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QUALITY BY DESIGN BASED DEVELOPMENT OF LUMATEPERONE TRANSDERMAL PATCH

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ABSTRACT

Objective: The current study is oriented on the design and development of a Transdermal Patch for Lumateperone, a BCS Class I drug, utilizing the Quality by Design (QbD) principle. **Methodology:** The study was aimed to demonstrate the QbD approach's feasibility and effectiveness by integrating the product and determining the targeted sustain release profile. The Quality Target Product Profile was defined, CQAs were identified, and risk assessments was carried out by using various tools such as Ishikawa diagram, risk estimation matrix and Failure modes and effects analysis. Each factor's Risk Priority Number was determined separately. Main effect screening design was used, with independent variables Eudragit RL-100/RS-100 and Tween 80 as material attributes that influence responses such as thickness, folding endurance and drug content. The optimized formulation was checked for the in vitro skin permeability and skin irritation test. **Results:** The results of the main effect screening design of 12 formulations revealed that the combined action of all variables had a substantial impact on CQAs and could predict the optimal formulation with maximum global desirability of 0.6231. Statistically significant models were observed for thickness(mm) (R2=0.98), folding endurance (R2=0.87), and drug content (%) (R2=0.98).

The optimized formulation confirms with good permeability characteristics and stability. **Conclusion:** Lumateperone transdermal patch was successfully formulated using Quality by Design. The study's optimal formulation outcomes were evident, as they confirmed the usefulness for addressing the issues associated with the oral route and enabling patient compliance for Antipsychotic treatment.

Keywords: Risk Priority Number; Transdermal Patch; Lumateperone; Quality by Design; Main Effect Screening Design

INTRODUCTION

Schizophrenia affects 1% of the global population and can be caused by both hereditary and environmental factors **[1]**. Individuals with delayed cortical migration in the perinatal period are at higher risk for developing schizophrenia **[2]**. It is characterized by adolescent growth. Positive symptoms in young adulthood include hallucinations, delusions, disorganized speech, and catatonic behaviour, while negative symptoms include affective blunting, alogia, apathy, anhedonia, asociality, and inattention. Many people with schizophrenia continue to struggle with self-care, despite available medications **[3-4]**.

The World Health Organization appraisal that schizophrenia affects around 24 million population globally. The condition is curable, with earlier intervention being more beneficial. More than half of people with schizophrenia do not receive adequate care. 90% of untreated schizophrenia cases occur in underdeveloped nations **[5]**.

Antipsychotic drugs are widely used to treat schizophrenia and other psychiatric disorders, including bipolar disorder. However, their effectiveness can be hindered by adverse effects, which vary depending on patient characteristics and the drug being employed **[6]**.

Lumateperone is an alkyl phenyl ketone anti-psychotic drug utilized by adults for managing schizophrenia. It is also prescribed either as a monotherapy or in conjunction with lithium or valproate for the treatment of depression linked to bipolar disorder (manic depression). It is an FDA-approved BCS Class-I anti-psychotic drug that is slightly soluble in water. Soluble with Organic solvents like, ethanol, Dimethyl sulfoxide (DMSO), and dimethyl formamide and sparingly soluble in aqueous buffer. It has a lipophilic nature at a pH of 7.4 and exhibits high permeability across the gut and the blood-brain barrier, attributed to its MDR1 (marked multidrug resistance protein 1) permeability characteristics. There is a requirement for an efficacious topical formulation that should be safe and patient friendly **[7]**.

Transdermal administration of drugs has numerous benefits over oral delivery, that includes improved patient adherence, sustained plasma drug levels, bypassing hepatic metabolism, and lower intra-patient variability **[8]**. The oral route is not suited for drugs that undergo considerable first-pass metabolism, ensuing in low bioavailability. In the parenteral method, patients might refuse treatment due to invasiveness, and sterility can increase costs. Caregivers and doctors have hurdles while treating people with schizophrenia. To solve these disadvantages, a transdermal patch was created to improve bioavailability and prolong drug administration, resulting in lower dose frequency. Topical drug distribution makes it easier for caregivers to distribute drugs than other methods **[9]**.

All regulatory authorities for pharmaceutical products place a priority on quality. Customer satisfaction in terms of service, product, and procedure is what quality entails **[10]**. A more comprehensive approach given by quality by design (QbD) should be used to ensure product quality. Pharmaceutical QbD is a systematic approach to development that starts with established goals and emphasizes product and process understanding and control that utilizes strong research and quality risk management **[11]**. In pharmaceutical development, the QbD concept has evolved as a systematic method for the development that provides several benefits, including high-quality drug products with operational flexibility within optimized choices of critical factors, regulatory flexibility in drug product application approvals, and post-approval change management **[12]**. In the current study the QbD principles were used throughout the development of Lumateperone transdermal patch.

MATERIALS AND METHODS

Materials

Lumateperone received as a sample gift from Dr. Reddy's Laboratories, India. Eudragit RL 100 and Eudragit RS 100 (Ultra-Pure LAB CHEM Industries LLP), Tween 80 (SD Fine Chem PVT. LTD.), Ethanol (CDH Fine Chem Limited, Bengaluru), Potassium dihydrogen phosphate (Central Drug House (P) Ltd), and Sodium hydroxide flakes (Central Drug House (P) Ltd) were also included.

Methods

Quality Target Product Profile (QTPP)

The FDA outlines QTPP as product quality features that ensure safety and effectiveness. QTPP should only provide patient and performance related information **(Table 1)**. The QTPP should solely encompass information on product performance that is relevant to the patient **[13]**.

Table 1: QTPP of TP

QTPP elements	Target	Justification
Dosage type	Sustained release Transdermal patch	Increase skin permeability and improve bioavailability.
Dosage form	Transdermal patch	Ease of administration
pH	5-8	Ideally, the formulation's pH should be adjusted to match the skin's physiological pH. This change might affect both skin irritation and formulation retention on the skin.
Route of administration	Topical	Patient compliance
Dosage strength	1.8 mg	A unit dose of Lumateperone is included to demonstrate therapeutic efficacy.
Stability	At least 12 months shelf life at room temperature	To assess the degradation pattern of the drug and excipients in the formulation.
Container closure system	Triple laminated Aluminium child resistant sack	Appropriate container closure method to achieve the appropriate shelf life while retaining Transdermal patch integrity during shipment.
Skin condition	Low Skin irritation	Drugs and adhesives applied to the skin should cause no or minimal irritation while yet providing therapeutic benefit.

