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Development and Evaluation of a Pediatric Paracetamol, Chlorpheniramine Maleate, and Phenylephrine Hydrochloride Syrup Using a QbD-Based RP-HPLC Analytical Method

Vikram **Gharge**[1*], Anup **Kulkarni**[1], Mangesh **Jagdale**[1], Deepti **Masne**[2], Anant **Patil**[2], Mahadev **Lohar**[1],

[1] Formulation and Development Department, Zuventus healthcare limited, MIDC Hinjawadi, Pune – 411057, India

[2]Analytical and Development Department, Zuventus healthcare limited, MIDC Hinjawadi, Pune – 411057, India

***Corresponding Author**: Vikram Gharge
Email: Vikram.gharge@zuventus.com

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ABSTRACT

Background: The fixed-dose combination (FDC) syrup of Paracetamol (PCM), chlorpheniramine Maleate (CPM), and Phenylephrine Hydrochloride (PPH) is widely used as an antipyretic and analgesic medication to manage pain and common cold symptoms.

Objective: the study aims to develop a sugar-free syrup formulation of PCM, CPM, and PPH using a Quality by Design (QbD) approach. The goal is to create a stable, effective product tailored for pediatric use.

Methods: The formulation was developed using QbD principles, focusing on excipient compatibility which was confirmed through preformulation studies. A method for detecting Ethylene Glycol (EG) and Diethylene Glycol (DEG) was developed and validated, with precision, intermediate precision, specificity, accuracy, linearity, and robustness assessed. Additionally, a precise RP-HPLC method was developed for the real-time stability assessment of PCM, CPM, and PPH. Design of Experiments (DoE) was employed to optimize method parameters, such as flow rate and mobile phase composition, using a YMC Triart C18 column with a gradient elution method.

Results: The sugar-free syrup formulation remained stable at 6-month accelerated study, demonstrating linear stability. The RP-HPLC method provided a clear resolution of the active compounds optimized conditions: a gradient elution with Sodium phosphate buffer (pH 3.0) as mobile phase A and Acetonitrile (70:30) as mobile phase B, at a flow rate of 1.2 mL/min. The method was precise, accurate, and specific.

Conclusion: The study successfully developed a stable, sugar-free syrup formulation of PCM, CPM, and PPH, meeting pediatric requirements. The validated RP-HPLC method proved effective for quality control, highlighting the success of applying QbD principles in pharmaceutical development.

Keywords: Antipyretics, Design of Experiment, Common Cold, Excipients, diethylene glycol.

INTRODUCTION

Most multi-component drug formulations usually contain two or more active ingredients that combine to produce the combined therapeutic action of the treatment. When the selective agents have distinct modes of action that result in additive or synergistic efficacy, this approach is advantageous. The market is filled with numerous multi-component syrup formulations that include Phenylephrine Hydrochloride (PPH), Paracetamol (PCM), and chlorpheniramine Maleate (CPM) either as the only active ingredients or as one of the drug's many active ingredients. These medications are typically used as antipyretic-analgesic medications to treat pain and the common cold [1]. IUPAC name of the Paracetamol N-(4-hydroxyphenyl)acetamide, N-(4-hydroxyphenyl) ethanamide. The empirical formula C8H9NO2 is an antipyretic and non-opioid analgesic that is used to treat mild to moderate pain and fever. The 3-(4-chlorophenyl)-N, N-dimethyl-3-pyridin-2-ylpropan-1-amine is the IUPAC name of the chlorpheniramine Maleate (CPM). The empirical formula for CPM is $C_{20}H_{23}ClN_2O_4$, CPM is a H-1 receptor blocker. CPM is an antihistamine that helps alleviate symptoms of allergy, hay fever, and common cold. (R)-1-(3-hydroxyphenyl)-2-methylamino-ethanol hydrochloride is the IUPAC name of Phenylephrine Hydrochloride (PHE). The empirical formula for PHE is $C_9H_{13}NO_2HCl$. Phenylephrine is an alpha-adrenoceptor agonist that reduces nasal congestion and promotes the drainage of sinus cavities [2].

To separate each active component from multi-component medicine formulation, pharmaceutical companies employ extraction techniques that need that need multiple and repeated extraction. This has caused scientists to create several of strategies to aid in the simple and rapid study of medication with several components. Numerous researcher have sought to develop different RP-HPLP procedure because HPLC is a preferred technology [3-4].

MATERIALS AND METHODS

Chemicals and reagents

Materials

Phenylephrine Hydrochloride, chlorpheniramine Maleate and Paracetamol were used as active substances from Zuventus Healthcare Ltd., Pune, India. Disodium Edetate, Sodium Benzoate, Citric acid Monohydrate, Sodium Citrate, Neotame, Sorbitol, Xanthan Gum, Menthol, Polyethylene Glycol 4000, Colour Sunset yellow supra, Flavour Juicy Orange Oil, Sodium Dihydrogen Orthophosphate Monohydrate, Orthophosphoric acid, Acetonitrile and Methanol were provided by Zuventus Healthcare Ltd., Pune, India. The water used was obtained by using the Millipore MilliQ Plus water purification system.

Equipment

Formulation equipment Batch was manufactured with help of equipment**'s** like Homogeniser (Make - Remi Motors), Remi stirrer (RQT 124 A) (Make - Remi Motors); for heating: Hot plate (Make-Tarsons), for filling of syrup: Auto Dosing Machine (Make- Thermolab) and

sealing of bottle: Semi Auto Ropp Cap Sealing machine (Make- Svelte).

Analytical equipment

Liquid chromatography analysis was carried out on a Waters HPLC (Waters Corporation, Milford, MA, USA) equipped with a Photodiode Array Detector (PDA) at 220 nm. Empower3 software was used to process and monitor the output signal. Studies on photostability were conducted in a Newtronics photo-stability chamber. Studies on thermal stability were conducted in a Metalab dry-air oven.

Chromatographic condition

Separation was accomplished on an YMC Triart C18 column (250 mm x 4.6 mm, 5 µm) with flow rate of 1.0 mL/minute, and the detection wavelength was 220 nm using the following gradient: program (time in min)/(%Mobile Phase-B): 0/4, 8/4, 34/40, 36/90, 40/90, 41/4, 50/4. The following solutions were prepared: Buffer solution of Sodium Dihydrogen Orthophosphate Monohydrate (0.044 M) pH 3.0 with Orthophosphoric Acid; Mobile Phase-A, same as buffer and Mobile Phase-B, ACN: MeOH (80:20, v/v). The column temperature was maintained at 40 °C and the injection volume was 20 µL with a sample cooler at 5°C. Mixture Mobile Phase A and Methanol in the proportion (70:30 v/v), respectively, used as a solvent or diluent. DoE and Statistical analysis was performed using "Design-Expert®" software, version 9.0.1.0 (StatEase, Inc., Minneapolis, MN, US).

