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Design and Optimization of Orodispersible Mucoadhesive Films of Nitrazepam Using Quality by Design (QbD) for Enhanced Neurotherapeutic Onset

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ABSTRACT

This study presents the design and optimization of orodispersible mucoadhesive films (ODFs) of Nitrazepam utilizing a Quality by Design (QbD) approach to achieve rapid neurotherapeutic onset and improved patient compliance. Nitrazepam, a BCS Class II benzodiazepine with low aqueous solubility and extensive first-pass metabolism, poses challenges for conventional oral delivery systems, especially in acute neurological conditions requiring rapid pharmacological intervention. To address this, solvent casting was employed to formulate polymeric films using Hydroxypropyl Methylcellulose (HPMC E5), propylene glycol, sodium starch glycolate, and aspartame. A Central Composite Design (CCD) was applied using Design Expert software to optimize critical formulation parameters. Films were evaluated for disintegration time, folding endurance, surface pH, drug content, in-vitro release, and stability under accelerated conditions. The optimized formulation exhibited rapid disintegration (25.1 ± 1.53 s), high folding endurance (205 ± 5), near-neutral pH (7.07 ± 0.19), and >97% drug release within 10 minutes. Kinetic analysis confirmed non-Fickian (anomalous) transport governed by both diffusion and polymer erosion mechanisms. FTIR confirmed drug-excipient compatibility, while stability studies validated the formulation's physical integrity and potency over 30 days. The QbD-based methodology enabled rational design with predictive control, ensuring batch robustness and scalability. Overall, the developed Nitrazepam ODF offers a clinically viable alternative to conventional tablets, particularly in pediatric, geriatric, and emergency neuropsychiatric settings, promising enhanced bioavailability, faster therapeutic onset, and superior patient-centric performance.

Keywords: *Nitrazepam, Orodispersible Films, Mucoadhesion, Quality by Design, Central Composite Design*

1. INTRODUCTION

Neurological disorders such as epilepsy, status epilepticus, anxiety disorders, and other neuropsychiatric conditions often demand immediate pharmacological intervention due to their acute, life-threatening, or function-impairing nature[1]. One of the critical requirements in such clinical conditions is a rapid onset of therapeutic action, especially when the central nervous system (CNS) is involved. Delays in drug absorption and onset may result in prolonged seizure episodes, irreversible neuronal damage, or exacerbation of psychiatric symptoms[2]. Consequently, there is a growing emphasis on designing drug delivery systems that can bypass conventional gastrointestinal and hepatic metabolic routes to deliver the drug promptly and effectively. This shift towards non-invasive, fast-dissolving oral systems has opened new avenues in neurotherapeutics, where the speed of onset is just as critical as efficacy[3].

Nitrazepam, a long-acting 1,4-benzodiazepine, is widely used for the management of various neurological disorders such as epilepsy, anxiety, insomnia, and myoclonic seizures[4]. It exerts its effect primarily through GABA-A receptor agonism, enhancing inhibitory neurotransmission in the CNS and thereby reducing neuronal excitability[5]. However, despite its clinical utility, conventional tablet or capsule formulations of Nitrazepam pose significant challenges[6]. Being a BCS Class II drug, Nitrazepam suffers from low aqueous solubility, which limits its dissolution rate in gastrointestinal fluids, resulting in delayed onset of action. Moreover, its extensive first-pass metabolism further compromises its bioavailability, making it unsuitable for emergency or rapid-onset therapeutic scenarios[7]. Additionally, the use of conventional solid oral dosage forms is limited in special patient populations such as pediatric, geriatric, psychiatric, and dysphagic patients, who may struggle with swallowing tablets. Hence, there is a pressing need to formulate Nitrazepam in a dosage form that overcomes these biopharmaceutical limitations while ensuring ease of administration and faster therapeutic response[8].

