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Stability Indicating Method Development and Validation of Irbesartan and Hydrochlorothiazide with Stress Degradation

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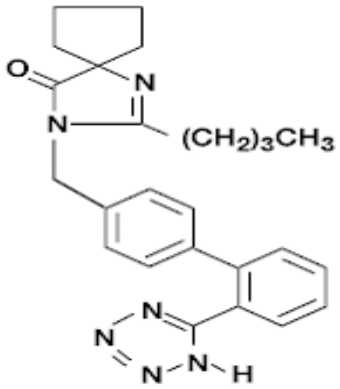
ABSTRACT

Irbesartan and Hydrochlorothiazide were subjected to different ICH prescribed stress conditions like acidic, alkaline, oxidation, reduction, thermal and Photostability condition and found that degraded peaks did not interfere with the peaks of drug under the study. A HPLC system LC Shimadzu UFLC-2000 Prominance LC-20AD Binary Gradient System, SPDM 20A detector with Rheodyne injector and EnableC18 G column 250 x 4.6mm, 5µm. Injection volume of 20µL was injected and eluted with the mobile phase consists of a mixture of 50 mm Ammonium acetate: Acetonitrile (70:30% v/v) effluent was monitored at 235 nm using PDA detector. The method was linear over the concentration range of 150-350 µg/ml (r^2 = 0.999) with a limit of detection and quantitation of 0.019 and 0.053 µg /ml for Irbesartan, and range of 15-35 µg/ml (r^2= 0.999) with a limit of detection and quantitation of 0.023 and 0.070 µg/ml for Hydrochlorothiazide. The method was validated for linearity, range, precision, accuracy, specificity, selectivity and intermediate precision.

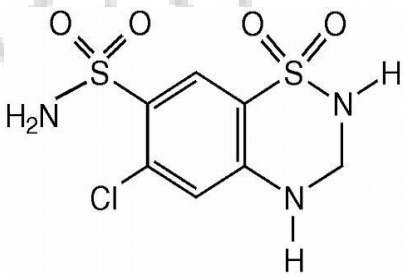
INTRODUCTION

Pharmaceutical chemists have to rely on forced degradation samples to develop SIMs [1-4]. The ability of forced degradation studies (also called stress studies) to forecast real-time degradation has been the object of several studies. Formal stability assessment of pharmaceuticals is typically done at three distinct times during development and commercialization: during development, to support the safety and efficacy claims of investigational new drugs; at registration, to ascertain the quality and shelf-life of the marketed product and its ingredients; and finally during the commercialization phase, to ensure the quality of the production and to support site or other changes to the product. Stability information on both drug substance and drug products is required as part of the registration dossier and serves to assign/confirm the shelf-life, determine appropriate storage conditions, define supply chain management, and assure that the quality of the product is unchanged from the time of manufacture to the time of administration to the patient.

DRUG PROFILES [7-8]



IRBESARTAN



HYDROCHLOROTHIAZIDE

PARAMETERS	IRBESARTAN	HYDROCHLOROTHIAZIDE
IUPAC NAME	*2-butyl-3-({4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1,3-diazaspiro[4.4]non-1-en-4-one*	*6-chloro-1, 1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7- Sulfonamide*.
MOLECULAR FORMULA	$C_{25}H_{28}N_6O$	$C_7H_8ClN_3O_4S_2$
MOLECULAR WEIGHT	428.5294 g/mol	297.74 g/mol
SOLUBILITY	Slightly soluble in alcohol and methylene chloride and practically insoluble in water	Slightly soluble in water and soluble in alcohol.
CATEGORY	Anti-hypertensive	Anti-hypertensive, Diuretic
CHEMICAL NATURE	Weak acid	Neutral
BIOAVAILABILITY	60–80%	Variably absorbed from GI tract
METABOLISM	Minimal hepatic	Does not undergo significant metabolism (>95% excreted unchanged in urine).
HALF LIFE	11–15 hours	5.6-14.8 hours

MATERIALS & METHOD [5-6]

A stability indicating HPLC method for simultaneous estimation of Telmisartan and Hydrochlorothiazide was developed and validated. The chemicals were Acetonitrile; HPLC grade was procured from (SD Fine-Chem Ltd), Ammonium acetate, AR grade, Millipore water, Irbesartan (Hetero Pharma), Hydrochlorothiazide (Aurobindo Pharma) and The tablets Xarb- H

manufactured by Piramal Health care Pvt Ltd, India were procured from local market.

