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Quality-By-Design (QBD) Approach in Developing a Thermoresponsive In-Situ Nasal Gel Containing Nanosized Antiviral Agents

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Abstract

Design of patient acceptable and effective drug delivery systems is a major concern area in pharmaceutical research field especially when the aim is management of nasal and respiratory infections. This paper was an attempt to design and optimize a thermoresponsive in-situ nasal gel made with nanosized antiviral agent using Poloxamer 407, Poloxamer 188, and HPMC as variables of the formulation. To determine the impact of these variables on the gelation temperature, viscosity and drug release, a Box- Behnken design was used together with Response Surface Methodology (RSM). ANOVA showed the effect of three excipients to be significant ($p < 0.05$), and the R 2 values were over 0.95, which represents considerable stability of the model. Optimized formulation displayed gelling temperature in the physiological range, a favorable drug delivery (gel) viscosity tailored to administrable in nasal cavity through nasal spray, and sustained drug release which was supported by predictive modelling and in-vitro tests. The results indicate the possibility of increasing drug bioavailability and mucosal adhesion and developing a fast onset of therapeutic effects with this formulation, so it should be considered one of the candidates in clinical translation.

Key Words:

Thermoresponsive gel, in-situ nasal delivery, nanosized antiviral agents, Poloxamer 407, Poloxamer 188

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1. INTRODUCTION

Respiratory viral diseases are a cause of major concern in the world and they lead to high morbidity and mortality rates during seasonal outbreaks and pandemic. The drawback related to serum delivery methods of the conventional antiviral agents is that the antiviral agents have low bioavailability[1], give an immediate clearance effect and also have systemic side effects that diminish the therapeutic efficiacy. More recently, intranasal dosing has become an interesting

alternative to non-invasive delivery due to the ability to place the drug directly into the respiratory tract with potential high speed of onset[2]. Thermoresponsive in situ gels showed that the liquid to gel conversion at physiologic temperature conditions results in enhanced retention in the nasal cavity and drug release rate maximizing antiviral properties[3]. Drug stability, passage through mucosa and specific activity may also be enhanced by incorporating nanosized antiviral agents into such systems. As directed by Quality-by-Design (QbD) approach[4], the main purpose of the current study is the formulation, optimisation and testing of the nanosized thermoresponsive in-situ nasal gel with antiviral effect to assure the highest therapeutic effect and provide the safety and patient adherence.

1.1.Background information

Development and emergence of respiratory viral diseases that challenge the overall public health of the world like influenza, coronaviruses, as well as respiratory syncytial virus are significant threats with high transmission rate and with few treatment alternatives available[5]. Conventional oral or injectable antivirals are notorious with low bioavailability, first-pass metabolism and systemic side effects that have given rise to poor therapy responses. Intranasal delivery means that the drug has quick access to the respiratory system by passing through the systemic defenses and yields the drug instantaneously[6]. Pre-emerging thermoresponsive in-situ gels were described as a new method of improving mucosal retention and prolonging the delivery of drugs, with nanometric-sized antiviral agents showing better permeability[7], stability and antiviral efficacy. With the implementation of the Quality-by-Design (QbD) strategy, one will be able to optimize the formulation systematically, providing reproducibility, safety and efficacy of the advanced nasal delivery systems.

1.2.Statement of the problem

However, with the increased prevalence of respiratory viral infection and the drawbacks of the traditional antiviral delivery vehicle, a gap still exists in the development of effective targeted-efficiency intranasal drugs and delivery systems that can prolong drug release and increase the effects of antivirals[8]. Current nasal sprays or solutions may be lost to mucociliary action as soon as they are introduced into the nose hence less therapeutic effect. In addition, the clinical potential of numerous antiviral drugs is hampered by few solubilities, stability, and bioavailability issues[9]. This knowledge gap highlights the imperative need to formulate an in-situ nasal gel, development of which has been informed using a systematic Quality-by-Design (QbD) process, with a scientifically optimised thermoresponsive gel containing nanosized proprietary antiviral agents, to enhance local retention of drugs[10], increase patient adherence and maximise the cytoprotective activity on respiratory viral infections.