Critical Quality Assessment (CQA)

A CQA is outlined as "a physical, chemical, biological, or microbiological attribute which must be within an acceptable limit, range, or distribution to guarantee the product quality" **[14]**. Changes in formulation or process factors could impact CQAs, which are subsets of QTPP. Critical material attributes (CMAs) are also known as crucial elements since they directly affect the CQAs. CMAs are described as a feature of an input material that includes physical, chemical, biological, or microbiological elements which must be inside predefined limits to assure the required quality of the beneficial materials being produced **[15]**. Critical process parameters (CPPs) are associated with the specific procedures used to produce a drug product and have a direct impact on CQAs. CPPs are also important factors that may affect process efficiency and product quality discrepancies **[16]**. The CQAs of TP are provided in **Table 2**.

Table 2: CQAs of TP

Quality attributes of drug product	Target	Is this CQAs?	Justification
Appearance	colour and shape	No	The fabrication of the product into a patch does not directly relate to its efficacy and safety.
Odour	Odourless	No	Odor does not impact safety and effectiveness directly, but it can influence a patient's acceptance.
Drug content	100%	Yes	It is a vital parameter for the design of a dosage form and is considered critical.
Weight uniformity	130-140 mg	Yes	Variations in weight uniformity can affect safety and effectiveness.
Moisture content	< 6%	Yes	Water content can affect product deterioration and microbiological growth, impacting the safety and stability of the product.
Thickness (mm)	0.13-0.45mm	Yes	The thickness of the film influences drug release.
Folding Endurance	150-275	Yes	A lower value indicates a reduction in the film's brittleness.
% Drug release	≥ 85%	Yes	To achieve prolonged drug release.

Quality Risk Management (QRM)

The FDA signifies QRM as a systematic method for evaluating, communicating, reviewing, and regulating risks associated with the quality of a drug product across its entire life cycle. The goal of QRM is to identify risks associated with a process or event, assess their significance, and take appropriate steps to mitigate such risks if they are deemed unacceptable **[17]**.

In order to establish the QbD technique for assessing risk in the transdermal patch of lumateperone, we evaluated CMA and CPP, which have an influence on CQA by the application of Risk estimation tools. The Ishikawa diagram was created using JMP® software to identify probable causes and contributing elements that impact the product's CQAs **(Figure 1) [18]**. The FMEA tool was used effectively to calculate RPN (Risk Priority Number). To select high-risk components, a Risk Estimation Matrix (REM) table was constructed **(Table 3, 4 and 5)** to identify and express the relation between CQA vs QTPP and CQA vs CPP. This matrix demonstrates the potential hazards associated with material and process factors which may have a substantial influence on the product's CQAs. Each aspect's risk level was classified as low (1), medium (3), or high (9). The RPN calculated for each factor signifies the level variance and its effect on output uniformity.

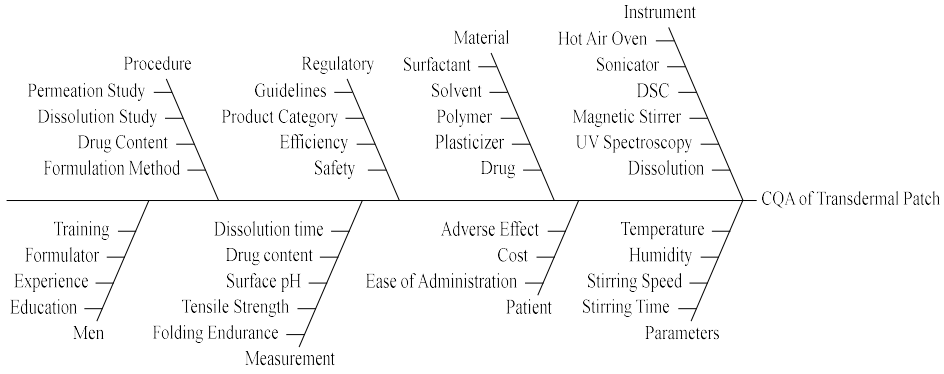

Figure 1: Fishbone diagram

Table 3: CQA vs. QTPP Table of REM

CQA	Dosage type	Dosage form	pH	Route of administration	Dosage strength	Stability	Container closure system
Thickness	9	9	1	9	1	3	1
Appearance	1	1	1	1	1	1	3
Odour	1	1	1	1	1	1	3
Drug content	3	3	3	9	9	9	1
Uniformity of weight	3	9	1	3	9	3	1
Moisture content	9	9	3	3	3	3	3
Folding Endurance	3	9	1	9	1	9	1
% drug release	9	9	3	9	9	3	1

Table 4: CQA vs. CPP Table of REM

CQA	Drug [Mixing]	Polymer [Mixing]	Surfactant [Mixing]	Plasticizer [Mixing]	Solvent [Mixing]	Stirring Time [Mixing]	Stirring Temperature [Mixing]	Stirring Speed [Mixing]
Thickness	1	9	9	9	9	3	3	3
Appearance	1	3	1	3	1	1	1	1
Odour	1	1	1	1	1	1	1	1
Drug content	9	9	3	1	9	9	1	3
Uniformity of weight	3	9	9	3	3	9	1	9
Moisture content	1	3	3	3	3	1	1	1
Folding Endurance	3	9	9	9	3	1	1	3
% drug release	9	9	9	9	3	3	1	9

Table 5: CPP Occurrence / Uncertainty Table of REM

CPP Grouped	Occurrence	Detection Uncertainty
Drug [Mixing]	3	3
Polymer [Mixing]	9	9
Surfactant [Mixing]	9	9
Plasticizer [Mixing]	9	9
Solvent [Mixing]	3	3
Stirring Time [Mixing]	1	1
Stirring Temperature [Mixing]	1	1
Stirring Speed [Mixing]	1	1

Design of Experiment - Main effects screening design (MESD)

Design of experiment (DoE) is comprehensive research that determines how the final formulation's performance is influenced by the combination of material and process factors. In the current study, the impact of multiple independent factors on dependent variables was investigated utilizing a MESD. The MESD is an experimental approach that aims to identify a few relevant factors from a large number of probable ones.