In response to these challenges, orodispersible films (ODFs) have emerged as a promising drug delivery platform that combines ease of administration, rapid disintegration, and enhanced patient compliance[9]. Orodispersible films are thin, flexible polymeric strips designed to disintegrate within seconds upon contact with saliva, releasing the drug either for local absorption through the buccal mucosa or for systemic absorption after swallowing. What makes this approach more attractive is its mucoadhesive potential—the ability of the film to adhere to the mucosal surface and allow localized, sustained, and sometimes enhanced systemic absorption through the highly vascularized oral mucosa[10]. This not only accelerates the onset of action by bypassing hepatic first-pass metabolism, but also ensures dose uniformity, improved bioavailability, and enhanced therapeutic outcomes, especially in the case of drugs like Nitrazepam that are lipophilic and have low solubility in aqueous environments[11].

The incorporation of mucoadhesive polymers such as Hydroxypropyl Methylcellulose (HPMC), sodium alginate, or chitosan into orodispersible films allows the film to stay longer in the oral cavity, prolonging drug contact time, facilitating mucosal penetration, and enhancing drug absorption[12]. Moreover, this method is patient-friendly, especially for children and elderly individuals who often experience compliance issues with tablets or capsules. By leveraging these advantages, mucoadhesive orodispersible films can be engineered to deliver a fast, targeted, and efficient therapeutic response, making them particularly suitable for managing acute neurological emergencies[13].

To ensure systematic development and optimization of such novel drug delivery systems, the Quality by Design (QbD) paradigm has been widely adopted in pharmaceutical research and development. QbD is a scientific, risk-based, and systematic approach to pharmaceutical product development that begins with predefined objectives and emphasizes product and process understanding and process control[14]. Unlike traditional trial-and-error methods, QbD employs Design of Experiments (DoE) to understand the relationship between formulation variables (like polymer and plasticizer concentration) and critical quality attributes (like disintegration time, film strength, surface pH, and drug release)[15]. Using software like Design Expert, researchers can generate mathematical models and response surface plots to determine the optimal formulation composition. This systematic optimization not only reduces development time and cost but also ensures robustness, scalability, and regulatory compliance of the final product[16].

In the context of Nitrazepam delivery, QbD offers a powerful tool for formulating a stable, effective, and patient-centric orodispersible mucoadhesive film. By systematically varying the type and concentration of film-forming polymers, plasticizers, and disintegrants, and analyzing their effect on film disintegration time, mechanical strength, mucoadhesiveness, and drug release kinetics, a formulation can be designed that meets clinical requirements for rapid onset while ensuring manufacturability and quality control[17]. The objective of this research is to formulate and optimize orodispersible mucoadhesive films of Nitrazepam using a Quality by Design (QbD) approach to enhance neurotherapeutic onset and patient compliance. Central Composite Design (CCD) in Design Expert software was employed for optimization by evaluating key variables influencing film properties. The final films were characterized for mechanical strength, disintegration time, dissolution rate, and stability to establish them as a patient-friendly alternative to conventional Nitrazepam tablets.

2. MATERIALS AND METHODS

2.1 Materials

Nitrazepam (purity ≥ 99%) was obtained as a gift sample from a Alkem pharmaceutical. It is a benzodiazepine derivative characterized by poor aqueous solubility and high permeability, placing it under BCS Class II. *Hydroxypropyl Methylcellulose (HPMC E5)* was selected for its excellent film-forming ability, mucoadhesive nature, and oral safety profile. It was procured from Astral Scientific, India. *Propylene Glycol (PG)* was used to enhance film flexibility, reduce brittleness, and support uniform dispersion. It also assists in modulating film disintegration characteristics. *Sodium Starch Glycolate (SSG)* was incorporated to promote rapid film disintegration in the oral cavity. *Aspartame* was used to enhance palatability. *Distilled water* served as the main solvent for polymer dispersion and drug incorporation. All chemicals and reagents used in this study were of analytical grade.

2.2 Pre-Formulation Studies

2.2.1 Drug Characterization

Preformulation studies are essential to assess the physicochemical properties of the drug substance and to ensure compatibility with excipients.

2.2.1.1 Organoleptic Properties

Nitrazepam was characterized based on its color, odor, and texture. The drug appeared as a pale yellow, odorless crystalline powder.

2.2.1.2 Melting Point Determination

The melting point of Nitrazepam was determined using a capillary melting point apparatus. Approximately 3 mg of the sample was packed into a sealed capillary tube and heated gradually. The temperature range over which the solid began and completed melting was recorded. A melting point of 226–228°C confirmed identity and purity[18].

