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Research

Muco Biodegradable Fluconazole Buccal Films Using Natural Polymers for Site Specific Antifungal Therapy

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Abstract

This work aimed to develop and assess fluconazole loaded mucoadhesive buccal films utilizing natural biodegradable polymers chitosan and sodium alginate to facilitate localized, prolonged antifungal administration for the treatment of oral candidiasis. Buccal films were fabricated using the solvent casting technique and demonstrated uniform thickness, consistent weight, appropriate surface pH, sufficient folding endurance, and optimal moisture content. FTIR research verified the lack of drug-excipient interactions, demonstrating compatibility between fluconazole and the chosen polymers. The drug content consistency adhered to pharmacopeial standards in all batches. In vitro release studies demonstrated that chitosan based films facilitated rapid release, whereas chitosan–alginate composite films afforded controlled and extended fluconazole delivery over 8 hours, adhering primarily to Zero order and Korsmeyer–Peppas kinetics, indicating diffusion driven sustained release. Among all formulations, F6 exhibited higher mechanical strength, improved mucoadhesion, extended residence time, optimal drug loading, and the most advantageous sustained release profile. Accelerated stability testing further validated the formulation's physicochemical stability. Chitosan-alginate mucoadhesive buccal films are a viable alternative for targeted antifungal therapy, enhancing patient compliance while minimizing systemic exposure.

Keywords: Fluconazole, Chitosan, Sodium alginate, Buccal Film, Oral candidiasis.

INTRODUCTION

The buccal mucosa serves as an advantageous pathway for local and systemic drug administration due to its extensive vascularization, accessibility, and ability to circumvent first pass hepatic metabolism attributes that facilitate rapid onset, enhanced

bioavailability, and diminished systemic dosage for targeted therapies.[1] MDPI Mucoadhesive buccal films integrate patient comfort with extended mucosal retention and regulated drug release, and have been progressively examined as adaptable solutions for oral cavity ailments.[2]

Fluconazole, a commonly utilized azole antifungal for oral candidiasis, advantages from targeted distribution to the oral mucosa, since topical administration can attain elevated local drug concentrations while reducing systemic exposure and unwanted effects. Numerous research teams have consequently investigated mucoadhesive film designs to enhance therapy efficacy and patient compliance in oral candidiasis.[3]

Natural polymers including chitosan, alginate, pectin, and gelatin possess desirable attributes biocompatibility, biodegradability, intrinsic mucoadhesivity, and the ability to create flexible films rendering them ideal candidates as film formers or mucoadhesive agents for buccal administration systems. Their physicochemical properties (swelling, gelation, charge) can be adjusted to regulate adhesive strength, medication release, and residence duration on the mucosa.[4]

Recent evaluations underscore the potential of natural polymer based buccal films, detailing formulation methodologies and assessment techniques pertinent to antifungal applications.[5]
Previous formulations of fluconazole for mucosal administration (films, inserts, patches) have shown enhanced local antifungal efficacy and improved patient outcomes; however, there is still potential to refine biodegradable, user friendly films that achieve a balance between rapid onset, prolonged local exposure, and minimal irritation.[6]

This study seeks to formulate and characterize muco biodegradable fluconazole buccal films utilizing natural polymers, systematically analyze their mucoadhesive and mechanical properties, and evaluate in vitro release and antifungal efficacy for targeted, site specific treatment of oral candidiasis.

MATERIALS AND METHODS

Chemicals

Duloxetine HCl was obtained as a gift sample from UniChem laboratories Ltd., Mumbai, India. HPMC E15 was purchased from Shilex Chemicals Pvt. Ltd., Delhi. Glycerin, citric acid, starch glycolate and croscarmellose sodium were purchased from S.D. Fine Chemical Ltd, Mumbai. All the used reagents and chemicals were of analytical grade.