The trials were designed using the statistical program JMP 18.0.1 (Statistical Analysis program; SAS Institute Inc., North Carolina, USA).

Analysis of variance (ANOVA) was employed to assess the relation among the independent variables (factors) like Eudragit RS100 or Eudragit RL100 (%) (X1) and Tween 80 (%) (X2) and the dependent variables (responses) such as Percentage Drug Content (Y1), Folding endurance (Y2), and thickness (mm) (Y3). **Table 6 and 7** shows variables with their limits in MESD and Responses in the MESD respectively.

Table 8 shows DoE runs with defined dependent variables, as well as the additional components necessary to create the TP. Every formulation batch received an arbitrary set of tests. Each formulation was created in line with the 12 trial runs that were given.

A main effects screening strategy is an experimental approach that aims to identify a few relevant factors from a large number of probable ones.

Table 6: Variables and their limits in MESD

Variables	Limits					
Polymer	Eudragit RL 100 5%	Eudragit RL 100 7%	Eudragit RL 100 10%	Eudragit RS 100 5%	Eudragit RS 100 7%	Eudragit RS 100 10%
Tween 80	3%		5%		7%	

Table 7: Responses in the MESD

Responses	Goal	Lower limit	Upper limit
% Drug content	Maximize	95	100
Folding Endurance	Target	150	275
Thickness in mm	Target	0.11	0.45

Development of TP- Lumateperone

The transdermal patches were made using the solvent casting evaporation process. The various polymer ratios were mixed in to a 15 ml of ethanol. The polymeric dispersal was agitated by a magnetic stirrer for approximately 10 min to produce an opaque solution. Specified quantity of Tween 80 added to the aforesaid solution. 1.8 mg of drug was added and mixed using a magnetic stirrer until a homogenous solution was formed, which was then transferred to a petri plate and placed an inverted funnel to regulate solvent evaporation and prevent patch cracking. It was set aside overnight. Dried TP were removed from the petri plate, sliced, and kept in the desiccator **[19-20]**.

Checking the Critical Quality Attributes

Determination of % Drug Content

The drug content of the patch was determined by dissolving a 2*2 cm^2 section of the patch in 50 ml of pH 7.4 phosphate buffer. The resultant solution was then filtered and analysed using UV-visible spectroscopy at a wavelength of 223 nm. This process was repeated three times to estimate the average drug content **[21]**.

Determination of Folding Endurance

A 2*2 cm^2 (4 cm^2) patch was uniformly cut and repeatedly folded at the identical point until it broke. The number of folds the patch withstood without splitting determines the folding endurance value. This test was conducted three times to calculate the average and standard deviation, which were then recorded **[22]**.

Thickness (mm)

The thickness of each TP was gauged using a screw gauge at five distinct positions on the patch, and the average thickness was calculated. This process was repeated three times to note the average and standard deviation **[23]**.

Model fit

The responses from all 12 formulations of lumateperone TP were integrated into the design to assess model fit. Data was statistically assessed by applying a multiple regression model with the zero intercept. Statistically significant models were identified for % drug content, folding endurance, and thickness (mm). Variables with p-values less than 0.05 were deemed statistically significant. The JMP software

facilitated the design, analysis, and generation of numerous 3-D and surface plots. The overview of effects for the entire model plus the prediction profiler for each response were used to optimize the design's independent variables. Using the generated and verified models, the design space was established across all individual acceptance criteria for each Critical Material Attribute (CMA). Following the prediction profiler, confirmatory trials were run for each response to validate the model.

Optimization by using prediction profiler and matching the predicted and experimental values

The prediction profiler created for the responses was used to optimize the design's independent variables. The design space was defined by evaluating the unique acceptability zones of each CMA after the models were built and validated. Confirmatory tests for individual responses were performed to verify the model, following the guidelines of the Prediction profiler.

Evaluation of optimised transdermal patch

The thickness, folding endurance and drug content of the optimized formulation was determined as per the procedure discussed in the section of checking the CQAs.

Surface pH

A pH meter was used to measure the TP surface pH. With the aid of water, the patch was slightly moist. By touching the electrode to the patch's surface, the pH was determined. The process was carried out three times, and the average and standard deviation were recorded **[24]**.

Weight variation

Weight variation was determined by weighing TP on a computerized balance. It was conducted on 5 TP, and an average weight was computed **[24]**.

Moisture content

A desiccator containing calcium chloride(fused) was utilized to determine moisture content. Patches for evaluation were weighed and placed in a desiccator for 24 hrs. After 24 hrs, the patches were reweighed and the moisture content of patches was estimated by deducting the final weight from their initial weight **[24]**.

$$\text{Percentage moisture content} = \frac{Initial\ weight - Final\ weight}{Final\ weight} * 100$$

Moisture uptake

The weighted patches were placed in desiccators containing saturated potassium chloride solution which helps to maintain 84% relative humidity for 24 hours at room temperature. The percentage of moisture absorption was identified by deducting the end weight from the initial weight **[25]**.

$$\text{Percentage moisture uptake} = \frac{Final\ weight - Initial\ weight}{Initial\ weight} * 100$$

***In vitro* drug release study**

The release study was carried out by using Franz diffusion cell with a 50 ml receptor compartment and a 5 ml donor compartment. The orifice has a 4mm

diameter. The TP was placed on a membrane that is semipermeable and coupled to a diffusion unit. The receptor cavity was filled with a pH 7.4 phosphate buffer solution and kept at 37 ± 1 °C. The mixture was continually stirred. To maintain sink conditions, samples (1 ml) were removed from the medium at specified intervals and replenished with the equivalent volume of new phosphate buffer solution. The samples were assessed spectrophotometrically at 223 nm, and the drug release percentage was computed **[26]**.

***Ex vivo* skin permeation study**

The abdomen skin of rats was positioned between two compartments of diffusion cell: donor and receptor. The receptor compartment having 50 mL capacity was filled with 7.4 pH phosphate buffer. The TP was affixed to the skin. This setup was installed on a stirrer. A magnetic stirrer was used to agitate the Phosphate buffer solution in the receptor compartment at a temperature of 32 ± 0.5 ºC. Drug content was measured using a spectrophotometer after samples were collected at various time periods. After each sample removal, an equivalent amount of buffer solution was reintroduced. A graph was created to visualize the cumulative amount of drug penetrated over time **[27]**.

