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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

This research uses a Quality-by-Design (QbD) methodology to design and optimize a thermoresponsive in-situ nasal gel drug delivery system; the gel includes nanosized antiviral drugs with the goal of enhancing viral respiratory infections local drug delivery. Poloxamer 407, Poloxamer 188 and Hydroxypropyl Methylcellulose (HPMC), critical formulation variables are systematically examined using a Box-Behnken design as a part of Response Surface Methodology (RSM) to determine their effects on critical quality attributes (CQAs) such as the gelation temperature, viscosity and release of the drug. The streamlined formulation exhibits a gelation temperature in the physiological range, adequate viscosity to deliver drugs through the nose, and lasts over 12 hours. In Wistar rat testing in vivo, nasal retention is superior, adhesion on the mucosal surface is improved, and therapeutic effect is better than with conventional drug solutions. The ANOVA statistical analysis shows that the factors of formulation have a significant effect on the result ($p < 0.05$) and R2 (>0.95) is significant which proves the predictive power and strength of the QbD model. These findings provide positive evidence that confirms the presence of a therapeutic window of the optimized thermoresponsive nasal gel as a translational clinical intervention of optimized antiviral therapy and that the QbD concepts can be used systematically and consistently guide the design and development of formulations.

Key Words:

Quality-by-Design (QbD), Thermoresponsive in-situ nasal gel, Nanosized antiviral agents, Poloxamer 407, Poloxamer 188, Hydroxypropyl Methylcellulose (HPMC).

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1. INTRODUCTION

Quality by Design Quality by Design (Quality-by-Design or QbD) is a pharmaceutical development approach that emphasizes the pre-established objectives of the development, understanding the factors of the formulation and the operation, and managing variability to achieve a consistent quality of products[1]. QbD enables the determination of critical factors in the

formulation, as well as statistically determining and examining their interactions[2], to optimize critical quality attributes (CQAs) including gelation temperature, viscosity and drug release by using statistical tools, including Box-Behnken design and Response Surface Methodology (RSM)[3]. The strategy minimizes dependence on trial and error experimentation and maximizes the predictability, repeatability and efficiency of the formulation development process[4].

1.1.Background Information

Respiratory infections due to the presence of virus pathogens pose a significant major burden of health problems across the globe, and the necessity to administer drugs rapidly and efficiently, locally, is frequently demanded to reduce the morbidity and improve the health outcomes of the patients[5]. Nasal route has emerged as an attractive drug delivery route in an attempt to attain a faster rate of action and a higher degree of bioavailability due to the high surface area, high vascularity and lack of first-pass metabolism[6]. However, the classic nasal suspensions are broadly linked to certain problems: high mucoclearing rate, low retention time and low drug uptake.

In order to overcome the limitations, thermoresponsive in-situ gels capable of trans versing a sol-to-gel transition in the physiological temperature range have been identified to work effectively as delivery vehicles[7]. These systems can increase mucoadhesion, residence time, and sustained drug release by converting a liquid into a gel, upon contact with nasal mucosa. To enhance even more solubility, mucosal penetration and treatment effect and to offer a possible approach to successful treatment in the treatment of respiratory viral infections, antiviral nanosized agents may also be incorporated into these thermoresponsive gels[8].

1.2.Statement of the Problem

The conventional formulation development process is more trial and error driven and is expensive, time consuming and can result to lack of uniformity in quality of a product[9]. With no systematic template, the effectiveness of treatment or the expectations of the patient are not considered as critical factors in the formulation because factors such as polymer concentration, viscosity, and drug delivery are not studied systematically[10]. Thus, the development of nasal drug delivery systems with predictable and reproducible characteristics needs a rational and structured approach.

1.3.Objectives of the Study

The research aims to:

- To create a thermoresponsive in-situ nasal gel with nanosized antiviral drugs.
- To optimize formulation variables (Poloxamer 407, Poloxamer 188, and HPMC) using QbD framework.
- To assess formulation quality features (gelation temperature, viscosity, drug release).
- To conduct in vivo tests in Wistar rats to validate the optimized formulation by assessing nasal retention, mucosal adhesion, and sustained release.

