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Website: www.aarf.asia Email : editor@aarf.asia , editoraarf@gmail.com

DEVELOPMENT OF STABILITY INDICATING UV SPECTROSCOPY METHOD FOR THE ESTIMATION OF APREMILAST IN PHARMACEUTICAL FORMULATION

[1]Sabiha Sabeen, [2]Syeda Kulsum, [3]G Vidya Sagar

[1]College Of Applied medical sciences, Prince Sattam Bin Abdul Aziz University, Wadi Al Dawasir, Riyadh-K.S.A.
[2]Research Scholar, Rayalaseema University, Kurnool,Andhra Pradesh, India.
[3]Professor and Principal, Srinivasa Rao College of Pharmacy, Visakhapatnam, Andhra Pradesh, India.

ABSTRACT

Apremilast is a drug for the treatment of certain types of psoriasis and psoriatic arthritis. It may also be useful for other immune system related inflammatory diseases. The drug has maximum absorbance at 220nm.The optical characteristic of drug was found within Beer's law limits 20-100 µg/ml, Correlation coefficient is 0.999.The drug sample was analyzed by UV spectroscopy using methanol as solvent and the average content of drug present in the formulation was found to be 99.7%. The force degradation studiesof Apremilast tablet was done. Stress degradation performed by hydrolysis procedure under alkaline condition by using 0.1M NaOH was found to be 13.3% . Stress degradation by hydrolysis under acidic condition by using o.1M HCl and product degradation was found to be 8.2%. Dry heat induced degradation was done by using 80^{0c} temperature was found to be 14.5 % for 26 hrs. Oxidative degradation was done by using hydrogen peroxide and product degradation was found to be 12.5%. Photolytic degradation was found to be 10.7% for 4hrs.

KEYWORDS: Apremilast, UV Spectroscopy, Validation, Forced Degradation.

INTRODUCTION

Apremilast is chemically *N*-{2-[(1*S*)-1-(3-Ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1*H*-isoindol-4-yl}acetamide(fig 1) is a drug for the treatment of certain types of psoriasis and psoriatic arthritis [1,2]. It may also be useful for other immune system related inflammatory diseases. Apremilast is a small molecule inhibitor of PDE4, an enzyme that breaks down cyclic adenosine monophosphate (cAMP)[3,4]. In inflammatory cells, PDE4 is the dominant enzyme responsible for this reaction. The chemical structure of Apremilast was shown in Fig-1.Literature survey reveals that a LC-UV method was developed for the determination of process-related impurities in apremilast. But there was no reported method for the Forced degradation studies of Apremilast by using UV spectroscopy. So the present work is to carryout the force degradation studies along with its pH degradation studies. The method was validated according to the ICH guidelines. Forced degradation studies may help facilitate pharmaceutical development as well in areas such as formulation development, manufacturing, and packaging, in which knowledge of chemical behavior can be used to improve a drug product.

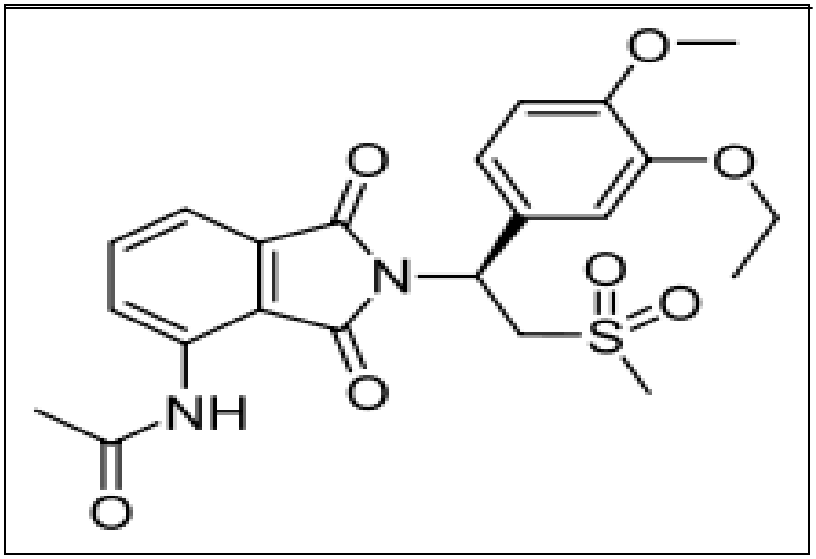

FIG 1: STRUCTURE OF APREMILAST

MATERIALS AND METHODS

DEVELOPMENT AND VALIDATION OF UV SPECTROSCOPIC METHOD

INSTRUMENT

Absorption spectral measurements were carried out with a UV – Visible spectrophotometer (Shimadzu Model 1700) using UV Probe software version 2 was employed with spectral bandwidth of 1 nm and wavelength accuracy of 0.3 nm (with automatic wavelength correction with a pair of 5 cm matched quartz cells.