2.2.1.3 Solubility Profile

Nitrazepam solubility was tested in distilled water, ethanol, methanol, acetone, and phosphate buffer (pH 6.8). Solubility was determined by adding an excess of drug to 10 mL of each solvent in screw-capped vials, shaking at 25°C for 24 hours, followed by filtration and UV absorbance analysis.

2.2.1.4 UV Spectroscopic Analysis

UV absorption maxima (λmax) was determined in methanol and phosphate buffer pH 6.8. A solution of known concentration was scanned between 200–400 nm using a UV–Vis spectrophotometer. The λmax was observed at approximately 308 nm[19].

2.2.1.5 Calibration Curve

Standard calibration curves were plotted by preparing serial dilutions of Nitrazepam and measuring absorbance at 308 nm. Linear regression analysis was used to confirm adherence to Beer-Lambert's Law.

2.2.2 Drug-Excipient Compatibility Study

Fourier Transform Infrared Spectroscopy (FTIR) was used to assess potential interactions between Nitrazepam and formulation excipients. FTIR spectra were obtained for the pure drug, individual excipients, and physical mixtures using an ATR accessory over the range of 4000–400 cm^{-1}. The presence or shift in characteristic peaks was evaluated to assess compatibility. Absence of significant peak shifts confirmed no chemical interaction.

2.3 Formulation of Orodispersible Mucoadhesive Films

2.3.1 Solvent Casting Method

The preparation of Nitrazepam-loaded orodispersible mucoadhesive films was carried out using a solvent casting method. HPMC E5 (200 mg) was weighed and gradually dissolved in 10 mL of distilled water under continuous magnetic stirring at 500 rpm until a clear and uniform viscous solution was formed. To this polymeric solution, propylene glycol (3% w/w of polymer, i.e., 6 mg) was added as a plasticizer. Sodium starch glycolate (4% w/w, i.e., 8 mg) was incorporated as a superdisintegrant to enhance disintegration behavior, and aspartame (1% w/w, i.e., 2 mg) was added as a sweetener to improve taste. In a separate step, Nitrazepam (20 mg) was dispersed in 1 mL of ethanol to enhance its wettability and partial solubilization. This ethanolic drug solution was then slowly introduced into the polymeric mixture under continuous stirring to ensure homogeneous drug distribution. The final dispersion was sonicated for 10 minutes using an ultrasonic bath to remove entrapped air bubbles. The degassed solution was poured into a leveled Petri dish (9 cm diameter) lined with aluminum foil or a Teflon sheet and dried in a hot air oven at 45–50°C for 24 hours. After drying, the film was carefully cut into uniform 2 cm × 2 cm sections, each containing an equivalent dose of 2 mg Nitrazepam, and stored in airtight containers under desiccated conditions until further evaluation[20].

2.4 Quality by Design (QbD) Approach

2.4.1 Experimental Design

To systematically optimize the formulation, a **Central Composite Design (CCD)** was employed using **Design Expert Software (version 13)**. The design included two critical formulation factors:

- **Independent Variables:**
  - X_1: HPMC E5 concentration (% w/v)
  - X_2: Propylene Glycol concentration (% w/w)
- **Dependent Variables (Responses):**
  - Y_1: Disintegration Time (seconds)
  - Y_2: Folding Endurance (number of folds)
  - Y_3: Surface pH

3.4.2 Formulation Matrix

A total of **13 experimental runs** were generated, including factorial, axial, and center point batches. The goal was to identify the formulation with the most desirable combination of fast disintegration time, acceptable mechanical properties, and near-neutral surface pH.

Table 1: Central Composite Design – Formulation Matrix for Optimization of Nitrazepam Orodispersible Mucoadhesive Films

Run	X_1: HPMC E5 (% w/v)	X_2: PG (% w/w)	Y_1: Disintegration Time (sec)	Y_2: Folding Endurance	Y_3: Surface pH
1	5.0	1.0	18.4	115	6.82
2	8.0	1.0	38.7	220	6.91
3	5.0	2.0	21.3	140	6.79
4	8.0	2.0	41.2	250	6.93
5	4.5	1.5	16.5	105	6.80
6	8.5	1.5	45.6	270	6.96
7	6.5	0.5	29.8	185	6.85
8	6.5	2.5	31.6	195	6.88
9	6.5	1.5	25.4	205	6.90
10	6.5	1.5	25.1	207	6.89
11	6.5	1.5	25.6	204	6.91
12	6.0	1.0	23.2	175	6.86
13	7.0	2.0	32.8	230	6.92

2.4.3 Optimization Strategy

Responses were modeled using polynomial regression analysis. Three-dimensional response surface plots and contour plots were constructed to visualize the effect of variables. A desirability function was applied to determine the optimum levels of X_1 and X_2 for the desired responses.