Steady state flux (µg/cm²/hr)

The steady state flux (Jss) is the rate of drug diffusion over a permeable membrane. After attaining the steady state of drug penetration, the flux was estimated using the following equation **[28]**.

$$\textbf{Jss}= \frac{\textit{Amount of drug permeated}}{\textit{Unit area}} * \textit{time}$$

Permeability coefficient (cm/hr)

The permeability coefficient (Kp) was determined by following equation **[28]**.

$$\textbf{Kp}= \frac{\textit{Jss}}{\textit{Total donar concentration of formulation}}$$

Stability studies

Stability studies for optimized formulation were conducted in compliance with the International Conference on Harmonization (ICH) criteria. The formulation underwent stability testing in aluminum foil at room temperature for three months. Samples were taken periodically (15 days, 1 month, and 3 months) and analysed for any changes in the folding endurance and drug content. These tests were performed on three different batches of optimized formulation **[29]**.

Scanning electron microscopy

The samples were examined using a Scanning Electron Microscope (SEM). Prior to analysis, the samples were coated using the sputtering process at 7 amps for 300 seconds. The goal of this study was to examine the surface characteristics of the ideal patch **[30]**.

RESULTS AND DISCUSSION

Results obtained from the QbD tools

The QbD method was utilized to explore the QTPP and CQAs of the proposed product.

The Figure 2 provide the heatmap for CQA vs CPP (process steps) where it helps to understand the sum of RPN with in CQA/CPP combination. Due to the efficiency of the preparation process, material qualities like polymer (RPN-729), surfactant (RPN-729), and plasticizer (RPN-729) significantly impact the outcomes like drug release, drug content, folding endurance and thickness more than process attributes. In the production of the TP, process attributes such as stirring speed (RPN-1), stirring temperature (RPN-1), and stirring time (RPN-1) were assigned lower priority in this study due to their negligible effect on product variability. The RPN score obtained for all the selected CQAs and process attributes (CMA and CPP) associated with the development of transdermal patch were represented in the **Figure 3 and 4**.

