

DEVELOPMENT AND CHARACTERIZATION OF PULLULAN-BASED ORODISPERSIBLE FILMS OF ALMOTRIPTAN MALATE WITH SUPERDISINTEGRANT OPTIMIZATION

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ABSTRACT

Almotriptan Malate requires rapid systemic delivery for acute migraine management to overcome disease-induced gastric stasis and dysphagia. This study aimed to systematically develop and optimize pullulan-based orodispersible films (ODFs) enhanced with superdisintegrants. A 3-factor, 3-level Box-Behnken Design (BBD) was utilized to optimize the concentrations of pullulan, crospovidone, and glycerol. Films were prepared via the solvent casting method and evaluated for mechanical strength, disintegration time, and in vitro dissolution. Solid-state characterization was conducted using FTIR, DSC, XRD, and SEM. The optimized formulation (4.2% w/v pullulan, 7.5% w/w crospovidone, 21.5% w/w glycerol) exhibited a rapid disintegration time of 19.25 seconds and excellent mechanical resilience (tensile strength: 3.72 MPa). In vitro studies demonstrated >91% drug release within 5 minutes, driven by Fickian diffusion. Solid-state analyses confirmed the complete amorphization and uniform molecular dispersion of the drug without any chemical incompatibilities. Furthermore, the formulation maintained robust physical and chemical integrity throughout 3 months of accelerated stability testing. In conclusion, the statistically optimized pullulan-crospovidone ODF presents a highly effective, patient-centric delivery platform for rapid therapeutic intervention in migraine therapy.

KEYWORDS: Almotriptan Malate; Orodispersible films; Pullulan; Box-Behnken Design; Superdisintegrants; Amorphization.

1. INTRODUCTION

Migraine is a complex neurological disorder characterized by severe and throbbing head pain that is frequently accompanied by autonomic symptoms like nausea, vomiting, and sensory sensitivity (Goadsby, Lipton, & Ferrari, 2002). Treating these acute attacks requires immediate therapeutic intervention to prevent the escalation of pain. Almotriptan Malate is a highly selective serotonin 5-HT_{1B/1D} receptor agonist and serves as one of the most effective oral triptans available for acute migraine management (Ferrari, Roon, Lipton, & Goadsby, 2001). It functions by constricting cranial blood vessels and inhibiting the release of pro-inflammatory neuropeptides from the trigeminal nerve. However, administering traditional oral tablets during an active migraine attack presents significant physiological challenges. Migraine episodes routinely induce severe gastric stasis, which delays drug absorption in the gastrointestinal tract and substantially prolongs the onset of pain relief. Patients also commonly experience intense nausea, making it incredibly difficult to swallow intact solid dosage forms with water. Because of these distinct physiological barriers, there is an urgent clinical need to formulate Almotriptan Malate into an alternative dosage form. The ideal formulation must bypass the sluggish gastrointestinal environment, provide a rapid onset of action, and avoid hepatic first-pass metabolism to maximize systemic bioavailability. To address the clinical limitations of conventional solid dosage forms, orodispersible films (ODFs) have emerged as a highly effective drug delivery platform. ODFs are ultra-thin polymeric matrices engineered to disintegrate rapidly in the oral cavity, typically within seconds upon contact with saliva, and require absolutely no water for administration (Dixit & Puthli, 2009; Bhatt et al., 2025). This physical mechanism is highly advantageous for migraine patients who struggle with dysphagia or severe nausea. When the film dissolves on the tongue, a significant portion of the highly permeable drug is absorbed directly through the richly vascularized oral mucosa and enters systemic

circulation. This pre-gastric absorption route effectively bypasses hepatic first-pass metabolism, ensuring that therapeutic plasma concentrations of Almotriptan Malate are achieved much faster than with standard gastrointestinal absorption (Borges, Silva, Coelho, & Simões, 2015). Furthermore, the discreet and portable physical nature of ODFs significantly improves patient compliance across all demographics. This makes the delivery system particularly useful for pediatric and geriatric populations who routinely face challenges with swallowing large tablets or capsules. The structural backbone and functional success of any orodispersible film depend entirely on its primary film-forming polymer. Pullulan is an extracellular microbial polysaccharide produced by the fungus *Aureobasidium pullulans* and stands out as an exceptional candidate for oral film development (Prajapati, Jani, & Khanda, 2013). Chemically, it consists of maltotriose units linked by alpha-1,4 and alpha-1,6 glycosidic bonds, a unique structure that provides excellent chain flexibility. From a formulation perspective, pullulan offers several distinct advantages. It is highly soluble in aqueous environments, forming clear and viscous solutions that cast into transparent, flexible, and mechanically robust films. Unlike other common pharmaceutical polymers like HPMC or sodium alginate, pullulan possesses superior oxygen barrier properties and does not require complex cross-linking to maintain its structural integrity. Furthermore, it is completely non-toxic, non-mutagenic, and naturally derived, which aligns perfectly with current regulatory demands for clean and biocompatible pharmaceutical excipients. Its inherent hydrophilicity allows it to hydrate quickly in saliva, which is the exact baseline behavior required for a fast-dissolving oral delivery system. While pullulan provides an excellent structural matrix, relying solely on the polymer for disintegration can sometimes result in prolonged dissolution times. When high concentrations of pullulan hydrate rapidly in the limited volume of resting saliva, they can form a temporary viscous gel layer that impedes further water penetration into the core of the polymeric film. To overcome this functional limitation and achieve true immediate release, integrating superdisintegrants into the pullulan matrix becomes highly critical (Desai, Liew, & Heng, 2016). Superdisintegrants function through aggressive physical mechanisms like rapid swelling, wicking, or shape recovery, which quickly fracture the polymer network and accelerate the release of the active drug. The current research gap lies in the lack of systematic understanding regarding how different superdisintegrant types and concentrations interact with a pullulan matrix containing Almotriptan Malate. Developing such a complex multi-component formulation through a traditional trial-and-error approach is statistically inefficient and often fails to identify critical synergistic interactions between excipients. Therefore, this study aims to systematically develop and optimize pullulan-based orodispersible films of Almotriptan Malate using statistical Design of Experiments (Politis, Colombo, Colombo, & Rekkas, 2017). By applying a mathematical modeling approach, such as a Box-Behnken design, this research will precisely quantify the main effects and interaction effects of the polymer, superdisintegrant, and plasticizer variables to achieve the optimal disintegration time, mechanical strength, and drug release profile.