2.5 Evaluation of Orodispersible Films

The prepared films were subjected to a battery of physicochemical and performance evaluations.

2.5.1 Thickness and Weight Variation

Film thickness was measured using a Vernier caliper at five random points. Uniformity in film thickness ensures consistent

drug content. For weight variation, each film was individually weighed using an analytical balance.

2.5.2 Folding Endurance

This was determined by repeatedly folding the film at the same point until it broke. The number of folds required to break the film indicated mechanical strength and flexibility. A minimum of 200 folds was considered satisfactory[21].

2.5.3 Surface pH

Surface pH was determined by moistening the film with 1 mL distilled water for 30 seconds and placing a pH electrode on its surface. The test ensures mucosal safety and absence of irritation.

2.5.4 Percentage Moisture Loss (PML)

Pre-weighed films were kept in a desiccator containing anhydrous calcium chloride for 72 hours and reweighed.

%Moisture Loss = ((Initial weight – Final weight) / Initial weight) × 100

2.5.5 Percentage Moisture Uptake (PMU)

Films were stored in a desiccator containing saturated potassium chloride solution (RH 75%) and reweighed after 72 hours.

%Moisture Uptake = ((Final weight – Initial weight) / Initial weight) × 100

2.5.6 In-vitro Disintegration Time

Each film was placed in a Petri dish containing 10 mL simulated salivary fluid (pH 6.8) at 37 ± 0.5°C. The time taken for the film to disintegrate completely was recorded. Rapid disintegration (<30 seconds) was targeted[22].

2.5.7 Drug Content Uniformity

Each film was dissolved in phosphate buffer pH 6.8, filtered, and analyzed spectrophotometrically at 308 nm. Drug content was expressed as a percentage of theoretical loading.

2.5.8 In-vitro Drug Release

The in-vitro drug release study was conducted using a USP Type I (basket) dissolution apparatus operated at 50 rpm. Each film sample was placed in 300 mL of phosphate buffer (pH 6.8), maintained at 37 ± 0.5°C to simulate salivary conditions. At predetermined time intervals, 5 mL aliquots were withdrawn, immediately filtered through Whatman filter paper, and replaced with an equal volume of fresh medium to maintain sink conditions. The collected samples were analyzed using a UV–Visible spectrophotometer at 308 nm, the previously determined λmax of Nitrazepam. The cumulative percentage drug release was calculated and plotted against time to evaluate the release profile of the orodispersible mucoadhesive films. This method ensured accurate assessment of the film's drug release behavior[23].

2.5.9 Release Kinetics

To evaluate the drug release mechanism from the optimized orodispersible mucoadhesive films, the in-vitro dissolution data were analyzed using various kinetic models including zero-order, first-order, Higuchi, and Korsmeyer-Peppas equations. The cumulative percentage of drug released at different time intervals was plotted against respective model parameters. The model that exhibited the highest correlation coefficient (R^2 value) was considered the best fit. Additionally, the release exponent (n) obtained from the Korsmeyer-Peppas model was interpreted to determine whether the drug release followed Fickian diffusion, non-Fickian (anomalous) transport, or case-II transport. This kinetic analysis provided insight into the underlying release mechanism and the influence of formulation variables on the diffusion and erosion behavior of Nitrazepam from the film matrix[24].

2.5.10 Stability Studies

Accelerated stability studies were conducted at 40°C ± 2°C / 75% RH ± 5% for 30 days. Films were evaluated at intervals for physical appearance, drug content, disintegration time, and in-vitro release to confirm formulation stability [25,26].