Formulation: Quality by design based development

Pharmaceutical Quality by Design (QbD) has evolved significantly following the introduction of ICH guidelines Q8 (R2) (Pharmaceutical Development), Q9 (Quality Risk Management or QRM), Q10 (Pharmaceutical Quality System), and Q11 (Development and Manufacture of Drug Substances). These guidelines offer comprehensive direction on the implementation and breadth of QbD [5]. According to the FDA, QbD is defined as a systematic approach to development that commences with predefined objectives, focusing on understanding product and process through robust scientific principles and effective quality risk management. QbD facilitates the development of robust processes and enhances comprehension of product and process dynamics, thereby supporting pharmaceutical product lifecycle management. QbD provides numerous benefits to the generic drug industry, including reduced incidence of batch failures, enhanced understanding of risks, decreased product recalls, and expedited product launches. Gradually becoming standard practice in the pharmaceutical sector, the value of QbD is increasingly recognized by manufacturers, promoting its integration into product development processes. QbD has expanded its application into related fields such as analytical QbD, and the pharmaceutical industry anticipates the ongoing advancement and enhancement of this approach [6].

Quality target product profile for formulation

The Quality Target Product Profile (QTPP) is a forward-looking synopsis detailing the attributes of a drug product that impact its quality. It functions as a critical link between patient requirements and product quality**. Table 1** illustrates the QTPP specific to a liquid syrup formulation, delineating the essential elements of the QTPP along with the corresponding target specifications and rationale for each element [7-8].

Table 1-Elements of QbD

QTPP	Target	Justification
Description	An orange colour clear liquid.	Organoleptic property
Assay	95 -105%	Affects therapeutic efficacy of the formulation
pH	Between 4.0 and 6.5 at 25°C	Stability of Product
Weight per mL	1.10 to 1.30 at 25°C	Solid content

Critical quality attributes formulation

Critical Quality Attributes (CQAs) are identified from the Quality Target Product Profile (QTPP) through impact and severity analysis. This determination hinges on two fundamental questions:

1. Does a change in formulation and/or process parameters influence the quality attribute of the product? (Impact analysis)

2. Would failure to meet the quality attribute significantly impact the efficacy and safety of the product in the patient? (Severity analysis)

If both questions yield an affirmative response for a specific QTPP element, it qualifies as a Critical Quality Attribute (CQA). Conversely, if either question is answered negatively, the QTPP element does not classify as a CQA. This method has been employed to establish the critical quality attributes for liquid syrup preparation [**Table 2**][9-10].

Table 2 : Critical Quality Attributes for Liquid Syrup Preparation

QTPP element/quality attribute	Target	Impact analysis [a]	Severity analysis [b]	Is the quality attribute critical or not critical?
Dosage form	Liquid	No	No (Dosage form is decided)	Not critical
Route of administration	Oral	No	No route of administration is already decided	Not critical
Dose strength	125 mg/5 mg/1 mg	Yes	Yes	Critical, but related to assay
Viscosity	Optimum (1000–50,000 mPa s)	Yes	Yes	Critical
pH	Well-matched with formulation	Yes	Yes	Critical
Microbial content	As per compendial requirements.	No	Yes	Critical
Container closure system	Pet Bottle	No	Yes	Not Critical

[a] Does change in formulation and/or process parameters affect the quality attribute of the product?

[b] Does failure to meet the quality attribute severely affect the efficacy and safety of the product in the patient?

Preparation of Syrup:

The Phenylephrine Hydrochloride, Chlorpheniramine Maleate and Paracetamol syrup were prepared as described by Singh et al. [11].

Polyethylene glycol screening studies:

Polyethylene Glycols (PEGs) are commercially accessible in molecular weight ranges spanning from 200 to 10,000,000 g/mol. PEGs with molecular weights between 200 and 600 are typically transparent liquids, while those with molecular weights of 1000 and higher are predominantly semi-crystalline solids under ambient conditions. The solubility of API in the solid PEG was investigated by meticulously adding increasing amounts of solid PEG. At the same time, material heated in a water bath at temperature 70-75°C. This approach was continued until no further crystals of API were visually observed in the syrup and were noted as the endpoint. These results confirm by physical observation.

Xanthan gum screening studies

Xanthan gum (XG) is a high molecular weight exopolysaccharide with branched polymeric chains that is also well-soluble in water and biocompatible [12-13]. Prototype batches of syrup were prepared by solution preparation technique. The formulations were prepared using Xanthan Gum with at concentration 0.15% to 0.35% w/v in the solution. Testing were done by physical as well as with chemical analysis.

Formula Optimization (Preparation of syrup)

On the basis of a literature search, excipients were selected. Pre-formulation study was carried out to check the compatibility on ingredients. The study result shows the all active compounds were compatible with excipients. In formulation Sorbitol is used as a cosweetener & non crystalizing agent. Sodium benzoate as a preservative, Edetate disodium as a chelating agent. Neotame is an artificial sweetener. Sodium citrate and Citric acid as buffering agents. Xanthan Gum as a viscosity modifier. Polyethylene Glycol 4000 is used as a co-solvent for dissolving Paracetamol. For flavoring, menthol and Juicy Orange oil were used. Sunset yellow supra coloring agent is incorporated. Water is used as a solvent.

Various trials were performed during formulation development. Taste, clarity and viscosity were focused during development. Artificial sweetener influencing the taste. Xanthan Gum control the viscosity. Polyethylene Glycol 4000 influencing the clarity. Formulation designed based on the experimental results data.

Full Factorial design

A full factorial experimental design was utilized to optimize response variables by systematically varying two factors at three levels each. The factors investigated were the concentrations of Polyethylene Glycol (PEG) and Xanthan Gum, which were appropriately coded. Response variables such as viscosity, dissolution characteristics, and drug release profiles were assessed within this experimental framework. The study involved a comprehensive evaluation of these two factors F across their respective levels, with experimental trials conducted for every conceivable combination. Throughout the investigation, all other variables related to formulation and processing were kept constant to ensure consistency and isolate the effects of the factors under investigation.

