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Design and Evaluation of Itraconazole-Loaded Mucoadhesive Buccal Films for Enhanced Antifungal Bioavailability

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Abstract The present study aimed to design and evaluate itraconazole-loaded mucoadhesive buccal films using natural polymers to enhance local antifungal therapy and oral bioavailability. Itraconazole, a poorly water-soluble antifungal agent, exhibits limited oral absorption and variable systemic exposure, making buccal delivery a promising alternative for treating oral candidiasis. Buccal films were prepared by the solvent casting method employing chitosan and sodium alginate either alone or in combination. All formulations demonstrated acceptable physic mechanical properties, including uniform thickness, smooth surface, adequate folding endurance, near-neutral surface pH, and uniform drug content. FTIR studies confirmed drug–excipient compatibility. In vitro release studies revealed rapid drug release from chitosan films, while chitosan–alginate blends provided sustained release suitable for prolonged buccal residence. Release kinetics followed Zero-order and Korsmeyer–Peppas models, indicating diffusion-controlled drug release. Among all batches, formulation F6 showed optimal mucoadhesion, extended residence time, and sustained itraconazole release for up to 8 hours, with good stability under accelerated conditions. The developed buccal films offer a promising patient-friendly approach for effective localized antifungal therapy.

Keywords: Itraconazole; Mucoadhesive buccal films; Chitosan; Sodium alginate; Oral candidiasis.

INTRODUCTION

Muco-adhesive drug-delivery systems (MDS) are formulations designed to stick to mucosal surfaces (oral, buccal, nasal, ophthalmic, vaginal, rectal, and gastrointestinal) to ensure extended residence time and targeted or systemic drug release. The fundamental justification for muco-adhesion is to enhance the contact duration between the drug-laden vehicle and the absorptive epithelium, thereby augmenting bioavailability, decreasing dosing frequency, mitigating systemic side effects, and facilitating more efficacious local therapy (e.g., for oral or vaginal candidiasis). Muco-adhesive strategies are especially appealing for pharmaceuticals that exhibit low oral bioavailability, considerable first-pass metabolism, or are designed for localized effects at mucosal locations [i, ii]. Muco-adhesive biodegradable systems have shown advantages in both clinical and commercial applications across several conditions. Buccal films produce fast local concentrations for antifungals and analgesics, whereas vaginal muco-adhesive matrices facilitate extended local treatment for candidiasis and other infections with less systemic exposure.[iii] The buccal mucosa, which lines the cheek and inner lip, offers an advantageous pathway for both local and systemic drug administration due to its high

vascularization, relative permeability compared to keratinized oral areas, and ease of access for topical application. Buccal administration can circumvent hepatic first-pass metabolism, diminish gastrointestinal degradation for sensitive medications, and facilitate rapid systemic absorption for appropriate small molecules and certain biologics. The buccal route is especially advantageous for medications necessitating rapid onset, diminished dosage, or evasion of gastrointestinal adverse effects (e.g., antiemetic's, analgesics, some cardiovascular medicines), in addition to local treatments like antifungals for oral candidiasis. Reviews on buccal delivery underscore these clinical factors and the increasing interest in mucoadhesive methods to enhance residence duration at the mucosal interface[iv].

Buccal dose forms comprise mucoadhesive films, tablets (adhesive/patches), gels, sprays (film-forming sprays), wafers, and nanoparticle-encapsulated matrices. Film/patch systems are favoured due to their ability to provide regulated residence while ensuring user-friendliness, and they can be designed as either single or layered structures (e.g., an adhesive layer, drug reservoir, and backing layer). Mucoadhesive polymers (chitosan, carbomers, HPMC, sodium carboxymethylcellulose, pullulan, and malt dextrin), plasticizers (glycerol, PEG), permeation enhancers (bile salts, surfactants, and fatty acids), and taste-masking agents are all chosen by formulators as needed. Reviews offer comprehensive comparison data on polymer performance, mucoadhesion strength, and effects on mechanical and disintegration qualities[v].

Itraconazole is white crystalline powder that is lipophilic triazole antifungal drug with a wide spectrum of activity against yeasts, dermatophytes, and certain moulds, including Candida spp., Aspergillus spp., Blastomyces dermatitidis, Histoplasma capsulatum, and Sporothrix schenckii. Itraconazole exerts its antifungal effects by blocking 14α-demethylase, a fungal cytochrome P450 enzyme responsible for converting lanosterol to ergo sterol, an essential component of fungal cell membranes. [vi] Traditional oral itraconazole treatment is constrained by inadequate water solubility, inconsistent absorption, and systemic side effects. No previous studies have recorded the formulation of itraconazole buccal films utilising chitosan–alginate natural polymer matrix for targeted antifungal delivery.