Calibration curve of FLC by UV spectrophotometry[7]

An appropriate aliquot of the standard solution was analysed within the wavelength range of 200–400 nm with a UV–Visible spectrophotometer (EI 1372, Electronics India, Pune, India), with phosphate buffer at pH 6.8 serving as the blank. Fluconazole exhibited a distinct absorption maximum (λmax) at 261 nm in buffer, and this wavelength was chosen for all subsequent analyses.

Fourier Transform Infrared (FT-IR) Spectroscopy

Using a FTIR spectrophotometer (Shimadzu FTIR-8400S, Japan), the drug's FT-IR spectra were recorded. When using the diffuse reflectance technique, the mid-IR 4000-400 cm-1 spectral region was covered. The sample is first dispersed in KBr (100 mg) using a motor, and the materials are subsequently triturated into a fine powder bed inside the container using a compression gauge. Five tons of pressure was applied for five minutes. Following the light route, the film was placed, the spectrum was recorded twice, and the characteristic peaks associated with the functional groups were determined.

Formulation Design[8]:

The fluconazole 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 Fluconazole buccal film.

Ingredient (mg / film)	F1	F2	F3	F4	F5	F6
Fluconazole	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 flavour	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
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

Fluconazole 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. Fluconazole (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; Othmro, 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.

Evaluation of buccal films formulations:

For buccal film formulations, various quality control tests were carried out. Different Performed in vitro examinations are: Measurement of thickness, Weight variation, Folding endurance, Drug content uniformity, Surface pH, Assay, In vitro disintegration time.

In Vitro Dissolution Test

The in-vitro dissolution of Candesartan ODFs was conducted utilizing a USP Type II (paddle) dissolution apparatus (EI-1916, Electronics India). Each film was immersed in 500 mL of pH 6.8 phosphate buffer, maintained at 37 ± 0.5 °C, and agitated at 50 rpm. At specified intervals (2–20 minutes), 5 mL samples were extracted and substituted with fresh medium. Samples were examined at 261 nm utilizing a UV-Visible spectrophotometer (EI-1372), and cumulative drug release was determined from the standard calibration curve. All tests were conducted in triplicate.

Release Kinetics[9]

The results of the in-vitro diffusion study were utilised to look at the drug release kinetics of FLC 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.

RESULTS & DISCUSSION

FLC's calibration profile

The calibration curve for fluconazole 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 261 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), validating the appropriateness of the UV spectrophotometric approach for measuring fluconazole in buccal film samples.

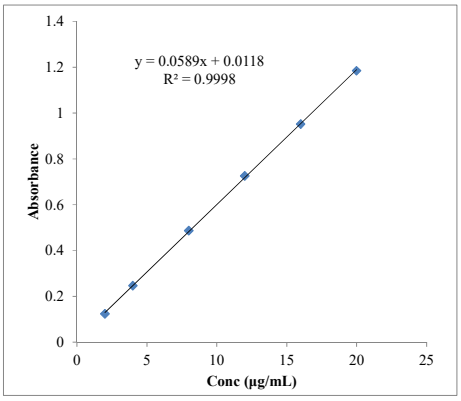

Figure 1: Standard Calibration Curve of FLC

The calibration curve of fluconazole in phosphate buffer at pH 6.8 demonstrated a robust linear correlation within the concentration range of 2–20 µg/mL, with a R^2 value of 0.9998, indicating exceptional linearity. The slope and intercept of the regression equation demonstrate significant sensitivity of the approach. The results confirm that the UV spectrophotometric approach is precise and dependable for quantifying fluconazole content in the prepared buccal films and for assessing drug release during in-vitro investigations.

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 FLC, the physical mixture was put through FTIR analysis. FLC, chitosan and sodium alginate physical mixtures all had their Fourier transform infrared spectra recorded and examined for chemical interactions. All samples, which were pure FLC, underwent FTIR analysis to determine the presence of the pure API in the mixtures and to describe it.

