RESEARCH PAPER

Development, Characterization, and In-Vitro Evaluation of Antihistaminic Oral Thin Films of Loratadine

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ABSTRACT

Background: Loratadine, an antihistamine of 2nd generation, is widely advised for management of allergic conditions but suffers from delayed onset of action in conventional oral dosage forms. Oral thin films (OTFs) offer a promising alternative, ensuring rapid drug release, improved patient compliance, and easy administration without water.

Methods: Loratadine OTFs were developed using solvent casting method and optimized through a 3^2 full factorial design, with Hydroxypropyl Methylcellulose (HPMC K4M) and Chitosan as independent variables. Preformulation studies included organoleptic assessment, FTIR, UV spectrophotometry, melting point, solubility, and calibration curve construction. The films were evaluated for physicochemical properties (transparency, thickness, surface pH, appearance, weight variation, elongation, tensile strength, folding endurance, drug and moisture content), dissolution profile, in-vitro disintegration time, and surface morphology using scanning electron microscopy (SEM). Statistical optimization was led using DesignExpert® software, and kinetics of drug release were analysed via Higuchi, Korsmeyer–Peppas, first-order, and zero-order models.

Results: Optimized batch (F3) exhibited desirable mechanical strength (0.92 N/mm²), high folding endurance (194 ± 3.94), surface pH within physiological range (7.4), and high drug content (99.12%). It showed a speedy in-vitro disintegration time of 12 seconds along with cumulative medication release of 98.22% within 25 minutes. Drug release followed Higuchi and Korsmeyer–Peppas models, revealing diffusion-controlled and anomalous transport mechanisms. SEM analysis revealed a smooth, homogenous surface morphology, confirming uniform drug distribution. Statistical modeling confirmed significant influence of polymer concentrations on disintegration time, drug content, and release profile ($p < 0.005$, desirability = 0.922).

Conclusion: The developed Loratadine OTFs demonstrated excellent physicochemical properties, rapid disintegration, and high drug release, making them a promising platform for fast-acting antihistaminic therapy. This formulation strategy holds potential for enhancing therapeutic efficacy and patient compliance in allergic condition management.

Keywords: Loratadine, Oral Thin Films, 3^2 Full Factorial Design, In-vitro Dissolution, Antihistaminic, Higuchi Model

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INTRODUCTION

Allergic conditions constitute a major public health issue globally, impacting people of all ages and contributing to a considerable burden on healthcare systems[1-3]. These conditions arise due to hypersensitive immune responses to otherwise harmless environmental antigens, like animal dander, dust mites, pollen, and certain foods. Common allergic manifestations include rhinitis, urticaria, conjunctivitis, asthma, and atopic dermatitis[4-6]. Among the pharmacological interventions available, antihistamines are the most frequently prescribed agents, acting by antagonizing the histamine H_1 receptor to alleviate symptoms like nasal congestion, sneezing, itching, along with watery eyes[7-8]. The second-generation antihistamines, exemplified by loratadine, have been favored for their non-sedating profile, long duration of action, and improved safety in comparison with first-generation counterparts[9-10].

Conventional oral dosage forms, specifically tablets and capsules, remain the most broadly utilized means of delivering antihistaminic medications owing to their convenience, cost-effectiveness, and stability[11-12]. However, these dosage forms have inherent limitations, particularly for patient populations such as pediatrics, geriatrics, and individuals with dysphagia (difficulty in swallowing). The need for water to facilitate swallowing, relatively slow onset of action due to gastrointestinal dissolution and absorption, and the possibility of first-pass metabolism can compromise therapeutic outcomes[13-15]. In the context of allergic reactions, where rapid symptom relief is often desired, delays associated with conventional oral administration may reduce patient satisfaction and compliance[16-17].

Oral thin films (OTFs) have emerged as an innovative and patient-centric drug delivery platform which addresses several shortcomings of conventional oral dosage forms.

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These fast-dissolving, polymer-based films are designed for disintegrating swiftly on saliva contact, enabling release of drugs and absorption via oral mucosa[18-19]. This route can bypass a portion of the hepatic 1st-pass metabolism, potentially improving bioavailability besides reducing the required dose[20-21]. OTFs offer the additional benefit of portability, discreet administration without water, and improved compliance in patients with swallowing difficulties. Moreover, the rapid onset of action provided by OTFs is particularly advantageous for acute allergic symptoms, where timely therapeutic intervention is critical[22-23].

From a manufacturing standpoint, OTFs offer formulation flexibility, compatibility with a wide range of APIs, and their ability to incorporate taste-masking agents, flavors, and sweeteners to enhance patient acceptability[24-25]. These advantages have led to their increasing adoption in therapeutic areas including antiemetics, analgesics, cardiovascular agents, and antihistamines.