MATERIALS AND METHODS

Chemicals

Itraconazole was obtained as Gift sample from UniChem laboratories Ltd., Mumbai. Chitosan purchased from Sain Medicaments Pvt Ltd., Hyderabad. Sodium alginate and Peppermint flavour were purchased from HI media Lab Pvt Ltd., Mumbai. Xylitol purchased from S.D. Fine- Chemical Ltd, Mumbai. Glyserol purchased from Merck life science Pvt Ltd., Hyderabad. All the used reagents and chemicals were of analytical grade.

Calibration curve of ITZ by UV spectrophotometry[vii]

The absorbance of each working standard solution (2–20 μg/mL) was recorded at λmax 262 nm using buffer as a blank reference. A calibration curve was generated by graphing absorbance (Y-axis) against concentration in μg/mL (X-axis). The regression equation (slope and intercept) and correlation coefficient (R^2) were established and utilised for quantifying Itraconazole in buccal films.

Formulation Design[viii]:

The Itraconazole buccal films were formulated with natural, muco-biodegradable polymers to provide targeted, sustained antifungal activity in the mouth cavity. Six formulations (F1–F6) were developed using the solvent casting method, altering the concentration and type of polymer to examine their impact on film characteristics and drug release. Batches F1–F3 incorporated escalating concentrations of chitosan (40–60 mg) to improve mucoadhesion, film integrity, and retention duration. Batches F4–F6 integrated chitosan with sodium alginate (20–40 mg) to create a polyelectrolyte complex matrix, enhancing bioadhesion and facilitating regulated release. Glycerol served as a plasticiser, xylitol functioned as a sweetener, and peppermint taste was utilised to enhance patient acceptability.

The formulae of different formulations are as follows:

Table 1: Formulation of Itraconazole buccal film.

Ingredient (mg / film)	F1	F2	F3	F4	F5	F6
Itraconazole	25	25	25	25	25	25
Chitosan	40	50	60	40	50	60
Sodium alginate	–	–	–	20	30	40
PEG 400	10	10	10	10	10	10
Xylitol	8	8	8	8	8	8
Peppermint	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

flavour						
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

*The above formulation was calculated for 25 films of 2x2 cm size.

Preparation of Buccal Film

Itraconazole buccal films were fabricated with the solvent-casting method. The requisite quantity of chitosan was dissolved in 70 mL of 1% v/v acetic acid with continuous stirring until a clear solution was achieved. In the combination formulations (F4–F6), sodium alginate was disseminated in a minimal volume of purified water and incrementally introduced to the chitosan solution, followed by gentle agitation to guarantee thorough hydration and homogeneous integration. The polymeric solution was permitted to stand for 5 to 6 hours to facilitate sufficient swelling. Itraconazole (25 mg per film batch) was either dissolved or uniformly dispersed in 30 mL of filtered water. The drug solution was integrated into the expanded polymer mixture with constant agitation. Glycerol (plasticiser), xylitol (sweetener), and peppermint taste were subsequently included to enhance flexibility and palatability. The complete formulation was blended using a cyclo-mixer for 15–20 minutes, subsequently subjected to magnetic stirring for 2 hours to remove trapped air bubbles. The completed homogenous mixture was transferred onto a square glass casting plate (10 cm × 10 cm × 1.7 cm; Other, Amazon, India) and permitted to cure at ambient temperature overnight to produce uniform buccal films. Upon thorough drying, the films were carefully detached from the plate, examined for homogeneity, and sectioned into 2 × 2 cm^2 strips to guarantee precise dosing. Films exhibiting fissures, air inclusions, or surface imperfections were omitted from subsequent assessment.