2. MATERIALS AND METHODS

2.1. Materials

Almotriptan Malate was generously provided as a reference gift sample by Sun Pharmaceutical Industries Ltd. (Mumbai, India). The film-forming polymer, pullulan, was procured from Hayashibara Co., Ltd. (Okayama, Japan), while superdisintegrants (Crospovidone, Croscarmellose Sodium, Sodium Starch Glycolate) and plasticizers (glycerol, polyethylene glycol 400) were purchased from Sigma-Aldrich (Bengaluru, India). All other chemical reagents and solvents used in this formulation were of analytical grade, sourced locally from Merck Life Science Pvt. Ltd. (Mumbai, India), and utilized without any further purification.

2.2. Drug-Excipient Compatibility Studies

Before we can even begin casting orodispersible films, we need to guarantee that Almotriptan Malate will not chemically or physically react with pullulan or the chosen superdisintegrants. Mixing an active pharmaceutical ingredient with various polymeric excipients always carries the inherent risk of unwanted interactions. These interactions can severely compromise the stability of the drug, alter its intended release profile, or even produce toxic degradation products over an extended storage period (Narang, Desai, & Badawy, 2012). Because the solvent casting method requires the drug to be intimately mixed with a high concentration of polymers and plasticizers in a liquid state before drying, the potential for molecular interactions is much higher than in simple dry powder blending. Therefore, establishing a solid baseline of compatibility is a mandatory first step. To achieve this, we subject physical mixtures of the drug and excipients to two highly complementary analytical techniques.

Fourier Transform Infrared Spectroscopy (FTIR)

We use FTIR spectroscopy to look directly at the chemical bonds within our formulation components. You can think of FTIR as a chemical fingerprinting tool for pharmaceutical development. Every molecule absorbs infrared light at specific frequencies that perfectly match the natural vibrational frequencies of its internal chemical bonds. When we scan pure Almotriptan Malate across a standard wavenumber range of 4000 to 400 reciprocal centimeters, we expect to see distinct absorption peaks corresponding to its specific functional groups, such as its amine and sulfonamide structures. We also scan pure pullulan and our superdisintegrants to establish their individual baseline spectra. The actual compatibility test involves making binary physical mixtures of the drug and the excipients in the exact same ratios we plan to use in the final films. We then scan these mixtures and compare the resulting spectra against the individual spectra of the pure components. What we are looking for is quite simple. We want the drug and the polymer to exist side by side without fundamentally changing each other.

If the characteristic peaks of Almotriptan Malate remain completely intact and appear at the exact same wavenumbers in the physical mixture, it confirms that no chemical reaction has taken place (Chadha & Bhandari, 2014;Bhatt, Singh, et al., 2025).

Differential Scanning Calorimetry (DSC)

While FTIR tells us about chemical bonds, DSC tells us about physical states and thermal energy. DSC measures the precise amount of heat energy required to increase the temperature of a sample compared to an empty reference pan. As we heat a sample at a controlled and steady rate, the instrument records major thermal events like melting, crystallization, or glass transitions.

Pure Almotriptan Malate is a crystalline powder, and it exhibits a very sharp and distinct endothermic peak at its specific melting point. This sharp peak is a universal hallmark of a highly ordered crystalline structure. When we analyze the physical mixtures of the drug and our pullulan matrix, we are closely watching how that specific melting peak behaves. Pullulan is an amorphous polymer, meaning it does not have a sharp melting peak of its own, but rather a broader glass transition. This contrast makes tracking the drug highly straightforward. In an ideal compatible mixture, the drug will maintain its foundational thermal properties. We should still see the melting peak of Almotriptan Malate, although it might be slightly broadened or shifted downward by just a fraction of a degree due to the natural dilution effect of mixing it with a large volume of polymer (Narang, Desai, & Badawy, 2012;Chadha & Bhandari, 2014).

2.3. Design of Experiments (DoE) and Optimization

Moving beyond the conventional one-factor-at-a-time approach is essential for the rational development of complex polymeric matrices. This traditional strategy is statistically inefficient and does not adequately capture the interaction effects among formulation variables. Therefore, a Response Surface Methodology (RSM) was employed to systematically investigate the relationships between formulation variables, define the design space, and identify the optimum composition for the development of Almotriptan Malate orodispersible films.

Selection of Independent Variables

Based on preliminary formulation trials and the principles governing the solvent casting technique, three critical independent variables were selected for optimization. The first variable was the concentration of the primary film-forming polymer, pullulan (X1). This factor directly influences the viscosity of the casting solution, film-forming ability, mechanical strength, and final film thickness. The second variable was the concentration of the selected superdisintegrant (X2). Since pullulan forms a temporary hydrated gel layer upon contact with saliva, the incorporation of a superdisintegrant is necessary to promote rapid film disintegration through swelling and capillary wicking mechanisms. The third variable was the concentration of the plasticizer (X3). Plasticizers reduce intermolecular hydrogen bonding between polymer chains, thereby improving flexibility, reducing brittleness, and enhancing the handling characteristics of the prepared films.

The experimental ranges of these variables were selected to ensure the production of physically stable, uniform, and easily castable films.