The concentration of these Polyethylene Glycol and Xanthan Gum excipients were taken in consideration during experimental work. Two different levels of concentrations are as follows in **Table 3.**

Table 3. Variables and their levels used in Plackett–Burman design.

Sr. No	Excipients	Concentration used in % W/V Level 01	Concentration used in % W/V Level 02
01	Polyethylene glycol	4.50	2.5
02	Xanthan gum	0.5	0.25

Two level variation evaluate the product, finally conclude and develop the fixed dose combination of syrup which is sugar free and stable formulation over the time period. Stability of the product is defined on the basis of 6-month stability study data.

Phenylephrine Hydrochloride, Chlorpheniramine Maleate, Paracetamol, Edetate disodium, Sodium Benzoate, Menthol, Propylene Glycol, Sorbitol Solution 70% , Colour Sunset Yellow Supra, Citric Acid Monohydrate, Sodium Citrate, Polyethylene Glycol 4000, Neotame, Xanthan Gum (FNCS), Flavour Juicy Orange Oil IFF, Purified Water these ingredient were used for preparation of liquid syrup.

Preparation of standard and sample

Preparation of Standard solution

Prepare 500 ppm Phenylephrine Hydrochloride standard solution and 640 ppm Paracetamol Standard Solution in diluent and use as standard stock A. Prepare 250 ppm Chlorpheniramine Maleate standard solution in diluent and use as standard stock B. Mixed standard solution prepared by diluting 5.0 mL of standard stock solution A & 2.0 mL of standard stock solution B up to a 50 mL with diluent.

Preparation of Test solution for Chlorpheniramine Maleate & Phenylephrine HCl

Transfer sample equivalent to 125mg of Paracetamol in to a 100mL clean and dry volumetric flask, add about 70mL of diluent and sonicate. Dilute to volume with diluent and mix. Filter the solution through 0.45µm nylon filter paper (Stock solution C).

Preparation of Test solution for Paracetamol

Diluted 5.0 mL of stock solution C up to a 100 mL with diluent and mix.

Design of Experiments (DoE)

MINITAB® employs a 3^3 full factorial analytical design as a type of design of experiment applied by MINITAB®. The model was used to create the design. The flow rate (mL/min) (X1), gradient time point (min) (X2), and mobile phase composition (Acetonitrile: Methanol%)

(X3), which changed on three levels, were the variables chosen based on the risk analysis [14]. The experimental data were fitted using the statistical module of the Design Expert software and the chosen experimental design. The same program was used to calculate the statistical parameters.

Analytical method: Assay

Considering the literature search, its preliminary studies & quality parameter of the products defines the CQAs of the analytical method based on experimental & practical knowledge. The CQAs of the analytical method are denoted by the following features: Assay of active ingredients, pH, related substance, & microbial limit test of formulation. Based on study chemicals & reagents like Sodium Dihydrogen Orthophosphate Monohydrate, Orthophosphoric acid, Acetonitrile, Methanol were used for evaluation. All chemicals were used having HPLC grade high purity [15].

The composition of some of these goods can now be simultaneously assessed using a variety of chromatographic techniques. The development of these approaches often focuses on the One-Factor-At-a-Time (OFAT) method, which is based on the trial-and-error method. The parameters that affect the analytical procedure that have been evaluated within a suitable range (or levels) are approached using the trial and error method, while the other factors are kept constant. To create a reliable system for quality assessments, the QbD approach is applied [16].

Quality by Design approach for Analytical advance.

Identification of the Quality Target Product Profile (QTPP), evaluation of Risk Factors, and Critical Quality Attributes (CQAs). The QTPP contains the qualities that have a direct relevance to the quality, safety, and effectiveness attributes of the medicinal product, in accordance with current ICH Q8 (2) standard [17].

Design of Experiments (DoE)

The model (Minitab 3^3 Full factorial design) was used to create the design. The flow rate (mL/min) (X1), gradient time point (min) (X2), and mobile phase composition (Acetonitrile: Methanol%) (X3), which changed on three levels, were the variables chosen based on the risk analysis.

The experimental data were fitted using the statistical module of the Design Expert software and the chosen experimental design. The same programme was used to calculate the statistical parameters [18].

Formulation

Polyethylene glycol screening studies

For higher drug dissolution and drug distribution in the formulation the selction of solid and PEG was critical in formulating an effective preparartion. The solubulity of API in various concentration are summarized in tablets in Table 3. Also the API are completely soluble in all the formulation confirmed by testing method.

Xanthan gum screening studies

In the realm of fasibility, formulation preparaed using Xanthan gum various

concentarion in the formulation and summarized in **Table 3**. The effect of Xanthan gum concentration which provide the formulation as thickening agent; use of higher and lower which affect the viscosity of formulation.

Optimization of Syrup using a hybrid design - Full Factorial design

An experimental factorial design employing two factors at three levels (-1, 0, +1), similar to a 22 factorial design, was chosen for this study. This design is well-regarded for its efficiency in second-order experimentation, allowing for the estimation of main effects and interactions with a reduced number of experimental runs. Moreover, it enables the modeling of quadratic response surfaces, which is not feasible with traditional two-level factorial designs. This approach was implemented to systematically investigate the variables of interest.

The developed analytical method was utilized to evaluate the formulated product. RP-HPLC was employed for assay determination, while GC was used to quantify the content of Ethylene Glycol (EG) and Diethylene Glycol (DEG). The results of these analyses are summarized in the accompanying table, demonstrating satisfactory outcomes.

Analytical method for assay and EG_DEG analysis validated as per ICH guideline.

Assay Method validation

Precision and intermediate precision

The precision of the method was assessed through its repeatability by injecting six individual preparations of a syrup sample containing Paracetamol (PCM) 125 mg, Phenylephrine Hydrochloride (PPH) 5 mg, and Chlorpheniramine Maleate (CPM) 1 mg per 5 ml of syrup. Intermediate precision was also evaluated. The %RSD (Relative Standard Deviation) for each test concentration was calculated and found to be less than 2.0% RSD.