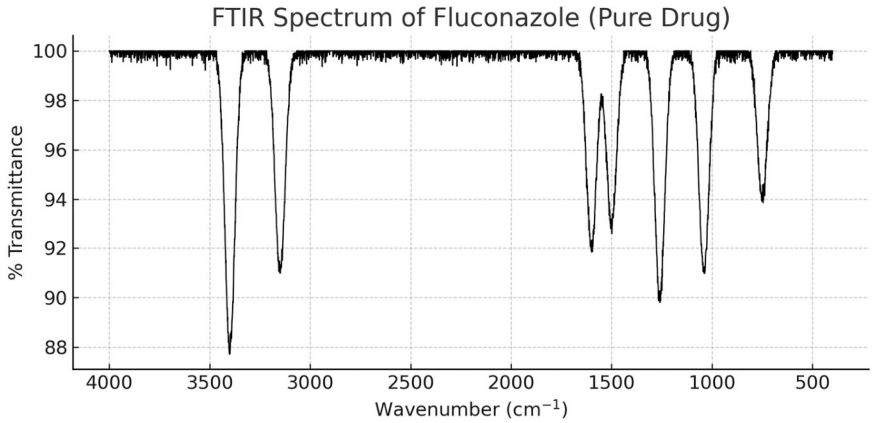

Figure 2: FTIR Spectral analysis of pure FLC.