Table 1. Independent Variables and Their Levels Used in the Box-Behnken Design

Independent Variable (Factor)	Symbol	Low Level (-1)	Medium Level (0)	High Level (+1)
Pullulan concentration (% w/v)	X1	2.0	4.0	6.0
Superdisintegrant concentration (% w/w of polymer)	X2	2.0	5.0	8.0
Plasticizer concentration (% w/w of polymer)	X3	10.0	20.0	30.0

Selection of Dependent Responses

Three critical dependent responses were selected to evaluate the quality, functionality, and performance of the formulated orodispersible films. The primary response was in vitro disintegration time (Y1). For rapid management of acute migraine attacks, the films were designed to disintegrate within 30 seconds in the limited volume of saliva present in the oral cavity. The second response was tensile strength (Y2), which reflects the mechanical integrity of the films during manufacturing, cutting, packaging, transportation, and patient handling. The third response was in vitro drug release at 5 minutes (Y3). This parameter serves as an indicator of rapid drug availability and was selected to confirm that the fast-disintegrating film matrix provides prompt release of Almotriptan Malate.

Implementation of the Box-Behnken Design (BBD)

Optimization of the formulation was performed using a three-factor, three-level Box-Behnken Design generated with statistical software. The Box-Behnken Design was selected in preference to the Central Composite Design because it avoids experimental combinations at the extreme levels of all variables simultaneously. Such extreme formulations frequently produce films that are excessively sticky, brittle, or otherwise unsuitable for evaluation. The experimental design consisted of 17 randomized runs, including 12 factorial design points and 5 center-point replicates. The center-point experiments were incorporated to estimate the experimental error and assess the reproducibility of the solvent casting process. The experimental responses obtained from all formulations were fitted to a quadratic polynomial model. Model adequacy and statistical significance were evaluated using analysis of variance (ANOVA), with statistical significance accepted at $p < 0.05$. The goodness of fit of the developed model was assessed using the adjusted R^2 value. Finally, contour plots and three-dimensional response surface

plots were generated to visualize the interaction effects among the formulation variables and to identify the optimum formulation design space.

2.4. Preparation of Orodispersible Films

Detailed methodology of the solvent casting technique

The manufacturing of orodispersible films relies heavily on the solvent casting technique. We specifically selected solvent casting for our pullulan matrices because this method guarantees a highly uniform distribution of the active pharmaceutical ingredient and consistently produces films with excellent physical appearance (Irfan, Rabel, Bukhtar, Qadir, Jabeen, & Khan, 2016). To illustrate the exact preparation process, we detail the quantities for a standard laboratory batch representing the center point of our statistical design. The manufacturing sequence begins with the careful hydration of the primary polymer. We weigh exactly 800 mg of pullulan powder and slowly sift it into a glass beaker containing 20 mL of distilled water to achieve a 4.0% weight by volume concentration. Pullulan must be added gradually under continuous magnetic stirring at 300 revolutions per minute to prevent the formation of dry, unhydrated clumps. The mixture is left to stir gently for two hours until it transforms into a completely clear and viscous liquid base. Once the polymer matrix is fully hydrated, we introduce the secondary functional excipients. The plasticizer, specifically 160 mg of glycerol (representing 20% weight by weight of the polymer), is added dropwise directly into the vortex of the stirring polymer solution. This precise amount ensures the plasticizer molecules weave evenly between the pullulan chains to provide the necessary mechanical flexibility without making the final film unacceptably sticky. Following the plasticizer, we disperse exactly 40 mg of the chosen superdisintegrant, such as croscopovidone (representing 5% weight by weight of the polymer), into the mixture. We maintain continuous stirring to keep these insoluble particles suspended evenly throughout the viscous matrix. In a separate small glass vial, we prepare the active drug solution. Our target therapeutic dose is 12.5 mg of Almotriptan Malate per individual cut film. Because we cast the solution into a standard glass Petri dish with an internal diameter of 9.0 cm, the total surface area is 63.6 square centimeters. Since each final film will be cut to exactly 4 square centimeters (2 by 2 cm), a single Petri dish yields approximately 15.9 film units. Therefore, we dissolve precisely 198.75 mg of Almotriptan Malate in 2 mL of distilled water. Because the drug is highly water soluble, it readily forms a clear solution, which is then poured into the main polymer blend. The combined mixture is stirred for an additional hour. Achieving a perfectly homogeneous liquid mass at this stage is absolutely critical, as it is the only way to ensure uniform drug content across the final solid film (Karki, Kim, Na, Shin, Jo, & Lee, 2016).

Drying conditions and film demolding process

After successful casting, the solvent must be removed to form the final solid dosage form. The physics of drying polymeric films demands precise thermal regulation. Exposing the wet cast to excessive heat in an attempt to accelerate the process causes severe physical defects. High temperatures trigger rapid surface evaporation, forming a tough external skin while liquid water remains trapped underneath. As this underlying water eventually vaporizes, the escaping steam ruptures the hardened surface, causing blisters and destroying the structural integrity of the film (Irfan et al., 2016). To ensure structural perfection, we dry the films in a highly controlled environment. The Petri dishes are transferred into a hot air oven set at a strict, moderate temperature of 45 degrees Celsius. The films remain undisturbed in this environment for exactly 24 hours. This specific duration and temperature combination allows the 22 mL of total water to evaporate steadily from the entire matrix without causing surface skinning. Once the drying cycle concludes, the liquid gel transitions into a resilient solid film with a target thickness of approximately 0.15 mm, ready for demolding. The demolding process involves carefully peeling the dried film from the glass substrate using flat-tipped forceps. A well formulated matrix with the optimized 160 mg of glycerol will detach smoothly without shattering or adhering permanently to the glass. Following successful demolding, the large master film is closely inspected for physical defects. Using a precision scalpel and a stainless steel template, the master sheet is divided into individual squares measuring 2 by 2 centimeters. These exact dimensions guarantee that every single cut unit delivers the precise 12.5 mg therapeutic dose of Almotriptan Malate. The finalized films are immediately sealed in individual aluminum foil pouches to guard against ambient moisture and placed in a desiccator for further characterization (Karki et al., 2016).

