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Using Green Chemistry Concepts in Developing and Validating Analytical Methods for Meropenem in Parenteral Dosage Form: A Quality by Design Point of View

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KEYWORDS

Green Chemistry, Validation, Eco-friendly, Spectrophotometric, Meropenem, Quality by design.

ABSTRACT:

Introduction: Green chemistry, typically referred to as ecologically sustainable chemistry, constitutes a field of inquiry situated within the context of chemistry, wherein the primary objective is to mitigate the adverse impacts related to chemical processes and products.

Objectives: The objective is to promote the advancement of sustainable and eco-friendly treatments by decreasing or completely removing the utilisation of toxic chemicals, minimising the production of hazardous materials, and saving energy and resources. This study observed linearity with a range of concentration between 02-12µg/mL for Meropenem (MPM).

Methods: The method of solving concurrent equations was utilised to ascertain the concentrations of the medication. The recovery percentage from the parenteral dosage form was determined to be 100.2% along with a standard deviation (SD) of ±0.085, with a sample size of 6. The recovery rates observed in the accuracy study ranged from 99.6-100.66% on average. The observed percentage relative standard deviation (%RSD) demonstrated a value that was much below 2% throughout intra-day evaluations, suggesting a noteworthy degree of precision in the proposed methodology.

Results: The findings from statistical analyses of the technique the validation outcomes indicate that the suggested procedures are suitable for implementation inside the facilitated quality control laboratories.

Conclusions: The present methodology is deemed appropriate for the quantitative analysis of MPM in parenteral dosage formulations, since it effectively eliminates any potential interference from frequently used additives. Hence, this approach can be employed for regular analytical objectives.

1. Introduction

To reduce the negative effects on the natural world resulting from the manufacture and dissemination of chemicals, a multidisciplinary approach known as "green chemistry" has been settled. Regarding the sake of reducing waste, saving assets, and increasing the use of organic items, the optimum focus of this study is the development of environmentally friendly alternatives that substitute traditional procedures utilising chemicals. Meropenem (MPM), denoted by its IUPAC (International Union of Pure and Applied Chemistry) symbol (4R,5S,6S)-3-(((3S,5S))-(5-(Dimethyl carbamoyl)-(3-(thiophene)thio)-6-((R)-1hydroxyethyl)-4-methyl-7-oxo-1-azabicyclo[3.2.0]Heptanoic acid 2 carboxylate. The broad-spectrum antibiotic, hept-2-ene-2-carboxylic acid which is innovative, used to treat bacterial illness [1-3]. It kills pathogens by its attachment to penicillin-binding proteins (PBPs) in their cell walls thus blocking the synthesis of cell wall cross-linked peptidoglycans [4]. It is used to treat meningitis (an inflammation of the tissues that surround the spinal cord and brain) as bacterial infections of the skin and stomach [5-7].

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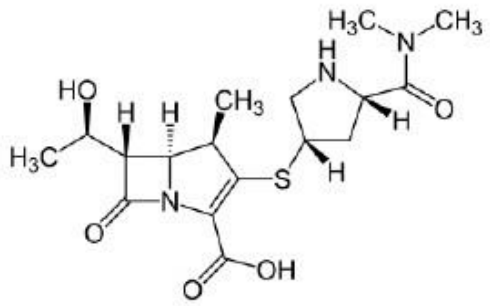

Figure 1. Chemical structure of MPM

MPM in injectable forms & biological samples is estimated throughout UV-visible spectroscopy [8], HPLC [9, 10] and LC-MS [11] method. The disclosed UV spectrophotometric approach, however, has a number of limitations. These include a limited linearity range, no Sandell's sensitivity, and no presentation of the molar extinction coefficient. As a result Quality-by-Design (QbD) strategy was implemented to the advancement of a novel as well as developed UV spectrophotometric method for quantification of MPM through parenteral preparation.

A holistic strategy, QbD, that incorporates excellence throughout every aspect of the operation to guarantee the desired outcome is achieved. QbD is a framework for systematic creativity that conforms, to the standards set out by International Council for Harmonisation (ICH) of Technical Requirements, for Pharmaceuticals for Human Use, in particular ICH-Q8-(R2). This approach begins with clearly defined objectives and places a strong focus on comprehending and maintaining both the final outcome and its structure. This strategy's technique is based on good scientific concepts and incorporates measures that lower risks, guaranteeing the results' accuracy and dependability [12]. After Food and Drug Administration (FDA) launched its "Pharmaceutical Current Good Manufacturing Practises (cGMPs) for the 21st Century" in 2002, QbD has been launched [13]. There are six stages involved in implementing the empirical QbD Perspective and achieving a dependable and high-quality analysis approach with increased resilience [14].

