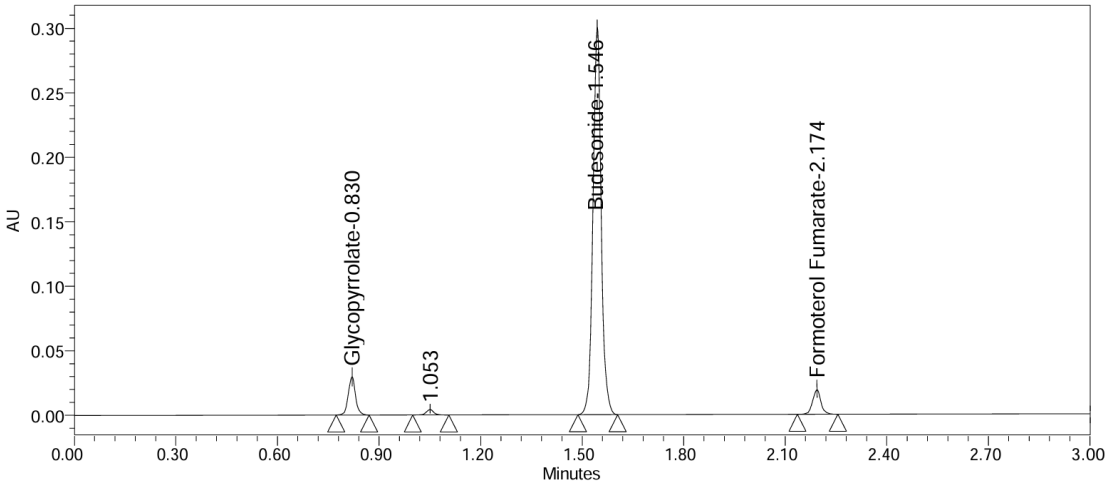
Peak Results

	Sample Name	Name	Area	USP Tailing	USP Plate Count	USP Resolution
1	Photolytic deg	Glycopyrrolate	171035	1.08	6519	
2	Photolytic deg	Budesonide	2693833	1.14	18540	6.82
3	Photolytic deg	Formoterol Fumarate	82593	0.99	5427	5.36



Peak Results

	Sample Name	Name	Area	USP Tailing	USP Plate Count	USP Resolution
1	Reduction deg	Glycopyrrolate	170648	1.03	6540	
2	Reduction deg	Budesonide	2701696	1.17	18529	6.86
3	Reduction deg	Formoterol Fumarate	80249	0.95	5454	5.41



Peak Results

	Sample Name	Name	Area	USP Tailing	USP Plate Count	USP Resolution
1	Thermal deg	Glycopyrrolate	169091	1.05	6571	
2	Thermal deg		265704	0.86	9124	2.86
3	Thermal deg	Budesonide	2499312	1.17	18512	4.03
4	Thermal deg	Formoterol Fumarate	81151	0.98	5436	5.29

SUMMARY

Forced degradation studies are indispensable in the development of stability-indicating and degradant-monitoring methods as part of a validation protocol. Forced degradation studies also provide invaluable insight in investigating degradation products and pathways of drug substances and products. Given that no specific set of conditions will be applicable to all drug substances and products, the pharmaceutical scientist should ensure the stress conditions are consistent with product decomposition under normal manufacturing, storage, and intended use conditions.

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