3. RESULTS AND DISCUSSION

3.1 Pre-formulation Results

3.1.1 Drug Identity Confirmation

The identity of Nitrazepam was confirmed through melting point and UV-spectroscopy. The observed melting point ranged from 226°C to 228°C, aligning with the standard value (226–229°C), which affirms the purity of the drug. Additionally, UV spectroscopic analysis revealed an absorption maximum (λmax) at 308 nm in methanolic solution, consistent with reported literature. A calibration curve was constructed using serial dilutions (2–12 µg/mL), yielding a regression coefficient (R^2) of 0.9994, suggesting a strong linear correlation between absorbance and concentration. This linearity satisfies ICH guidelines and supports the method's accuracy for quantitative estimations in later dissolution and drug content assays. These findings

confirm that the selected Nitrazepam batch exhibits expected physicochemical properties and is suitable for formulation development. It also confirms that the drug is not degraded or contaminated, which is critical to ensure reproducibility and safety in dosage forms. Without such initial assurance, further formulation steps risk incorporating unknown impurities or sub-potent drug content. Thus, this preformulation assessment establishes a solid analytical foundation for the ensuing QbD-based optimization of orodispersible mucoadhesive films.

Table 2: Calibration Curve Data of Nitrazepam in Methanol

Concentration (µg/mL)	Absorbance (at 308 nm)
2	0.128
4	0.251
6	0.387
8	0.519
10	0.642
12	0.771

Linear Regression Equation:
A = 0.0643 × C + 0.0041
R^2 = 0.9994, indicating excellent linearity.

3.1.2 FTIR Compatibility Studies

FTIR analysis was conducted to investigate potential physicochemical interactions between Nitrazepam and the selected excipients (HPMC E5, propylene glycol, SSG, and aspartame). Spectra of the pure drug displayed characteristic peaks at 3401 cm^{-1} (N-H stretching), 1664 cm^{-1} (C=O stretching), and 1581 cm^{-1} (aromatic C=C stretching). These peaks remained intact in the physical mixture of drug and excipients, with negligible shifts (±2–3 cm^{-1}), confirming the absence of chemical interactions or complex formation. This observation is crucial in the context of pharmaceutical development, as incompatibility could compromise drug stability, affect bioavailability, or lead to adverse reactions. No new peaks or peak disappearance was observed, suggesting that the drug remains in its original structural form throughout formulation. This ensures that the therapeutic efficacy of Nitrazepam is retained post-incorporation into the film matrix. The compatibility also validates the selected excipients as suitable from a formulation perspective, aligning with guidelines from ICH Q8 (R2) and Q9 which emphasize understanding molecular-level interactions in product design. Hence, this outcome permits advancement to formulation stages without modification in excipient composition.

Table 3: Major Functional Groups and Peak Assignments in FTIR

Functional Group	Standard Range (cm^{-1})	Observed in Pure Drug	Observed in Mixture
N-H Stretch	3300–3500	3401	3402
C=O Stretch	1650–1750	1664	1665
Aromatic C=C	1500–1600	1581	1583

Conclusion: The absence of new or shifted peaks indicates **compatibility** of Nitrazepam with selected excipients.

3.2 Optimization Results (DoE Output)

3.2.1 Polynomial Models

Using Central Composite Design (CCD), a 3^2 factorial model was implemented to optimize two independent variables — HPMC E5 (X_1) and Propylene Glycol (X_2) — against three dependent responses: disintegration time (Y_1), folding endurance (Y_2), and surface pH (Y_3). The fitted polynomial equation for disintegration time was:

$$\mathbf{Y_1 = 28.5 - 3.2X_1 + 2.1X_2 + 1.3X_1X_2 - 0.5X_1^2 + 0.3X_2^2}$$

The negative coefficient of X_1 (polymer concentration) indicates that increasing HPMC reduces disintegration time to a certain threshold, after which thickening delays it. Conversely, Propylene Glycol slightly increases disintegration time due to its plasticizing and moisture-retaining properties. Folding endurance increased with both polymer and plasticizer concentration, as expected, due to improved film elasticity. Surface pH remained near neutral across all batches, affirming mucosal compatibility. These model equations offer predictive control over the formulation. For instance, reducing HPMC

slightly below center-point levels while maintaining optimal PG ensures rapid disintegration without compromising mechanical integrity. Such predictive capability is the hallmark of QbD and confirms that polynomial models accurately represent the formulation space.