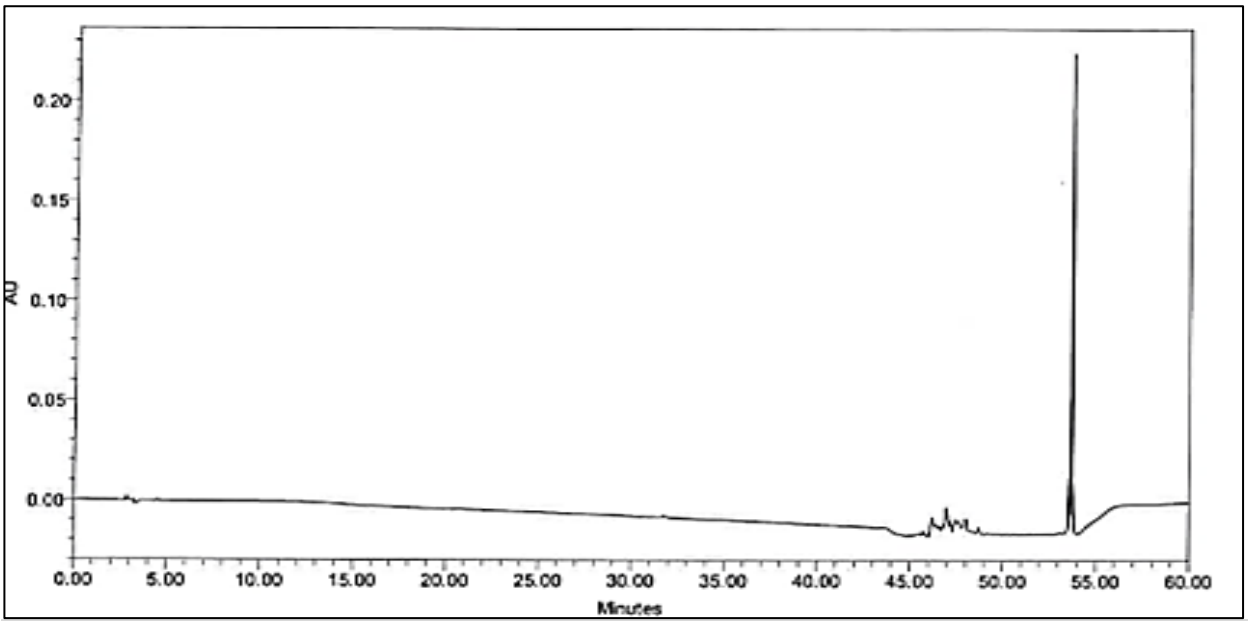


Figure . 1 Blank Solution

Specificity refers to the ability to accurately assess the analyte in the presence of potential interfering components such as impurities, degradation products, and matrix components. Chromatograms of placebo syrup preparations and sample preparations were compared, revealing no peak interferences at the retention times corresponding to CPM, PPH, and PCM. The peaks of the placebo and sample were well resolved. (Refer Figure 1-4)