1.3.Objectives of the study

- To develop and optimize a thermoresponsive in-situ nasal gel formulation containing nanosized antiviral agents
- To evaluate the physicochemical properties and performance of the optimized formulations
- To apply statistical modeling and Response Surface Methodology (RSM)

- To assess the short-term stability of the optimized thermoresponsive nasal gel

2. METHODOLOGY

The purpose of the study was to systematically design and formulates an optimal in-situ thermoresponsive nasal gel that entails the use of nanosized antiviral agent via the Quality-by-Design (QbD) strategy. QbD approach was used to define and regulate the critical formulation and process parameters in order to obtain a robust, effective and safe product. The used methodology combined the experimental design, risk assessment and the statistical modeling to achieve reproducibility, stability and improved delivery of drugs in the form of nasal drop.

2.1. Description of Research Design

The sequential experimental plan was selected with the risk assessment tools (Ishikawa diagram, Failure Mode Effect Analysis) in addition to Design of Experiments (DoE) applied to optimize the formulations. The study proceeded along the procedure of QbD framework:

1. The Quality Target Product Profile (QTPP) Definition.
2. Determination of Critical Quality Attributes (CQAs) of the gel.
3. The process of identifying Critical Process Parameters (CPPs) and Critical Material Attributes (CMAs).
4. Depending experimental trials using a central composite design (CCD) to determine the impact of independent variable on the performance of the products.

2.2. Sample Details

Sample batches of thermoresponsive gels were prepared for experimental purposes. Three model nanosized antiviral agents were used in preliminary trials:

- Favipiravir nanosuspension
- Ribavirin nanocrystals
- Remdesivir-loaded lipid nanoparticles

Polymeric excipients such as Poloxamer 407, Poloxamer 188, and hydroxypropyl methylcellulose (HPMC) were used to induce thermoresponsive behavior. All chemicals and excipients were of analytical or pharmaceutical grade.

2.3. Instruments and Materials Used

The following instruments were used during the study:

- High-Pressure Homogenizer – for particle size reduction.
- Dynamic Light Scattering (DLS) Analyzer – for measuring particle size and polydispersity index.
- Brookfield Viscometer – for viscosity determination.
- Fourier-Transform Infrared (FTIR) Spectrometer – for compatibility studies.
- Differential Scanning Calorimetry (DSC) – for thermal analysis.
- UV-Visible Spectrophotometer – for drug content and in-vitro release analysis.

- Texture Analyzer – for gel strength measurement.

2.4. Procedure and Data Collection Methods

Step 1: Risk Assessment

The literature and expert input were used to identify potential formulation and process variables that would impact on the performance of the gels. Ishikawa mapping was done and the parameters with the potential risk were identified under the Short listing of parameters with risk using Failure Mode Effect Analysis (FMEA).

Step 2: Preparation of Nanosized Antiviral Agents

Each antiviral agent was processed using high-pressure homogenization to achieve nanosized particles (<200 nm). Particle size, PDI, and zeta potential were recorded.

Step 3: Gel Formulation Development

Cold method and dispersion of Poloxamer and HPMC in chilled water were prepared followed by addition of antiviral suspension nanosized antiviral.

Step 4: DoE-Based Optimization

Poloxamer 407 concentration, Poloxamer 188 concentration and HPMC concentration were utilized as the independent variables and thegelation temperature, viscosity, and drug release profile were the dependent responses in a Central Composite Design (CCD).

Step 5: Characterization of Optimized Gel

The optimized formulation was evaluated for:

- Gelation temperature and time
- Viscosity at different temperatures
- pH compatibility with nasal mucosa
- In-vitro drug release and permeation studies using Franz diffusion cells
- Stability studies under ICH guidelines

2.5.Data Analysis Techniques

Design-Expert software was used to analyze the results of the experiments. The relationship between independent and dependent variables was defined with the help of polynomial regretting models. Statistical significance was found in ANOVA, where $p< 0.05$ was indicated as significant. Optimal formulation conditions were sought after using Response Surface Methodology (RSM). The verification of stability data by similarity factor (f2) analysis with respect to release profiles was done with statistically comparison values.

3. RESULTS

The Quality-by-Design (QbD) scheme allowed the development of the thermoresponsive formulation and optimization of the antiviral agent loaded nanosized in-situ nasal gel. An in-depth knowledge of how formulation variables influence critical quality attributes was generated by the experimental trials that were based on the Central Composite Design (CCD). The results provided below reported the outcomes of formulation of nanosized antiviral preparation, development of gel formulation, optimization and the final characterization of the accepted formulation.