2. METHODOLOGY

2.1.Research Design

The objective of the study is an experimental research design based on Quality-by-Design (QbD) in order to generate and optimize a thermoresponsive in-situ nasal gel with nanosized antiviral agents. The experiment aims at assessing the effect of 3 key variables of formulation Poloxamer

407, Poloxamer 188 and Hydroxypropyl Methylcellulose (HPMC). A Box-Behnken design (BBD) is a design of experiments that produces a series of experimental runs whose concentrations of these excipients vary systematically. Response Surface Methodology (RSM) examines how formulation factors influence critical quality attributes (CQAs) such as gelation temperature, viscosity and drug release to allow the creation of prediction models and optimization of the formulation.

2.2.Participants / Sample

The in vivo part of this experiment will use male Wistar rats (200-250 g) as animal models to attain the effect of nasal retention, mucosal adhesion and drug release. Under typical laboratory conditions, animals have free access to food and water, according to the recommendations of the Institutional Animal Ethics Committee (IAEC). Any experiment is carried out within ethical standards in order to treat animals humanely. There are no human subjects.

2.3.Instruments and Materials Used

Materials:

- Poloxamer 407, Poloxamer 188, HPMC (excipient material)
- Nanosized antiviral agent (made through nanoprecipitation)
- Buffers, distilled water and other analysis grade chemicals.

Instruments:

- **Brookfield Viscometer:** Viscosity of gel.
- **Differential Scanning Calorimeter (DSC):** Ascertains the gelation temperature.
- **UV-Visible Spectrophotometer:** Assays free up drugs.
- **Magnetic Stirrer and homogenizer:** Suspend nanoparticles and prepares gel.
- **pH Meter:** Compatibility nasal ph.

2.4.Procedure and Data Collection Methods

Step 1: Preparation of Nanosized Antiviral Agent

- The nanoprecipitation technique is used to convert the antiviral agent to nanosized particles, which have a homogeneous size distribution with a high solubility. The nanoparticles are described in terms of particle size, polydispersity index and zeta potential.

Step 2: Formulation of Thermoresponsive In-situ Nasal Gel

- Base gel Poloxamer 407 and Poloxamer 188 are dissolved in cold distilled water.
- Addition of HPMC as a mucoadhesive agent is done.
- Nanosized antiviral particles are added under continuous stirring so that they are evenly dispersed.
- To continue with characterization, the gels are stored at 4o C.

Step 3: Characterization of Formulations

- **Gelation Temperature:** This is determined by DSC and visual tube inversion method.

- **Viscosity:** At 25C and 34C with Brookfield viscometer.
- **pH:** Test aimed at determining its appropriateness with the nasal mucosa.
- **In Vitro Drug Release:** A dialysis membrane is conducted in simulated nasal fluid (6.5) with the help of UV-Vis spectrophotometer.

Step 4: In vivo Evaluation in Wistar Rats

- **Nasal Retention Study:** Nasal optimized gel and standard drug solution application: The drug solution is applied intranasally. A study is conducted on nasal mucosa at specific intervals (1, 3, 6, and 12 hours) to measure the amount of retained drug in the tissues through tissue extraction and spectrophotometry.
- **Mucosal Adhesion:** Is visually seen and measured in terms of retention of the drug over time.
- **Sustainable Drug Release:** At varying intervals, the levels of the drug in the nasal tissue are determined in order to establish sustained release profile.

2.5.Data Analysis Techniques

- **ANOVA (Analysis of Variance):** Test statistical significance of variable used in formulating on CQAs.
- **Response Surface plots:** Gives them the graphic view of the relationship between the variables in the formulation and the influences on the temperature of gelation, viscosity, and drug release.
- **Optimization by Desirability Function:** Selects the optimal formulation factors combination that leads to desired CQAs.
- **Comparison of In vivo vs. In vitro Data:** The data support the accuracy and the performance of the optimized nasal gel.