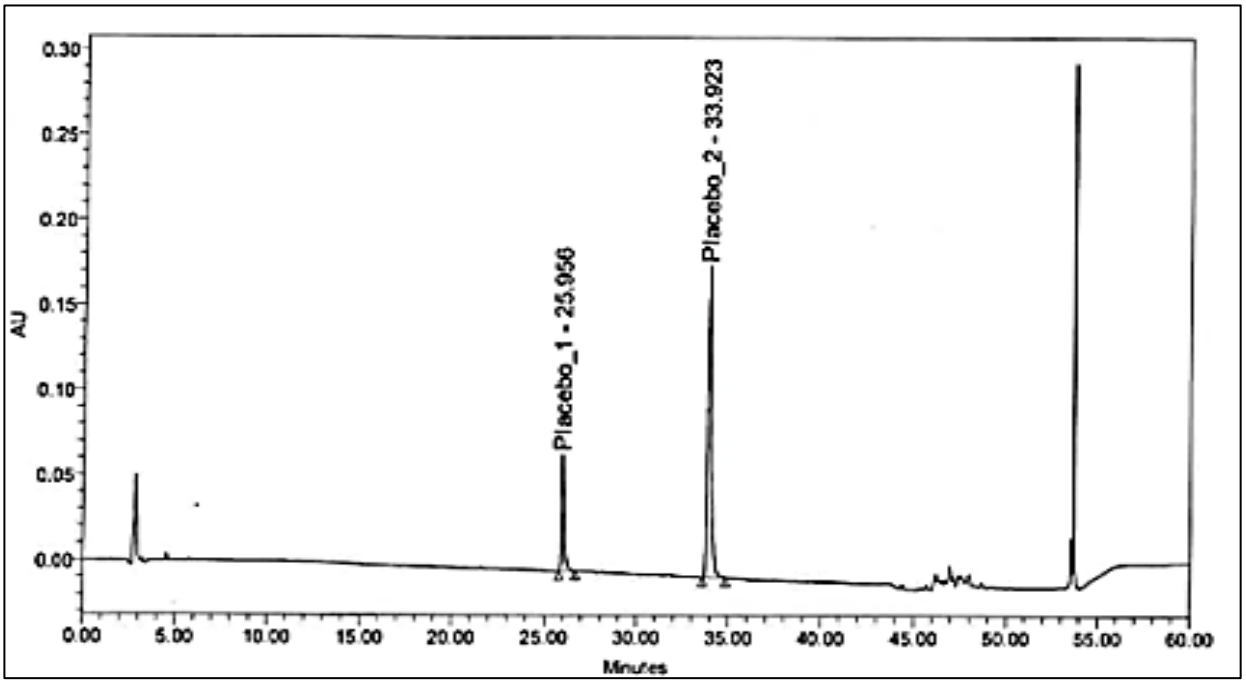


Figure. 2 Placebo

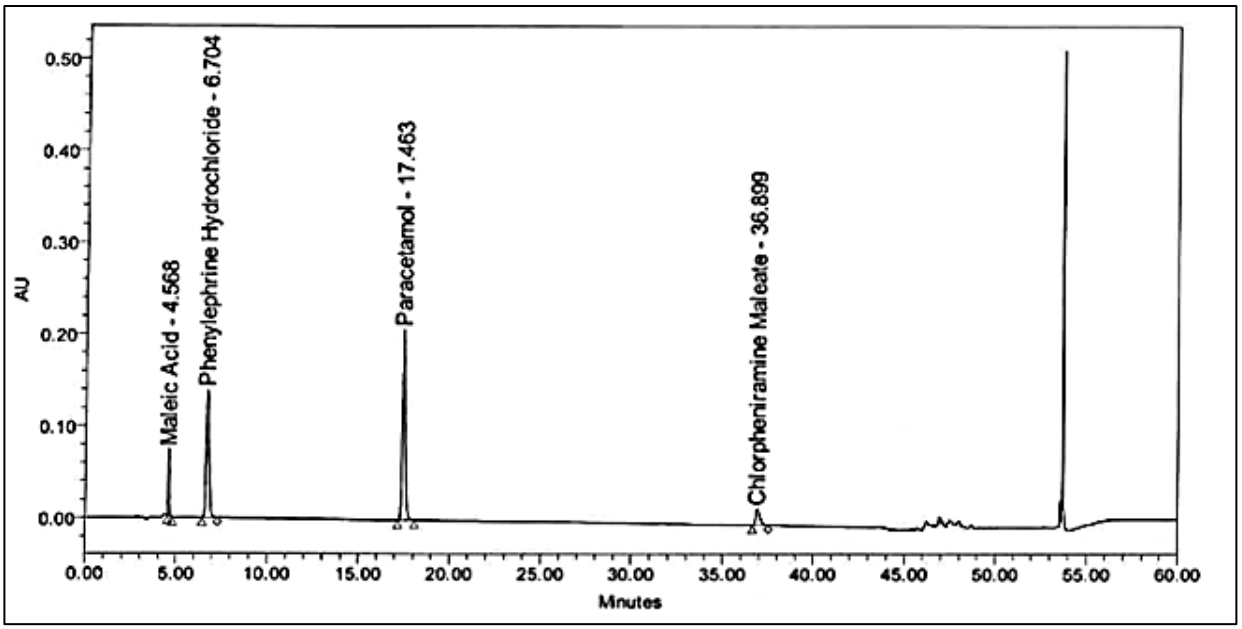


Figure. 3 Standard Solution

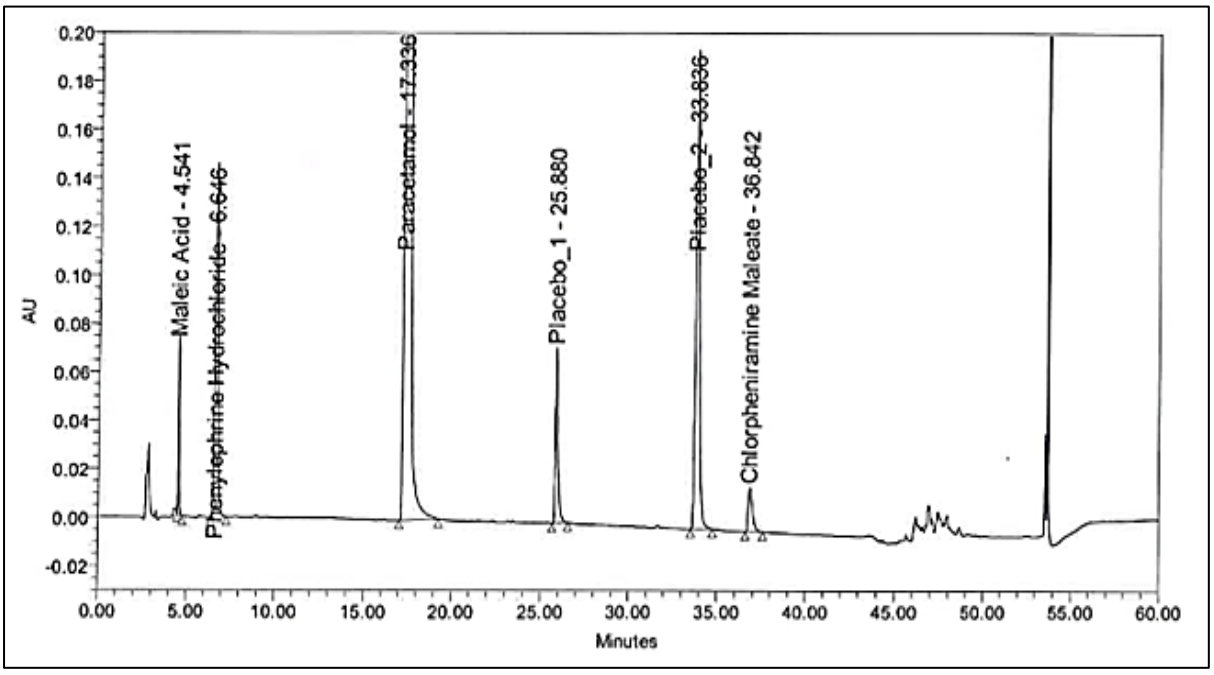


Figure. 4 Test solution

Forced degradation

Specificity studies were conducted on syrup samples and individual active drug substances.
to assess their identification and indication capabilities. Intentional degradation experiments were performed under stress conditions including acid (0.1 N HCl at 60 °C for 60 minutes),
base (0.5 N NaOH at 60 °C for 60 minutes), oxidation (30% H2O2 at 60 °C for 60 minutes),

photolytic (UV exposure of not less than 200 watt hours per square meter for 1 hour, visible light exposure of not less than 1.2 million lux hours), and thermal (70 °C for 24 hours) stress conditions.

The performance of the proposed method was evaluated using a photodiode array (PDA) detector on stressed samples.

During stress testing, degradation of Phenylephrine Hydrochloride was observed under acid and alkali conditions, while Chlorpheniramine Malate degradation occurred under alkali conditions. Peak purity was confirmed for Paracetamol (PCM) and Phenylephrine Hydrochloride (PPH) and Chlorpheniramine Maleate (CPM) under each degradation condition. The assay of stressed samples was calculated relative to a qualified reference standard, and the mass balance approached 99.1%, accounting for assay percentage, the sum of all compounds, and the sum of all degradants, respectively.

Accuracy

The accuracy of the assay method was evaluated through standard addition and recovery experiments using real samples. This assessment was conducted in triplicate, employing three concentration levels spanning from 50% to 150% of the target concentration for Paracetamol (PCM), Phenylephrine Hydrochloride (PPH), and Chlorpheniramine Maleate (CPM).