Loratadine is a non-sedating H_1 receptor antagonist of 2nd-generation, commonly utilized in the management of chronic urticaria and allergic rhinitis. This drug is regarded as a Class II substance within the BCS, defined by its superior permeability besides little solubility. While its pharmacokinetic profile—marked by a relatively long half-life of approximately 8–14 hours—allows for once-daily dosing, its limited aqueous solubility can restrict dissolution rate and bioavailability in conventional solid oral dosage forms. This limitation is particularly relevant for fast-acting therapy, where dissolution is the rate-limiting step. Developing a formulation that enhances the dissolution profile of loratadine can improve therapeutic efficacy, especially in the initial onset phase[26-29].

Polymeric excipients serve a significant function in establishing mechanical strength, disintegration time, as well as drug release profile of OTFs[30-31]. HPMC K4M and Chitosan were chosen as primary film-forming agents in this study due to their complementary functional attributes. HPMC K4M is a semi-synthetic, hydrophilic polymer with exceptional film-forming ability, mechanical strength, and controlled hydration properties. Its compatibility with a extensive range of APIs and excipients, along with its non-toxic and non-irritant nature, makes it a preferred polymer for OTFs. The viscosity grade K4M offers a balanced profile of flexibility and tensile strength, essential for the physical integrity of thin films[32-33].

Chitosan, a natural cationic polysaccharide derived from chitin, possesses bioadhesive properties that enhance mucosal retention and drug absorption. Its ability to form hydrogen bonds with mucosal surfaces can prolong the residence time of the film, potentially enhancing local drug absorption. Furthermore, chitosan exhibits antimicrobial properties and can modulate film disintegration rates through its hydrophilic yet structurally rigid backbone[34-35]. The combination of HPMC K4M and Chitosan allows for tailoring the film's disintegration time, tensile strength, and dissolution characteristics, making it possible to optimize patient-centric attributes such as rapid onset and ease of administration.

The current study was undertaken with the objective of developing, characterizing, as well as optimizing mouth-dissolving oral thin films of loratadine for rapid antihistaminic action. The overarching goal was to create a formulation that overcomes the solubility-related limitations of loratadine while leveraging the advantages of the OTF platform to enhance patient compliance and therapeutic performance.

The specific objectives were:

To perform preformulation studies on loratadine, including physicochemical characterization and compatibility assessment with selected excipients.

To design and prepare loratadine OTFs using the solvent casting approach plus optimize formulation using a 3^2 full factorial design with HPMC K4M and Chitosan as independent variables.

To evaluate the prepared films for physicochemical parameters, mechanical properties, medication content uniformity, dissolution profile, and *in-vitro* disintegration time.

To analyze drug release kinetics using mathematical modeling and identify the dominant release mechanism.

To identify the optimized formulation based on statistical desirability and its potential for clinical application.

By addressing these objectives, this work aims to provide a robust, patient-friendly dosage form of loratadine that ensures rapid therapeutic onset and improved patient adherence in the management of allergic conditions.

MATERIALS AND METHODS

Loratadine (active pharmaceutical ingredients) was procured from Sigma Aldrich (India). HPMC K4M and Chitosan were obtained from Sigma Aldrich, serving as the primary film-forming agents. Other excipients included Polyvinyl Alcohol (PVA, Rankem), Glycerin (Rankem), Benzoic Acid (Sigma Aldrich), Sodium Benzoate (Merck), Citric Acid (Merck), Sucralose (Rankem), Sodium Lauryl Sulfate (Merck), Clove (Rankem), Crosscarmellose Sodium (Merck), and Crospovidone (Merck). All reagents as well as chemicals utilized were of analytical quality. Purified H_2O was obtained in-house and used throughout the study.

Preformulation Studies

Organoleptic Properties

Loratadine was evaluated visually for color, odor, texture, and taste. Loratadine appeared as a crystalline powder ranging from whitish to off-white color without any odor with a somewhat bitter taste.

Identification Tests

Infrared Spectroscopy (IR): Potassium bromide (KBr) was dried in oven for 1 hour at 60°C and mixed with each drug in a suitable proportion to form translucent pellets. IR spectra were recorded over the range 4000–400 per cm to recognize typical functional groups.

UV Spectrophotometry: Standard solutions of Loratadine were prepared in methanol and scanned between 200–400 nm to determine wavelength of maximum absorbance (λ_{max}). Loratadine showed λ_{max} at 252 nm.

Melting Point Determination

MP of Loratadine was checked by capillary approach utilizing a Thiele's tube assembly and found to be 135 °C, respectively, consistent with pharmacopeial standards.

Solubility Studies

Solubility was tested in distilled H_2O, methanol, phosphate buffer of 6.8pH, and buffer of 1.2pH. Loratadine was soluble in methanol and pH 1.2 buffer, sparingly soluble in H_2O, and slightly soluble in buffer of 6.8 pH.

Calibration Curve Preparation

Stock solutions (1000 µg/mL) of each drug were prepared in methanol and diluted to concentrations of 1, 2, 5, 7, and 10µg/mL. Absorbance was noted at respective λ_{max} to construct calibration curves, which demonstrated linearity in the tested range[36-38].