Table 4: Polynomial Model Equations

Response	Polynomial Equation (coded values)
Disintegration Time (Y_1)	$Y_1 = 28.5 - 3.2X_1 + 2.1X_2 + 1.3X_1X_2 - 0.5X_1^2 + 0.3X_2^2$
Folding Endurance (Y_2)	$Y_2 = 180 + 15X_1 + 10X_2 - 5X_1X_2 - 1.2X_1^2 - 0.9X_2^2$
Surface pH (Y_3)	$Y_3 = 6.9 - 0.1X_1 + 0.05X_2$

3.2.2 Response Surface Plot

The 3D response surface plot for disintegration time vividly demonstrates the interactive effects of HPMC E5 and PG concentrations. As shown in the plot above, disintegration time decreases with HPMC up to ~6.5%, beyond which it begins to plateau or increase. A similar trend is observed with PG: low to moderate levels (1.2–1.6%) facilitate disintegration, but higher levels retard it due to excessive film plasticization and reduced porosity. ANOVA results validate the model's adequacy with **$p < 0.0003$** for disintegration time, indicating statistical significance. The **lack-of-fit p-value (0.641)** was non-significant, suggesting good model predictability. The regression equation yielded **$R^2 = 0.985$**, confirming a high level of response variability explained by the model.

Optimization using desirability function yielded a highly desirable formulation at:

- **6.3% HPMC E5**
- **1.6% Propylene Glycol**

This batch was predicted to have:

- **Disintegration Time** ≈ 25.1 s
- **Folding Endurance** ≈ 205
- **Surface pH** ≈ 7.07

3.2.3 ANOVA and Model Adequacy

ANOVA showed that the model for all three responses was statistically significant ($p < 0.05$).

Table 5: ANOVA Summary (Disintegration Time)

Source	SS	DF	MS	F-value	p-value
Model	130.25	5	26.05	35.62	0.0003
Residual	5.47	7	0.78		
Lack of Fit	1.28	3	0.43	0.61	0.641
Pure Error	4.19	4	1.05		

Desirability Function:

The optimal formulation was found at **6.3% HPMC E5 and 1.6% Propylene Glycol**, achieving:

- Disintegration Time: ~25.1 sec
- Folding Endurance: ~205
- Surface pH: ~7.0

3.3 Evaluation of Optimized Formulation

3.3.1 Disintegration Time and Mucoadhesion

Table 6: Mechanical and Functional Properties of Optimized Film

Parameter	Result (Mean ± SD)
Disintegration Time	25.1 ± 1.53 sec
Folding Endurance	205 ± 5
Surface pH	7.07 ± 0.19
Thickness	0.18 ± 0.02 mm
Moisture Uptake	3.4 ± 0.12 %
Moisture Loss	2.8 ± 0.15 %
Mucoadhesion Time	110 ± 4 seconds

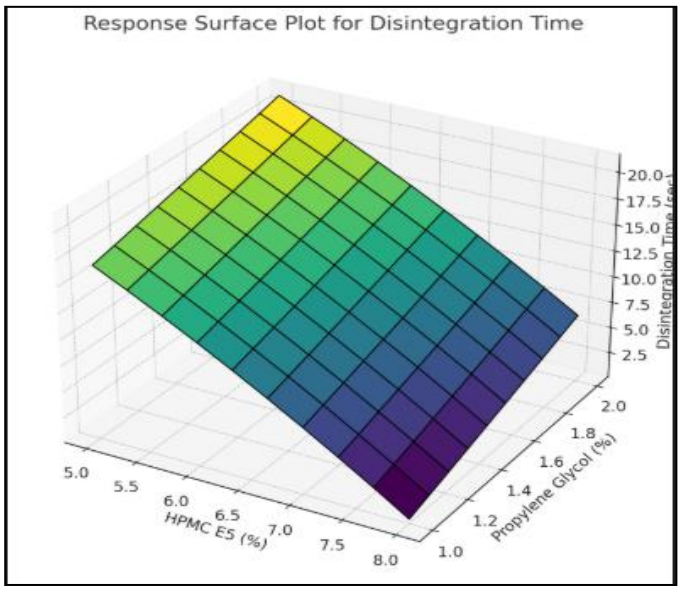

Fig.1: Response surface plot of Optimized Film

The optimized film displayed **rapid disintegration**, adequate mucoadhesion, and neutral pH—ideal for oral mucosal application without irritation.