Linearity

To assess linearity, solutions were prepared by diluting pure stock solutions of the drug substances to specified concentrations. Five concentration levels ranging from 50% to 150% of the specification level were prepared for PCM (31 ppm to 96 ppm), CPM (5 ppm to 15 ppm), and PPH (25 ppm to 85 ppm). The correlation coefficient obtained exceeded 0.999. Correlation coefficient of PCM, CPM and PPH found 0.9996, 1.0000and 0.9998 respctivly. Peak area data versus concentration was analyzed using least-squares linear regression, demonstrating a robust linear relationship between peak area and the concentrations of PCM, CPM, and PPH, respectively. Refer fig 5-7

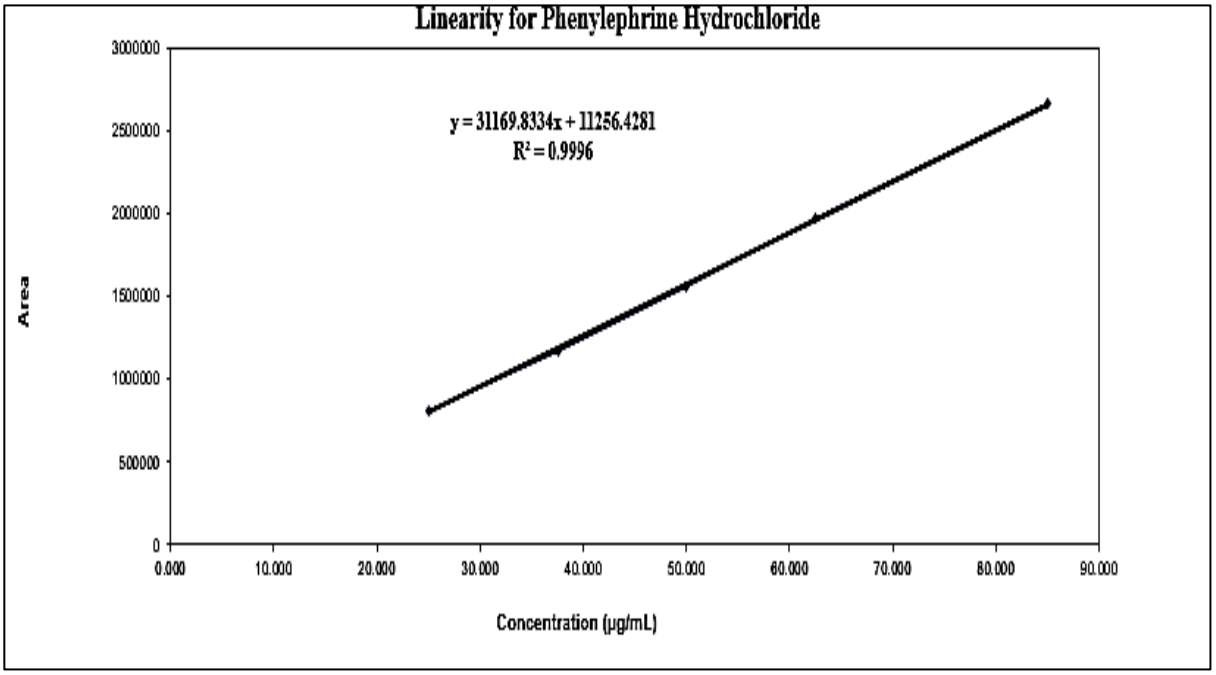


Figure. 5 Linearity for Phenylephrine Hydrochloride

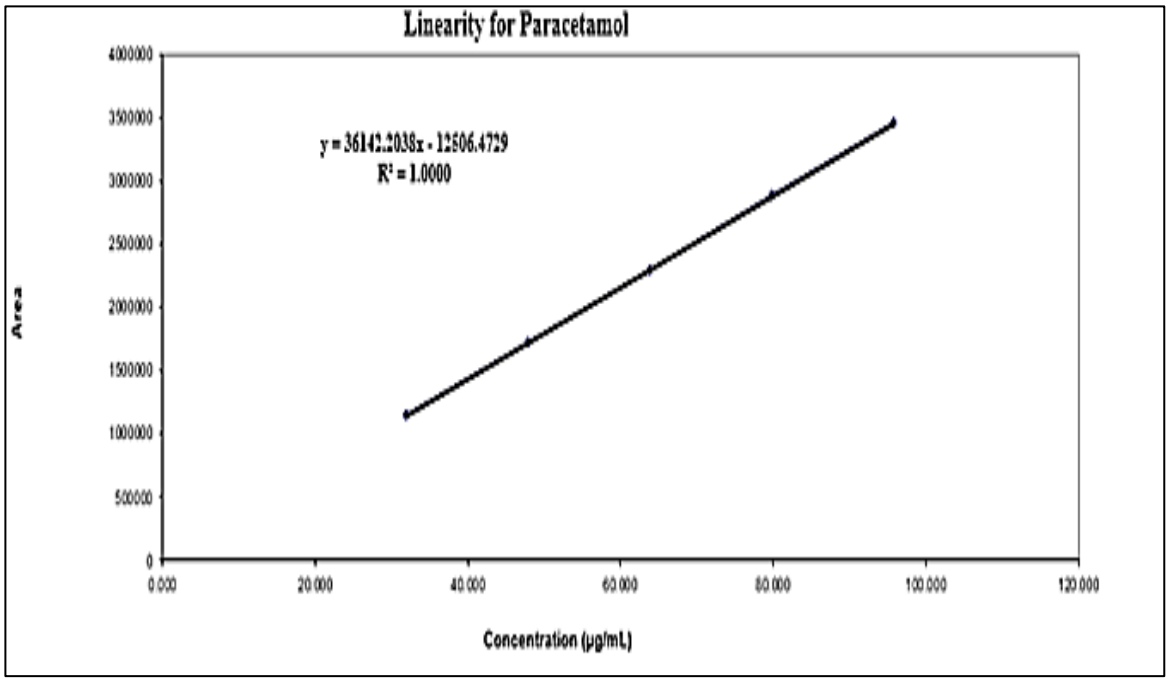
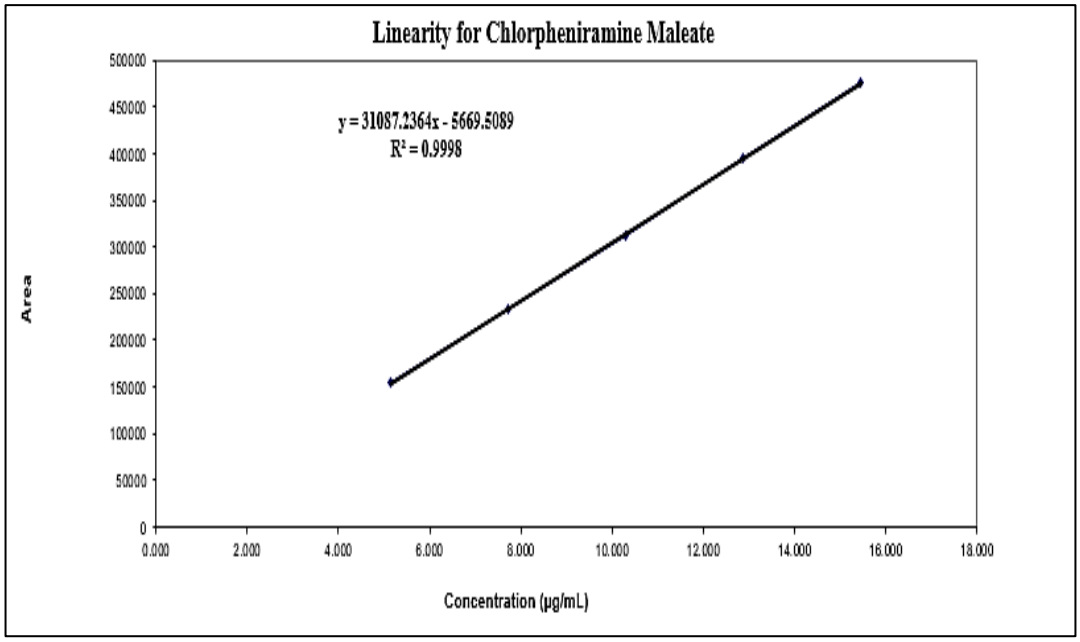