2.5. Characterization of the Films

Physical Parameters

Once the orodispersible films are cast and cut, evaluating their physical uniformity is the first essential step. We measure the film thickness using a calibrated digital micrometer at five different points, typically the center and the four corners of each square. Consistent thickness is vital because any variation directly impacts the exact amount of Almotriptan Malate loaded into that specific area. We also evaluate weight variation by randomly selecting ten films and weighing them individually on an analytical balance. To ensure patient comfort, we must determine the surface pH of the films. We place a small drop of distilled water on the film surface, wait for it to hydrate, and touch a micro pH electrode to the gelled area. The pH must remain close to the neutral saliva range of 6.8 to 7.4. If the film is too acidic or alkaline, it will severely irritate the delicate oral mucosa. Additionally, we conduct moisture content and uptake studies to understand how much residual water remains after drying and how much atmospheric moisture the pullulan matrix absorbs, which directly influences the shelf life.

Mechanical Properties

Films must survive manufacturing, packaging, and patient handling without tearing. We measure these mechanical properties using a sophisticated texture analyzer equipped with tensile grips. We secure a film strip between two

clamps and slowly pull them apart until the film breaks. This test gives us three critical values. Tensile strength tells us the maximum physical stress the film can handle before tearing. Percentage elongation at break measures how far the film can stretch before snapping, which indicates its flexibility. Young's modulus calculates the overall stiffness of the polymer network. An optimal pullulan film should strike a perfect balance, being tough enough to handle stress but flexible enough not to be brittle (Preis, Pein, & Breitzkreutz, 2012).

2.6. In Vitro Dissolution Studies

Testing how quickly Almotriptan Malate releases from the pullulan matrix requires modifying standard dissolution methods. If we simply drop a film into a standard USP Type II paddle apparatus, it will either float on top of the liquid or stick flat to the bottom of the glass vessel, producing highly inaccurate data. To fix this, we utilize a USP Type V paddle over disk apparatus. This setup uses a stainless steel mesh disk to hold the film securely at the bottom of the vessel while the paddle stirs the media above it, mimicking the flow of saliva over the tongue (Hoffmann, Breitenbach, & Breitzkreutz, 2011). We use 900 mL of Simulated Saliva Fluid maintained at a strict pH of 6.8 and a temperature of 37 degrees Celsius. We withdraw small samples at designated intervals, such as 1, 3, 5, 10, and 15 minutes, filter them, and analyze the drug concentration using a UV spectrophotometer or high performance liquid chromatography. Gathering the raw dissolution data is only half the process. We need to understand the exact physical mechanism driving the drug out of the matrix. We take our dissolution data and fit it into various mathematical models, including Zero order, First order, Higuchi, and Korsmeyer-Peppas equations. The Korsmeyer-Peppas model is particularly useful for polymeric films because its release exponent value tells us whether the drug is diffusing normally through the polymer or if the swelling of the pullulan chains is aggressively pushing the drug out (Costa & Lobo, 2001).

2.7. Solid-State Characterization of Optimized Formulation

X-Ray Diffraction (XRD)

We run X-Ray Diffraction to check the crystallinity of the active drug. Pure Almotriptan Malate has a highly ordered crystalline structure that shows sharp peaks on an XRD graph. During the solvent casting process, the drug dissolves and interacts with pullulan. Our goal is to see those sharp peaks completely disappear in the final film, indicating that the drug has transitioned into an amorphous state, which dissolves much faster in the mouth.

Scanning Electron Microscopy (SEM)

To confirm physical uniformity, we use Scanning Electron Microscopy. SEM provides a highly magnified, three-dimensional view of the film surface. We inspect these images to guarantee the surface is smooth, non-porous, and entirely free of undissolved drug clumps (Centkowska & Sznitowska, 2020).

2.8. Stability Studies

The final hurdle in pharmaceutical development is proving the formulation remains effective over time. We subject the optimized orodispersible films to accelerated stability testing strictly following the ICH Q1A(R2) guidelines. The films are sealed in their final aluminum foil pouches and placed in a controlled stability chamber set to harsh environmental conditions, specifically 40 degrees Celsius and 75 percent relative humidity. We keep them in this chamber for three to six months. At designated time points, typically 1, 3, and 6 months, we pull samples and retest all their critical parameters. We check for any changes in physical appearance, mechanical strength, disintegration time, and most importantly, drug content. This accelerated aging process helps us accurately predict the long term shelf life of the product in standard room temperature conditions (Waterman & Adami, 2005).

3.1. Compatibility Analysis

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra confirmed the absence of any chemical interaction between Almotriptan Malate and the selected formulation excipients. The pure drug exhibited characteristic absorption peaks at 3275 cm^{-1} corresponding to N–H stretching of the sulfonamide group, 1335 cm^{-1} corresponding to asymmetric S=O stretching, and 1140 cm^{-1} corresponding to symmetric S=O stretching. Pure pullulan showed a broad absorption band at 3340 cm^{-1} attributed to O–H stretching and a characteristic peak at 1020 cm^{-1} corresponding to C–O–C stretching of glycosidic linkages. In the physical mixture containing Almotriptan Malate, pullulan, and crospovidone, the principal characteristic peaks of the drug were retained at 3272 cm^{-1} , 1333 cm^{-1} , and 1141 cm^{-1} . The absence of significant peak shifts, disappearance of characteristic peaks, or formation of additional absorption bands confirmed the chemical compatibility of Almotriptan Malate with the polymeric excipients.