The implementation of the QbD methodology not only decreases the time required for developing a reliable analytical technique but is also considered financially efficient strategy to ensuring quality from the early stages of method development. For determining the optimum configuration domain for method efficiency, making it an integral part of paradigm, QbD, Design of Experiments (DoE), is widely regarded like a crucial tool. The use of rigorous experimental designs is the primary focus of this investigation; the overarching goal is to reduce the amount of variation that occurs in spectrophotometric aspect of MPM. Primary objective is to ascertain the finest selections. The investigation commenced with the implementation of a factor screening analysis utilising a fractional factorial design (FFD) in order to ascertain the key method parameters that exert an influence on performance. Subsequently, a central composite design (CCD), was employed to optimise the methodology, so ensuring its resilience and attaining predetermined objectives. The goal of the study was to come up with an innovative UV spectrophotometric method that was rigorous and reliable for determining the amount of MPM in parenteral formulations. We were able to accomplish this objective thanks to the effective application of QbD concepts throughout the method development process, followed by validation in accordance with ICH standards [15].

2. Materials and Methods

Reagents and Standards

MPM standardised sample with purity >99.5% was provided by Pfizer Ltd., India. Ethanol (EtOH) utilised in the preparation of our medication and reagent solutions came from Merck Ltd., Jamshedpur, India. As the marketed parenteral formulation of MPM (1gm) was accessible, it was purchased and analysed using the established procedure.

Instrumentation and Optical Characteristics

The spectrum investigations were carried out via a microprocessor-controlled single beam system and the LI-285 UV spectrophotometer (manufactured by Lasany, India), employing 10mm calibrated quartz cuvettes. To ensure precise measurements of reagents, a high-precision analytical instrument was employed. Ultrasonication (Enertech, India), was used to influence the dissolution of the parenteral dosage form.

Incorporation of Analytical Target Profile

It’s one of the comprehensive examinations of existing literary text sources & medication profiles, including

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physical as well as chemical features, were conducted to develop an analytical target profile. This profile encompasses a concise overview of the quality attributes associated with an analytical method. Ultimate focus of this study, was to create an analytical method that is efficient, accurate, and economical for estimating the concentration of MPM in its parenteral dose form. Hence, in accordance with the primary objective of this research, a UV spectrophotometric technique was employed to facilitate the expeditious analysis of MPM. The decision to employ the UV spectrophotometric method in drug analysis was motivated by its advantageous characteristics of simplicity and efficiency, which render it superior to more complex analytical techniques.

Incorporation of Risk Management & Cause-Effect Relationship

When it's important to see how different factors that might affect the performance of a method are connected, the Ishikawa fish-bone diagram is one of the easiest ways to do it. An Ishikawa diagram was made to learn more about how these factors might change the UV spectrophotometry properties for MPM. Researchers used Cause-Effect Risk Assessment Matrixes depending on the Control-Noise-Experimentation (CNX) method to figure out which factors are most likely to affect the study's statistical features. The study found lots of CMVs i.e., Critical Method Variables that were bridged to elevated end score, which suggests that they are high-risk variables. The composition of those CMVs encompasses variations in detection wavelength, solvent used, scan rate, sample integrity, sampling intensity, and pH of the sample. The CMVs were checked out by implementing screening design additionally in order to determine the crucial method parameters. Subsequently, response surface optimisation was conducted using an appropriate experimental design.

Screening of CMVs by FFD

To identify the variables with high risk, Design expert 11 software, version-11.0.4.0, USA, FFD has been utilized to screen critical variables. Several factors were chosen as essential method variables based on a comparison of the spectrum design, precision, and absorbance. Based on what was already known and the Ishikawa fish-bone diagram, prioritisation studies were used to figure out the detection wavelength, solvent type, & sample integrity. These factors further checked using direct observation. Design expert software was used to conduct an FFD experiment with a minimum of 5 trials (one serving as a centre point) to assess the technique variables of scan speed (X1), PH of the sample (X2), and interval of sampling (X3). Parameters were evaluated on both the higher and lower levels, as well as the program was further utilized in determining CMVs those affect the absorbance (Y) of the response variables. Significant parameters were identified by evaluating actual versus predicted values plot, prediction equation, pareto chart & fitting summary plot.