Figure. 6 Linearity for Paracetamol

Figure. 7 Linearity for Chlorpheniramine Maleate



Solution stability and mobile phase stability. The stability of PCM CPM and PPH sample solution & standard solution at room temperature for 72 h and measuring the % Recovery and absolute difference at every 12 h interval. The stability of mobile phase was also determined by analysing visual observation for turbidity.

Robustness

In all the deliberative varied chromatographic conditions (flow rate, column temperature and pH of mobile phase A), all analytes were adequately resolved and elution order as per method precision. %RSD for each test concentration was calculated and observed that the comparative results with method precision are less than 2.0% RSD.

Method Validation for EG DEG content

Precision and intermediate precision

Precision of the method verified by repeatability and checked by % RSD of Ethylene Glycol and Diethylene Glycol content results of six spiked test solutions n=6. The intermediate precision of the method was also evaluated. %RSD for each test concentration was calculated and observed that the results are more than 20.0% RSD. Ethylene Glycol 0.096 with 3.13%RSD and Diethylene Glycol 0.099 with 5.05% RSD. In intermediate precision found that the %RSD of 12 sample (Six of method precision and 6 of intermediate precision Ethylene Glycol 0.109 with 11.93%RSD and Diethylene Glycol 0.112 with 12.50% RSD002E.

Specificity is the ability to assess unequivocally the analyte products and matrix components. The peak due to *Analytes are well resolved from each other and any other peaks.

Accuracy

Standard addition and recovery experiments were conducted on real sample to determine accuracy of the EG-DEG method. The study was carried out in triplicate using four concentration levels from LOQ to 150% of test concentration for Ethylene Glycol and Propylene Glycol. Obtained results are very accurate at LOQ, 50%, 100% and 150% level for both Ethylene Glycol and Diethylene Glycol. For Ethylene Glycol LOQ level LOQ level 102.67% Recovery with 4.50 % RSD, 50% level 100.00 with 7.07 %RSD, 100% level 102.31% with 4.77 %RSD and 150% level 106.58 with 0.62 %RSD observed. For Diethylene glycol 89.33% Recovery with 6.84 % RSD, 50% level 94.00 with 2.13 %RSD, 100% level 96.00% with 1.80 %RSD and 150% level 94.70 with 2.10 %RSD observed.

Linearity test solutions were prepared by diluting the pure stock solutions of the drug substance to the required concentrations. The solutions were prepared at five concentration levels from LOQ to 150% of the specification level. (For EG and DEG LOQ is 25%). The peak area versus concentration data treated by least-squares linear regression analysis. The results show that good correlation between the EG and DEG. See figure 8,9.