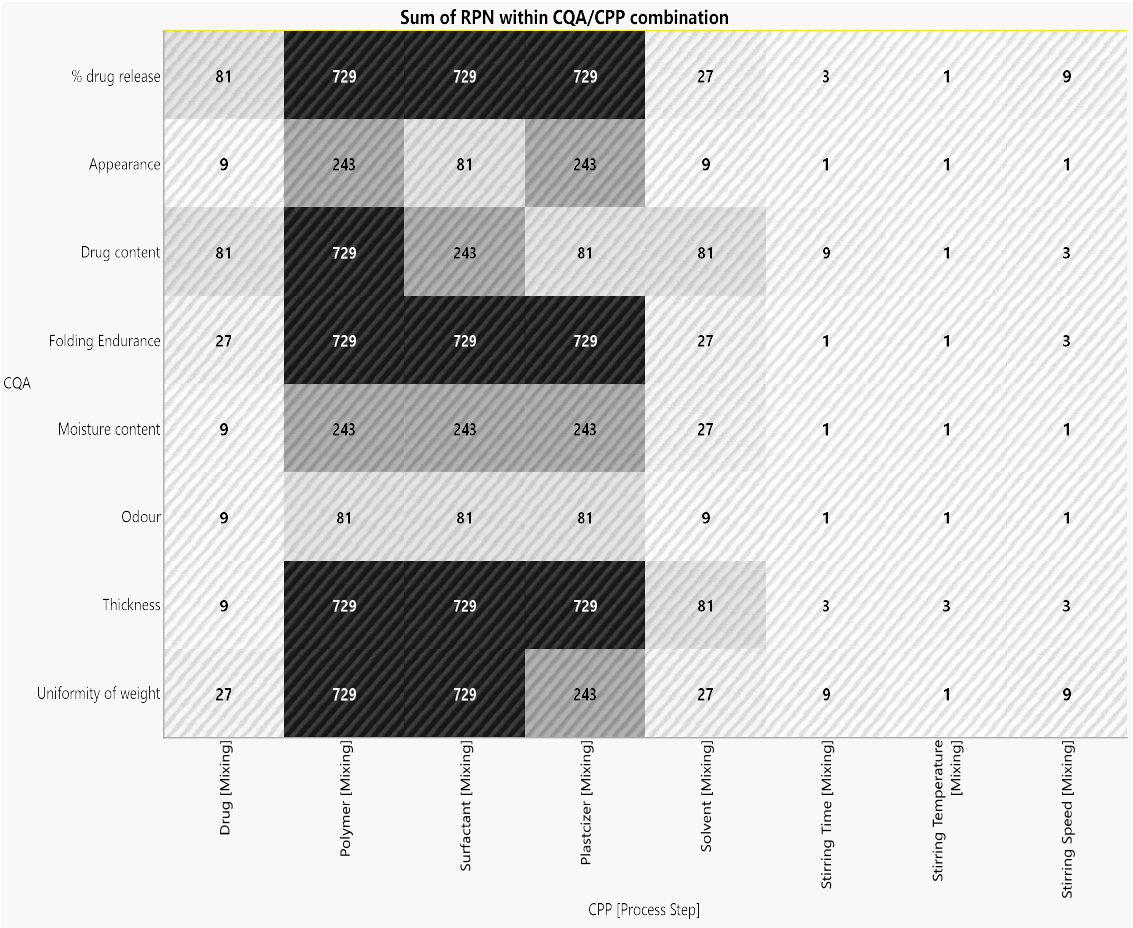

Figure 2: CQA vs. CPP heatmap

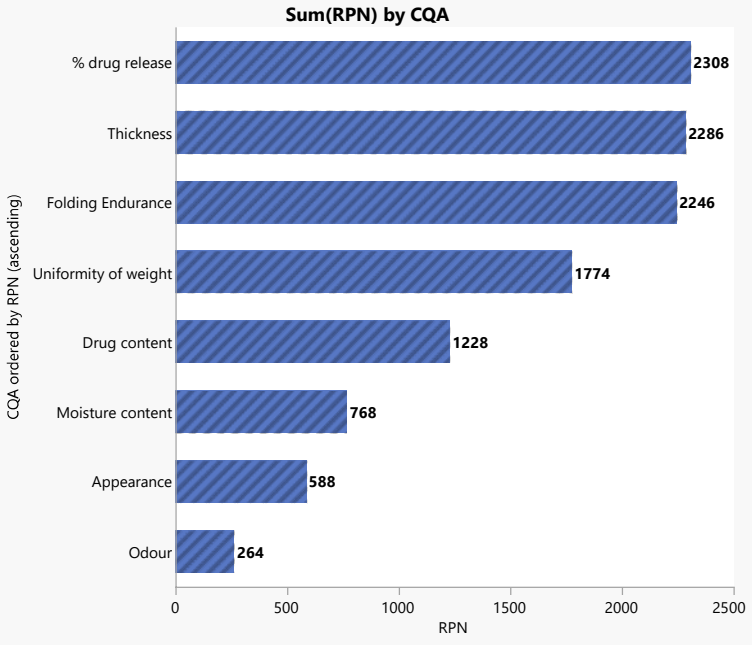

Figure 3: Pareto chart of CQA

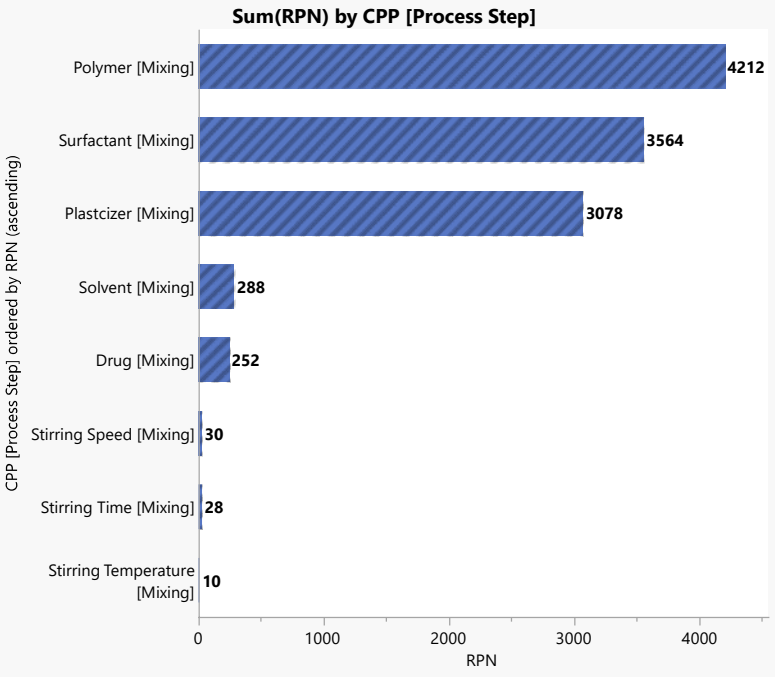

Figure 4: Pareto chart of CPP overall

The factors that significantly impact the quality of film formulations as evidenced by the risk assessment are given utmost consideration. Consequently, the identified CQAs for Lumateperone test product include folding endurance, thickness, and percentage of drug content. A screening design was implemented to investigate the effect of each independent variable on individual responses.

Table 8: Composition of Lumateperone Transdermal patch and Evaluation report of CQA's for all 12 formulations

Formulation	Polymer (%)	Tween 80 (%)	Solvent	Drug content (%)	Thickness (mm)	Folding endurance
F1	Eudragit RL 100 - 10	5	Ethanol	94.5 ± 0.264	0.12 ± 0.36	172 ± 2
F2	Eudragit RL 100 - 5	5		101.5 ± 0.35	0.103 ± 0.0005	110 ± 5.567
F3	Eudragit RL 100 - 7	7		105.2 ± 0.1	0.1 ± 0.017	109 ± 3.605
F4	Eudragit RS 100 - 7	5		98 ± 0.312	0.116 ± 0.007	173.6 ± 3.511
F5	Eudragit RS 100 - 5	7		101 ± 0.624	0.103 ± 0.002	165.3 ± 3.511
F6	Eudragit RL 100 - 7	5		102.1 ± 0.264	0.103 ± 0.001	165 ± 2.645
F7	Eudragit RS 100 - 5	3		86.4 ± 0.124	0.106 ± 0.001	193.3 ± 4.041
F8	Eudragit RS 100 - 10	7		65 ± 0.624	0.123 ± 0.002	175 ± 4.582
F9	Eudragit RS 100 - 10	3		60 ± 0.624	0.120 ± 0.001	282 ± 24.576
F10	Eudragit RS 100 - 7	3		84.5 ± 0.7	0.116 ± 0.0005	168 ± 4
F11	Eudragit RL 100 - 10	7		90.61 ± 0.925	0.121 ± 0.002	160 ± 3
F12	Eudragit RL 100 - 5	3		94.58 ± 2.658	0.105 ± 0.0005	156 ± 6.244

Model Fit

Statistical study of the characterisation data with regression models obtained significant models for drug content, folding durability, and thickness. **Figure 4** depicts the actual vs expected plot for the selected CQAs. The R-square value and p-value determined from all responses are used to assess model fit. The predictive models **(Figure 5, 6, and 7)**, % Drug Content (R^2=0.98 and p-0.003), Folding Endurance (R^2=0.87 and p-0.111), and Thickness (mm) (R^2=0.98 and p-0.003), were statistically significant, indicating goodness of fit.