3.1. Risk Assessment Findings

The Ishikawa diagram and FMEA revealed Poloxamer 407 concentration, Poloxamer 188 concentration, HPMC concentration, and homogenization pressure were the high risk factors in the performance of the gel. The main parameters that were chosen as critical quality attributes (CQAs) in the process of optimization were gelation temperature, viscosity, and in-vitro drug release.

Table 1: Risk Priority Ranking from FMEA Analysis

Parameter	Risk Score	Criticality Status
Poloxamer 407 concentration	36	High
Poloxamer 188 concentration	32	High
HPMC concentration	28	High
Homogenization pressure	26	High
Mixing temperature	18	Medium
Cooling rate	15	Low

The Failure Mode and Effect Analysis (FMEA) revealed that product cannot withstand the high-risk factors like Poloxamer 407 concentration, Poloxamer 188 concentration, HPMC concentration, and homogenization pressure with a risk score greater than 25 showing they have a vital impact on the product performance. The parameters that fall into medium and low risk groups, i.e., mixing temperature and cooling rate, were taken into account but were deemed not to have significant effect on desired properties of the gel. The precedence facilitated the simplification of experimental design since optimizing of the variables was concentrated on the most influential ones.

3.2. Preparation of Nanosized Antiviral Agents

The obtainable particle sizes of all three antiviral agents were less than the target 200 nm and polydispersity indices were also low, which had a uniformly distributed particle size. The values of the zeta potentials showed sufficient colloidal stability.

Table 2: Particle Size and Stability Parameters of Nanosized Antivirals

Antiviral Agent	Particle Size (nm)	Polydispersity Index	Zeta Potential (mV)
Favipiravir nanosuspension	168	0.22	-28
Ribavirin nanocrystals	152	0.19	-25
Remdesivir lipid nanoparticles	178	0.21	-27

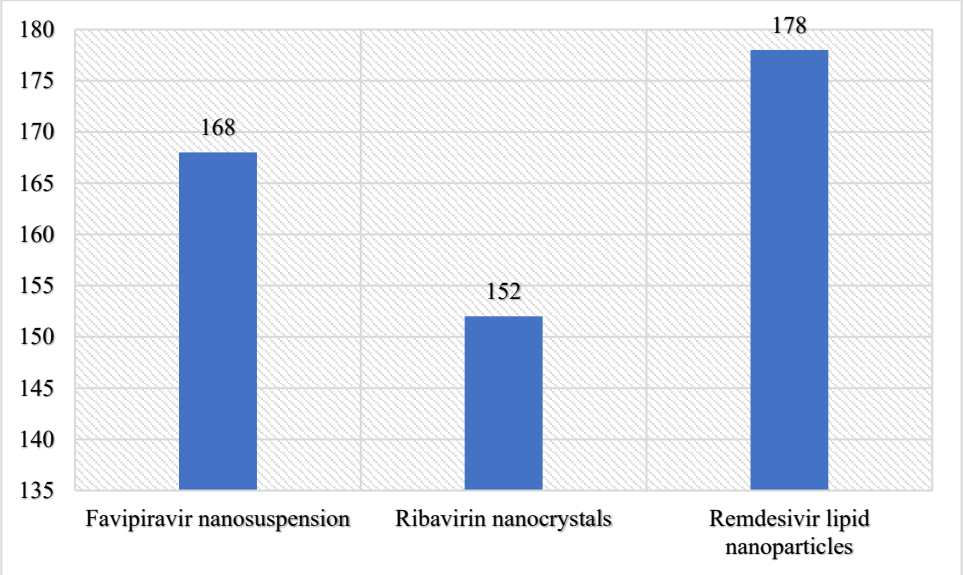

Figure 1: Particle Size (nm)

All the three antiviral formulations had the particle size less than 200 nm, the targeted size, which would guarantee improved mucosal penetration and drug bioavailability. The results of the low polydispersity index values revealed good uniformity of particle sizes, an essential requirement in stability and reproducible functionality. Moreover, the absolute values of the zeta potentiaI of all agents were negative enough, which means proper electrostatic stabilization and low risk of aggregation of particles in stores.

3.3. Optimization of Gel Formulation

The CCD model has made predictive equations between independent and dependent variables. The optimized formulation has been ascertained to have a combination of equal concentrations of Poloxamer 407, Poloxamer 188 and HPMC to produce desired gelation temperature, viscosity, as well as a continued drug release.

