

A Novel Eco-Compatible Green UV-Spectroscopic Analytical Method Development and Validation for Apremilast Estimation in Bulk, Marketed Formulation and in Nanovesicles

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ABSTRACT

Background: The proposed study focuses on developing and validating a sensitive and simple UV-spectroscopic technique for apremilast quantification in bulk drug, commercial tablet, cubosomes and transferosomes. **Materials and Methods:** The optimum conditions for analysing apremilast were developed with methanol and phosphate buffer pH 6.8. It shows maximum absorbance at 230nm wavelength. QC standards were used for determining several validation parameters for analytical methods, including accuracy, precision, LOD, LOQ, robustness and ruggedness. In accordance to ICH Q2 (R1) guidelines, the validated technique was applied to quantify apremilast in commercial tablets, bulk, cubosomes and transferosomes. **Results and Discussion:** Apremilast exhibited a maximum absorption at a wavelength of 230 nm. Calibration curve was plotted at concentration ranging from 0.2-1.0 µg/mL, with linear equation of $y = 0.8017x + 0.0105$ and coefficient of variance was observed to be 0.998. The detection limits and quantification limits were found to be 0.09 µg/mL and 0.28 µg/mL respectively. Repeatability and precision results were within (2%) acceptable ranges. Apremilast recovery in marketed formulations, cubosomes and in transferosomes was found to be between 100.47%, 99.97% and 98.35 respectively. **Conclusion:** The proposed analytical technique was observed to be novel, eco-friendly, reliable and precise for quantifying apremilast in bulk, commercial tablets, cubosomes and transferosomes. It can be used in the pharmaceutical industry for apremilast in various formulations.

Keywords: Apremilast, UV Spectrophotometric Method, Analytical Method Validation, Cubosomes, Transferosomes.

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INTRODUCTION

Psoriasis is a persistent autoimmune inflammatory skin condition affecting around 2% of the total world population. It exhibits the presence of erythema, red scaly patches that can appear on the scalp, elbows, knees and trunk. Psoriasis causes discomfort, fluster and social isolation for those affected (Raharja *et al.*, 2021). The disease tends to follow a prolonged course and individuals are prone to recurrences, necessitating ongoing medication for effective control (Zeng *et al.*, 2021).

Apremilast (N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide) is a Phosphodiesterase 4 (PDE4) inhibitor that has shown significant efficacy in managing plaque psoriasis (Mullick *et al.*, 2021).

Apremilast, focuses on central inflammatory signalling pathways and regulates the expression of different inflammatory mediators that plays a important role in the inflammatory process (Mulleria *et al.*, 2021). It is a potent inhibitor of Phosphodiesterase-4 (PDE-4), exerts its influence by selectively elevating intracellular cyclic Adenosine Monophosphate (cAMP). This orchestrated increase in cAMP levels prompts release of anti-inflammatory cytokines-interleukin-10 (IL-10), while concurrently suppressing pro-inflammatory mediators like Tumour Necrosis Factor-alpha (TNF-α), Interleukin-23 (IL-23), Interleukin-12 (IL-12) and leukotriene B4 (Mondal *et al.*, 2019).



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Apremilast is orally administered and is absorbed rapidly. It is insoluble in water, slightly soluble in ethanol and soluble in acetone (Patel *et al.*, n.d.). The peak plasma concentration is reached after 2-3 hr. Apremilast has a bioavailability of approximately 73%, $t_{1/2}$ of 6-9 hr and a mean apparent volume of distribution of 87 L (Bubna, 2016).

Kolsure *et al.*, (2022) developed a novel RP-HPLC technique to determine apremilast in pharmaceutical formulations and in bulk. The method employed acetonitrile: potassium dihydrogen phosphate buffer (pH 3.0, 60:40 v/v) with 1 mL/min flow rate. An Agilent 1120 LC compact system with a binary gradient and UV-Absorbance Detector was employed. The HPLC method demonstrated sharp symmetric peaks for Apremilast with minimal tailing and a desired elution profile, validated for accuracy in pharmaceutical dosage forms (Kolsure *et al.*, 2022).

Shakeel *et al.*, validated an eco-friendly HPTLC technique for Apremilast, employing "RP-18 silica gel 60 F254S HPTLC plates" and (65:35, v/v) ethanol: water and was assessed by ChlorTox, Analytical Eco-Score. This method demonstrated reliability in estimating apremilast across various formulations. With a linear range of 100-600 ng/band, it contributes to sustainable pharmaceutical analysis, offering insights into critical variables and eco-conscious practices for Apremilast determination (Shakeel *et al.*, 2024).