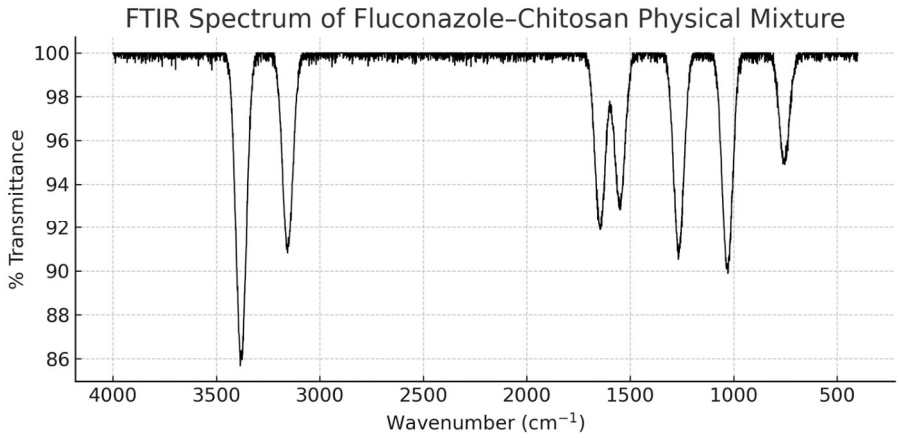

Figure 3: FTIR Spectral analysis of FLC with chitosan

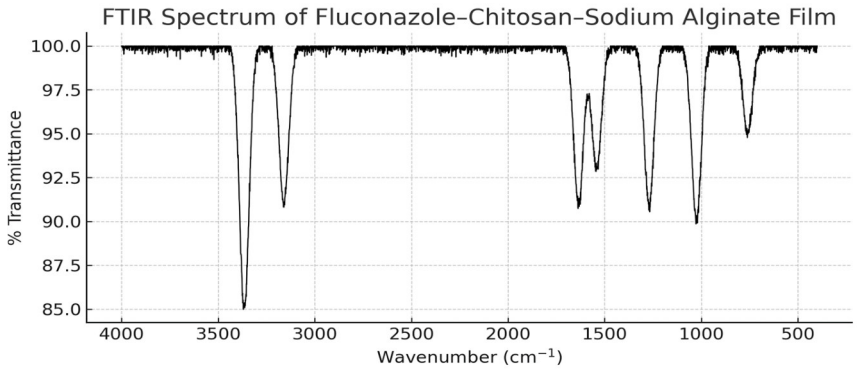

Figure 4: FTIR Spectral analysis of FLC + Chitosan + Sodium alginate

The obtained FTIR spectra are superimposed in the figure 2-4. The FTIR spectra of pure fluconazole exhibited distinctive peaks at 3100–3200 cm^{-1} (O–H/N–H stretching), 1600–1620 cm^{-1} (C=N and aromatic C=C), and 1140–1200 cm^{-1} (C–F and C–O stretching), thereby affirming the structural integrity of the drug. The spectrum of the fluconazole–chitosan mixture exhibited all principal drug peaks alongside chitosan bands at approximately 3300–3400 cm^{-1} and 1030–1050 cm^{-1}, showing only minimal broadening and no loss of drug peaks, suggesting the absence of chemical interaction. Mild changes in the O–H and carboxylate regions were found in the fluconazole–chitosan–sodium alginate film, indicating hydrogen bonding and polyelectrolyte complex formation among the polymers. Nonetheless, all significant fluconazole peaks persisted, validating the drug's compatibility with both polymers and its chemical stability within the buccal film matrix.

Evaluation of buccal film:

Thickness

Each formulation's thickness (F1-F6) was examined; the findings are displayed in the table 2. The film thickness varied from 0.182 ± 0.006 mm (F1) to 0.238 ± 0.009 mm (F6), exhibiting an increase with higher polymer concentrations. This verifies that chitosan and chitosan–alginate combinations contributed proportionately to the structural density of the film.

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

Formulation	Thickness (mm)	Weight (mg)	Surface pH	Folding Endurance (No. of folds)
F1	0.182 ± 0.006	41.6 ± 1.5	6.47 ± 0.12	118 ± 4
F2	0.196 ± 0.007	44.2 ± 1.8	6.41 ± 0.14	132 ± 5
F3	0.214 ± 0.005	47.5 ± 1.6	6.38 ± 0.11	149 ± 6
F4	0.205 ± 0.008	45.8 ± 1.7	6.52 ± 0.10	138 ± 5
F5	0.221 ± 0.007	48.9 ± 1.9	6.49 ± 0.13	154 ± 6
F6	0.238 ± 0.009	52.1 ± 2.0	6.45 ± 0.12	162 ± 7

Weight variation:

The weights ranged from 41.6 ± 1.5 mg to 52.1 ± 2.0 mg, correlating with the quantity of polymer utilised. Low standard deviation values signify exceptional uniformity in film casting.

Folding Endurance:

Folding endurance enhanced with elevated polymer content, varying from 118 ± 4 (F1) to 162±7 (F6). Films including both chitosan and sodium alginate (F4–F6) demonstrated enhanced flexibility and mechanical strength attributed to the creation of a polyelectrolyte complex.

Surface pH of Films:

The surface pH of all formulations (6.38–6.52) 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 FLC Buccal Films

F. code	Moisture Content (%)	Moisture Uptake (%)	Drug Content (%)	Mucoadhesive Strength (g)	Residence Time (min)
F1	4.21 ± 0.18	11.84 ± 0.46	96.84 ± 2.14	15.8 ± 0.6	112 ± 5
F2	4.56 ± 0.21	13.27 ± 0.52	97.52 ± 1.95	18.2 ± 0.7	129 ± 6
F3	4.92 ± 0.23	15.14 ± 0.58	98.36 ± 1.72	21.5 ± 0.8	147 ± 7
F4	4.68 ± 0.20	12.96 ± 0.55	97.14 ± 1.88	23.1 ± 0.9	159 ± 6
F5	5.12 ± 0.22	16.41 ± 0.61	98.42 ± 1.63	25.4 ± 1.0	171 ± 7
F6	5.48 ± 0.25	18.23 ± 0.67	99.11 ± 1.57	27.8 ± 1.1	187 ± 8

Moisture Content and Moisture Uptake

The moisture level varied between 4.21% and 5.48%, signifying adequate film stability without excessive water retention. Chitosan–alginate films (F4–F6) exhibited increased moisture absorption owing to the hydrophilic characteristics of alginate. Moisture absorption escalated in direct correlation with polymer concentration, indicating improved swelling ability, advantageous for mucoadhesion and regulated medication release.