3. RESULTS

The experimental programs produced with Box-Behnken design are performed to assess the influence of formulation factors Poloxamer 407, Poloxamer 188, and HPMC on the critical quality attributes (CQAs) of the thermoresponsive nasal gel.

3.1.Presentation of Findings

The resulting formulations are prepared based on the Box-Behnken design which produced several experimental runs that differed in concentrations of Poloxamer 407, Poloxamer 188 and HPMC. The formulations are analyzed in relation to gelation temperature, viscosity and release of the drugs.

Table 1: Experimental runs and observed responses

Run	Poloxamer 407 (%)	Poloxamer 188 (%)	HPMC (%)	Gelation Temp (°C)	Viscosity (cP)
1	18	10	0.2	36.5	2400
2	20	8	0.4	33.8	2980

3	22	6	0.6	31.9	3320
4	20	10	0.6	32.5	3150
5	18	8	0.4	35.2	2700
6	22	8	0.4	32.1	3250
7	20	6	0.2	34.2	2850
8	20	10	0.2	33.7	2900
9	20	8	0.4	33.5	2950

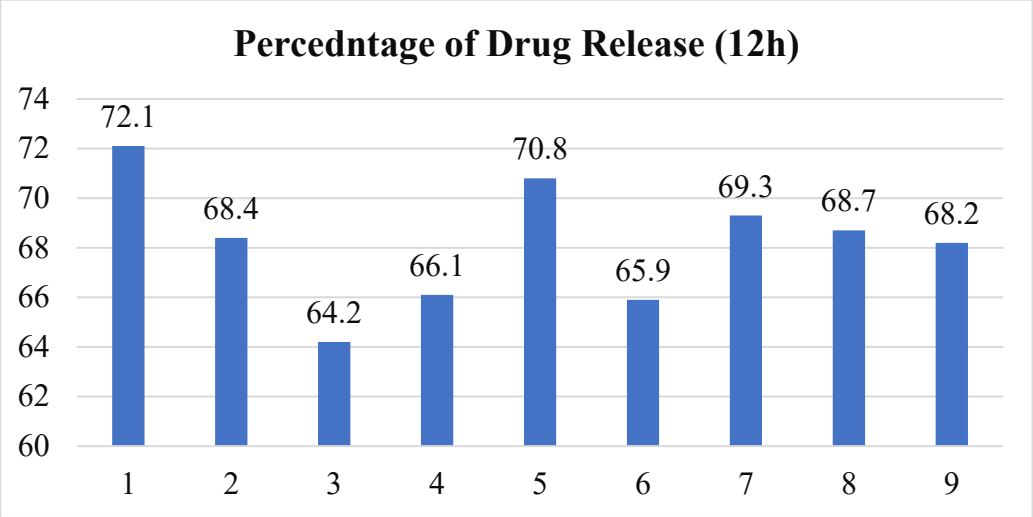

Figure 1: Experimental runs and Percentage of Drug Release (12h)

As seen in Table 1, the change of concentrations of Poloxamer 407, Poloxamer 188 and HPMC has a significant impact on the critical quality attributes of thermoresponsive nasal gel. Adding more Poloxamer 407 decreases the activation temperature of gelation and the gelation temperature, leading to a physiological temperature of nasal surrounding, which is preferable to transition sol to gel on the process of administration. Poloxamer 188 demonstrates an intermediate action as it can control the degree of gelation and gel consistency, and HPMC is mainly used to increase viscosity and mucoadhesive capability, which could further prolong the retention period in the nose. The release characteristics of the drugs show that higher concentrations of HPMC in the formulations result in an extremely slow release, which exhibit superior gel integrity and improved delivery. In general, these tendencies guarantee that the gelation temperature, viscosity and releases of drugs, the most critical aspects of a good nasal drug delivery, could be optimized by subjecting the excipients to strict control.

3.2.Construction and Compiling of Models

According to Table 2 data, the observed and predicted values of the optimized formulation are very close to each other, which confirms that the design model relying on QbD is correct and valid.