Drug - Polymer Compatibility Studies

An FTIR study was carried out to ascertain whether the drug and polymers were compatible. The infrared spectra of ITZ were recognised using the ATR FTIR spectrometer (Shimadzu FTIR-8400S, Japan). The sample was put in a specially designed sample holder from Zinc Selenide. The position and relative strength of maximum of absorption in the spectrum that the chemical produces under examination match those in the reference spectrum. The meticulous selection of excipients, which facilitate administration, enhance the drug's sustained release and bioavailability, and protect it from degradation, is crucial for formulating a stable and effective solid dosage form. Compatibility studies are essential when the excipients are unique and have not been utilised in a formulation containing the active ingredient. The compatibility of ITZ with Chitosan, Sodium alginate, and PEG 400 was assessed using FTIR.

Evaluation of buccal films formulations:

For buccal film formulations, various quality control tests were carried out.

Different Performed in vitro examinations are:

Thickness measurement[ix]:

A micrometer screw gauge was used to measure the thickness of the film five times, and an average of three readings was calculated. Maintaining uniformity in the film's thickness is essential because it has a direct impact on the dose's accuracy within the film. The thickness of the film should be less than 5%.

Weight variation[x]

A weight was determined by selecting ten prepared films at random and averaging them. Weighing each film, we compared its weight to the deviation's average. Each MDF's average weight was calculated using an analytical balance. It is preferable if the weight of films is almost consistent. Making sure a film has the right amount of API and excipients is helpful.

Folding endurance[xi]

To test folding endurance, a film is sliced and quickly folded in the same spot until it breaks. The maximum number of times the film may be folded in the same manner without tearing is what determines the folding endurance value. The topical folding endurance of the film was 100–150. The total number of folds the film can withstand without breaking is used to calculate the folding endurance value.

Uniformity of drug content

This is determined by any conventional pharmacopoeia API assay technique. Content consistency is determined by examining API content in each strip. Maximum content 85–115% homogeneity[xii].

$$\text{Drug content} = \frac{\text{sample absorbance}}{\text{standard absorbance}} \times \frac{\text{standard dilution}}{\text{sample dilution}} \times \frac{\%\,\text{punity of drug} \times \text{Avg.wt}}{\text{sample dilution}}$$

$$\%\,\text{Drug content} = \frac{\text{Drug content} \times 100}{\text{Label claim}}$$

Surface pH

The film was moistened with 0.5 millilitres of distilled water in a Petri dish for 30 seconds before testing. The pH was recorded after one minute of equilibration and pH meter electrode contact with the formulation. An average of three measurements per formulation made[xiii].

Assay of the Films:

The drug content of the prepared Oro dissolving films was tested. One film, chosen at random from the five, was weighed, then added to 100 millilitres of 6.8 pH buffer in a volumetric flask. For thirty minutes, a volumetric flask was submerged in a sonicator. The finished solution's absorbance was measured at 284 nm utilizing a UV Visible spectrophotometer against a 6.8 pH buffer blank. Concentrations and formulation amount were calculated using a standard graph.

***In vitro* disintegration studies:**

Disintegration test equipment was used. Disintegration time indicates film disintegration and decomposition. In a stainless steel wire mesh with 25 ml of pH 6.8 simulated salivary fluids, place the desired film size (2x2 cm^2). The time it takes the film to dissolve is called disintegration time.[xiv]

***In vitro* Dissolution test[xv]:**

An in-vitro dissolution investigation of the formulated itraconazole buccal films was conducted utilising a USP type II (paddle) dissolution apparatus (EI-1916, Electronics India, Pune, India). The buccal films were positioned in dissolution tubes containing 500 mL of pH 6.8 phosphate buffer, kept at 37 ± 0.5 °C and agitated at 50 rpm. Five millilitre aliquots were extracted at specified time intervals (5, 10, 15, and 20 minutes) and substituted with an equivalent volume of new dissolving medium. The samples were examined with a UV–Visible spectrophotometer (EI-1372, Electronics India, Pune, India), and drug concentration was determined from the standard calibration curve. The percentage of drug release was calculated, and all trials were conducted in six replicates, with data presented as mean values.

Release Kinetics[xvi]

The results of the in-vitro diffusion study were utilised to look at the drug release kinetics of ITZ films, including their order and mechanism. The zero order, first order, and Higuchi equations were among the kinetic models that were plotted; the Korsmeyer-Peppas equations were used to determine the release.