CHEMICALS

Apremilast API supplied by Mehta API Pvt Ltd, India and used as such. Methanol used was from Qualigen fine chemicals Ltd, India. Water used was generated by double distillation.

SELECTION OF SOLVENT

Solutions of apremilast was prepared in different solvents like water, methanol, ethanol, acetonitrile and UV spectrum of each were recorded by scanning between 200-400 nm. Better absorbances were observed for the drug when methanol is used as a solvent.

PREPARATION OF STANDARD SOLUTIONS

Standard stock solutions of Apremilast was prepared by dissolving 10 mg of the drug in water and the volume was made up to 100ml in a standard flask. From the stock solution, concentrations ranging from 20-100 µg/ml was prepared for apremilast and scanned in the UV region.

PREPARATION OF SAMPLE SOLUTION

Twenty tablets (apremilast) are powdered and the average weight was calculated. A quantity equivalent to 10 mg of drug was dissolved in Methanol. Finally the volume was made up to get a working concentration of 60µg/ml. Absorbances were noted at 220 nm. A spectrum of Apremilast is seen in fig:2

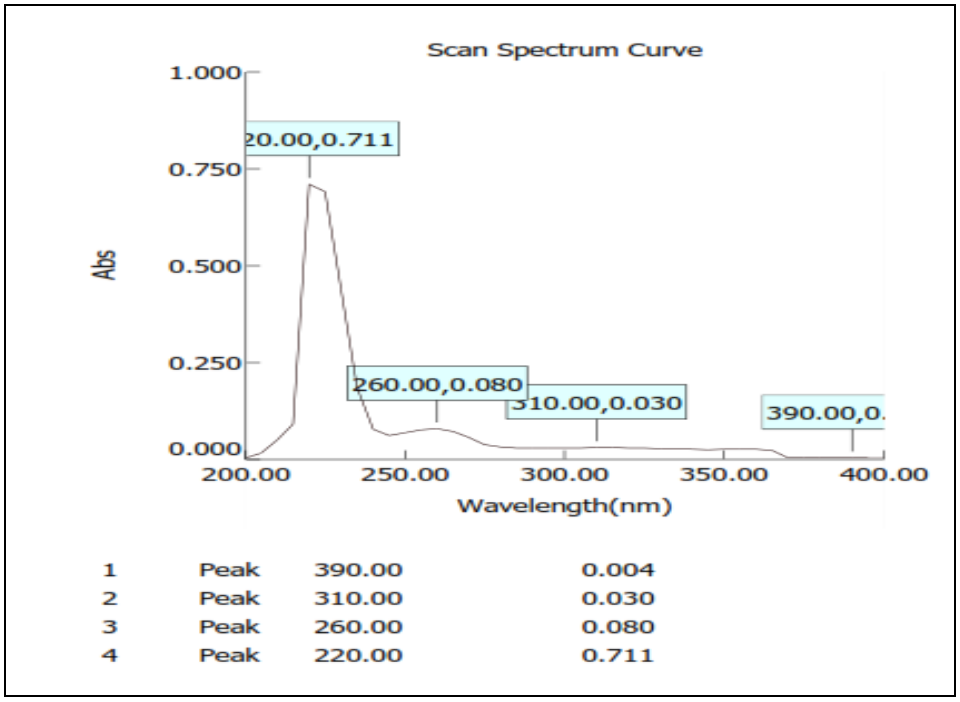

FIG 2: SPECTRUM OF APREMILAST

VALIDATION OF THE METHOD

LINEARITY

Apremilast was found to be linear in a concentration range of 20-100µg/ml. The absorbances of these solutions were noted at wavelengths 220 nm. Calibration curves were plotted using concentration Vs absorbance at wavelength of 220 nm and the slope, intercept and correlation coefficient values were found to be 0.008, 0.007 and 0.999 respectively.

PRECISION

Precision studies were performed by preparing the standards six times and measuring absorbances of the drug at 220 nm. Low RSD values indicate that the method is precise[5].

ACCURACY

In order to ensure the suitability and reliability of proposed method, recovery studies were carried out. To an equivalent quantity of formulation powder (10mg), a known quantity of standard Apremilast was added at 50% 100% and ,150 % level and the contents were re-analysed by the proposed method.

Drug	Amount (mg/tab)		% label claim	% RSD*
	Labeled	Found		
APREMILAST	75	74.8	99.90	0.53

TABLE 1 : ANALYSIS OF FORMULATION

FORCED DEGRADATION STUDIES

Forced degradation of Test sample was performed under acidic, alkaline, heat, photolytic and oxidative stress conditions.