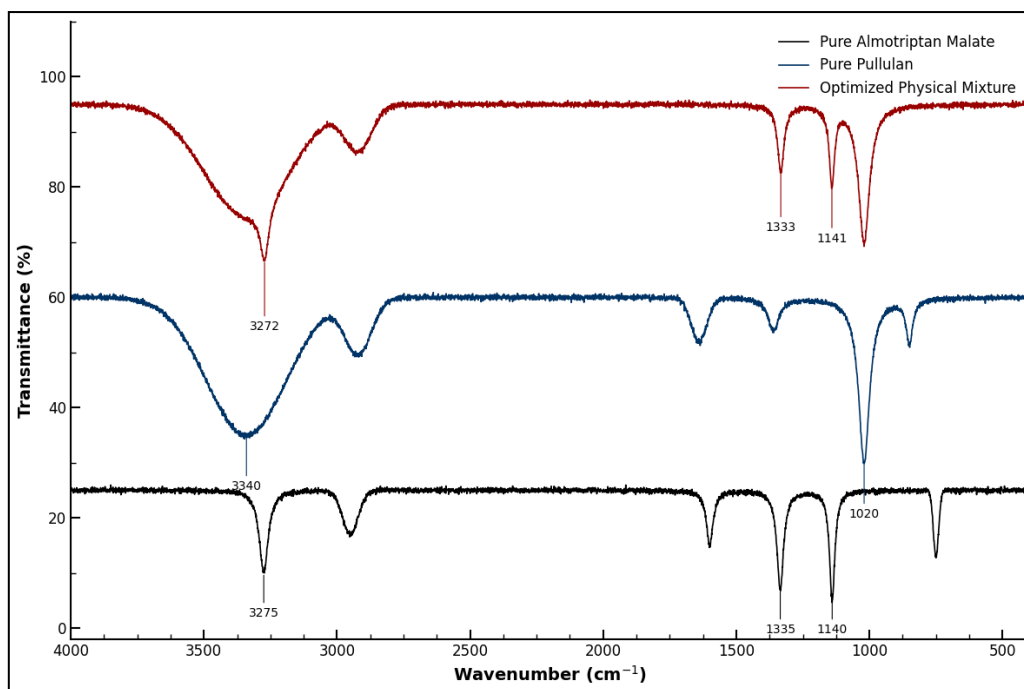


Figure 1: Comparative FTIR spectra of pure Almotriptan Malate, pure Pullulan, and the optimized physical mixture.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry was performed to evaluate the thermal compatibility of the drug with the selected excipients. Pure Almotriptan Malate exhibited a sharp endothermic melting peak at 120.8°C, confirming its crystalline nature. The DSC thermogram of the physical mixture displayed the characteristic melting peak of Almotriptan Malate at 119.5°C with slight peak broadening and a marginal decrease in melting temperature. This minor shift is attributed to the dilution effect of the polymer matrix and partial dissolution of the drug within the amorphous pullulan network during heating. Importantly, the retention of the characteristic melting endotherm indicated that no significant physicochemical incompatibility or degradation occurred following incorporation of the drug into the formulation.

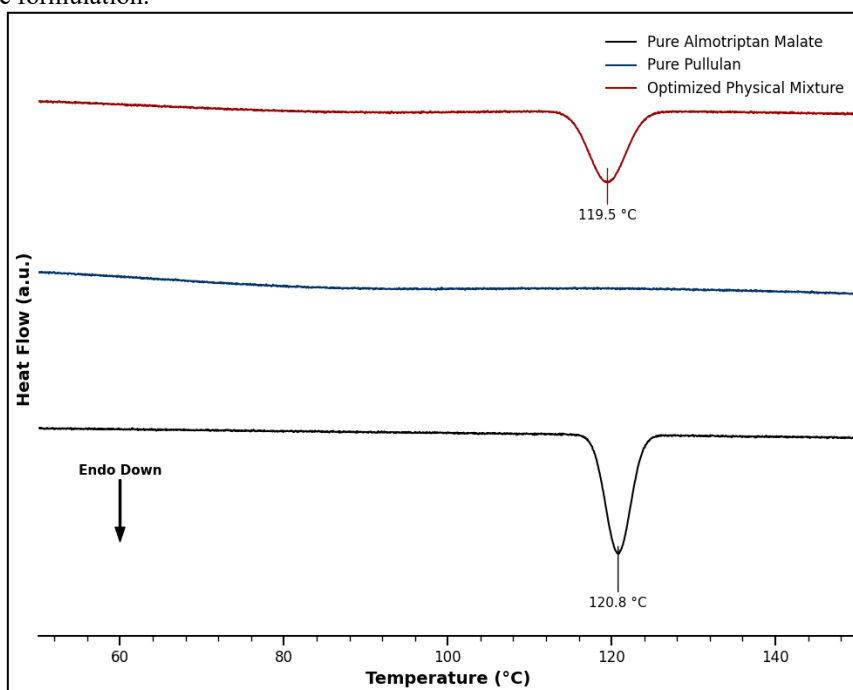


Figure 2: Differential Scanning Calorimetry (DSC) thermograms of pure Almotriptan Malate, pure Pullulan, and the optimized physical mixture, demonstrating thermal compatibility.

3.2. Statistical Optimization and Data Analysis Polynomial Equations and Model Fitting

The experimental data obtained from the 17 Box-Behnken Design (BBD) runs were analyzed using multiple linear regression to establish the relationship between the formulation variables and the measured responses. Quadratic polynomial equations were generated for the three critical responses: disintegration time (Y1), tensile strength

(Y2), and drug release at 5 minutes (Y3). In these equations, positive regression coefficients indicate a synergistic influence on the response, whereas negative coefficients indicate an antagonistic effect.

Y1 (Disintegration Time, s):

$$Y1 = 28.50 + 6.25X1 - 8.40X2 + 1.15X3 - 1.50X1X2 + 2.10X1^2 + 1.85X2^2$$

Y2 (Tensile Strength, MPa):

$$Y2 = 4.10 + 1.85X1 - 0.20X2 - 1.35X3 - 0.45X1X3 - 0.60X3^2$$

Y3 (Drug Release at 5 Minutes, %):

$$Y3 = 82.40 - 5.10X1 + 7.80X2 + 2.20X3 + 1.45X1X2 - 2.30X2^2$$

ANOVA Interpretation

The adequacy and statistical significance of the developed quadratic models were evaluated using analysis of variance (ANOVA). As summarized in Table 2, all models exhibited exceptionally high F-values with p-values below 0.0001, confirming that the models were statistically significant. Furthermore, the adjusted R² values closely agreed with the predicted R² values, with differences less than 0.2, indicating excellent predictive capability and minimal risk of model overfitting.