Forced Degradation Studies for Irbesartan and Hydrochlorothiazide

Forced degradation studies for Irbesartan and Hydrochlorothiazide were carried out in acidic, alkaline, oxidation, thermal and in UV condition.

Degradation Studies of Irbesartan and Hydrochlorothiazide in Acidic Condition

Forced degradation studies for Irbesartan (100 µg/mL) and Hydrochlorothiazide (100 µg/mL) were carried out in 0.1N HCl at room temperature for a period of 4 hrs, and at 60^0c for 1 hr.

The acidic degradation of standard Irbesartan drug in 0.1 N HCl was found to be 31.94 % at (60^0c), 1 hour giving rise to a degraded peak at a retention time of 9.5 min. Whereas the degradation of Hydrochlorothiazide in 0.1 N HCl was found to be 30.02 % at (60^0c), 1 hr giving rise to a degraded peak at a retention time of 3.1 min.

Degradation Studies of Irbesartan and Hydrochlorothiazide in Alkaline Condition

Forced degradation for Irbesartan and Hydrochlorothiazide were carried out in 0.1N NaOH at room temperature for a period of 4 hrs, and at 60^0c for 1 hr. The alkaline degradation of standard Irbesartan was found to be 18.41 % degraded in 0.1N NaOH at (60^0c) 1 hr giving rise to a degraded peak at the retention time of 9.49 min. Whereas the degradation of standard drug Hydrochlorothiazide in alkaline medium was found to be 35.63 % degraded in 0.1N NaOH at 6^{th} hr giving rise to a degraded peak at the retention time of 3.07 min.

Degradation Studies of Irbesartan and Hydrochlorothiazide in Oxidation Condition

Forced degradation for Irbesartan and Hydrochlorothiazide were carried out in 3 % Hydrogen peroxide. The oxidation degradation of standard Irbesartan was found to be stable. Whereas the degradation of standard drug Hydrochlorothiazide in oxidation condition was found to be 20.59 % degraded in oxidation condition at 2^{nd} hr, 33.91 % at 4^{th} hr giving rise to a degraded peak at the retention time of 1.9 min.

Degradation Studies of Irbesartan and Hydrochlorothiazide in Thermal Condition at 60°C

Thermal degradation studies for Irbesartan and Hydrochlorothiazide was carried out in hot air oven at 60°C for two days. Thermal degradation of standard drug Irbesartan and

Hydrochlorothiazide was found to be stable for 48 hr after exposing the drug to 60^0C in hot air oven with no degradation peaks.

Degradation Studies of Irbesartan and Hydrochlorothiazide in Photostability Condition

Photostability degradation study for Irbesartan and Hydrochlorothiazide were carried out in Photostability chamber by exposing to UV light for 48 hrs. The data obtained is presented below Photolytic degradation of standard drug Irbesartan and Hydrochlorothiazide was found to be stable for 48 hr after exposing the drug to UV light with no degradation peaks.

Separation Studies

A stability indicating HPLC method was developed for the simultaneous estimation of Irbesartan and Hydrochlorothiazide using a C18 column (Enable C-18 G, 250 mm x 4.6 mm, 5 µm), mobile phase consisting of Acetonitrile : Ammonium acetate buffer (pH: 5.5) in ratio of 30:70 flow rate of 1.5 mL/ min, PDA detection at wavelength of 235 nm. The retention time of Irbesartan and Hydrochlorothiazide was observed at 7.1 and 3.3 min respectively. The developed method was then validated by using various parameters like accuracy, precision, linearity, specificity, ruggedness and robustness etc. as per ICH guidelines and reported in Table No. 1.