Method optimization & Robustness study Implementing CCD

The CCD was used to make sure that the method for finding the best method conditions was reliable [16]. As a result of the screening studies, 13 dummy runs were ready using at the least five central points chosen rely on CCD to find the best CMVs, such as the sample's pH (A) & sampling interval (B). As the answer variable, absorbance at 336nm was used to look at the results of the experiments. For all the tests, a normal MPM of 10µg/mL was used.

Design of Expert software was used to fit experiment data into mathematical model applying Multiple Linear Regression Analysis (MLRA). This model could explore main and interaction effects. To analyse the model, only significant coefficients (p value<0.05) from analysis like ANOVA were used for framing the polynomial equations & analyse parameters for instance R2, adjusted R2, & Predicted Residual Sum of Squares (PRESS) respectively. Multiple profilers were used to evaluate the model's viability, including projection profilers, interaction profilers, and three-dimensional response surface profilers. Using a numerical desirability function, we were able to find the optimal solution by striking a balance between the many factors under consideration. The area of the design was then demarcated off according to this [17].

Method Control Strategy

The design space formed by the DoE methodology was used to inform the development of control strategies for the method, enclosed by the marginally changes in method performances were enabled to retain method's resilience.

Preparation of Standard Stock Solution

To make the MPM standard stock solution (1000µg/mL), 10 mg of MPM was dissolved in enough EtOH to make

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10 mL. To make 100 g/mL standard solutions, five mL of above prepared stock solution transferred, to a fifty mL volumetric flask, & the content was filled with water to make fifty mL [18].

Parenteral Dosage Form Analysis

Meronem 1000/Pfizer Ltd.'s labelling claim for its MPM parenteral formulation is 1 gm. For injection, 1 gramme of MPM should be diluted in 20 millilitres of water, as directed on the packaging. After the solution was ready, 0.2 millilitres (the weight equivalent of 10 milligrammes) was transferred to a 10 millilitre volumetric flask and brought to 10 millilitres with EtOH. For thirty minutes, the material was ultrasonicated. Whattmann filter paper was used to further filter this solution for particles. In order to analyse the filtered solution, it was diluted further with EtOH. Using a calibration curve based on the concentration of standard MPM, we were able to calculate the amount of medication in the sample solution.

3. Method Validation

The Specificity

The specificity of UV spectrophotometric method, was appraised by determining drug's presence in the formulation excipients. The spectrums were assessed in order to see if there was any potential interference caused by the excipients [19].

Linearity

In order to create a range of concentrations from 2 to 12 g/mL, multiple aliquots were collected with working standard solution of MPM and placed within distinct 10 mL volumetric flasks before diluting by using EtOH at the end of the process. At a wavelength of 336 nm, UV absorption was measured. For the purpose of determining whether or not the results are linear, a calibration curve was created by placing the absorbance & the concentration (in g/mL) on the Y-axis & X-axis respectively [20].

Precision & Accuracy

In order to assessing the methodology precision, recovery experiments were being conducted with three different levels: 80%, 100%, & 120% of the test solution of MPM (10µg/mL), utilising the standard dilution technique. Recovery researches were conducted in duplicate for every degree. Standard medication, MPM mixed up with the recovery solution was computed by plotted calibration curve. In order to evaluate intra-day precision, replicates of total six of a constant conc. of MPM (10µg/mL) were reviewed within a single day, as well as subsequently, the %RSD values were computed [21-23].

4. Results

In this current research, Ultraviolet spectrophotometric (UV Spectrophotometry) method was established for the purpose of determining the amount of MPM in a parenteral formulation. In order to obtain the variable parameters that would be needed for constructing the final spectrophotometric settings, the QbD method was put into practise. For the purpose of determining the technique variables, a conventional Ishikawa fish-bone diagram was constructed. The physical evaluation of the variables involved in the procedure was carried out. It was discovered that the medication did not dissolve in either acetone or ether. MPM was soluble in EtOH, chloroform, alcohol, and acetone, but it was insoluble in water. However, in this case, EtOH was chosen as an acceptable solvent system for the continuation of the investigations. The standard MPM solution reaches its maximum absorption (λmax) in EtOH at a wavelength of 336nm (Fig. 2); this wavelength was chosen as the detecting wavelength.