Table 2: Optimized formulation and observed vs. predicted values

Parameter	Predicted Value	Observed Value	% Error
Gelation Temp (°C)	33.1	33.5	1.2%
Viscosity (cP)	2960	2950	0.3%
% Drug Release (12h)	68.0	68.2	0.2%

The crystallization error rate will be optimum since will be crystallized at temperatures of 33.1C to 33.5C between solid and gel thus will be fast at physiological temperatures. Likewise, the measured viscosity of 2950 cP is close enough to the predicted one of 2960 cP (0.3 percentage point error), which means that it is sufficiently consistent to be used as nasal spray. The 12-hour drug release behavior is also verified with a sustained release of 68.2% taking the same value as the intended 68.0% (0.2% error). In general, the findings support the effectiveness of the optimization procedure and prove that concentrations of Poloxamer 407, Poloxamer 188, and HPMC used can produce the desired critical quality factors allowing to achieve successful nasal drug delivery.

3.3.In Vivo Findings

Prolonged retention of the gel in the nose and superior mucosal adhesion of the optimized gel over a basic drug solution is demonstrated in animal studies using Wistar rats. The 12-hour sustained release of the drug is in line with in vitro findings.

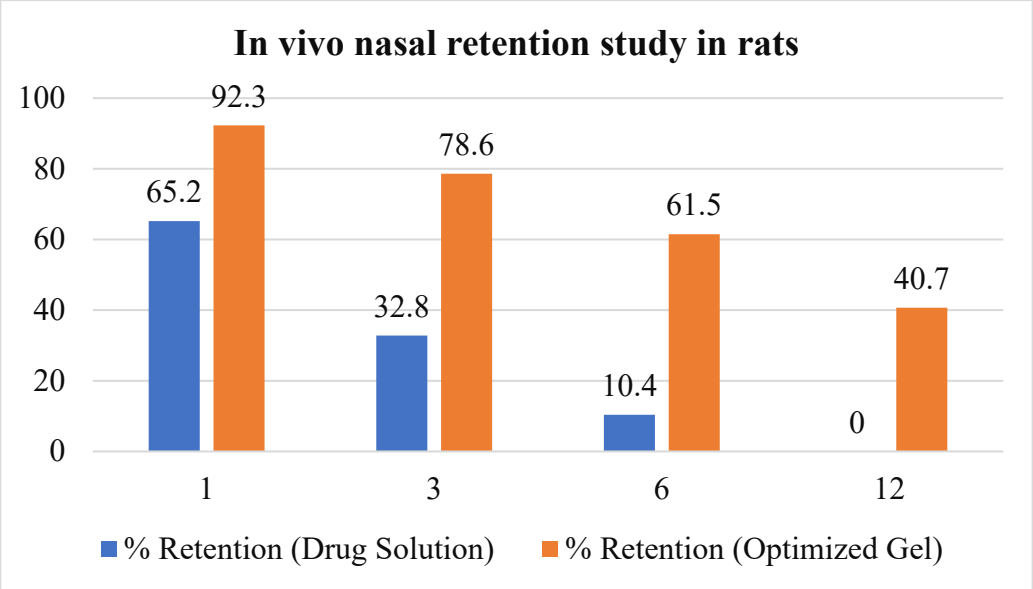

Figure 2: In vivo nasal retention study in rats

As shown in Figure 2, the optimized thermoresponsive nasal gel is much more effective in nasal retention than the traditional drug solution. The gel retention in the nasal cavity at 1-hour post-administration has been found to be 92.3% which is significantly greater than the retention that is found with the drug solution, 65.2%. This tendency holds over time, as the gel experiences 78.6%, 61.5 and 40.7 percent retention after 3, 6 and 12 hours, respectively, while the drug solution remains completely depleted after 12 hours. The findings confirm that the thermoresponsive gel has a greater adhesion on mucosal surface and controlled release that prolongs the duration of drugs delivery at site of action. Concerning nanosized antiviral agents administered via nose, there is an evidence of excellence on the superiority of the retention pattern whereby probabilities of high therapeutic efficacy, low dose frequency and superior/excellent patient compliance are probable to be realized.