The objective of the proposed project was to develop and validate a stability indicating HPLC for simultaneous estimation of Irbesartan and Hydrochlorothiazide in bulk drugs marketed formulation and to carry out the forced degradation of the drugs and study the effect of degraded products on the development method.

RESULTS AND DISCUSSION

Forced degradation studies was carried out at different stress conditions like acidic, alkali, oxidation, thermal, and photolytic condition for Irbesartan and Hydrochlorothiazide, and to study whether the degraded products interfere with the method and the results were presented in Table No. 2.

Table No.1: Validation Parameters of the HPLC Method [5-6]

Parameters		Irbesartan	Hydrochlorothiazide	Acceptance criteria
Specificity		No peak were interrupting the original peaks		No interference by degraded compounds
LOD (ng/mL)		1.035(µg/mL)	0.007(µg/mL)	-
LOQ (ng/mL)		3.137(µg/mL)	0.0216(µg/mL)	-
Linearity range		5 – 250 µg/mL	5 – 120 µg/mL	-
Precision	System	0.2 %	1.27 %	NMT 2%
	Method	1.11 %	1.12%	
	Inter day	0.64 %	0.22%	
	Intra day	1.50%	0.84 %	
R0bustness	1.3 mL/min	100.13 %	100.29 %	90-110 %
	1.7 mL/min	100.69%	99.321.98 %	
	233 nm	99.80 %	99.31.56 %	90-110 %
	237 nm	100.14 %	100.3 %	
Accuracy (% Recovery)		99.83-100.15 %	99.97–100.2 %	90-110 %
	No of plates (N)	15845.15	9491.15	>6000
	HETP	9.410	15.758	-
	Asymmetry			<1
	Resolution	21.02		-

Table No. 2: Forced Degradation Studies for Irbesartan and Hydrochlorothiazide.

Degradation condition	Drug Peak Area at Control		Drug peak area at Stressed Cond.		Rt of degraded Products		% Degradation	
	IRB	HCTZ	IRB	HCTZ	IRB	HCTZ	IRB	HCTZ
Acidic 0.1N HCl	40869	2097654	31009	1469825	9.5	3.1	31.93 %	30.01%
Alkaline 0.1N NaOH	40892	2090942	35098	1350092	9.49	3.07	18.40 %	35.63%
Oxidation 3% v/v H_2O_2	408691	2090429	40910	1386735	.....	1.89	.....	33.90%
Thermal Condition	40501	2091009	40350	2089673	.....	.....	.....	.....
Photostability	41009	2090146	40389	2080709	.....	.....	.....	.....

In acidic condition, standard drug of Irbesartan and Hydrochlorothiazide were found to be 31.04 % and 30.02 % degraded at 1st hour of 60^0c.

In alkaline condition, standard drug of Irbesartan and Hydrochlorothiazide were found to be 18.41 % and 35.63 % degraded at 1st hour of 60^0c.

In oxidative condition, standard drugs of Irbesartan were found to be stable and Hydrochlorothiazide was found to be 20.59 % degrade at 2nd hr, 33.91 % degraded at 4th hour.

In thermal studies, standard drugs of Irbesartan and Hydrochlorothiazide were found to be stable at 60^0C for 48 hr.

In photostability studies, standard drugs Irbesartan and Hydrochlorothiazide were found to be stable after 48 hr.

From the data of degradation studies, it was found that Irbesartan and Hydrochlorothiazide were found to be degraded in all stress conditions. And there is no interference of degraded peaks with the standard drug peaks.

Hence stress testing should be given importance for such combination of drugs and quantification of degraded products of such drugs helps us to maintain the quality, safety and efficacy of drugs in formulations.

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