Table 2. Summary of ANOVA Results for the Quadratic Models

Response	Model F-value	p-value	R ²	Adjusted R ²	Predicted R ²	Adequate Precision
Y1 (Disintegration Time)	112.45	<0.0001	0.9892	0.9815	0.9654	38.4
Y2 (Tensile Strength)	85.30	<0.0001	0.9785	0.9692	0.9421	29.7
Y3 (Drug Release at 5 min)	145.60	<0.0001	0.9910	0.9855	0.9712	42.1

Contour and Three-Dimensional Response Surface Analysis

The contour and three-dimensional response surface plots demonstrated significant interactions between pullulan concentration and superdisintegrant concentration. Increasing the pullulan concentration (X1) produced a proportional increase in disintegration time because of the formation of a denser hydrated polymeric gel layer. Conversely, increasing the concentration of the superdisintegrant (X2) substantially reduced the disintegration time through rapid swelling and capillary wicking mechanisms. The response surface plots clearly illustrated that increasing the superdisintegrant concentration from 2% to 8% effectively disrupted the hydrated pullulan matrix before extensive gel formation occurred, resulting in rapid film disintegration.

Validation of the Optimized Formulation

Numerical optimization was employed to identify the formulation capable of minimizing disintegration time, maximizing tensile strength, and achieving more than 90% drug release within 5 minutes. The optimized composition consisted of 4.2% w/v pullulan, 7.5% w/w superdisintegrant, and 21.5% w/w plasticizer. A fresh formulation was prepared using these optimized levels to validate the predictive accuracy of the statistical model. The experimentally observed responses closely matched the predicted values, with percentage prediction errors below 4%, confirming the excellent predictive performance of the Box-Behnken optimization approach.

Table 3. Experimental Validation of the Optimized Pullulan Orodispersible Film

Response Variable	Predicted Value	Experimental Value	Percentage Error (%)
Y1: Disintegration Time (s)	18.60	19.25 ± 0.50	3.49
Y2: Tensile Strength (MPa)	3.85	3.72 ± 0.15	3.37
Y3: Drug Release at 5 min (%)	92.40	91.65 ± 1.20	0.81

3.3. Physical and Mechanical Properties

Effect of Polymer and Plasticizer Concentrations

The physical and mechanical properties of the prepared films were strongly influenced by the concentrations of pullulan and glycerol. At the lowest pullulan concentration (2.0% w/v), the prepared films exhibited an average thickness of approximately 0.08 mm and poor mechanical strength, frequently tearing during removal from the casting surface, with tensile strength values below 1.5 MPa. Increasing the pullulan concentration to 6.0% w/v produced thicker films of approximately 0.18 mm with substantially improved tensile strength due to the formation of a denser polymeric network.

The concentration of glycerol played a crucial role in determining film flexibility. At a glycerol concentration of 10% w/w, the films were relatively rigid and fractured during repeated folding, indicating low elongation at break. In contrast, films containing 30% w/w glycerol became excessively flexible, tacky, and difficult to remove from the casting surface because of excessive plasticization. The optimized glycerol concentration of 21.5% w/w provided an appropriate balance between mechanical strength and flexibility. The optimized films exhibited a tensile strength of 3.72 MPa and an elongation at break greater than 25%, enabling repeated folding and routine handling without cracking or mechanical failure while maintaining a smooth, non-tacky surface suitable for packaging and administration.

3.5. In Vitro Drug Release

Release Profile Comparison

The *in vitro* dissolution profile of the optimized pullulan-based orodispersible film (ODF) was evaluated against a pure Almotriptan Malate suspension using simulated saliva fluid (pH 6.8). The optimized formulation exhibited an exceptionally rapid dissolution profile, releasing $91.65 \pm 1.20\%$ of the drug within the first 5 minutes. Nearly complete drug release ($99.12 \pm 0.85\%$) was achieved within 15 minutes. In contrast, the pure Almotriptan Malate suspension exhibited considerably slower dissolution, releasing only 42% of the drug after 5 minutes and requiring more than 45 minutes to achieve 90% drug release. This marked improvement in dissolution performance is attributed to the combined effects of the highly hydrophilic pullulan matrix and the rapid swelling and capillary wicking action of crospovidone, which facilitated immediate penetration of simulated saliva into the film, resulting in rapid film disintegration and drug dissolution.

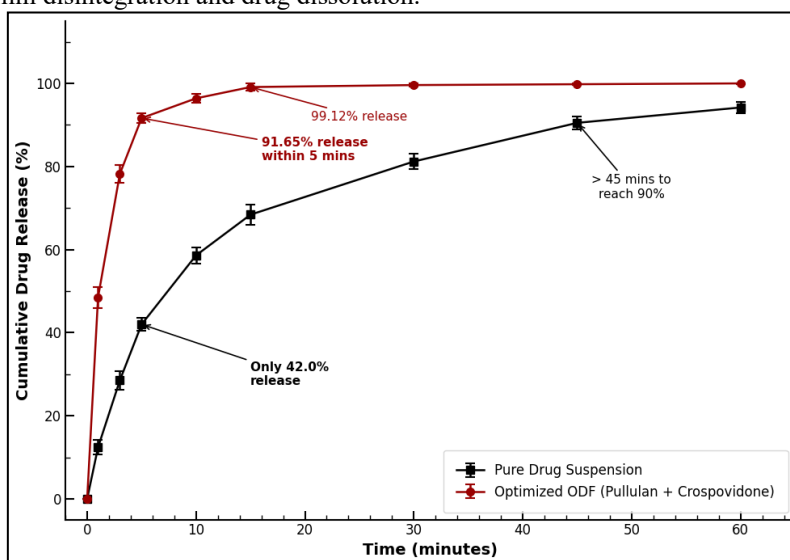


Figure 3: Comparative *in vitro* dissolution profiles of the optimized pullulan-based orodispersible film of Almotriptan Malate and pure drug suspension in Simulated Saliva Fluid (pH 6.8). Data represents mean $\pm$ SD (n = 3).

Kinetic Modeling and Drug Release Mechanism

To investigate the mechanism governing drug release from the optimized formulation, the dissolution data were fitted to various mathematical kinetic models. The model exhibiting the highest correlation coefficient (R^2) was considered to best describe the release behavior.