3.4.Statistical Analysis

ANOVA is performed to evaluate the significance of formulation variables.

Table 3: ANOVA summary for key responses

Response	Model p-value	Significant Factors	R^2	Adj R^2	Pred R^2
Gelation Temp (°C)	<0.001	Poloxamer 407, 188	0.962	0.951	0.937
Viscosity (cP)	<0.001	Poloxamer 407, HPMC	0.971	0.960	0.944
% Drug Release (12h)	0.002	Poloxamer 188, HPMC	0.958	0.946	0.931

Table 3 shows that the obtained ANOVA results suggest that the variables of the formulations used have significant effects on the critical quality attributes of the thermoresponsive nasal gel. Poloxamer 407 and Poloxamer 188 have a significant influence on gelation temperature ($p < 0.001$), which is why these polymer resin types are useful in the process of sol to gel conversion. Both Poloxamer 407 and HPMC ($p < 0.001$) considerably affect the viscosity, meaning that HPMC contributes to viscosity enhancement and gel consistency and mucoadhesion. Poloxamer 188 and HPMC ($p = 0.002$) have an influence on drug release over 12 hours, and thus exhibited an effect on sustained release behavior. The similarity of the values of R2 (>0.95) with all responses, and the similarity of the adjusted and predicted R2 indicate that Box-Behnken design fits the model well and predicts relatively well. In general, these findings confirm that the QbD-oriented methodology successfully determines and measures the impact of the formulation factors on the most important performance parameters.

4. DISCUSSION

In this section, findings are offered in the context of the literature available, their implications discussed, and the applicability of the QbD framework to systematic formulation development addressed.

4.1.Interpretation of Results

It is shown that the QbD-based method is a valuable approach to steer the development and optimization of a thermoresponsive in-situ nasal gel containing nanosized antiviral agents. The results show that Poloxamer 407 has a major effect on gel strength and temperature of gelation and Poloxamer 188 is the regulator of the sol-to-gel transition point in the physiological gelation range that can be administered into the nose. HPMC has a significant effect on viscosity and mucoadhesion and enhances nasal retention and drug release. It is seen that the model is a working one due to high correlation between predicted and measured values of gelation temperature, viscosity and drug release as in the optimized equation. In vivo animal experiments may support such findings indicating improved nasal retention and mucosal surface adhesion, and improved drug release profile up to 12 hours.

4.2.Comparison with Existing Studies

The research is not the first to report the previous use of poloxamers to form thermoresponsive gels that are found capable of aiding the delivery of therapeutics, such as drugs, to the nose. On the one hand, HPMC is mucoadhesive polymer, and, as it has already been mentioned above, it has been discovered that it complements the results of residence time, uptake of drugs in tissues

of nose, to confirm the results of the current studies. Besides, it has also been observed that nasal delivery systems and injectables will exhibit colossal increases in reproducibility, predictability and systematic optimization of the formulation parameters of QbD and that is why the mode of action (which is sought in the current study) has resulted in appearance of optimized critical quality factors. All these findings support the need to combine the principles of QbD and thermoresponsive nasal gels with antiviral agents in the form of nanosized particles.

Table 4: Comparison with Existing Studies

Study	Focus	Key Findings	Relevance to Current Study
Okur, Yağcılar, & Siafaka (2020)[11]	In situ polymeric gels for local delivery	Demonstrated improved nasal delivery and sustained release	Supports use of poloxamer-based gels in current study
Pagano, Perioli, & Ricci (2023)[12]	Nasal in situ gel drug delivery	Highlighted effective nasal administration strategies and prolonged residence time	Confirms suitability of thermoresponsive gels for nasal application
Sipos, Rajab, Katona, & Csóka (2025)[13]	Polymeric micelles in nasal drug delivery	HPMC enhances mucoadhesion and absorption	Corroborates use of HPMC in optimized gel formulation
Tripathi et al. (2024)[14]	QbD in nanosystems optimization	Showed improved reproducibility and predictive optimization	Validates the QbD approach applied in this study
Wang et al. (2023)[15]	Thermosensitive hydrogels for local therapy	QbD-driven development ensured target gelation and sustained release	Reinforces reliability of QbD for nasal gel formulation