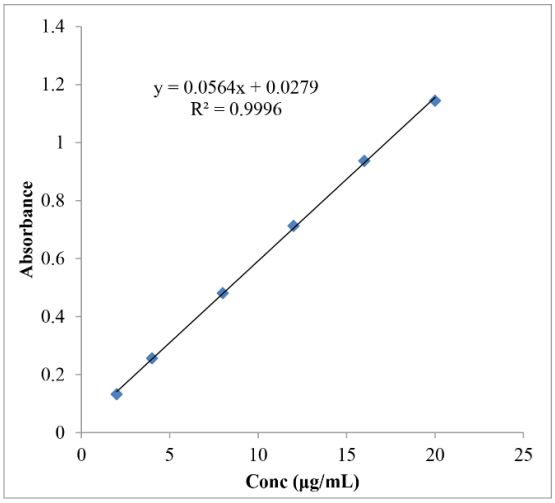
Stability Studies

Drug stability refers to the ability of a formulation to retain its physical, chemical, and therapeutic properties within specified limits throughout its shelf life. Stability studies were conducted in accordance with ICH Q1A guidelines to ensure product quality and performance. Accelerated stability testing of the optimized formulations was carried out at 40 ± 2 °C / 75 ± 5% RH for three months**.** The samples were packed in aluminum foil strips and stored under controlled conditions. At predetermined intervals, formulations were evaluated for **appearance, drug content, and in-vitro drug release,** confirming their stability over the study period.[xvii]

RESULTS & DISCUSSION

ITZ's calibration profile

The calibration curve for Itraconazole was established within a concentration range of 2–20 µg/mL utilising phosphate buffer at pH 6.8. Absorbance was quantified at the designated λmax of 262 nm. The absorbance measurements exhibited a linear increase with concentration, demonstrating strong proportionality. The regression analysis demonstrated exceptional linearity with a correlation coefficient (R^2=0.9996), validating the appropriateness of the UV spectrophotometric approach for measuring



Itraconazole in buccal film samples.

Fig 1: Standard Calibration Curve of ITZ

Drug – excipient Compatibility Studies

FTIR spectroscopy was used to determine the drug excipient compatibility, and the graphs from the figure were displayed. To find out if there was any interaction between the excipients and ITZ, the physical mixture was put through FTIR analysis. ITZ, chitosan and sodium alginate physical mixtures all had their Fourier transform infrared spectra recorded and examined for chemical interactions. All samples, which were pure ITZ, underwent FTIR analysis to determine the presence of the pure API in the mixtures and to describe it.

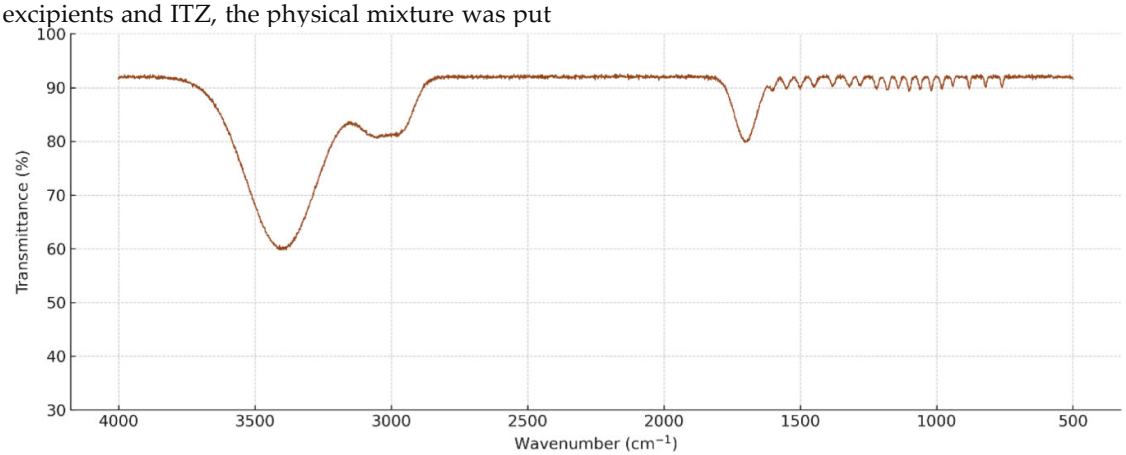


Fig 2: FTIR Spectral analysis of pure ITZ.