Ravisankar *et al.*, designed a UV-spectrophotometric method for quantifying apremilast, utilizing acetonitrile as a solvent. The method exhibited linearity in the concentration range of 2-10 µg/mL with a correlation coefficient (r^2) of 0.9983. Detection and quantification values were 0.00271 and 0.0082 µg/mL, respectively. Apremilast recovery analysis showed results between 96.80% and 98.28%. The technique was validated in accordance to the ICH Q1A (R2) guidelines, and is reliable for analysing apremilast in tablets and in bulk (Ravisankar *et al.*, 2017).

Cubosomes serve as biocompatible carriers for the drug delivery, constituting nanostructured liquid-crystalline particles composed of specific amphiphilic lipids in varying ratios. These bi-continuous cubic phases have distinctive physicochemical attributes, having undergone a reversed formation process (Sivadasan *et al.*, 2023). Cubosomes typically appear as nanoparticles with diameters ranging from 10 to 500 nm, presenting as spherical entities resembling dots. They are essentially nanostructured particles characterized by cubic crystallographic symmetry, formed through the amphiphiles or surfactant molecules (Harshini *et al.*, 2021).

Transfersomes represent a preferred form of ultra-deformable vesicles characterized by an aqueous core covered by a complex lipid bilayer. These vesicles exhibit a remarkable capability to traverse micro-porous barriers effectively, even when the pores are significantly smaller than the vesicle size (Harshini *et al.*, 2021). Essentially, these lipid aggregates are flexible, penetrate

intact mammalian skin and serve as carriers for non-invasive targeted drug delivery. They are capable to enable sustained release of therapeutic agents and can encapsulate hydrophobic and hydrophilic molecules, providing an advantage for delivering multiple drugs and phytochemicals simultaneously by the systemic route (Namrata *et al.*, 2022).

Different analytical techniques for determining apremilast have been documented in existing literature. These methods include HPLC and HPTLC. The mentioned approaches has its drawbacks, which involves manual steps prone to human errors, a multi-step process leading to slower analysis and lower sensitivity requiring higher analyte concentrations, time consumption and necessity for costly and expensive chemicals. UV analysis demonstrates higher sensitivity enabling the detection of apremilast at lower concentrations even in part per million levels. The use of green solvent in UV analysis aligns with environmentally conscious practices emphasizing the overall superiority of the UV analytical technique. The primary aim of this current research is to employ green solvent for the determination of apremilast.

MATERIALS AND METHODS

Materials

Apremilast was received from Unichem Pvt. Ltd., Goa as a gift sample. pH 6.8 phosphate buffer was prepared using disodium hydrogen and potassium dihydrogen phosphate, procured from SD Fine Chem Ltd., Mumbai.

Instrumentation

The determination of Apremilast was carried out by using UV-Spectrophotometer of Shimadzu UV-1900 with UV probe software. To weigh the samples accurately, a calibrated weighing balance was used during the experiment.

Selection of Wavelength

A UV-Spectrophotometer was utilized to scan a working standard of apremilast at 10 µg/mL concentration. The scanning range between 400 nm and 200 nm and the maximum absorption of the solution was observed at 230 nm (Figure 1).

Selection of solvent

Stock solution

A weighed amount of apremilast (100 mg) was dissolved in methanol by placing it in a volumetric flask (100 mL) and the volume was made upto 100 mL with pH 6.8 phosphate buffer. This gave a concentration of 1000 µg/mL and it was considered as a standard stock solution and the same was employed for serial dilutions.

Plotting of calibration curve

Serial dilutions containing concentrations of 0.2, 0.4, 0.6, 0.8 and 1.0 g/mL were prepared using Stock II. These solutions were

analysed and the absorbance was determined at 230 nm. The calibration curve was obtained by plotting concentration on the x-axis and absorbance on the y-axis. A regression equation was determined from the results.

Validation of the developed method

The UV method to determine the apremilast concentration was established and subsequently validated. Linearity, range, precision, robustness, accuracy, ruggedness, Limit of Quantification (LOQ) and Limit of Detection (LOD) were assessed. The validation was carried out using predetermined calibration standards (Matharoo *et al.*, 2024).

Linearity and range

Linearity is the ability of the analytical method to assess the data in direct correlation with the concentration of the analyte. To determine linearity, serial dilutions were prepared in the range of 0.2 to 1.0 µg/mL using the stock solution. These solutions were then analyzed at 230 nm and each measurement was conducted in triplicate (Chimagave *et al.*, 2022).