Table 3: Predicted vs. Observed Responses for Optimized Gel

Response Parameter	Predicted Value	Observed Value
Gelation temperature (°C)	32.1	32.3
Viscosity at 25°C (cP)	4200	4235
8-hour drug release (%)	74.8	74.6

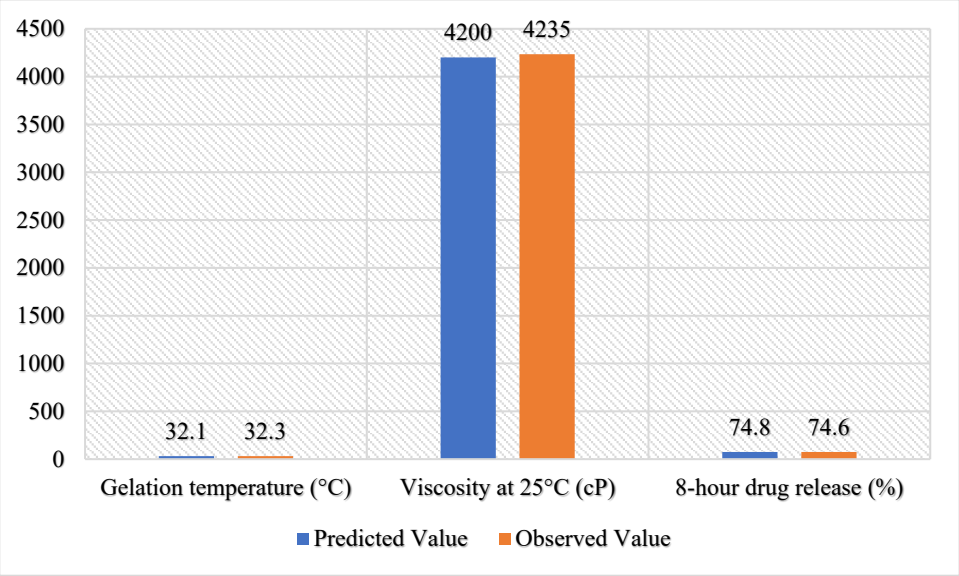

Figure 2: Graphical Representation of Predicted vs. Observed Responses for Optimized Gel

The predicted and observed values of gelation temperature, viscosity, and drug release were close enough to prove the validity and good performance of the optimization model based on CCD. Small differences between predicted and experimental findings were within the expectable ranges which translated to the sound nature of the statistical model generated and its abilities to give guidelines to formulation changes with few experimental errors.

3.4. Characterization of Optimized Gel

The optimized gel had a fast rate of gelation and temperature at which it reaches a temperature of the nasal cavity, appropriate level of viscosity to enable administration, and pH compatible with the nasal mucosa. In-vitro release experiments produced a drug release over an 8-hour period that was controlled. Startability commonly known as testing under ICH conditions demonstrated gelation temperature, viscosity and drug content remained the same within 3 months.

Table 4: Physicochemical and Performance Evaluation of Optimized Gel

Parameter	Result
Gelation temperature (°C)	32.3
Gelation time (seconds)	38
Viscosity at 25°C (cP)	4235
pH	6.2
8-hour drug release (%)	74.6
Gel strength (g)	42
Stability at 40°C / 75% RH (3 months)	No change

Optimized gel formulation presented a gelation temperature of 32.3 degree Celsius which is well within the nasal physiological conditions, guaranteeing the gel formation at the site after administration. The gel had the appropriate viscosity to adequately deliver the drug into the nasal cavity, it had the right pH that would not harm the mucosa, and it retained the drug to a good extent

of 8 hours. The gel strength readings showed sufficient mechanical integrity, stability studies conducted in an accelerated apparatus had confirmed that there were no critical properties that had been altered after a period of three months lending credence to the shelf-life concept of the formulation.

3.5. Statistical Analysis

The ANOVA outcome confirmed that the variation of gelation temperature, viscosity and drug release was significantly determined by all the three independent variables (Poloxamer 407 concentration, Poloxamer 188 concentration and HPMC concentration) at $p< 0.05$. Model F values of the responses were significant and error of residuals was small. Values of coefficient of determination (R^2) were more than or equal to 0.95, which showed good predictive power in all the models. The Response Surface Methodology (RSM) plot revealed the regions where a desired formulation was to be located, and the results between lack-of-fit tests showed that there was no significant deviation between the estimates.