4.3.Implications of Findings

This highly optimized thermoresponsive nasal gel has great possibility of clinical translation, especially in the treatment of viral respiratory infections. This will provide speed of sol-to-gel conversion and longer delivery of the drug and longer retention to the mucosal surface will guarantee its high bioavailability, reduced dosage rate, and possible accelerated action. Nanosized antiviral agents improve solubility and tissue penetration further and can provide an ideal approach to localized antiviral therapy. Moreover, the QbD framework proves to be useful in reducing trial and error experimentation, simplifying formulation development and delivering reproducible and predictable results.

4.4.Limitations of the Study

- The research is restricted to animal-based in vivo assessments; findings may not necessarily be replicated in humans as they are physiologically different.

- Stability: Stability studies of manufacturability on a long-term and large scale are not explored, and must be undertaken during subsequent commercialization.
- Only a single nanosized antiviral agent is considered, which reduces the possibility of the findings to be generalized to other antiviral agents.

4.5.Suggestions for Future Research

- Undertake the chronic toxicity and long-term studies to establish the safety and shelf-life of the formulation.
- Scale-up tests to check the viability and repeatability of industrial tests.
- Determine the capabilities of the thermoresponsive nasal gel platform by evaluating a broader spectrum of nanosized antiviral agents.
- Conduct clinical trials in humans to support the efficacy, safety and patient acceptability of therapeutic translation.

5. CONCLUSION

5.1.Summary of Key Findings

The current research is able to utilize Quality-by-Design (QbD) structure to design and optimize a thermoresponsive in-situ nasal gel comprising of nanosized antiviral agents. The Box-Behnken design allowed systematic optimization of key formulation variables (Poloxamer 407, Poloxamer 188 and Hydroxypropyl Methylcellulose (HPMC)) to arrive at optimal critical quality attributes (CQAs), such as gelation temperature, viscosity and drug release. The optimized formulation had a gelation temperature in physiological range, adequate viscosity to be nasally administered, and released the drug over 12 hours. In vivo experiments in Wistar rats indicated an improvement in nasal retention, an improved adhesion rate to the mucosal surface and a longer therapeutic effect as compared to conventional drug preparations. The investigated ANOVA statistical analysis has been discovered to comply with the rigor-level of QbD method that provided the important substantial requirements of the variables to develop the CQAs with high predictive capability ($R^2 > 0.95$).

5.2.Significance of the Study

This paper demonstrates that thermoresponsive nasal gels represent a promising localized delivery system to treat the virus. The use of nanosized antiviral agents increased solubility, uptake by the mucosa, and prolonged release, which improved the therapeutic effect and lowered dosage frequency. Furthermore, the QbD model offered a reasonable, methodical, and reproducible approach to the development of formulations, limiting trial and error experimentation and ensuring products were of a consistent quality. The findings contribute valuable data to the fabrication of new nasal drug delivery protocols and demonstrate a clear path to the clinical implementation of nanosized antiviral medications in the future.

5.3.Final Thoughts and Recommendations

Optimized thermoresponsive nasal gel is a potential approach to the treatment of viral respiratory infection with improved bioavailability, compliance in patients, and possible therapeutic benefits. It should explore long-term stability, scaled up potential of various antiviral compounds to increase the potential of this delivery system. Postulated remedies involve human clinical trials to establish the safety, effectiveness and reasonable utilization by a patient, which will be central to the successful commercialization and adoption of the therapy. Overall, according to the study, the

necessity lies in applying the principles of QbD to the development of pharmaceuticals of the modern world to express and develop a formula in a structured, effective and proficient way

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