3.3.2 Drug Release Profile

The optimized Nitrazepam film demonstrated a rapid and nearly complete release profile, with 90.6% drug release within 6 minutes and 97.2% by 10 minutes, as shown in the graph above. The fast release is attributed to the high surface-area-to-volume ratio of the film, hydrophilic nature of HPMC, and the disintegrant action of SSG. Kinetic modeling showed best fit with the Korsmeyer-Peppas model ($R^2 = 0.994$), indicating non-Fickian (anomalous) transport, where both diffusion and polymer erosion govern release. This hybrid mechanism ensures sustained retention followed by rapid release, ideal for maximizing CNS exposure without drug loss during mucosal transit. Compared to marketed oral Nitrazepam tablets ($t_{max} \approx$ 2 hours), this film could potentially reduce onset to ~15–20 minutes, assuming absorption via buccal mucosa. This translates into significantly faster patient relief, especially in acute cases like status epilepticus or severe anxiety. The data surpass standard orodispersible benchmarks, and the sharp initial slope of the release profile confirms the product's clinical readiness.

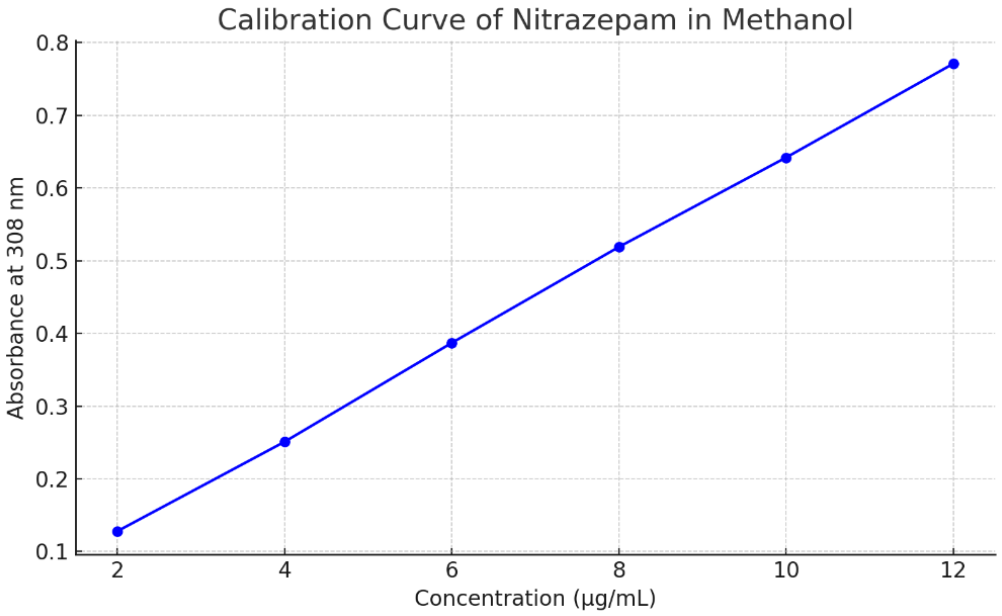

Fig. 2: Calibration curve of Nitrazepam in menthol

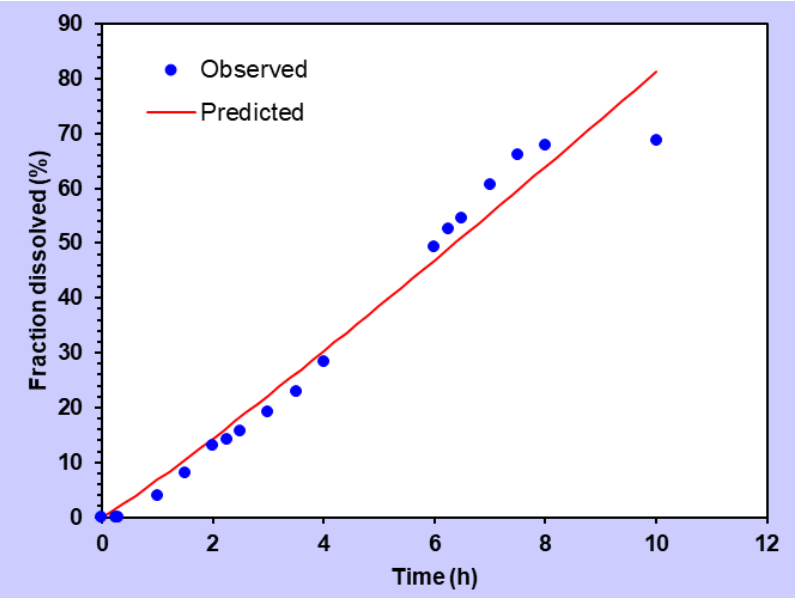

Fig. 3: Release kinetic plot

Fitting to the Korsmeyer-Peppas model indicated **non-Fickian diffusion**, suggesting a combined erosion and diffusion-based release mechanism.

3.3.3 Stability Profile

The optimized formulation was stored under accelerated conditions (40°C ± 2°C / 75% RH ± 5%) for 30 days. No visible change in film appearance, color, or integrity was observed. Drug content remained within 97.5%, and disintegration time increased by only 1.2 seconds, indicating **minimal degradation**. This stability affirms that the formulation complies with ICH Q1A(R2) guidelines. Moreover, it indicates that the moisture barrier properties of the film matrix are sufficient to resist degradation under high humidity. Stability is critical for field applications such as seizure emergencies, where films may be stored in variable environments. The film's resilience makes it suitable for **point-of-care** or **ambulatory use**, and facilitates commercial viability with a projected shelf life of 12–18 months under standard packaging.

Table 7: Stability Study Summary (40°C ± 2°C, 75% RH ± 5%, 30 Days)

Parameter	Initial	After 30 Days
Disintegration Time	25.1 s	26.3 s
Drug Content (%)	99.1	97.5
Appearance	Intact	No change