LOD and LOQ

The Detection Limit (LOD) is defined as the lowest concentration of an analyte that can be detected, though not necessarily quantified accurately. The Limit of Quantification (LOQ), is the smallest amount of the analyte that can be measured with acceptable precision and accuracy. These values were determined using the following equations: $LOD = 10 \times (s/m)$ and $LOQ = 3 \times (s/m)$, where s denotes the standard deviation of the measured response, and m is the slope of the calibration curve (Kulkarni and Deshpande, 2021).

Method Precision

The precision of an analytical method refers to how consistently it provides results under standard working conditions. To assess this, sample solutions were tested for intra-day and inter-day repeatability.

To measure intra-day precision, three replicates of a solution containing 0.8 µg/mL of Apremilast were analyzed at three distinct time periods during the day. The Relative Standard Deviation (RSD) was used to assess variability.

Inter-day Precision: Three replicates of a 0.8 µg/mL Apremilast solution were evaluated across three distinct days, and the percent RSD was obtained to examine the method's consistency over time (Prajapati *et al.*, 2020).

Ruggedness

In assessing Ruggedness was assessed, six separate solutions containing 0.8 µg/mL concentration of apremilast were prepared and the absorbance was measured at 230 nm by different analysts and using distinct instruments and then %RSD (Relative Standard

Deviation) for absorbance was calculated to ensure (Peerzade *et al.*, 2019).

Robustness

An essential component of method robustness is the development of analytical procedures capable of withstanding deliberate, minor variations in separation parameters without compromising performance. To assess robustness, specific parameters like slight changes in detector wavelength were systematically varied within a defined range and their quantitative impact on method accuracy and precision is evaluated (Peerzade *et al.*, 2019).

Accuracy

Recovery trials were conducted to determine accuracy and the sample's percent mean recovery was computed using a standardization approach at three different time points.

Three distinct levels of Apremilast solutions were prepared: 50%, 100% and 150%. For each level, three replicates were taken and recovery study was carried out.

Formulation of apremilast-loaded transferosomes

Apremilast ultradeformable nanoformulation was prepared by cold method. In one beaker, apremilast was dissolved in methanol and to this phospholipid and tween 80 was added. Millipore water was taken in another beaker. A constant temperature of 35°C was maintained throughout the process. Using a 22-gauge needle, the aqueous phase was then injected dropwise into the organic phase. This mixture was stirred at 750 rpm for 25 min. After uniform stirring the solution was kept stable for 45 min to form a cloudy solution. This mixture was subsequently subjected to probe sonication for 10 min and finally, the solution was stored at 3°C-4°C (Kudatarkar *et al.*, n.d.; Taleuzzaman, 2018).

Formulation of Apremilast-loaded cubosomes

Apremilast-loaded cubosomes were prepared by the homogenization method. In three separate beakers, water, Pluronic F-127 and Glyceryl-Monostearate (GMO-lipid) were taken. At a temperature between 45-65°C, GMO and Pluronic F-127 were melted on a hot plate. The molten drug-lipid mixture was added to melted Pluronic F-127 by using a magnetic stirrer. The pre-heated water was then added dropwise using a syringe to the mixture followed by homogenization at 15,000 rpm for 15 min and probe sonication for 10 min to form nano-sized dispersion, which was stored at 40°C for further characterization (Ravisankar *et al.*, 2017; Shetti and Jalalpure, 2022).

Analysis of Marketed Formulation

The developed UV spectrophotometric technique was employed for quantitatively determining apremilast in commercially available tablets (Aprezo). A sample of twenty tablets was precisely weighed and subsequently triturated into a fine powder.

The powder equivalent to 30 mg of apremilast was dissolved in methanol. The solution was then sonicated, filtered and further dilutions were made with 6.8 phosphate buffer to get a concentration of (10 µg/mL) within the linearity range and λ_{max} was measured at 230 nm. Finally, the drug content in the tablet was estimated (Farooq *et al.*, 2022).

Analysis of Apremilast in cubosomes and transferosomes formulation

Apremilast cubosomes and transferosomes were prepared at 30 mg in 30 mL. Dilutions were prepared by at 10 mL of preparation in 100 mL volumetric flask with methanol. Further, dilutions were prepared by 6.8 phosphate buffer.