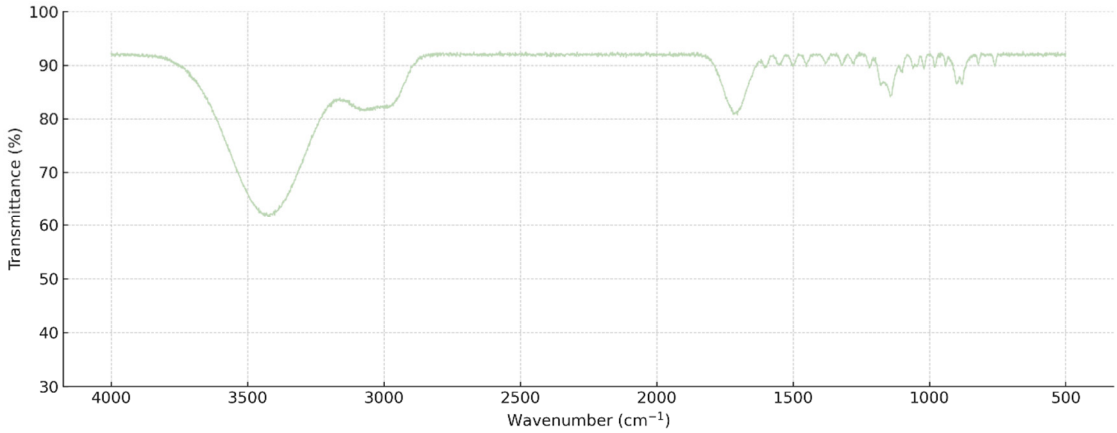


Fig 3: FTIR Spectral analysis of ITZ with chitosan

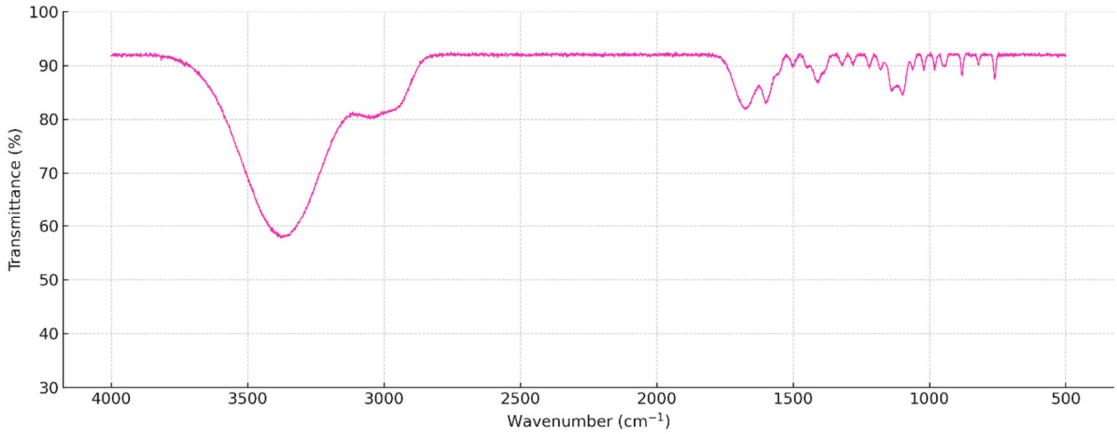


Fig 4: FTIR Spectral analysis of ITZ + Chitosan + Sodium alginate

The obtained FTIR spectra are superimposed in the figure 2-4. The FTIR spectrum of pure itraconazole exhibits distinctive bands, including a broad O–H/N–H area at around 3400–3200 cm^{-1}, aromatic/CH characteristics near 3050 and 2950 cm^{-1}, a significant trough around 1700 cm^{-1}, and a complex fingerprint in the range of 1600–750 cm^{-1}. The itraconazole–chitosan formulation exhibits bands shifted to higher wavenumbers, and the spectrum reveals additional polysaccharide-related signals (C–O–C region 1150 cm^{-1} and a glycosidic shoulder 890 cm^{-1}), indicative of hydrogen bonding and close physical association between the drug and chitosan. Incorporating sodium alginate (itraconazole–chitosan–alginate) results in a shift of major absorptions to lower wavenumbers, with the emergence of new bands associated with alginate carboxylate groups (asymmetric and symmetric COO^- stretches near 1590 and 1410 cm^{-1}). This is accompanied by an intensified saccharide-region intensity, suggesting synergistic polymer effects, enhanced hydrogen bonding/networking, and probable electrostatic interactions between itraconazole and the polyelectrolyte matrix, rather than the formation of new covalent bonds.