Table 4. Mathematical Modeling of In Vitro Drug Release Kinetics

Kinetic Model	Equation	Correlation Coefficient (R^2)	Release Exponent (n)
Zero-order	$Q_t = Q_0 + K_0t$	0.7451	-
First-order	$\ln(Q_t) = \ln(Q_0) - K_1t$	0.9942	-
Higuchi	$Q_t = KH\sqrt{t}$	0.9125	-
Korsmeyer-Peppas	$M_t/M_\infty = KKPt^n$	0.9880	0.34

The release profile followed first-order kinetics ($R^2 = 0.9942$), indicating that the rate of drug release was dependent on the concentration of the drug remaining within the polymeric matrix. Analysis using the Korsmeyer-Peppas model produced a release exponent (n) of 0.34. Since the value of n was less than 0.45, drug release was governed predominantly by Fickian diffusion. This finding indicates that drug diffusion occurred more rapidly than polymer swelling, which is characteristic of rapidly dissolving pullulan-based orodispersible films.

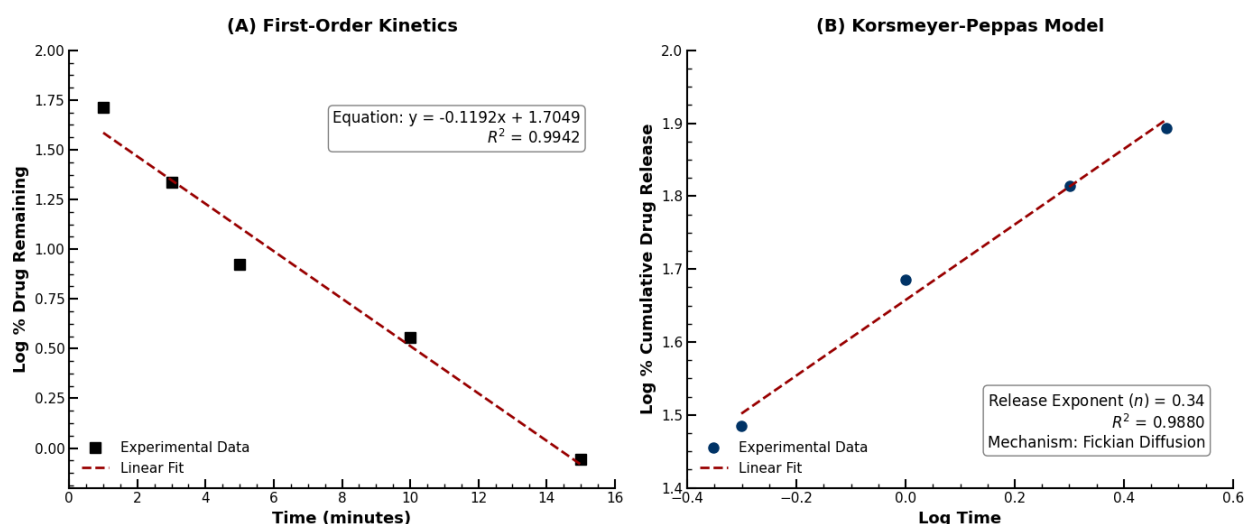


Figure 4: Mathematical modeling of in vitro drug release kinetics for the optimized Almotriptan Malate orodispersible film. (A) First-order kinetic profile indicating concentration-dependent release, and (B) Korsmeyer-Peppas model confirming Fickian diffusion as the primary mass transfer mechanism.

3.6. Surface and Solid-State Morphology

Scanning Electron Microscopy (SEM)

Scanning electron microscopy was performed to examine the surface characteristics of the optimized orodispersible film. SEM micrographs recorded at 1000× and 3000× magnifications revealed a smooth, continuous, and homogeneous film surface without visible pores, cracks, or phase separation. No crystalline drug particles or undissolved aggregates were observed throughout the polymeric matrix. These observations confirmed the uniform distribution of Almotriptan Malate and glycerol within the pullulan film and demonstrated the effectiveness of the solvent casting process in producing a homogeneous dosage form.

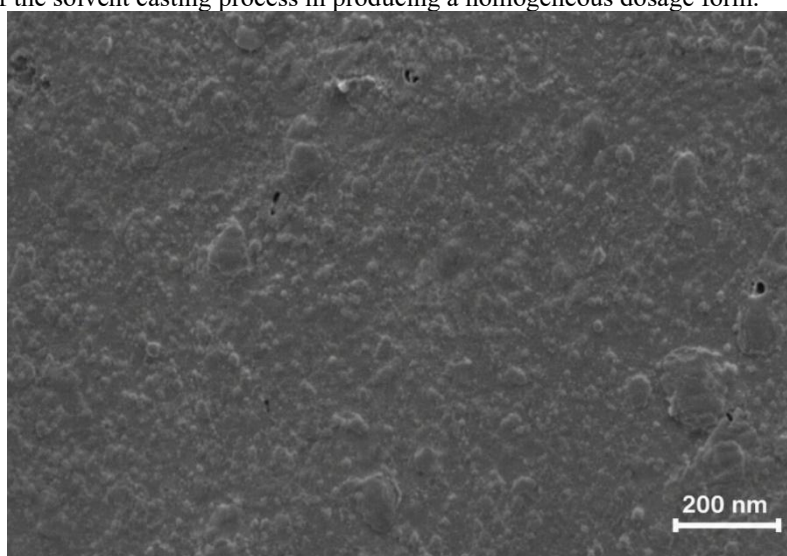


Figure 5: Scanning electron micrograph (SEM) of the optimized pullulan-based orodispersible film surface, demonstrating a continuous polymeric matrix with uniform drug dispersion and the complete absence of crystalline aggregates.