Percent Entrapment Efficacy

To measure the Encapsulation Efficiency (EE), the cubosomes and transferosomes dispersion containing apremilast (1 mL) was disrupted using 0.1 mL of 0.1% Triton X-100 in 2 mL pH 6.8 PBS for 5 min. The resulting solution underwent centrifugation at 3000 rpm for 5 min using a Centrifuge (Floor Model, 7000 Kubota, Japan). The supernatant was collected, diluted and analysed for apremilast estimation in cubosomes and transferosomes at 230 nm and % EE was determined (El-Shenawy *et al.*, 2020).

$$\%EE = \frac{\text{Total entrapped drug} - \text{Amount of drug in supernatant}}{\text{Total entrapped drug}} \times 100$$

Particle size analysis and determination of zeta potential

Cubosomes and transferosomes were assessed for particle size and zeta potential using the Malvern zetasizer. For analysis, 1 mL of Apremilast cubosomes solution was taken in 10 mL volumetric flask and diluted with solvent to make up the volume. Similarly, transferosomes were also analysed.

Transmission Electron Microscopy

Apremilast-loaded cubosomal and transferosomal formulations were individually prepared and applied onto carbon-coated copper grids for Transmission Electron Microscopy (TEM) analysis. Imaging was performed using a JEOL instrument operating at an accelerating voltage of 200 Kv (Jha *et al.*, 2020; Peram *et al.*, 2021).

RESULTS

A UV spectrophotometric method was developed utilizing a Shimadzu UV-1900 spectrophotometer equipped with UV Probe software for data acquisition and analysis. Apremilast was estimated with solvent system comprising of methanol and pH 6.8 phosphate buffer.

Determination of maximum wavelength

After scanning, the maximum wavelength of absorption was found to be 230 nm. The UV spectrum of apremilast is represented in Figure 1.

Linearity and Range

Linearity and range for apremilast were determined by analysing 0.2-1 µg/mL in triplicate, which were estimated at 230 nm with a correlation coefficient 0.9988.

Limit of Detection and Limit of Quantification

The Detection Limit (LOD) and Quantification Limit (LOQ) for apremilast were ascertained utilizing the standard deviation of the response and the slope approach, as outlined in the guidelines set forth by the International Conference on Harmonization (ICH). The resulting LOD and LOQ values were 0.09 µg/mL and 0.28 µg/mL, respectively, indicating that the developed UV spectrophotometric method is highly sensitive.

System precision

System precision was determined by conducting intraday and interday precision tests by examining six replicates (0.8 µg/mL) of apremilast solution. To assess the intra-day and inter-day precision, the solution was tested at three separate times within a single day and also across three different days. The findings showed an excellent repeatability, intra-day precision and inter-day precision of the proposed method. The %RSD was found to be less than 2% as depicted in Table 1.

Ruggedness

The ruggedness parameter was evaluated by repeating the suggested method with change in the analyst and the instrument. The percent RSD was less than 2%, indicating that the method was rugged.

Table 1: System precision.

Replicates	Concentration (µg /mL)	Absorbance
1	0.8	0.663
2	0.8	0.661
3	0.8	0.662
4	0.8	0.663
5	0.8	0.661
6	0.8	0.662
Average		0.662
SD		0.0008944
% RSD		0.1351098

Robustness

To evaluate the robustness of the developed method, the detection wavelength was deliberately varied. Apremilast was quantified at 235 nm and 225 nm and the corresponding results are presented in Table 2.

Accuracy

Accuracy of the developed method was determined by performing recovery experiments at three various levels (50, 100 and 150%) in which the percent mean recovery of the sample was calculated and was within the limits as tabulated in Table 3.

Analysis of Apremilast in tablets, cubosomes and transferosomes formulation

The newly developed analytical method was applied for the quantitative estimation of Apremilast content in the tablet dosage form, cubosomes and transferosomes formulation. The Apremilast content in tablets, cubosomes and transferosomes formulation was found to be 100.474, 99.9751 and 98.3535% respectively (Mavaddati *et al.*, 2015) .

Analysis of Apremilast loaded Cubosomes and Transferosomes

The drug-loaded cubosomes and transferosomes demonstrated nanoscale particle sizes with uniform distribution, as indicated by low PDI values. Entrapment efficiency was higher in transferosomes compared to cubosomes (Aygün *et al.*, 2020;

Table 2: Robustness (Change in wavelength).