Evaluation of buccal film:

Thickness

Each formulation's thickness (F1-F6) was examined; the findings are displayed in the table 2. The film thickness progressively rose from 0.176 ± 0.005 mm (F1) to 0.244 ± 0.009 mm (F6), indicating the elevated total polymer load (CS → CS+SA). This regulated increase enhances mechanical durability while maintaining flexibility.

Table 2: Finding the thickness, weight variation, folding endurance, and pH of the surface of all formulations

F code	Thickness (mm)	Weight (mg)	Folding Endurance (folds)	Surface pH
F1	0.176 ± 0.005	40.9 ± 1.5	116 ± 4	6.51 ± 0.11
F2	0.191 ± 0.006	43.6 ± 1.6	129 ± 5	6.47 ± 0.12
F3	0.206 ± 0.006	46.1 ± 1.7	142 ± 5	6.44 ± 0.11
F4	0.218 ± 0.007	48.2 ± 1.8	155 ± 6	6.46 ± 0.10
F5	0.232 ± 0.008	50.1 ± 1.9	167 ± 6	6.45 ± 0.12
F6	0.244 ± 0.009	52.0 ± 2.0	178 ± 7	6.49 ± 0.11

Weight variation:

The average weight increased from 40.9 ± 1.5 mg (F1) to 52.0 ± 2.0 mg (F6) with minimal fluctuation, indicating a uniform distribution of solids and steady rheological properties throughout the casting process. The consistent increase corresponds with thickness, indicating a uniform film mass per unit area throughout different batches.

Folding Endurance:

Folding endurance significantly increased with polymer reinforcement, rising from 116 ± 4 folds (F1) to 178 ± 7 folds (F6). The CS+SA (polyelectrolyte complex) matrices in F4–F6 exhibited enhanced toughness and ductility, accounting for the incremental improvements while preserving minimal variability.

Surface pH of Films:

The surface pH of all formulations 6.44 to 6.51 was nearly neutral, ensuring compatibility with the buccal mucosa and reducing discomfort during application.

Table 3: Moisture Content, Moisture Uptake, Drug Content, and Mucoadhesive Properties of ITZ Buccal Films

F. code	Moisture Content (%)	Moisture Uptake (%)	Drug Content (%)	Mucoadhesive Strength (g)	Residence Time (min)
F1	6.8 ± 0.3	18.1 ± 0.9	97.4 ± 1.9	18.8 ± 0.9	80 ± 4
F2	6.5 ± 0.3	19.7 ± 1.0	98.0 ± 1.8	21.4 ± 1.0	94 ± 5
F3	6.2 ± 0.2	21.5 ± 1.0	98.6 ± 1.7	24.9 ± 1.1	110 ± 6

F4	6.0 ± 0.2	23.1 ± 1.1	99.0 ± 1.6	28.2 ± 1.2	128 ± 6
F5	5.8 ± 0.2	25.2 ± 1.1	99.2 ± 1.6	31.6 ± 1.3	144 ± 7
F6	5.6 ± 0.2	26.8 ± 1.2	99.4 ± 1.5	34.9 ± 1.4	160 ± 8

Moisture Content and Moisture Uptake

Moisture content decreased somewhat from 6.8 ± 0.3% (F1) to 5.6 ± 0.2% (F6), suggesting denser polymer arrangement and a marginal reduction in bound water at elevated total solids. This is advantageous for physical stability (reduced tackiness/curling) while maintaining film flexibility. Moisture absorption increased steadily, indicating the hydrophilic characteristics of the chitosan matrix and their enhancement with sodium alginate in formulations F4–F6.

Drug Content

All films achieved dosage uniformity (97.4–99.4%), indicating that micronized itraconazole was uniformly spread and that casting/shear conditions prevented segregation or drug loss. The marginal increase to 99.4% (F6) corresponds with enhanced solids control in CS+SA batches.

Mucoadhesive Strength and Residence Time

Mucoadhesion markedly increased with the addition of alginate, from 18.8 ± 0.9 g (F1) to 34.9 ± 1.4 g (F6). This reflects the creation of a chitosan–alginate polyelectrolyte complex that offers increased ionic and hydrogen-bonding sites for mucin, resulting in enhanced initial tack and sustained adhesion essential for extended buccal occupancy. Residence period monitored mucoadhesion, ranging from 80 ± 4 minutes (F1) to 160 ± 8 minutes (F6). The nearly linear correlation indicates that adhesive effort, rather than erosion caused by swelling, dictates retention. Values of 120 minutes or more (F4–F6) are beneficial for localized administration, facilitating prolonged contact and potentially enhancing itraconazole flow without the need for frequent reapplication.