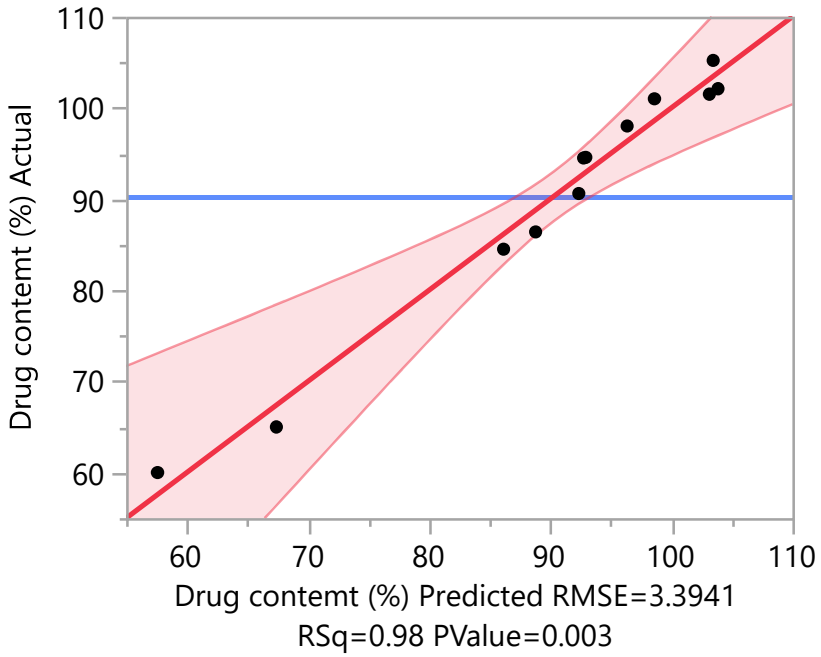

Figure 5: Leverage plots of Drug content

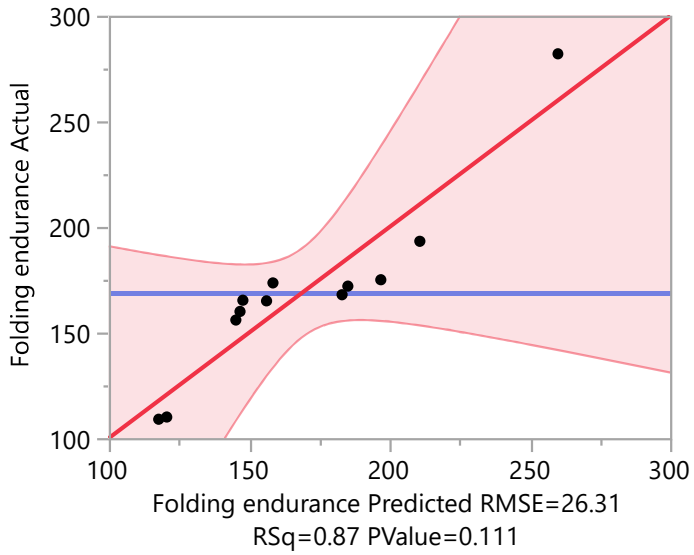

Figure 6: Leverage plots of Folding endurance

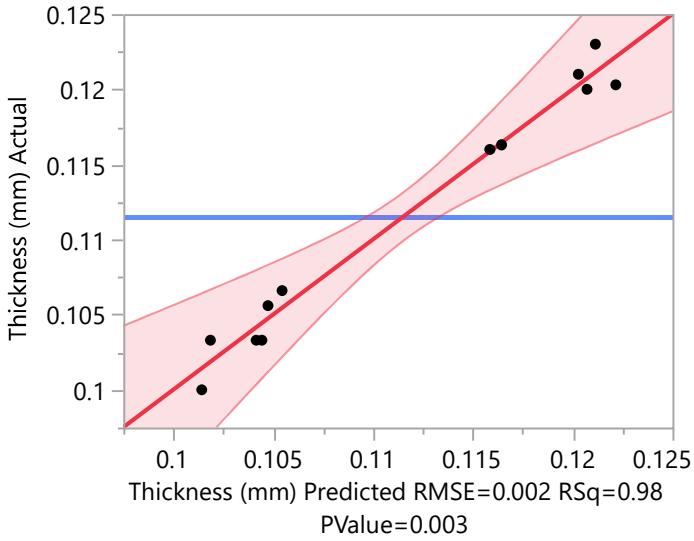

Figure 7: Leverage plots of Thickness

Statistical optimization of selected responses

The global desirability function of the prediction profiler was employed to optimize lumateperone TP simultaneously. The profiler illustrates a consistent relationship among various variables and responses, offering an extensive perspective on the variability among extreme values. **Figure 8** shows that the highest global desirability score of 0.6231 suggests a strong probability of meeting the target for all 3 responses. **Table 9** presents the percentage discrepancy between the experimental and predicted data, verifying the model's accuracy as it did not significantly differ.