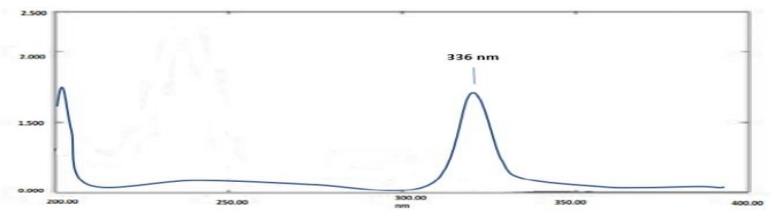

Figure 2. Typical UV absorption spectrum of MPM

Melting point test showed good sample integrity. However, sample PH, scan speed, sampling interval required for a thorough research for assessing their effects on technique robustness. Screening CMVs by

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scan speed, sampling interval, & sample PH was made easier using FFD. Actual vs. projected plots showed the model's fitness. Model p-value (0.0044), R2 (0.9177), & RMSE (Root Mean Square Error) (0.0021) indicated model suitability. Summary of fit showed anticipated R2 (0.4144) & adjusted R2 (0.8588).

The CCD was used to check how the CMVs changed the reaction absorbance. A UV spectrophotometer was used for 13 experiments that were done in a random order to get an answer that was free of bias and had at least five centre points. Table 1 shows the results of each experiment and the spectrophotometric range that was looked at.

Table 1. Experimental design matrix showing spectrophotometric range studied for robustness study and obtained responses

Run No.	Slit Width (A)	Sampling Interval (B)	Absorbance (Y)
1	1.25	1.25	0.29
2	1.25	1.25	0.29
3	1.25	2.31066	0.235
4	0.5	2	0.241
5	2.31066	1.25	0.31
6	1.25	1.25	0.29
7	1.25	1.25	0.29
8	0.5	0.5	0.224
9	1.25	1.25	0.29
10	1.25	0.18934	0.23
11	0.18934	1.25	0.24
12	2	0.5	0.3
13	2	2	0.32
Range	Low	High	
	0.5	2	
	0.5	2	

The null hypothesis (H0) was accepted based on a predetermined significance level of 0.05 for the p-value. A comprehensive examination of the CCD model was conducted, employing various statistical analytic techniques such as ANOVA, parameter estimations, and prediction profiler, to derive meaningful conclusions.

In Fig. 3 (A), perturbation plots display the anticipated models, independent factors impact on a given response, while fixing all other factors constant at a reference point. Degree of steepness in a slope or curve indicates the sensitivity of the reaction to a certain component. In the presented analysis in Fig. 3 (A), it was denoted that factor B, the sampling interval exhibited the greatest significant impact upon absorbance, following the sample pH. The actual versus predicted graphic showcases the baseline model (represented by blue points), revealing that the line obtained for the experimental data falls smoothly within the accuracy interval parameters (Fig. 3 (B)). The observed data exhibited a high degree of similarity to the expected data, this disproves the null hypothesis and proves the model's efficacy in describing data variation.

Response surfaces plots against slit width & sampling interval are illustrated in (Fig. 4) (slit width is plotted against the sampling interval). The analysis of perturbation plots & response plots, of optimization models revealed that factor had a huge impact on the absorbance of the analytes.

In addition, the analysis of variance (ANOVA) resulted in a P-value that was found to be less than 0.0011, which indicates that the model is suitable for addressing the variability observed in the data. This finding also suggests that the null hypothesis should be rejected.

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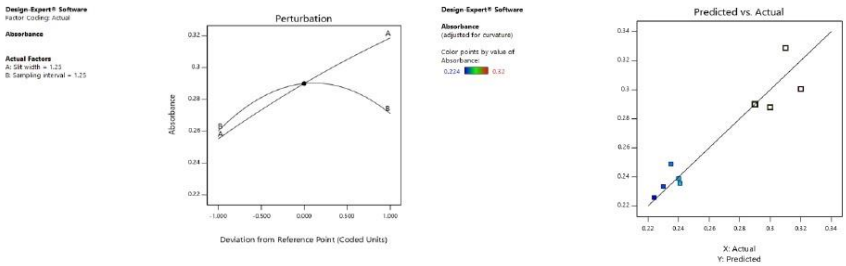
Additionally, the model's appropriateness was confirmed by the lowest value observed in anticipating PRESS.