Formulation Design

A 3^2 full factorial design was utilized for optimisation. 2 independent variables were selected:

X_1: HPMC K4M concentration (5%, 10%, 15%)

X_2: Chitosan concentration (15%, 20%, 25%)

Dependent variables (responses) included: medication content, in-vitro disintegration time, along with cumulative drug release (%CDR)[39-41].

Table 1: Factors and levels in 3^2 factorial design

Coded Level	X_1: HPMC K4M (%)	X_2: Chitosan (%)
-1	5	15
0	10	20
+1	15	25

Table 2: Formulation of Moth Dissolving Film of Loratidine utilizing 3^2 Full Factorial Design

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Loratidine	10	10	10	10	10	10	10	10	10
HPMC K4M	5	10	15	5	10	15	5	10	15
Chitosan	25	25	25	20	20	20	15	15	15
Glycerin	10	10	10	10	10	10	10	10	10
Polyvinyl Alcohol	15	10	--	15	10	-	10	15	--
Benzoic Acid	1	2	1	2	1	2	1	2	2
Sodium Benzoate	2	1	2	1	2	1	2	1	1
Citric Acid	5	5	5	5	5	5	5	5	5
Sucralose	3	3	3	3	3	3	3	3	3
Clove	2	2	2	2	2	2	2	2	2
Sodium Lauryl Sulfate	2	3	2	3	2	2	2	2	2
Crosscarmellose Sodium	3	3	3	3	3	3	3	3	3
Crospovidine	3	3	3	3	3	3	3	3	3
Purified H_2O	q.s.								

Preparation of Loratadine Oral Thin Films

OTFs were formulated by solvent casting method. HPMC K4M was dispersed in distilled H_2O and stirred at 1000 rpm at 60°C until hydrated. Chitosan was dispersed separately in an aqueous solution containing citric acid. Other excipients (plasticizers, sweeteners, flavors, preservatives) were dissolved in the polymer solutions. Loratadine, dissolved in appropriate solvent, was incorporated into polymer mixture with continuous stirring. Air bubbles were eliminated by vacuum, and solution was cast into molds then dried at ambient conditions. Dried films were cut into uniform strips, packed, and stored in desiccators until use[42-43].

Evaluation Parameters

Physical Appearance: Visual inspection for color, homogeneity, transparency, and surface defects.

Surface pH: Measured after moistening the film surface with distilled water.

Thickness: Measured at five points per film using a thickness gauge.

Weight Variation: Determined by weighing ten films individually and calculating mean ± SD.

Folding Endurance: Number of folds at the same point until breakage.

Tensile Strength: Determined using a custom tensile strength apparatus; calculated as force at break/cross- sectional area.

Percent Elongation: Measured by displacement before break under applied force.

Moisture Content: Measured by Karl Fischer titration.

Drug Content: Determined by dissolving film powder correspondent to 10 mg Loratadine in methanolic HCl and analyzing spectrophotometrically.

In-Vitro Disintegration Time: Recorded as time for complete disintegration in simulated salivary conditions.

In-Vitro Dissolution investigations: led in USP Dissolution Apparatus I, 50rpm, 900mL phosphate buffer of 6.8pH, 37±0.5°C, sampling at decided periods [44-46].

Statistical Optimization

Formulation optimization was performed using **DesignExpert® software** (Stat-Ease Inc., USA) applying response surface methodology (RSM). Quadratic models were generated for each response, and ANOVA was used to determine model significance. Optimized preparation was selected on basis of desirability criteria, targeting minimum disintegration time, high drug content, and maximum %CDR.

RESULTS AND DISCUSSION

Preformulation Studies

Organoleptic Properties

Loratadine was noticed as a crystalline powder, white to off-white color no odour, with slightly bitter taste. These attributes are in agreement with pharmacopeial specifications, indicating good quality and purity.

Identification Tests

FTIR Spectroscopy proved occurrence of functional moieties corresponding to ester carbonyl (~1677 cm^{-1}), aromatic C–H (~3029 cm^{-1}), aromatic C=C (~1603, 1566 cm^{-1}), alkyl C–H (~2954 cm^{-1}), ester C–O–C (~1211 cm^{-1}), and aryl chloride (~762 cm^{-1}). The spectrum matched the reference profile, confirming identity and chemical integrity.

UV Spectrophotometry identified λ_{max} at 252 nm in methanol, consistent with reported values, confirming the drug's spectral fingerprint.