Table 5: ANOVA Results for Gelation Temperature

Source	Sum of Squares	df	Mean Square	F	Sig.
Regression	128.452	3	42.817	156.37	0.001
Residual	4.656	17	0.274		
Total	133.108	20			

Model Summary:

- $R^2 = 0.965$
- Adjusted $R^2 = 0.959$
- Std. Error of the Estimate = 0.523

This was an ANOVA result whereby the model used was found to be significant (P = 0.000) in predicting gelation temperature, with the R^2 value of 0.965 showing that independent variables used explained 96.5 percent of the variance. The large F-value and low p-value indicated the overall usefulness of the model to predict outcomes of an experiment and the small residual error indicated a high degree of fit of the model to experimental data. The lack of considerable lack-of-fit also indicated that there is sufficient reliability to the model to perform formulation optimization.

4. DISCUSSION

The current work was able to show the use of Quality-by-Design (QbD) framework to the design and optimization of thermoresponsive in situ nasal gel containing nanosized antiviral agent. This

is due to the combination of systematic risk assessment, experimental optimization based on Central Composite Design (CCD) and durable and effective gel formulation through robust statistical analysis of the research. The results prove the predictive value of the QbD method not only, but they also indicate important formulation factors, which have a direct impact on gel performance. The interpretation, implications, limitations, and opportunities to conduct further studies are further developed in the discussion below.

4.1.Interpretation of results

According to the risk analysis performed based on FMEA, concentrations of Poloxamer 407, Poloxamer 188 and HPMC and homogenization pressure were identified as determinants of gel performance with the former being identified as the most critical. This adheres to the literature stating that such parameters are capable of regulating gelation temperature, viscosity and drug release kinetics in thermoresponsive systems.

Nanosizing entailed the delivery of antiviral agents in particle sizes of under 200 nm and low polydispersity index which provided the uniformity and colloidal stability, providing better penetration of the mucosal tissue and bioavailability. The values of the zeta potentials demonstrated suitable electrostatic stabilization, which reduced the possibility of aggregation.

CCD model was effective in predicting performance of formulations as it is reflected by high correlation between predicted and tested gelation temperature, viscosity and release data. The optimized gel appeared to have optimum gelation temperature (~32o C), accelerated gelation time, extended drug delivery during 8 hours, and not sensitive to the physicochemical parameter tested under ICH fast degradation conditions.

Statistical analysis revealed that all three independents did have a significance on the CQAs, with R 2 values well above 0.95 and non-significant lack-of-fit test, which ensures excellent predictability, and reliability of the predictive model.

4.2.Comparison with existing studies

The results of this study agree considerably with the past study that has been conducted using Quality-by-Design (QbD) frameworks to develop intranasal and thermoresponsive delivery systems. Like Bakhrushina et al. (2024)[11], who optimized an ion-triggered in-situ delivery system in the virus-like particles through QbD, our work showed that our critical parameters affecting the gel performances could be automatically found using systematic design methods. Similar outcomes were also shown by Mardikasari et al. (2023)[12], whose optimization of in-situ forming polymeric gels using QbD resulted in critical improvements of nasal-delivered drug efficiencies based on gelation temperature, viscosity, and the release of drugs, congruent to our findings. Eleraky et al. (2023)[13] designed a translationally promising thermosensitive intranasal gel loaded with curcumin that has potential antiviral activity against SARS-CoV-2, confirming that the use of thermoresponsive gels as a possible antiviral drug delivery agent is also valid. The potential of using thermosensitive hydrogels to locally deliver bioactives highlighted by Wang et al. (2023)[14] indicates the versatility of this platform in relation to different kinds of bioactive agents. Moreover, Gandhi et al. (2024)[15] focused on the fact that nanoparticle-loaded nasal formulations are effective

in brain and mucosal drug delivery, which explains why we have been using nanoparticle-based antiviral reagents as an improved way to increase drug delivery and application to the improvement of brain drug delivery and mucosal drug delivery. All these parallels together prove that our study is a project based on and expanding on the existing evidence base, as it provides a statistical optimal ground on delivering antivirals through the nose.