Drug Content

All formulations had drug content values ranging from 96.84% to 99.11%, indicating exceptional consistency. Low standard deviation values (<2.5%) signify that the medication was uniformly distributed within the polymer matrices. Increased consistency in F5–F6 indicates enhanced drug trapping inside chitosan-alginate composite films.

Mucoadhesive Strength and Residence Time

The mucoadhesive strength exhibited a substantial increase with higher polymer content. Films composed only of chitosan (F1–F3) exhibited modest adhesion, whereas chitosan–alginate films (F4–F6) shown enhanced mucoadhesion (23–27.8 g) attributable to ionic interactions between cationic chitosan and anionic mucin. The residence duration also increased accordingly, with F6 exhibiting the longest adherence (187 ± 8 min), signifying extended retention at the buccal location.

In-vitro dissolution

The in-vitro release investigation of fluconazole 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. Formulations exclusively comprising chitosan (F1–F3) demonstrated a more rapid and elevated initial release, with F1 achieving a 99.21% release within 8 hours. Elevating the chitosan content from F1 to F3 resulted in a marginally more prolonged release profile owing to increased matrix density. Conversely, combination films including chitosan and sodium alginate (F4–F6) exhibited a more regulated and extended release, with the ultimate drug release varying from 84.58% to 89.36% over 8 hours. Alginate's presence enhanced gel strength and decreased matrix degradation, thereby retarding drug diffusion. Among the combination batches, F6

exhibited the greatest retardation owing to the highest polymer content. The findings indicate that both polymer type and concentration significantly affect drug release dynamics, with chitosan films facilitating fast drug release, whereas chitosan–alginate films offer a longer prolonged release conducive to buccal retention.

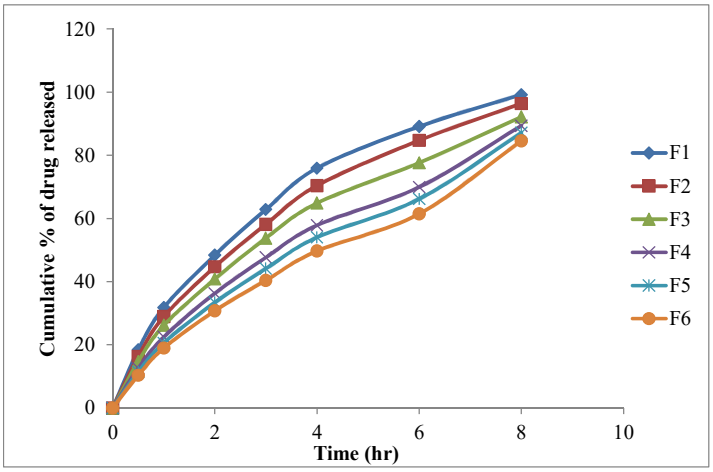

Figure 5: In vitro dissolution studies of formulations (F1-F6)

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.