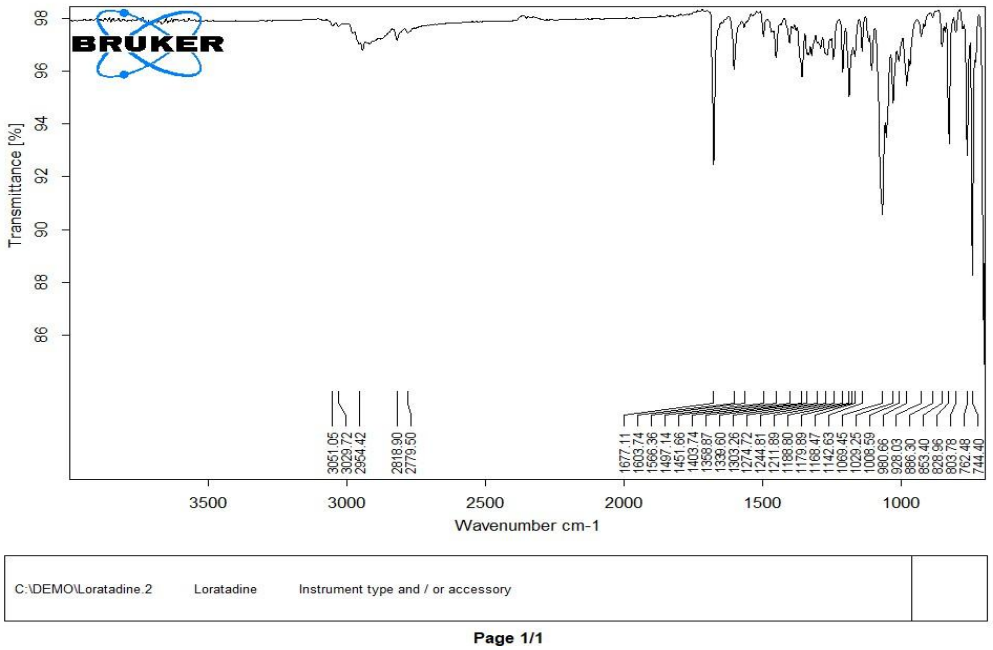

Figure 1: IR Spectra of Loratadine

Melting Point

The melting point was recorded at 135 °C, aligning with pharmacopeial standards, indicating crystalline nature and purity.

Solubility

Loratadine was soluble in pH 1.2 buffer and methanol, slightly soluble in pH 6.8 buffer, and sparingly soluble in water. This low aqueous solubility supports the need for formulation strategies enhancing dissolution rate.

Calibration Curve

The drug exhibited linear absorbance–concentration relationship between 1–10 µg/mL at 252 nm, with correlation coefficient (R^2) >0.99, validating UV spectrophotometry for quantitative analysis.

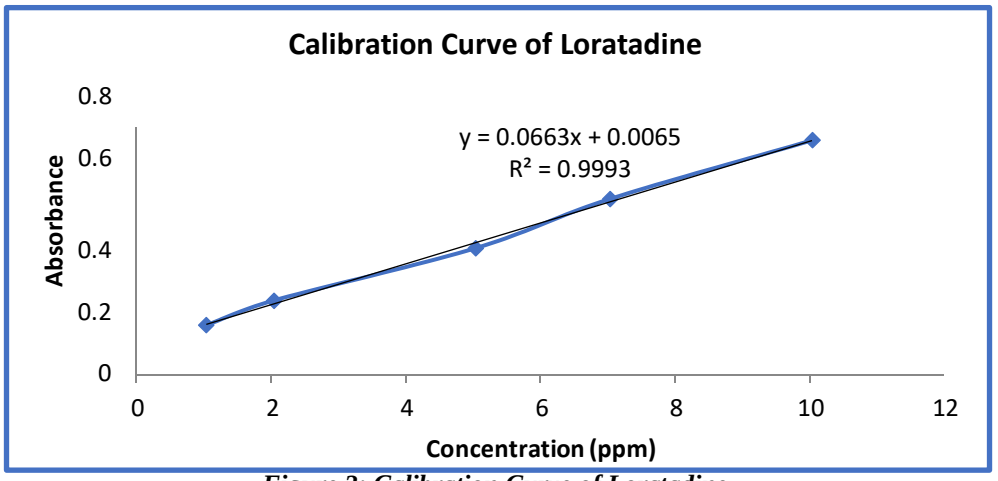

Figure 2: Calibration Curve of Loratadine

Formulation Evaluation

Physicochemical and Mechanical Properties

All nine factorial batches (F1–F9) produced films with smooth surfaces, uniform thickness (0.5–1.0 mm), and minimal weight variation (40.58–49.54 mg). Surface pH values ranged from 6.5 to 7.6, within physiological salivary range, ensuring minimal mucosal irritation potential.

Folding endurance exceeded 100 for all films, with the highest values in F3 (194 ± 3.94) and F9 (196 ± 1.15), confirming good flexibility.

Tensile strength ranged from 0.23 N/mm² (F2, F5, F6) to 0.92 N/mm² (F8), indicating variable mechanical robustness based on polymer ratios. Percent elongation was highest in F3 (8.76%) and F4 (8.23%), showing superior stretchability. Moisture content was nil for all films, favoring stability and reduced microbial growth risk.