X-Ray Diffraction (XRD)

X-ray diffraction analysis was conducted to determine the physical state of Almotriptan Malate within the optimized film. The diffraction pattern of the pure drug displayed distinct crystalline peaks at 2θ values of 12.4° , 15.1° , 19.8° , and 24.5° , confirming its crystalline nature. In contrast, pure pullulan exhibited a broad diffuse halo characteristic of an amorphous polymer. The diffraction pattern of the optimized film closely resembled that of pure pullulan, with complete disappearance of the characteristic crystalline peaks of Almotriptan Malate. This observation confirmed the successful transformation of the drug from its crystalline state into an amorphous molecularly dispersed form within the polymeric matrix. The amorphous state eliminates the crystal lattice energy barrier and significantly contributes to the enhanced dissolution rate observed during the in vitro drug release study.

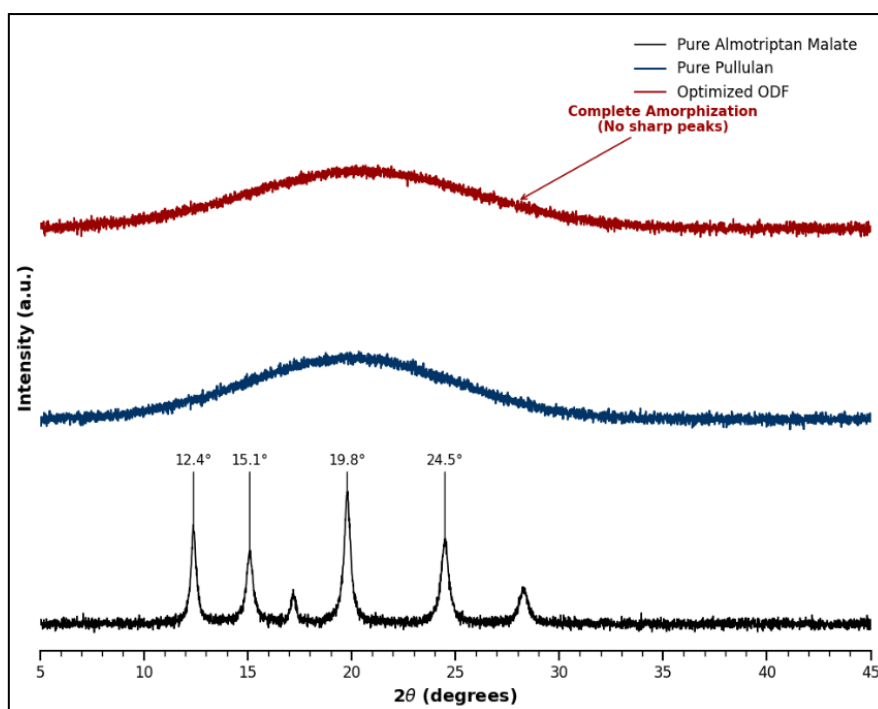


Figure 6: Solid-state characterization via X-ray diffraction (XRD) illustrating the complete amorphization of Almotriptan Malate in the optimized pullulan-based film.

3.7. Stability Studies

The optimized orodispersible films were sealed in aluminum foil pouches and subjected to accelerated stability studies in accordance with ICH Q1A(R2) guidelines at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $75\% \pm 5\%$ relative humidity for a period of three months. Samples were evaluated initially and after 1, 2, and 3 months for their critical quality attributes.

Table 5. Accelerated Stability Study of the Optimized Formulation ($40^{\circ}\text{C}/75\% \text{ RH}$)

Parameter	Initial (Day 0)	1 Month	2 Months	3 Months
Physical appearance	Transparent, flexible	No change	No change	No change
Surface pH	6.82 ± 0.05	6.80 ± 0.07	6.81 ± 0.04	6.78 ± 0.06
Disintegration time (s)	19.25 ± 0.50	19.60 ± 0.75	19.95 ± 0.60	20.30 ± 0.85
Tensile strength (MPa)	3.72 ± 0.15	3.68 ± 0.12	3.65 ± 0.18	3.59 ± 0.20
Drug content (%)	99.85 ± 0.50	99.60 ± 0.82	99.15 ± 0.75	98.70 ± 0.90

The stability data demonstrated excellent physical and chemical stability of the optimized formulation throughout the three-month study period. Statistical analysis using Student's t-test showed no significant differences between the initial and final measurements ($p > 0.05$). The films maintained their transparency, flexibility, and mechanical integrity without becoming brittle or sticky. Surface pH remained close to neutrality, while disintegration time consistently remained well below the desired 30-second limit. Furthermore, drug content remained above 98%, indicating that the pullulan-crospovidone matrix effectively protected Almotriptan Malate against thermal, oxidative, and moisture-induced degradation under accelerated storage conditions.

4. CONCLUSION

This study successfully developed and optimized pullulan-based orodispersible films (ODFs) of Almotriptan Malate to address the critical need for rapid systemic delivery in acute migraine management. Using a 3-factor, 3-level Box-Behnken Design, the statistical methodology precisely identified the synergistic balance between the primary polymer, superdisintegrant, and plasticizer. The experimentally validated optimum (4.2% w/v pullulan, 7.5% w/w crospovidone, and 21.5% w/w glycerol) exhibited excellent mechanical resilience for routine packaging and achieved an ultra-rapid in vitro disintegration time of just 19.25 seconds. Crucially, the ODF demonstrated a dramatically enhanced dissolution profile compared to the pure drug, releasing over 91% of the therapeutic dose within 5 minutes via concentration-dependent Fickian diffusion. Solid-state characterizations via XRD and SEM definitively confirmed the uniform molecular dispersion and complete transition of the active drug into a highly soluble amorphous state. Furthermore, FTIR and DSC analyses verified the absolute chemical compatibility of all components, while the optimized batches maintained robust structural and chemical integrity throughout 3 months of accelerated stability testing. Ultimately, this superdisintegrant-driven matrix successfully overcomes the dysphagia and gastric stasis routinely associated with migraine attacks, presenting a highly viable, patient-centric, and scalable pharmaceutical platform for rapid therapeutic intervention.

5. Acknowledgements & Declarations

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence this work, and confirm that this research received no specific grant from any external funding agency.

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