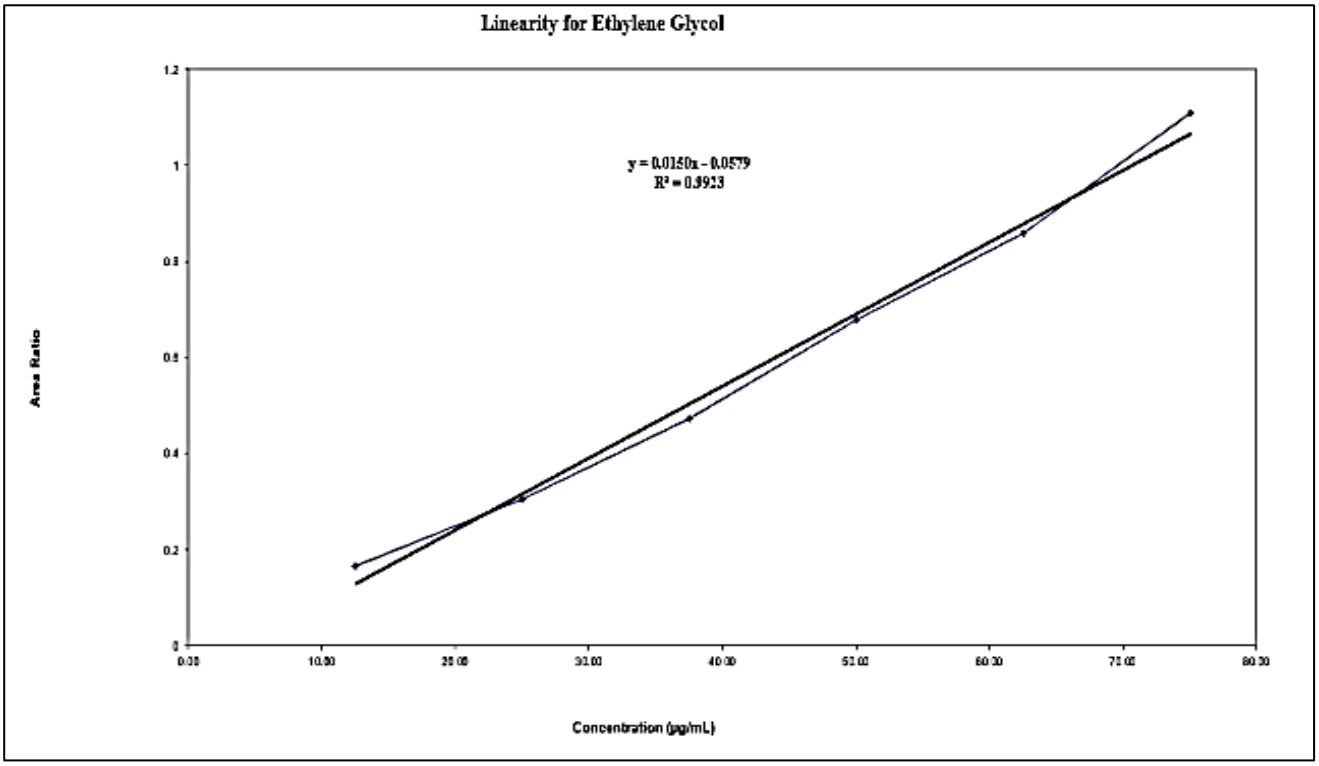


Figure . 8 Linearity for Ethylene Glycol

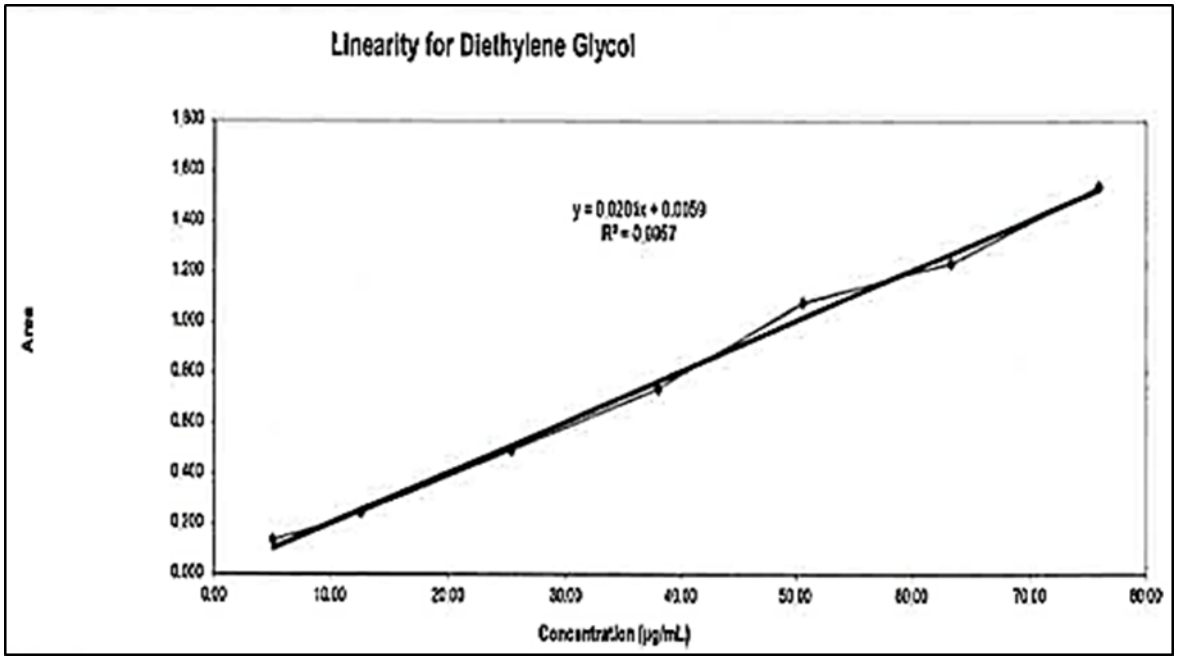


Figure.9 Linearity for Diethylene Glycol

Robustness In all the deliberative varied chromatographic conditions (flow rate, column temperature and change in column), all analyses were adequately resolved and elution order as per method precision.

Solution Stability % RSD of response of the standard solution injections from initial to 48 hours is within the acceptance criteria; hence standard solution is stable up to 48 hours at room temperature. From the above observation it is concluded that %RSD of results of Ethylene Glycol and Diethylene Glycol content are within acceptance criteria up to 48 hours, hence the test solution is stable up to 48 hours at room temperature.

Table 6 : Solution stability of Ethylene Glycol and Diethylene Glycol

Time (Hours.)	% of Ethylene Glycol	% of Diethylene Glycol
Initial	0.095	0.107
24Hrs.	0.094	0.096

48Hrs.	0.111	0.105
Mean	0.100	0.103
Standard deviation	0.0100	0.0060
% RSD	**10.00**	**5.83**

CONCLUSION

In conclusion, the present study successfully developed a sugar-free syrup formulation containing a fixed-dose combination of Paracetamol (PCM), Chlorpheniramine Maleate (CPM), and Phenylephrine Hydrochloride (PPH), tailored for pediatric use. The formulation was guided by Quality by Design (QbD) principles, aligning with the ICH guidelines Q8(R2), Q9, Q10, and Q11, which provided a comprehensive framework for development. Extensive preformulation studies confirmed the compatibility of all active compounds with the selected excipients. A robust analytical method was established for quantifying Ethylene Glycol (EG) and Diethylene Glycol (DEG) content, demonstrating precision, accuracy, and specificity. The method's precision and intermediate precision were validated through %RSD calculations, while specificity, accuracy, linearity, and robustness were thoroughly assessed. Additionally, a precise and accurate RP-HPLC method was developed for real-time estimation of PCM, PPH, and CPM, utilizing a Design of Experiments (DoE) approach to define Critical Method Attributes (CMAs). Stability studies confirmed that the product remains stable for up to six months with linear stability, ensuring its viability for clinical use. Overall, the study not only highlights the successful implementation of QbD principles but also provides a reliable analytical framework of successfully developed analytical RP-HPLC method by applying QbD approach.

Abbreviations

Fixed dose combination (FDC) of Paracetamol (PAR), Phenylephrine Hydrochloride (PPH) , Chlorpheniramine Maleate (CPM) , Design of Experiment (DoE).

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None

Conflict of interest

The authors have no Conflict of interest on this article

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