Table 3: Evaluation of MDF batches of Loratadine (F1 To F9) using factorial design

Batch	Appearance Transparency	Surface pH	Weight Variation (mg)	Thickness (mm)	Folding Endurance
F-1	Colorless, Transparent	6.8	40.58±0.421	1.0±0.014	147±0.448
F-2	Colorless, Transparent	7.3	42.75±0.376	0.8±0.074	185±2.154
F-3	Colorless, Transparent	7.4	48.96±0.846	0.7±0.085	194±3.945
F-4	Colorless, Transparent	7.6	44.45±0.231	0.5±0.069	161±3.652
F-5	Colorless, Transparent	6.9	40.64±0.345	0.7±0.065	135±2.497
F-6	Colorless, Transparent	6.7	42.17±0.654	0.9±0.017	165±2.465
F-7	White Opaque	7.2	49.54±0.348	0.7±0.046	174±1.764
F-8	Colorless, Transparent	7.1	43.34±0.135	0.9±0.074	144±3.864
F-9	White Opaque	6.5	42.46±0.453	0.8±0.025	42.46±0.453

Drug Content Uniformity

Drug content varied from 93.54% (F3, F4) to 99.12% (F8), all within pharmacopeial acceptance limits (±10%), indicating uniform distribution of Loratadine in the polymer matrix.

In-Vitro Disintegration

Disintegration times ranged from 12 s (F8) to 32 s (F3). Faster disintegration in F8 was attributed to optimal polymer–plasticizer balance, while prolonged disintegration in F3 related to higher thickness and folding endurance.

***In-Vitro* Dissolution Studies**

The dissolution profile demonstrated rapid and sustained release across all batches. Initial release at 2 min ranged from 14.56% (F9) to 31.98% (F2). By 15 min, most batches had released over 79%, and near-complete release was achieved at 25 min, with F3 reaching 98.22%.

Higher release rates in F1–F4 were associated with increased hydrophilic polymer content, improving wettability and disintegration.

Table 4: In-Vitro release of Loratadine

Time (min)	% Cumulative Drug release of Loratadine								
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**	**F-9**
0	00	00	00	00	00	00	00	00	00
2	27.14	31.98	29.87	25.56	19.98	17.44	21.98	18.34	14.56
5	39.23	43.56	42.34	41.87	34.78	31.32	36.55	39.98	29.28
10	66.87	67.45	63.65	64.45	51.55	53.23	49.23	50.65	59.91
15	86.57	82.27	81.34	79.12	69.12	67.87	73.67	74.12	74.45
20	94.54	91.97	96.64	92.66	86.45	85.54	90.17	89.96	88.66
25	97.53	97.43	98.22	96.95	95.32	94.23	90.74	93.65	98.43

Drug Release Kinetics

Kinetic modeling demonstrated that the release of Loratadine predominantly conformed to the Higuchi model across most batches, indicating a diffusion-controlled release mechanism. The Korsmeyer–Peppas model indicated release exponent (n) values amid 0.45-0.89, suggesting anomalous transport characterized by a combination of drug diffusion as well as polymer erosion.