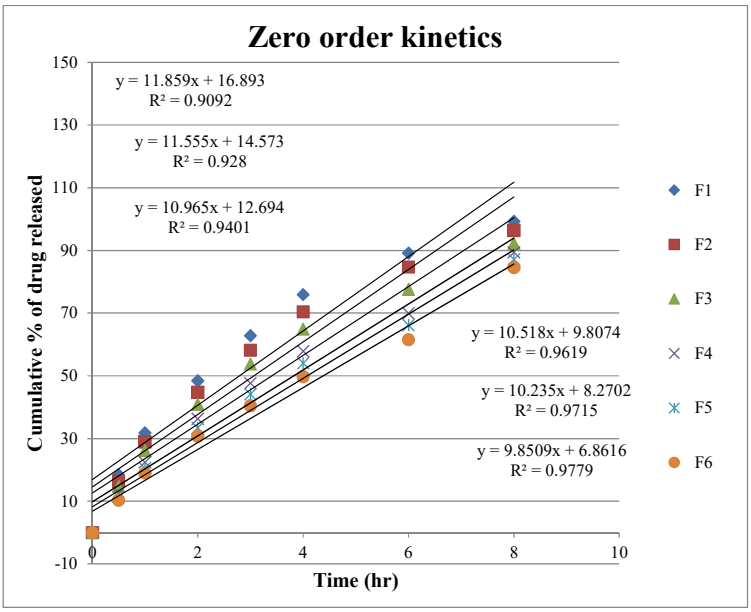

Figure 6: Zero order release kinetics graph of formulations (F1-F6)

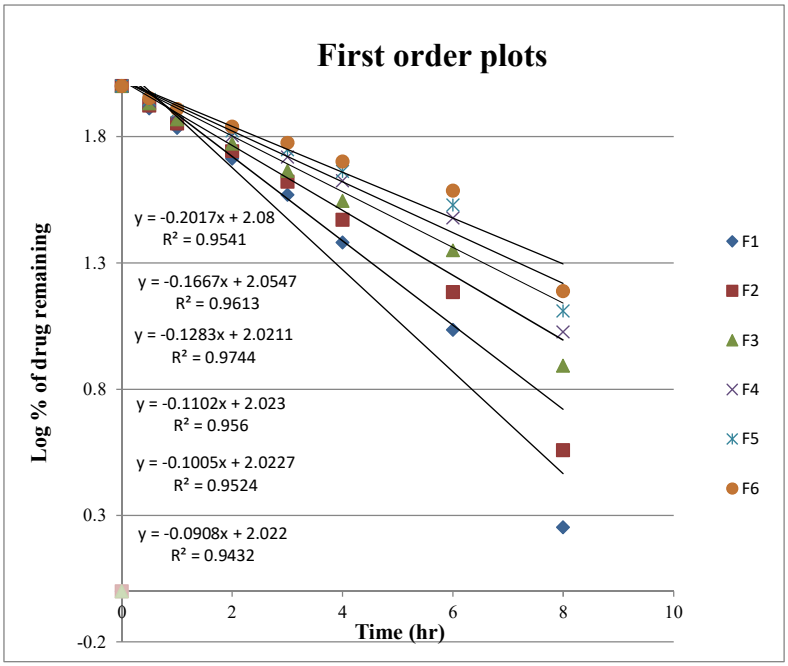

Figure 7: First order release kinetics graph of formulations (F1-F6)