The review of parametric estimations is vital in estimating the risk of variability from diverse variables. A p-value that is observed to be less than 0.05 indicates the availability of non-zero slope.

Sampling interval × sampling interval (B2) and slit width(A) became the greatest impacting method variables.

$$Absorbance\ (Y) = 0.2900 + 0.0317A + 0.0055B + 0.0008AB - 0.0031A^2 - 0.0244B^2$$

where, A=Slit Width, B=Sampling Interval.



A B

Figure 3 (A). Pertubation Plot, **3(B).** Predicted vs. Actual Plot

Table 2 displays the optical properties associated with the spectrophotometric technique. The method that was devised demonstrated both specificity and selectivity, since it was shown that the commonly utilised formulation excipients in the parenteral dose form did not interfere with the predicted procedure. The medication exhibited linearity, within a range of concentration 2-12µg/ml. The conducted regression analysis, on the linearity data demonstrated a satisfactory level of overall goodness of fit. The statistical measures, namely R2, adjusted R2, and predicted R2, yielded values of 0.9177, 0.8588 and 0.4144, respectively. The analysis of variance (ANOVA) indicated that the approach used for assessing linearity data was deemed adequate, as evidenced by a statistically significant p-value of less than 0.05. The recovery percentage from the parenteral dose form was determined to be 100.2% with a standard deviation of ±0.085, based on a sample size of 6.

5. Discussion

The recovery rates observed in the accuracy investigation exhibited an average range of 99.6-100.66%. In relation to intraday assessments, the %RSD exhibited a value well below 2%, indicating a notable level of precision in the suggested methodology. The obtained findings of the employed methodology fall within the predetermined range, indicating that the methodology is unaffected by the presence of additives.

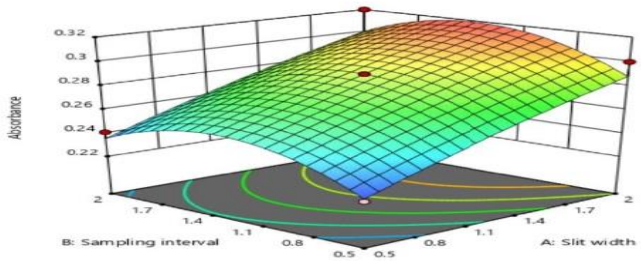


Figure 4. 3-D Response surface plot for absorbance against slit width Vs. sampling interval

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Table 2. Optical Characteristics and Summary of validation parameters

Parameters	Obtained Values
Wavelength (nm)	336
Linearity Range (µg/ml)	2-12
Sandell's sensitivity (µg/cm2 /0.001AU)	0.044
Molar extinction coefficient (ltr/ mol.cm)	0.87 * 105
Regression equation(Y=ax+b)*	0.0199x + 0.0304
Correlation coefficient(R2)	0.9998
Precision (% R.S.D., n=6)	0.39742914
Accuracy (% Recovery ± S.D.)	
80%	1.050156 ± 0.00411
100%	0.764868 ± 0.003266
120%	0.69786 ± 0.003266
% Range of error	
95% confidence limits	± 0.068
99% confidence limits	± 0.089

R.S.D. – Relative Standard Deviation; S.D. – Standard Deviation; A.U. - Absorbance Units,* is Y= ax+b, where Y = absorbance, a = slope, b = intercept and x is the concentration, † is average of three determinations at each level

6. Conclusion

An exact UV spectrophotometric approach for measuring MPM was made achievable due to the QbD methodology. The QbD procedure guaranteed a high quality of analysis. When establishing control techniques for the method and planning future trials to maintain making the method perform better, the researcher had to pay particular attention to the Sampling interval and slitwidth. Based on the data, the method seems to be new, easy, accurate, and precise. The created methods can be used in quality control labs, according to statistical studies of the method validation results. This technique can be used to find out the MPM of a parenteral dosage form without any problems from widely used fillers. Because of this, particularly this method can be implemented for normal analytical goals.

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