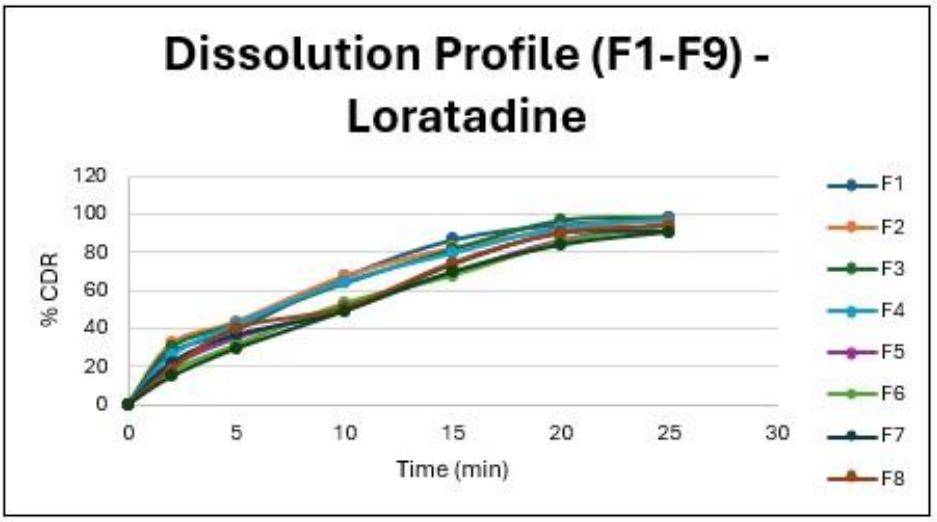

Figure 3: Dissolution Profile of Loratadine

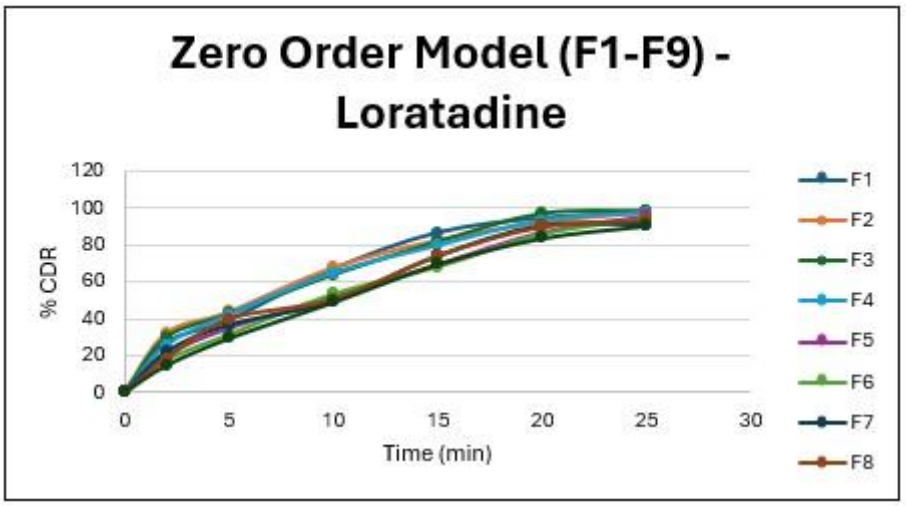

Figure 4: Zero Order Model of Loratadine

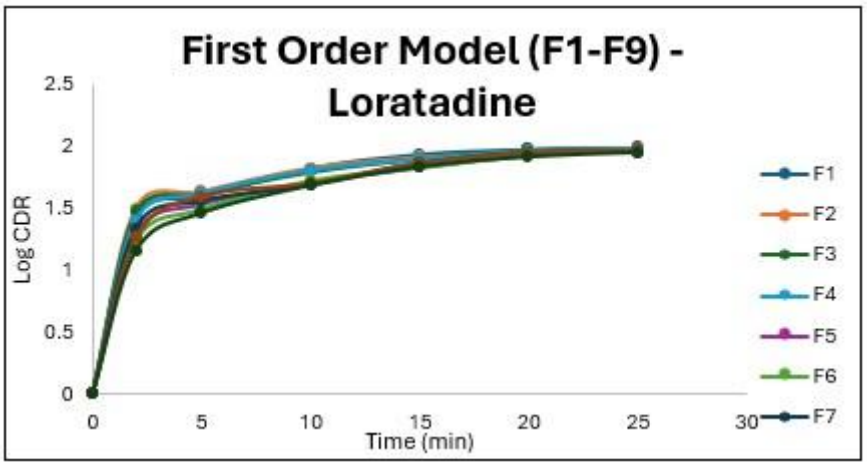

Figure 5: First Order Model of Loratadine

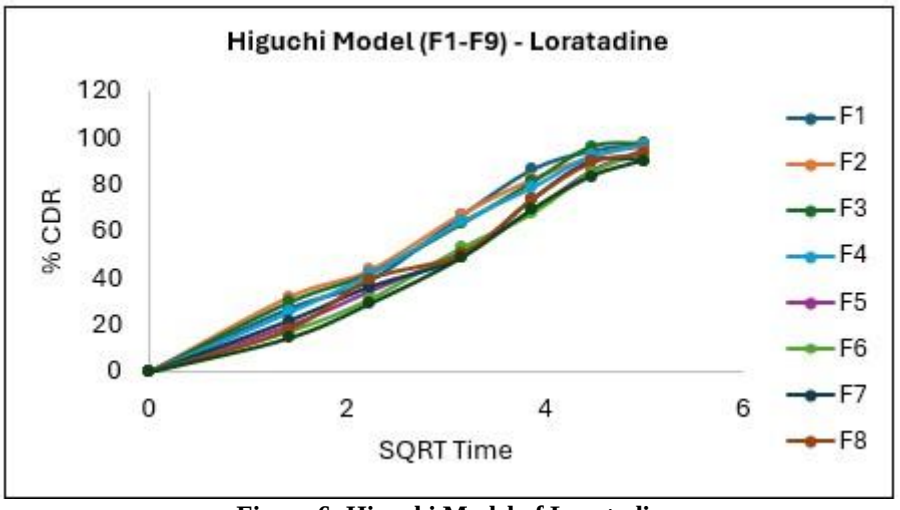

Figure 6: Higuchi Model of Loratadine

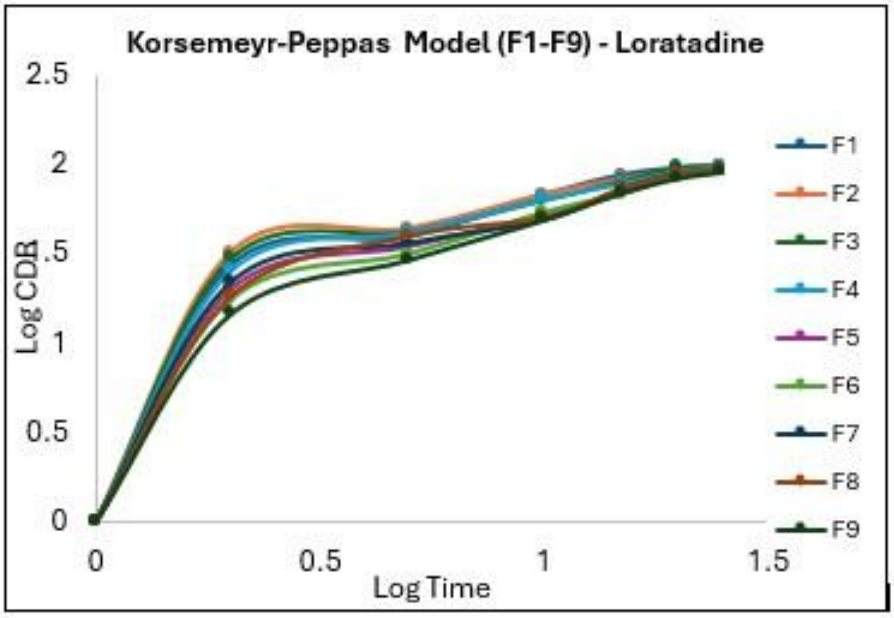

Figure 7: Korsemeyr-Peppas Model of Loratadine

Statistical Optimization

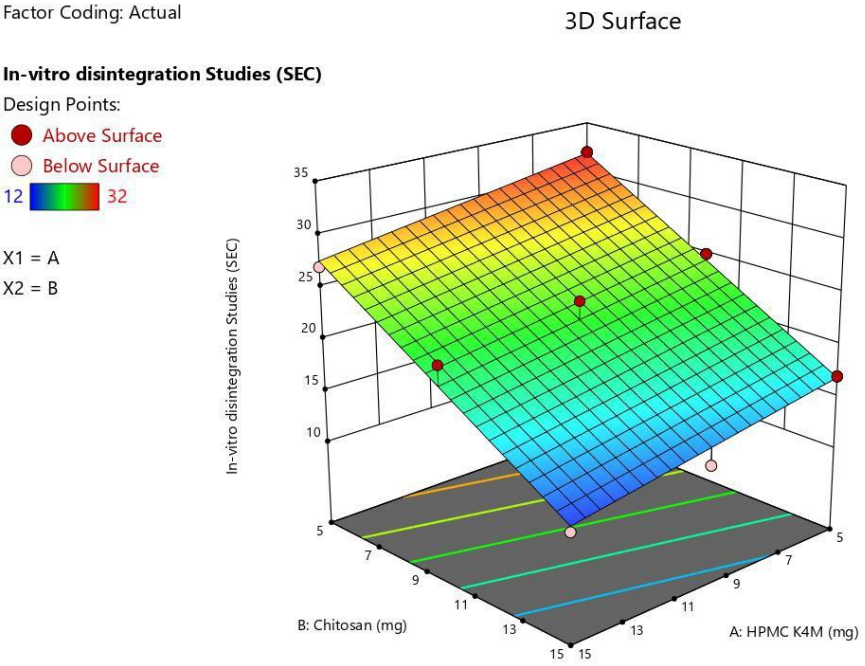

Figure 8: 3D Surface Plot Graph of In-vitro disintegration Studies of Loratadine

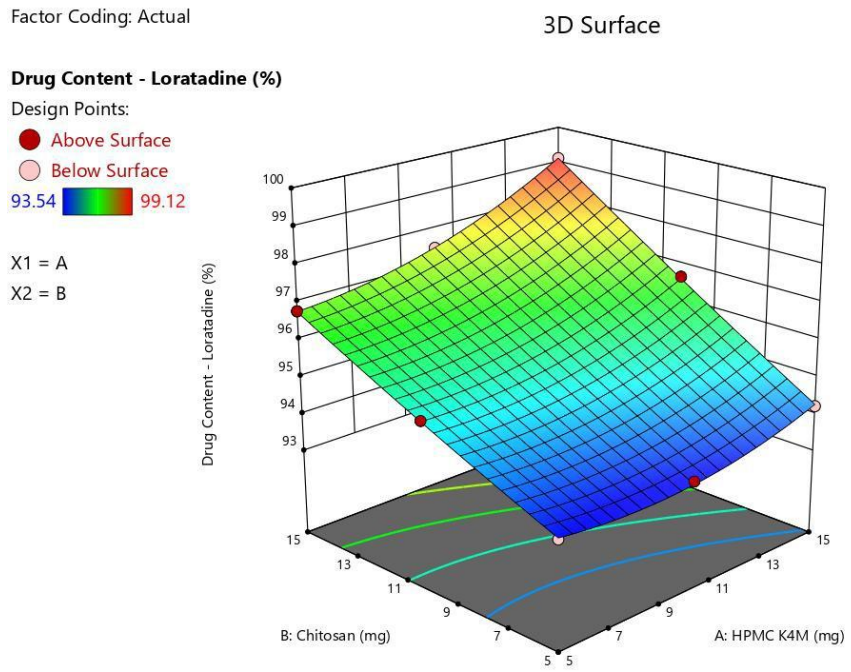

Figure 9: 3D Surface Plot Graph of Drug Content – Loratadine

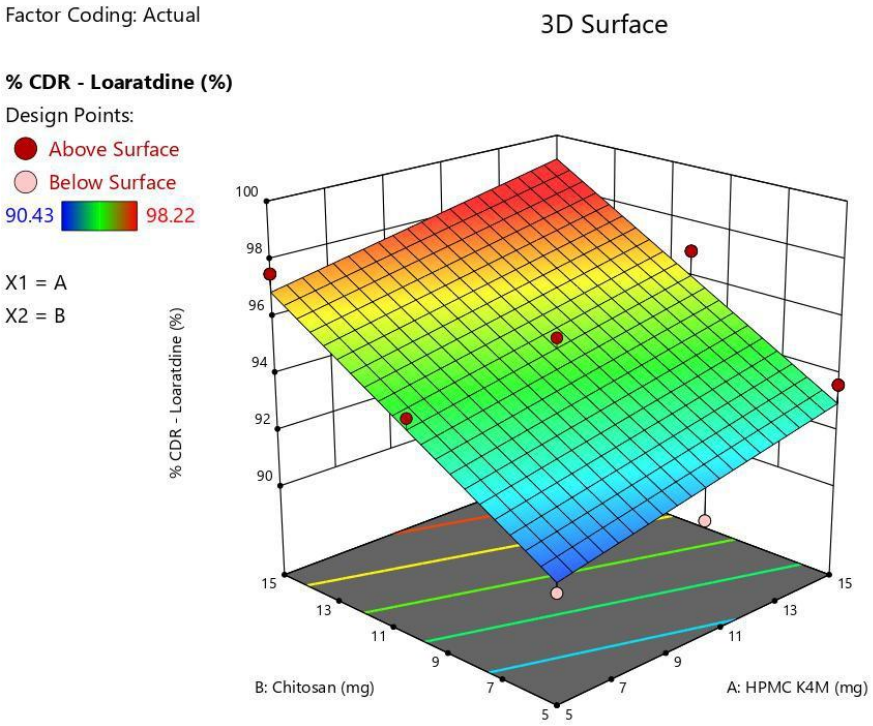

Figure 10: 3D Surface Plot Graph of % CDR – Loratadine

Table 5: Statistical analysis of generated model

Response	**F value**	**P value**	**R^2 value**	**Adequate precision**
In-vitro Disintegration Studies - Loratadine	26.14	0.0011	0.8971	13.5135
Drug Content – Loratadine	21.33	0.0019	0.8767	10.0436
%CDR – Loratadine	78.98	0.0001	0.9634	22.0095

Table 6: Solution Proposed by DesignExpert of Loratadine

No.	HPMC K4M	Chitosan	In-vitro Disintegration Studies (sec) Loratadine	Drug Content – Loratadine (%)	%CDR – Loratadine	Desirability
1	15.000	15.000	12.346	99.257	99.133	0.922