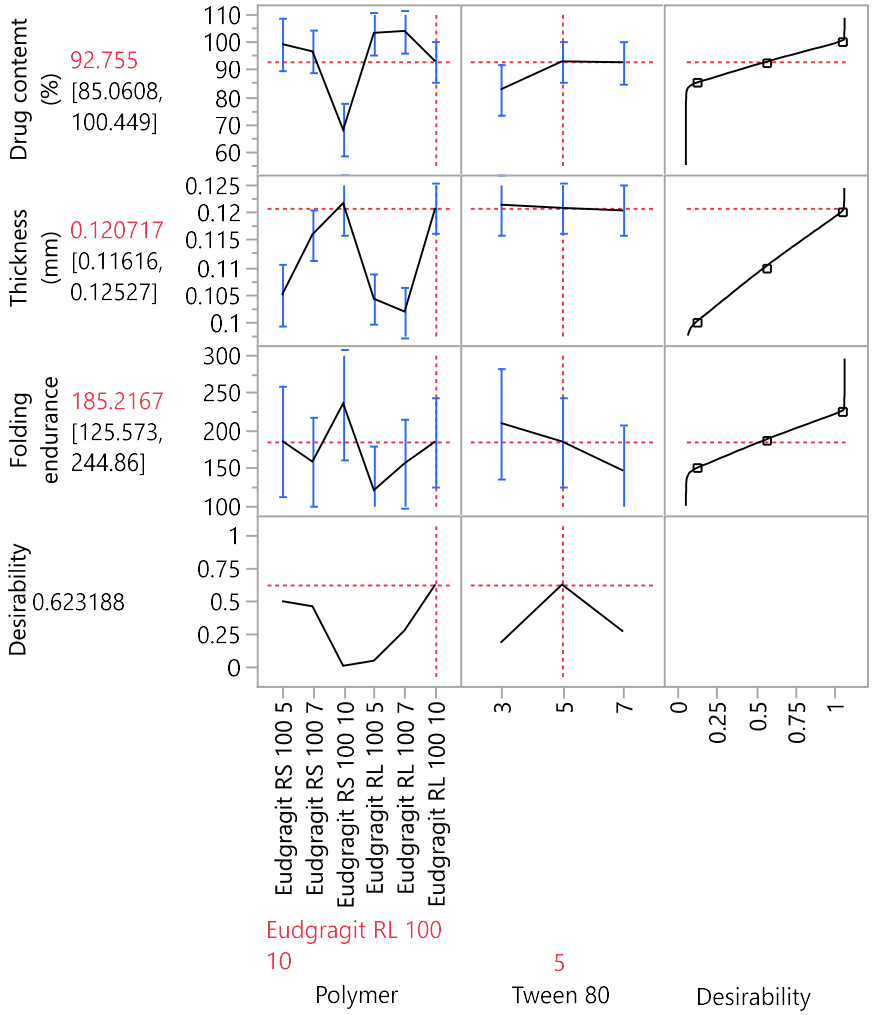

Figure 8: Prediction profiler for Optimized desirability

Table 9: Confirmatory experimental results as per the Prediction Profiler

Responses	Predicted value	Experimental value	Difference
% Drug content	92.755	91.167	1.712
Folding Endurance	185.216	173	6.599
Thickness in mm	0.120	0.116	3.333

Evaluation of optimal transdermal patches

Physical characterization of TP

The TP was found to be transparent, with excellent adhesive qualities and flexibility. The patch obtained was very thin, d an appealing appearance and was free of stains or dark spots.

Characterization of Optimized Formulation

Table 10 provides the summary of the results pertaining to pH, weight variation, percentage moisture content and uptake, drug content, folding endurance and thickness of the optimized formulations and confirms with tall the quality attributes.

Table 10: Results of Evaluation of TP

Optimized Formulation	Results
Surface pH	6.516 ±0.076
Weight Variation(mg)	± 2
% Moisture loss	8.856 ± 0.170
% Moisture content	4.622 ± 0.511
% Drug Content	91.167 ± 2.068
Folding Endurance	173 ± 6.557
Thickness (mm)	0.116 ± 0.00058

In-vitro drug release (%) of Transdermal Patch

The *in-vitro* drug release of the optimized Lumateperone TP shows 97.53% at 12 hours **(Figure 9)**. The diffusion mechanism in the *in-vitro* drug release contributed to a sustained and prolonged release of the drug.

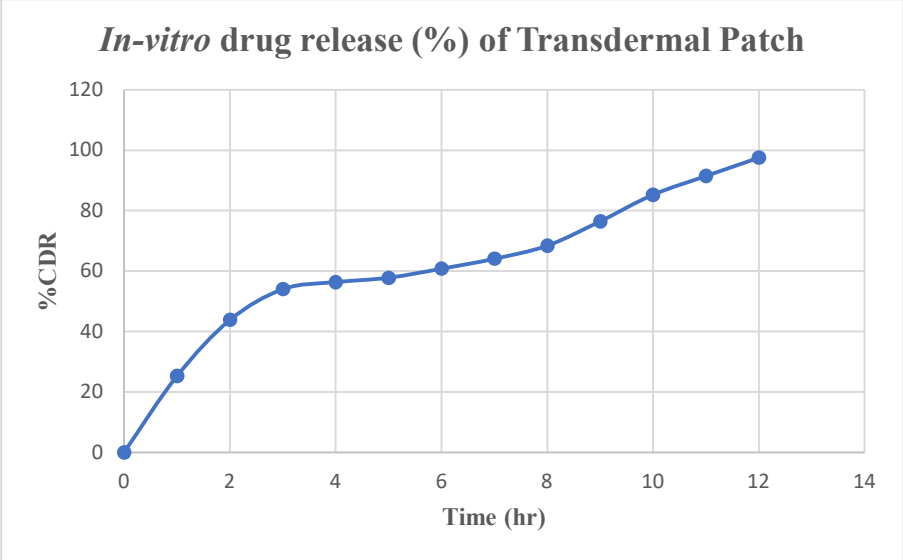

Figure 9: Plot of *In-vitro* drug release (%) of Transdermal Patch

Ex vivo Skin permeation (%) of Transdermal Patch

Optimized formulation was assessed by ex-vivo skin permeation studies to estimate the rate and amount of drug release over a period of 12-hour **(Figure 10)**. The impact of the stratum corneum on the skin's permeability was evaluated using rat abdominal skin with the help of Franz diffusion cell. The optimized Lumateperone TP obtained 96.934 % penetration at 12 hours. The Jss and Kp was found to be 5.816 and 2.908 respectively.

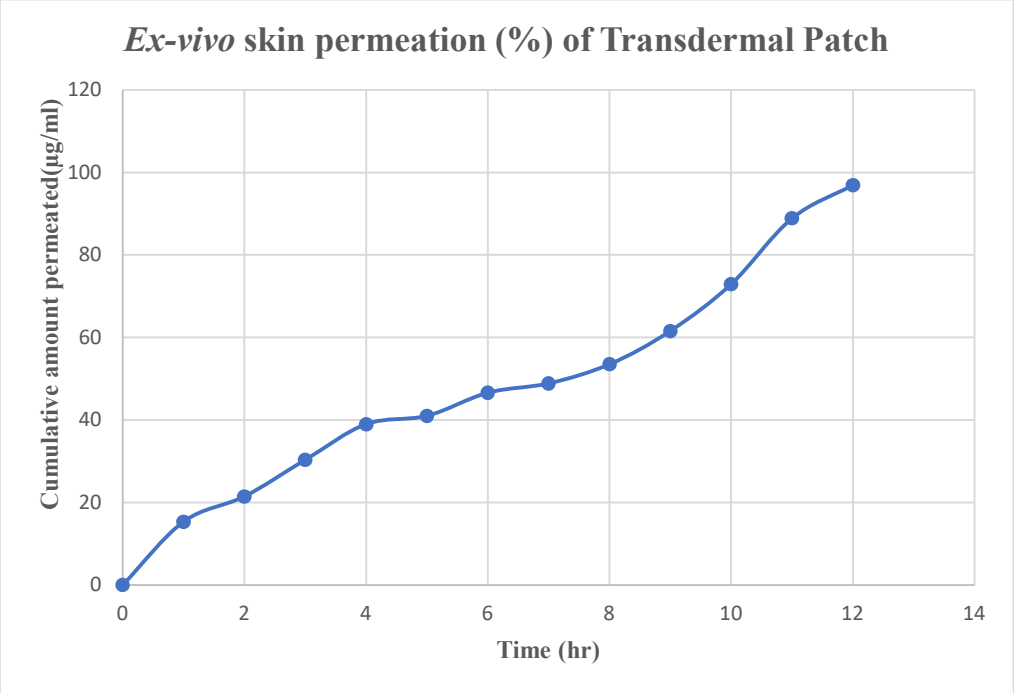

Figure 10: Plot of *Ex-vivo* Skin permeation (%) of Transdermal Patch

Stability studies

Stability studies were conducted over three months **(Table 11)**. The patch remained intact and not showed significant changes in drug content and folding endurance.

