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Identification of deactivation procedure for Trilaciclib

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Abstract

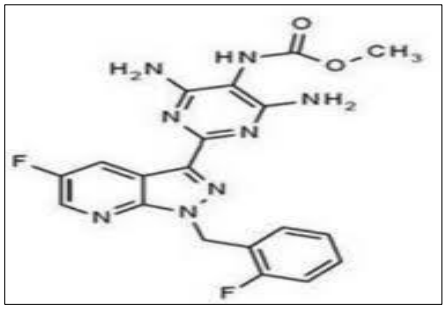
The Indian health-care facilities (HCFs) made some guidelines related to cytotoxic drugs so called cytotoxic policy for patient safety and health-care worker safety, and environmental monitoring program as per the available international guidelines. Trilaciclib is indicated for the treatment of patients with multiple myeloma and chemically it is a tetra peptide epoxy ketone and an analog of epoxomicin. Analytical method for the detection of Deactivating agent and concentration play an impartment role in the pharmaceuticals especially with cytotoxic molecules after completion of manufacturing and testing is mandatory to follow the safety protocol to dispose those materials. The present invention provides to identify the suitable deactivating agent for the neutralization of Trilaciclib injection 10 mg/mL and Trilaciclib API with respect to concentration and time. This method developed based by RP-HPLC.

Keywords: Trilaciclib; Deactivating Agent; Sodium Hypochlorite Solution; Parenteral dosage form; RP-HPLC; Cytotoxic waste

1. Introduction

Trilaciclib dihydrochloride, is a kinase inhibitor, chemically; he chemical name for trilaciclib is 2'-{[5-(4-methylpiperazin-1-yl)pyridin-2-yl]amino}-7',8'dihydro-6'H-spiro[cyclohexane-1,9'-pyrazino[1',2':1,5]pyrrolo[2,3-d]pyrimidin]-6'-one.

Trilaciclib has the following structure:



1.1. Mechanism of Action

Trilaciclib is a transient inhibitor of CDK 4 and 6. Hematopoietic stem and progenitor cells (HSPCs) in the bone marrow give rise to circulating neutrophils, RBCs, and platelets. HSPC proliferation is dependent on CDK4/6 activity.

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2. Material and methods

2.1. Materials

Trilaciclib API - A gift sample - Purchased from API vendor, Sodium hypochlorite solution – purchased from Nice chemical Pvt Ltd,Potassium dihydrogen phosphate, 1-Octane sulphonic acid sodium salt anhydrous, Orthophosphoric acid, Acetonitrile AR grade or equivalent, Water Ultrapure grade water.

2.1.1. Equipment(s)/instrument(s)

Volumetric flask, Measuring cylinders, Volumetric pipettes Glass, Class-A (both bulb and graduated), Micro pipettes-Ependorff, Balance with sensitivity of 0.01 mg, HPLC system Agilent, pH meter, Thermo scientific Column-Agilent Poroshell 120,EC-C18, (4.6 mm ×150 mm).

2.2. Methods

2.2.1. Assay Method[4,5]

Analytical method for the estimation of Trilaciclib in Drug substance and Drug product were developed by RP-HPLC.

Principle**:** Reverse phase liquid chromatography with gradient elution and UV detector

2.2.2. Buffer Preparation

Weigh accurately about 2.72 g of Potassium dihydrogen phosphate and 6.0 g of 1-Octane Octane sulphonic acid sodium salt anhydrous in 2000mL of water and mix well to dissolve completely and adjust the pH to 3.5 with dilute Orthophosphoric acid solution and filter through 0.22 µm filter.

Mobile phase A

Mix Buffer and Acetonitrile in the ratio of 1400:600(v/v) respectively. Sonicate and degas for 10 minutes.

Mobile phase B

Mix Buffer and Acetonitrile in the ratio of 600:1400(v/v) respectively. Sonicate and degas for 10 minutes.