Replicates	Concentration (mg/mL)	Absorbance at 235 nm	Absorbance at 225 nm
1	0.8	0.632	0.762
2	0.8	0.634	0.754
3	0.8	0.631	0.761
4	0.8	0.633	0.759
5	0.8	0.631	0.761
6	0.8	0.638	0.758
Average		0.6331667	0.75917
SD		0.0026394	0.00293
% RSD		0.4168641	0.38554

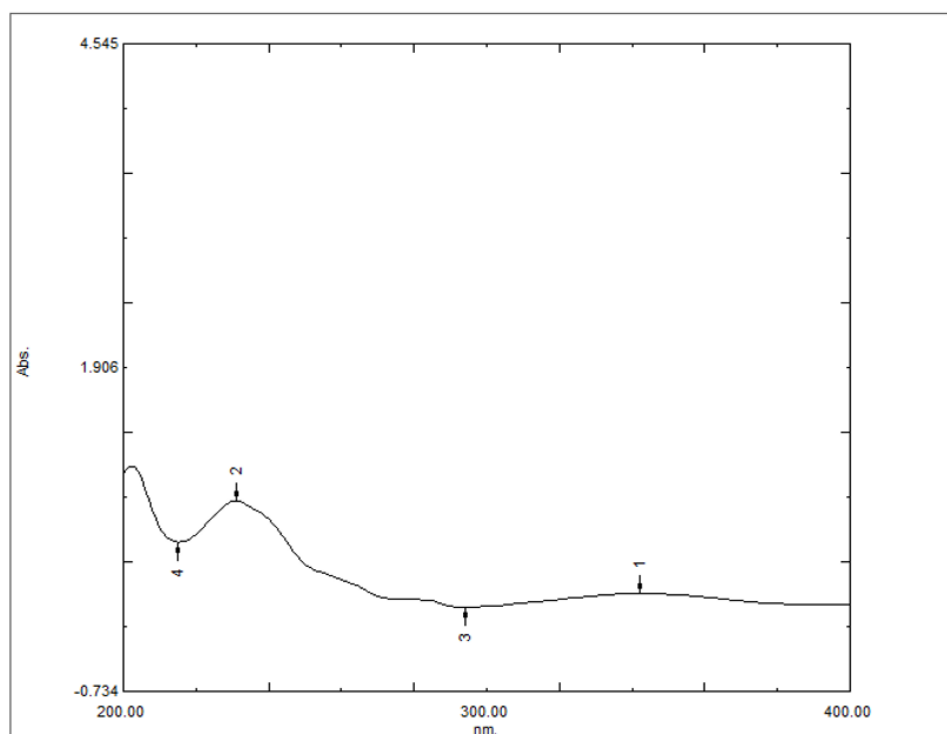


Figure 1: UV spectrum of Apremilast.

Table 3: Accuracy.

Concentration added µg/mL	Level	Concentration (µg/mL) standard	Concentration (µg/mL) Formulation	Absorbance	Concentration found	% Recovery
0.9	50%	0.3	0.6	0.735	0.899547	99.94964
		0.3	0.6	0.729		
		0.3	0.6	0.731		
1.2	100%	0.6	0.6	0.962	1.186437	98.86976
		0.6	0.6	0.959		
		0.6	0.6	0.964		
1.5	150%	0.9	0.6	1.223	1.513243	100.8828
		0.9	0.6	1.215		
		0.9	0.6	1.233		

Kurangi *et al.*, 2019). Zeta potential analysis confirmed good stability of both formulations. TEM images revealed spherical vesicles for transferosomes and a characteristic internal structure for cubosomes. These results highlight the suitability of both systems as promising nanocarriers.

DISCUSSION

This study presents a simple and eco-friendly UV-spectroscopic method for the estimating apremilast in various formulations. The method was developed using a methanol-phosphate buffer (pH 6.8) system and depicted consistent maximum absorbance at a specific wavelength of 230nm. It was also found to be accurate and robust under varied conditions. Application of the method to different formulations confirmed its reliability and versatility, with high recovery rates observed in all tested matrices. The method offers a cost-effective analytical approach for analysis of apremilast in both conventional and advanced drug delivery systems.

CONCLUSION

A simple, accurate and precise UV-visible spectrophotometric method for the estimation of Apremilast was successfully developed and validated. The method demonstrated excellent accuracy, precision and linearity and was found to be in accordance with the ICH validation guidelines.

The proposed methodology successfully quantified apremilast in bulk, pharmaceutical tablets, cubosomes and transferosomes without any interference from excipients commonly employed in apremilast formulations. Validation parameters adhered to the established acceptance criteria, further demonstrating the method's suitability for routine analysis.

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ABBREVIATIONS

cAMP: Cyclic Adenosine Mono Phosphate; **GMO:** Glyceryl Mono Oleate; **HPLC:** High Performance Liquid Chromatography; **HPTLC:** High Performance Thin Layer Chromatography; **ICH:** International Conference on Harmonization; **IL:** Interleukin; **LOD:** Limit of Detection; **LOQ:** Limit of Quantification; **PDE:** Phospho Diesterase Enzyme; **PDI:** Polydispersity Index; **rpm:** Rotations per minute; **RSD:** Relative Standard Deviation; **UV:** Ultraviolet.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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