Table 11: Stability studies table

Time	% Drug content			Folding endurance		
	B1	B2	B3	B1	B2	B3
0 days	91.24 ± 0.563	92.365 ± 0.603	91.851 ± 0.815	175 ± 2.51	173 ± 3.21	178 ± 2.08
15 days	91.115 ± 0.573	90.25 ± 0.585	91.335 ± 0.583	172 ±1.52	170 ± 2.51	173 ± 0.57
1 month	90.891 ± 0.489	90.124 ± 0.507	89.982 ± 0.216	170 ± 1	168 ± 3.51	169 ± 1.52
3 months	89.568 ± 0.288	90.056 ± 0.385	89.546 ± 0.257	169 ± 2	165 ± 0.57	167 ± 1.52

Scanning electron microscopy

SEM is useful for observing surface morphology and evaluating the stability of formulations.

Micrographs of the optimized TP (refer to **Figure 11**) shows that the drug was evenly distributed, and no free drug was seen. The patch's physical look remained in good condition.

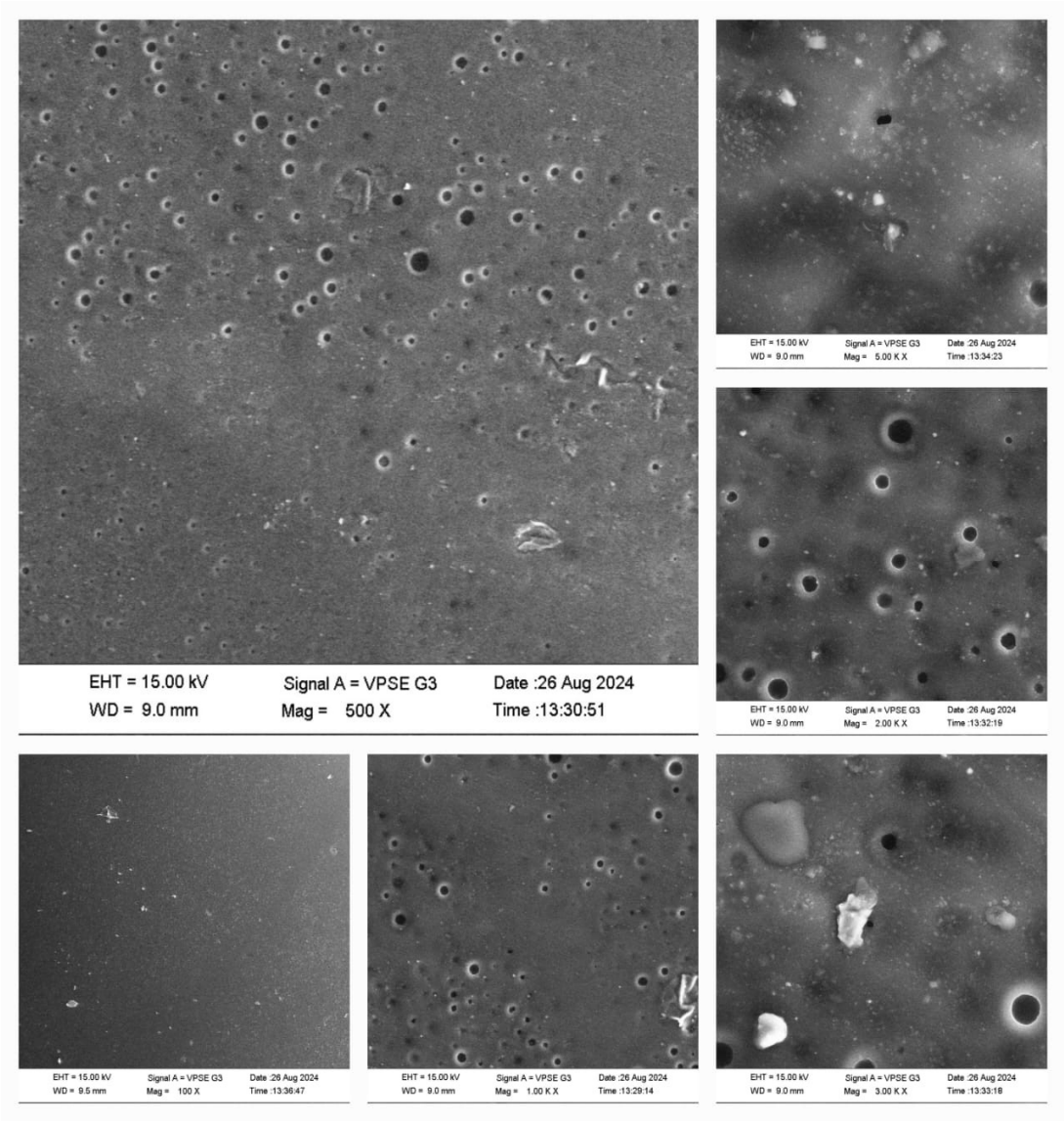

Figure 11: SEM of Optimised TP

CONCLUSION

The quality-by-design method was successfully applied to develop and optimize Lumateperone's Transdermal patch. JMP® software was used to build the experimental design trials using the appropriate experimental model. The formulation development in a quality by design framework ensured attainment of all the Critical Quality Attributes of the drug product. The fabricated transdermal patch facilitated the improved stability characteristics with enhanced permeability of hydrophilic drug lumateperone. The results demonstrate that Lumateperone's transdermal delivery technology has the potential to improve patient adherence, provide prolonged drug release, and increase bioavailability making it potential option for its administration.

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