Table 1 Chromatographic conditions

Column	**:**	**Agilent Poroshell 120, EC-C18 (4.6mm ×150 mm), 4 µm**
UV detection	:	210 nm
Flow rate	:	1.0 mL/min
Column temperature	:	35 °C
Auto sample temperature	:	10.0°C
Runtime	:	15 minutes
Injection volume	:	10 µL
Elution mode	:	Gradient

Table 2 Gradient Programme

Time (min)	**Mobile phase A (%)**	**Mobile phase B (%)**
0	30	70
12	40	60
13	30	70
15	30	70

Diluent: Prepare a degassed mixture of water and acetonitrile in the ratio of 30:70(v/v).

2.2.3. Standard preparation: (60 ppm)

Accurately weigh and transfer about10 mg of Trilaciclib WS/RS into a 25 mL volumetric flask and add about 10mL of acetonitrile to dissolve completely and make up to the volume with acetonitrile and mix well. Further transfer 3 mL of above solution to 20 mL volumetric flask dilute and make up to the volume with diluent and mix well.

2.2.4. Sample preparation: (60 ppm)

Accurately weigh and transfer about 2.0 g of Sample into a 50 mL volumetric flask and add about 20 mL of acetonitrile to dissolve completely and make up to the volume with acetonitrile and mix well. Further transfer 3 mL of above solution to 20 mL volumetric flask dilute and make up to the volume with diluent and mix well.

2.2.5. Procedure[6,7]

- Equilibrate the column using mobile phase to get a stable baseline.
- Inject blank (one injection) and standard preparation (five injections) into chromatographic system and check the system suitability parameters.

2.2.6. System Suitability:

- USP Tailing factor/Asymmetry for Trilaciclib peak from first injection of standard solution as recorded by software should be NMT 2.0.
- USP Plate count /Theoretical plates for Trilaciclib peak from first injection of Standard Solution as recorded by software should be NLT 2000.
- % RSD of Trilaciclib peak areas from five replicate injections of Standard Solution should be NMT 2.0
- If system suitability parameter pass, then inject sample solution into the chromatographic system and record the chromatograms.

Table 3 Sequence of Injections

S. No	Description of the solution	No. of Injections
1	Blank (Diluent)	1
2	Standard preparation	5
3	Sample preparation	2
4	Standard preparation (Bracketing)	1

2.2.7. Calculation for Assay[7,8,9]

Calculate the % of labeled amount of Trilaciclib by using the following formula:

$$\%\ \text{labelled amount of Trilaciclib} = \frac{AT}{AS} \times \frac{WS}{DS} \times \frac{DT}{WT} \times \frac{P}{100} \times \frac{100}{LC} \times Wt/mL$$

Where;
AT : Area of peak response of Trilaciclib in the sample Preparation
AS : Average area of peak response of Trilaciclib in Standard Preparation
WS : Weight of Standard taken in mg
DS : Dilution of standard solution
DT : Dilution for sample solution
WT : Weight of sample taken in g
P : % Potency of Trilaciclib Standard in % w/w on as is basis
LC : Label claim of Trilaciclib in Trilaciclib injection (in mg/mL)
Wt/mL : Weight per mL of Sample

2.3. Method for deactivating agent[1,3,9]

The analytical method used for the estimation of Trilaciclib in Drug substance and Drug product will be used to detect the concentration at the end. To determine the same different concentrations of Sodium hypochlorite with different exposure times were studied as per below data. Above samples of said concentration shall be separately filled into flint vials, stoppers and seal. Labelled the vials and performed analysis by HPLC. At which concentration and respective time the API gets neutralized was explained in the results & discussion mentioned below.

Table 4 Selection of concentration of deactivating agent for Trilaciclib Injection 10 mg/mL

Sample description	Deactivating agent (with %)	Amount of deactivating solution added	Amount of drug product to be added	Total volume	Final concentration of deactivating agent
Sample 1	5 % Sodium hypochlorite solution	NA	5 mL	5 mL	NA
Sample 2		1.67 mL	5 mL	6.67 mL	25.0 %
Sample 3		5 mL	5 mL	10 mL	50.0 %
Sample 4		15 mL	5 mL	20 mL	75.0 %
Sample 5		28.3 mL	5 mL	33.3 mL	85.0 %
Sample 6		95 mL	5 mL	100 mL	950 %