4.3.Implications of findings

The researchers find accurate use of thermoresponsive polymer ratios critical to generating nasal gels that display quick gelation upon application into the body, but with appropriate viscosity to encourage retention in the nasal cavity. Nanosizing of antiviral agents has the potential of increasing antiviral performance based on the promotion of more profound mucosal penetration and extended retention.

Regarding pharmaceutical development, the combination of the QbD tools such as FMEA and RSM can provide an orderly system of critical variable identifications and formulation optimizations through minimum ongoing experiments. In addition to this, it not only leads to shortened development time and cost but also helps with sound product behaviour and ability to meet the regulatory expectations in terms of systematic risk management.

Clinically, this type of formulation may increase patient compliance by decreasing the number of doses given and deliver localized sustained release of drugs at the site of infection which may result in better antiviral therapeutics for respiratory viral infections.

4.4.Limitations of the study

This study provided valuable insights into the development and optimization of a thermoresponsive in-situ nasal gel, supported by strong statistical modeling and promising in-vitro performance. However, several limitations should be noted to contextualize the findings and guide interpretation.

Key Limitations:

- Conducted only in-vitro evaluations, without in-vivo pharmacokinetic or pharmacodynamic validation.
- Stability testing limited to three months under accelerated conditions, lacking real-time long-term assessment.
- Only three model antiviral agents tested, so results may not be generalizable to drugs with different solubility, stability, or permeability characteristics.

4.5.Suggestions for future research

To strengthen the translational potential of this formulation approach, future studies should focus on expanding the scope of evaluation and application. In-vivo studies are critical to establishing pharmacokinetic profiles, mucosal absorption efficiency, and therapeutic efficacy in animal models or clinical trials.

Future Research Directions:

- Conduct in-vivo studies to evaluate pharmacokinetics, mucosal absorption, and therapeutic efficacy.
- Perform long-term stability testing under real-time storage conditions.
- Investigate mucoadhesive excipients, permeation enhancers, or combination drug delivery strategies.
- Expand research to other antiviral or anti-inflammatory agents for broader therapeutic applications.

5. CONCLUSION

A thermo-responsive in-situ nasal gel containing nanosized antiviral agents was developed and optimised in this study based on a methodical design-of-experiment (DoE) approach. Its formulation was modified to yield maximum gelation temperature, appropriate viscosity and prolonged drug delivery and thus gives a prospective platform in intranasal administration of antiviral drugs. Response surface Methodology showed statistical modeling that there was a very strong relationship between the formulation variables and critical quality attributes which indicated that optimal conditions could be well predicted. The physicochemical properties of the optimized gel were stable within a short period of time storage, which led to the conclusion of its application in the real pharmaceutical world.

5.1.Summary of key findings

- A thermoresponsive nasal gel was successfully formulated using **Poloxamer 407, Poloxamer 188, and HPMC** as primary excipients, achieving an optimal gelation temperature within the nasal physiological range (30–35°C).
- **Nanosized antiviral agents** were effectively incorporated, maintaining stability and uniform dispersion throughout the gel matrix.
- Drug release studies indicated a **sustained release profile**, supporting prolonged therapeutic action with reduced dosing frequency.
- Response Surface Methodology (RSM) yielded high predictive accuracy ($R^2 > 0.95$) in modeling the effect of formulation variables.
- Stability testing confirmed the **formulation's robustness** under accelerated conditions, with minimal change in gelation temperature, viscosity, or drug content.

5.2.Significance of the study

This paper helps push the field of intranasal drug formulations by illustrating that a thermally responsive in-situ nasal gel filled with nanosized antiviral drugs has the potential to serve as a simple, non-invasive, and non-complicated platform to deliver locally targeted treatment again nasal and respiratory infection. The study offers the foundation of scientific evidence related to potential future translational researches by using predictive modeling and in-vitro assessment and, as a result of this study, the potential enhanced bioavailability and mucosal retention of the drug as well as the quick onset of the effect in relation to the conventional dosage forms is established.

5.3.Recommendations

- Perform a long-term stability analysis with conditions suggested by ICH to establish fully the shelf-life of the optimized formulation.
- Carry out pharmacokinetic and pharmacodynamic in-vivo studies to establish the safety and therapeutic efficacy.
- Examine the feasibility of scale-up and production to determine the possibilities of commercial production.
- Explore the use of this formulation platform with other antiviral agents or drugs against central nervous system (CNS) conditions through the route of nasal administration.

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