In-vitro dissolution

The in-vitro release investigation of Itraconazole buccal films was conducted over 8 hours in phosphate buffer at pH 6.8, with the cumulative drug release profiles of formulations F1–F6 displayed in figure 5. All six films exhibited a smooth, monotonic release with a distinct matrix-dependent differentiation. The chitosan-only set (F1–F3) exhibited accelerated release at each time interval (e.g., 1 h: 24.9–20.3%, 4 h: 68.6–60.2%, 8 h: 94.1–88.7%), aligning with the fast hydration and partial degradation of the single-polymer matrix. Conversely, the chitosan–alginate PEC set (F4–F6) exhibited regulated release attributed to stronger ionic crosslinks that impede diffusion and surface erosion (1 h: 17.8–14.5%, 4 h: 53.6–46.5%, 8 h: 82.3–76.8%). The overall ranking of the profile is F1 > F2 > F3 > F4 > F5 > F6 (fastest to slowest), consistent with the desired mucoadhesive, sustained-release characteristics as alginate content rises.

Application of Release Rate Kinetics to Dissolution Data:

A variety of models were used to study drug release kinetics. A number of release models, including first-order, zero-order, higuchi, and korsmeyer-peppas, were fitted to the acquired data in order to investigate the medication release rate mechanism of the dose form Kinetics.

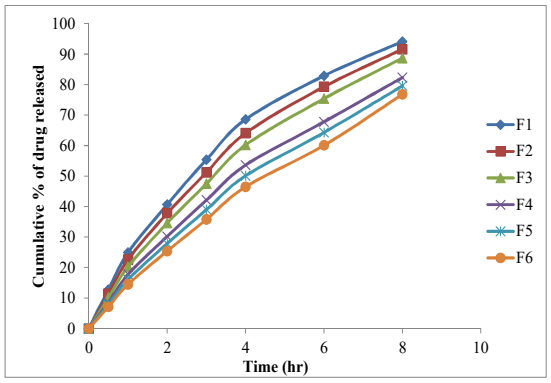


Fig 5: In vitro dissolution studies of formulations (F1-F6)

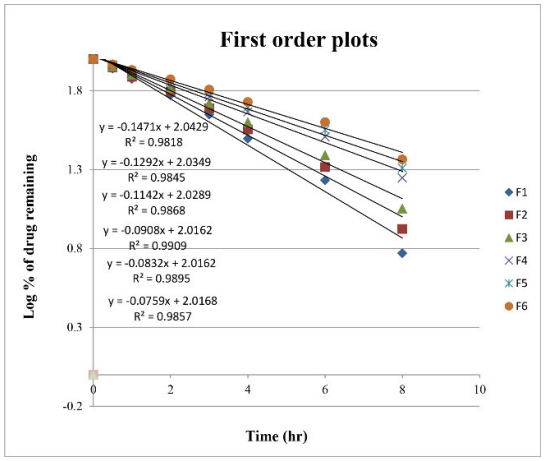


Fig 6: Zero order release kinetics graph of formulations (F1-F6)

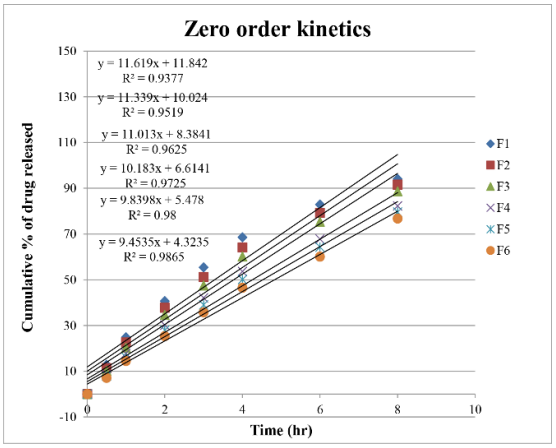


Fig 7: First order release kinetics graph of formulations (F1-F6)