Response Surface Methodology (RSM) analysis demonstrated that HPMC K4M and Chitosan concentrations significantly influenced disintegration time, drug content, and %CDR ($p < 0.005$). The optimized formulation, identified as F3, achieved:

Disintegration time: 12.35 s
Drug content: 99.26%
%CDR: 99.13%
with a desirability score of 0.922, making it the best candidate for rapid antihistaminic action.

The optimized Loratadine OTF formulation exhibited rapid disintegration, high drug content, and near-complete drug release within 25 minutes, with mechanical properties suitable for patient handling and compliance. Diffusion-based release, confirmed by Higuchi and Peppas models, along with uniform morphology, makes it a promising platform for fast-acting antihistaminic therapy.

CONCLUSION

The present study successfully developed plus optimized mouth-dissolving oral thin films (OTFs) of Loratadine using a 3^2 full factorial design with HPMC K4M and Chitosan as the primary film-forming polymers. Preformulation studies confirmed the drug's identity, purity, and compatibility with selected excipients through FTIR, UV, melting point analysis, and solubility profiling. The solvent casting method produced films with uniform thickness, minimal weight variation, acceptable surface pH, and high folding endurance, ensuring both mechanical integrity and patient acceptability.

Among the nine formulations, batch F3 appeared as the optimized formulation, displaying an excellent equilibrium of physicomechanical strength (tensile strength 0.92 N/mm^2), high folding endurance (194), rapid disintegration (12.35 seconds), and high drug content (99.26%). In-vitro dissolution studies demonstrated brisk and near-complete release of drug (99.13% within 25 minutes), fitting best to the Higuchi model, indicative of diffusion-controlled release. Korsmeyer–Peppas analysis revealed anomalous transport, suggesting a combined mechanism of drug diffusion and polymer erosion. SEM analysis confirmed smooth surface morphology and uniform drug dispersion without visible crystallinity.

Statistical optimization using DesignExpert® validated the significant influence of polymer concentrations on disintegration time, cumulative drug release, along with drug content, achieving a desirability score of 0.922 for the optimized batch.

Overall, the formulated Loratadine OTFs offer a patient-friendly, fast-dissolving, and effective substitute to conventional dosage forms meant for oral administration, especially advantageous for individuals facing trouble in swallowing or those requiring rapid relief from allergic symptoms. The approach can be extended to other poorly soluble drugs to enhance onset of action and improve therapeutic outcomes

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