Table 5 Duration of exposure of deactivating agent for Trilaciclib Injection 10 mg/mL

Sample description	Amount of deactivating agent	Amount of drug solution	Duration of exposure
Sample 7	28.3 mL	5 mL	10 min
Sample 8	28.3 mL	5 mL	20 min
Sample 9	28.3 mL	5 mL	30 min
Sample 10	95 mL	5 mL	45 min
Sample 11	95 mL	5 mL	60 min

Table 6 Duration of exposure of deactivating agent for Trilaciclib (API)

Sample description	Amount of deactivating agent	Amount of drug Substance	Duration of exposure
Sample 12	30 mL	10 mg	10 min
Sample 13	30 mL	10 mg	20 min
Sample 14	30 mL	10 mg	30 min
Sample 15	30 mL	10 mg	45 min

3. Results & Discussion

Table 7 Analytical results of selection of concentration of deactivating agent for Trilaciclib Injection 10 mg/mL

Sample description	Deactivating agent (with %)	Amount of deactivating solution added	Amount of drug product to be added	Total volume	Final concentration of deactivating agent	Description	Active/ Principal peak results
Sample 1	5 % Sodium hypochlorite solution	NA	5 mL	5 mL	NA	Complies	99.5 %
Sample 2		1.67 mL	5 mL	6.67 mL	25.0 %	Light yellow color solution	10.2 %
Sample 3		5 mL	5 mL	10 mL	50.0 %		14.3%
Sample 4		15 mL	5 mL	20 mL	75.0 %		4.0 %
Sample 5		28.3 mL	5 mL	33.3 mL	85.0 %		3.8 %
Sample 6		95 mL	5 mL	100 mL	950 %		2.3 %

Table 8 Analytical results of Duration of exposure of deactivating agent for Trilaciclib Injection 10 mg/mL

Sample description	Deactivating agent (with %)	Amount of deactivating agent	Amount of drug solution	Total volume	Duration of exposure	Description	Active/ Principal peak results
Sample 7	5 % Sodium hypochlorite solution	28.3 mL	5 mL	33.3 mL	10 min	Light pale yellow color solution	4.1 %
Sample 8		28.3 mL	5 mL	33.3 mL	20 min		4.0 %
Sample 9		28.3 mL	5 mL	33.3 mL	30 min		4.0 %
Sample 10		95 mL	5 mL	100 mL	45 min		2.3 %
Sample 11		95 mL	5 mL	100 mL	60 min		Not Detected

Table 9 Analytical results of Duration of exposure of deactivating agent for Trilaciclib (API)

Sample description	Deactivating agent (with %)	Amount of deactivating agent	Amount of drug Substance	Duration of exposure	Description	Active/Principal peak results
Sample N	5 % Sodium hypochlorite solution	30 mL	10 mg	10 min	Light pale yellow color solution	Not Detected
Sample O		30 mL	10 mg	20 min		Not Detected
Sample P		30 mL	10 mg	30 min		Not Detected
Sample Q		30 mL	10 mg	45 min		Not Detected

4. Conclusion

Inference: Trilaciclib Injection 10 mg/mL was tested for deactivating agent with Sodium hypochlorite solution (with 5 % w/v active chlorine).

Based on the analytical results it was concluded that the drug product was completely deactivated with 95% Sodium hypochlorite exposure to the Trilaciclib Injection 10 mg/mL after 60 min

Based on the analytical results it was concluded that the drug substance (Trilaciclib API) was completely deactivated in the ration of 3 ml: 1 mg (Sodium hypochlorite: drug substance) upon exposure of after 20 min.

Recommendations

- Trilaciclib Injection 10 mg/mL: From the above conclusion, 5 % Sodium hypochlorite solution with 95% Sodium hypochlorite exposure to the Trilaciclib Injection 10 mg/mL for 60 minutes was recommended for deactivation of Trilaciclib for Injection 10 mg/mL.
- Trilaciclib (API): From the above conclusion, 1 mg of Trilaciclib was completely deactivated with 3 ml of 5 % Sodium hypochlorite solution for minimum exposure of 20 min was recommended for Trilaciclib.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

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