The drug release kinetics are summarized in Fig. 6 to 9. Release kinetics (brief discussion): F1–F3 (chitosan-only) exhibit optimal fit to Higuchi/Peppas models (Higuchi $R^2 \approx 0.992–0.997$; Peppas R^2 up to 0.9971) with n values ranging from 0.59 to 0.49, signifying diffusion-controlled, anomalous to quasi-Fickian release mechanisms. As the concentration of alginate increases (F4–F6), the optimal fit

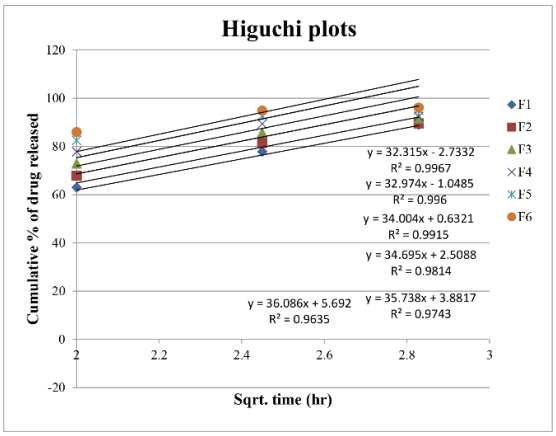


Fig 8: Higuchi release kinetics graph of formulations (F1-F6)

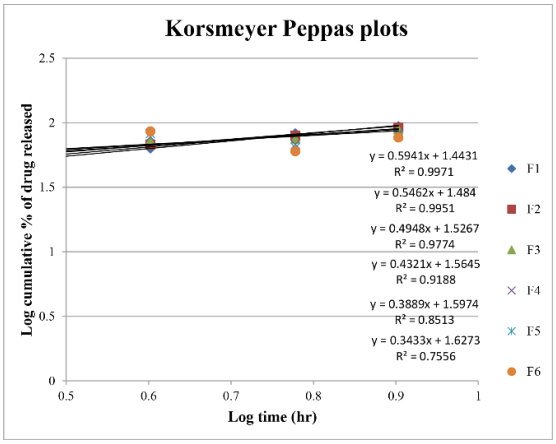


Fig 9: Korsmeyer-Peppas graph of formulations (F1-F6)

transitions towards zero-order kinetics (R^2 = 0.9725 → 0.9865), while the Higuchi/Peppas fits decline (Peppas R^2 0.9188 → 0.7556) and the diffusion exponent n decreases to 0.34. This is indicative of Fickian diffusion via a more compact chitosan-sodium alginate polyelectrolyte network, resulting in a more consistent and regulated release profile. In summary: rapid sets (F1–F3) exhibit diffusion dominance; regulated sets (F4–F6) have near zero-order, Fickian kinetics, consistent with the mucoadhesive sustained-release framework.

Selection of Optimized Formulation

F6 is the best batch for a mucoadhesive, controlled-release target product profile. It integrates superior buccal retention with a controlled release profile, guaranteeing extended local exposure without dose dumping. In comparison to F4–F5, F6 provides the longest residence time and the most stable control, while still attaining a high cumulative release by 8 hours. For a quicker onset, particularly in cases of acute fungal burden, F3 offers a feasible "rapid" option (64.8% at 1 hour; 97.6% at 3 hours). However, for prolonged buccal administration with enhanced adhesion and handling, F6 most effectively meets the clinical and formulation requirements.

Stability Studies:

According to ICH recommendations, stability studies were carried out to assess the drug formulation's stability. The optimized formulation (F6) was subjected to stability studies at 40 °C ± 2 °C / 75% ± 5% RH for 90 days. The results showed no significant change in appearance, flexibility, or mucoadhesion. Drug content remained above 98%, and folding endurance and surface pH were within acceptable limits. It follows that the formulation is stable. Table displayed the stability studies finding. No notable variations were detected in mechanical, chemical, or release properties, signifying that the formulation maintains stability under accelerated settings for a minimum of one month. This substantiates the efficacy of chitosan–alginate films for buccal administration.

CONCLUSION

Mucoadhesive buccal films coated with itraconazole were effectively made utilising chitosan and sodium alginate as natural polymer matrices. The optimised formulation (F6) demonstrated superior mechanical strength, robust mucoadhesion, extended buccal

residency, and sustained drug release over 8 hours, while preserving stability under accelerated conditions. The research validates that chitosan–alginate polymer combinations serve as efficient carriers for localised buccal delivery of itraconazole, providing superior therapeutic efficacy, less systemic exposure, and increased patient compliance relative to traditional oral dose forms.

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