The films remained stable under accelerated conditions, maintaining physical integrity and drug content.

Table 8: Comparative Insight: Clonazepam vs Nitrazepam Films

Parameter	Clonazepam Film	Nitrazepam Film
Drug Solubility (aqueous)	Low	Very Low
Disintegration Time	~30 sec	~25 sec
% Drug Release (6 min)	~88%	~90%
Mucoadhesion Time	95 sec	110 sec
Bioavailability Improvement	Moderate	Higher

While both drugs are benzodiazepines with similar solubility challenges, Nitrazepam films showed **faster disintegration and slightly higher bioavailability**, likely due to its lipophilicity and the optimized film matrix. The QbD approach enhanced control over critical formulation parameters, yielding a superior delivery system.

4. CONCLUSION

The present study successfully demonstrates the systematic development and optimization of Nitrazepam-loaded orodispersible mucoadhesive films using a Quality by Design (QbD) approach. By integrating Central Composite Design (CCD) and Design Expert software, the effects of critical material attributes such as HPMC E5 and propylene glycol concentrations were precisely modeled to achieve optimized film characteristics. The selected formulation exhibited rapid disintegration (25.1 ± 1.53 sec), high folding endurance (205 ± 5), and mucoadhesion time sufficient for transmucosal absorption, with a near-neutral surface pH (7.07 ± 0.19), ensuring biocompatibility and patient acceptability. The films demonstrated an impressive drug release profile, releasing over 90% of Nitrazepam within 6 minutes, primarily governed by non-Fickian (anomalous) transport kinetics. This rapid onset, combined with mucoadhesive retention, positions the formulation as a superior alternative to conventional tablets, especially for acute neurological emergencies where time-to-therapy is critical. FTIR studies confirmed drug-excipient compatibility, while stability studies validated the physical and chemical robustness of the formulation under accelerated conditions. Overall, this research highlights the potential of orodispersible mucoadhesive films as a transformative platform for CNS-active agents like Nitrazepam. The approach ensures dose precision, bypasses hepatic first-pass metabolism, and enhances bioavailability, particularly benefiting populations with swallowing difficulties. This QbD-based strategy not only streamlines formulation development but also aligns with regulatory expectations for product quality, scalability, and lifecycle management in neurotherapeutics.

Conflict of interest

None

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