STOCK SOLUTION PREPARATION

Twenty Tablets were weighed and powdered. Tablets powder having weight equivalent to 22 mg was weighed accurately and taken in a 10 ml volumetric flask. To it 5 ml of the mobile phase was added and sonicated for 15 minutes to dissolve the drugs. The volume was made up to 10 ml with mobile phase. The resulting solution was then filtered through a 0.45 µm membrane filter to prepare a stock solution of the tablet sample. Further dilution was done by diluting 0.3 ml of stock solution to 10 ml mobile phase. The concentration of apremilast in the solution was 30 µg/ml .

ACID HYDROLYSIS

Forced degradation in acidic media was performed by adding 3 ml 0.1 M HCl to 10 ml of stock solution and the mixture is heated at 60°C for approximately 26hrs and the solution is neutralized by addition of 0.1 M NaOH. The prepared solution is placed and spectrum was recorded. The study indicates that the drug under study was degraded and assay results shows that mostly Apremilast (8.2%) and the drug were well separated from the degradation products.

ALKALINE HYDROLYSIS

Forced degradation in basic media was performed by adding 3 mL 0.1 M NaOH to 10 mL of stock solution and the mixture is heated at 60°C for approximately 26hrs and the solution is neutralized by addition of 0.1 M HCl. The prepared solution is placed and spectrum was recorded.

The results of alkaline hydrolysis indicates that some degradation occurred and assay results shows that apremilast (13.3%)and the drugs were well separated from the degradation products.

OXIDATIVE DEGRADATION

To 1.5 ml of the stock solution of Apremilast(1000µg/ml), 1 ml of 30% w/v of hydrogen peroxide added in 10 ml of volumetric flask and the volume was made up to the mark with methanol. The volumetric flask was then kept at room temperature for 15 min. For the blank, 1 ml of the 30 % w/v of hydrogen peroxide was kept at normal condition for overnight in 10 ml of volumetric flask. Both solutions were heated on boiling water bath to remove the excess of hydrogen peroxide. Finally, after 15 minutes dilutions were made from the stock solution to achieve the required concentration (30µg/ml). The solution was then taken in a cuvette and analysed in UV. From the observation it was found that apremilast (12.5%) was found stable i.e, no significant spectrum were found. So it is stable in the above condition.

THERMAL DEGRADATION

To study the effect of temperature an aliquot of stock solution was kept at 80^0C for 26 hrs. 10ml of resulting solution was injected into HPLC and spectrum was recorded. From the observation it was found that Apremilast was found to be degraded by (14.5%)

PHOTOLYSIS

To study the effect of photolysis, an aliquot of stock solution was exposed to UV light for 4hrs.10ml of resulting solution was injected into HPLC and chromatograms were recorded.From the observation it was found that Apremilast was found (10.7%) stable i.e, no significant peaks were found. So it is stable in the above condition. Summery on degradation studies was given in Table

Stress Condition	Sample- apremilast		
	Absorb	%Assay	%Degradation
Acidic	1.161	91.8	8.2
Alkaline	1.192	86.7	13.3

Photolytic	1.266	87.5	12.5
Thermal	2.102	95.5	14.5
Oxidative	2.090	90.3	10.7

*TABLE 2:*RESULTS OF STRESS DEGRADATION STUDIES

RESULTS AND DISCUSSION

Apremilast was freely soluble in Methanol. The drug has maximum absorbance at 220nm.The optical characteristic of drug was found to be Beer's law limits 20-100 µg/ml, and Correlation coefficient is 0.999. The drug sample was analyzed by UV spectroscopy using methanol as solvent and the average content of drug present in the formulation was found to be 99.9%. The %RSD was found to be 0.53. The force degradation studies of Apremilast tablet formulation was done on Stress degradation by hydrolysis under alkaline condition by using 0.1N NaOH was found to be 13.3% 2 hrs. Stress degradation by hydrolysis under acidic condition by using 0.1N HCl and product degradation was found to be 8.2% for 2 hrs. Dry heat induced degradation was done by using 800°c temperature was found to be 14.5% for 2 hrs. Oxidative degradation was done by using hydrogen peroxide and product degradation was found to be 10.7%. Photolytic degradation was found to be 12.4% for 4hrs.

CONCLUSION

The estimation of Apremilast was done by UV Method. The results obtained on the validation parameters met ICH and USP requirements. It inferred that the method found is simple, accurate, precise and linear. The method was found to be having suitable application in routine laboratory analysis with high degree of accuracy and precision.

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