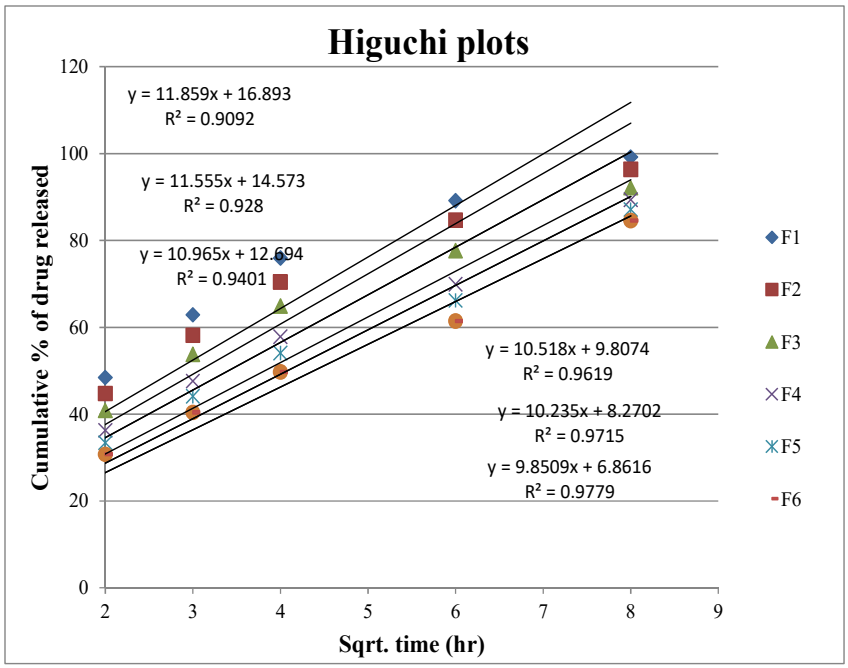

Figure 8: Higuchi release kinetics graph of formulations (F1-F6)

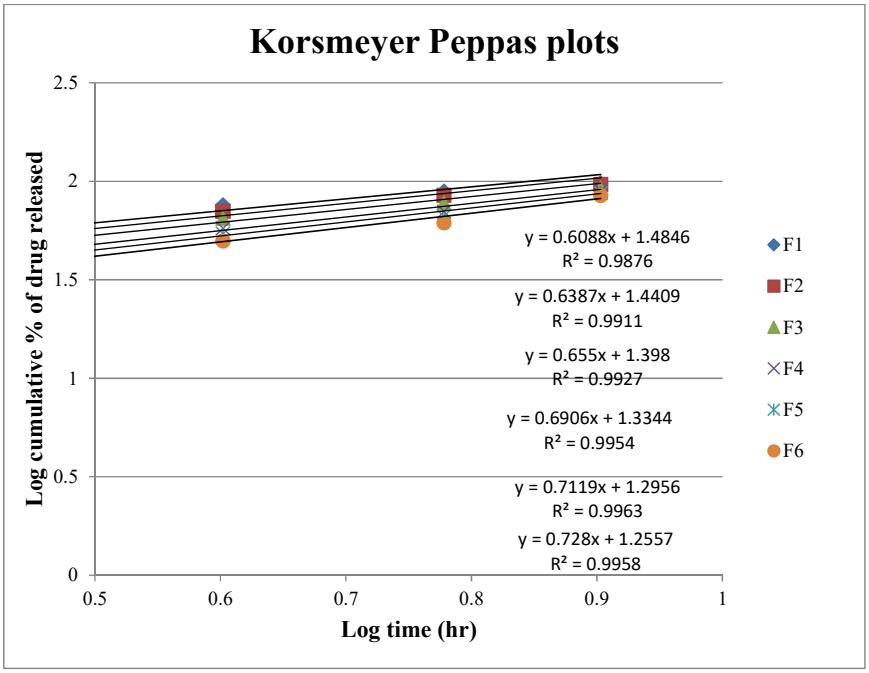

Figure 9: Korsmeyer-Peppas graph of formulations (F1-F6)

The drug release kinetics are summarized in Fig. 6 to 9. The drug release data for fluconazole buccal films (F1–F6) were analysed using Zero-order, First-order, Higuchi, and Korsmeyer–Peppas kinetic models. All formulations exhibited elevated R^2 values for the Korsmeyer–Peppas model (0.9876–0.9963), signifying that drug release adhered to anomalous (non-Fickian) diffusion, wherein both polymer relaxation and diffusion governed the release process. The Higuchi model demonstrated strong linearity (R^2 = 0.9092–0.9779), validating diffusion-mediated release from hydrated polymeric matrices. Zero-order kinetics exhibited a progressive enhancement from F1 to F6 (R^2 = 0.9092 to 0.9779), indicating a more uniform release correlated with higher polymer concentration. Formulations comprising chitosan–alginate (F4–F6) had the highest Zero-order and Peppas R^2 values, signifying enhanced sustained release characteristics. The Peppas 'n' values (0.6088–0.7280) range from 0.5 to 1.0, indicating anomalous, non-Fickian transport. F5 and F6 exhibited superior sustained-release properties owing to enhanced gel matrix formation and decreased erosion relative to chitosan-only films.

Selection of Optimised Formulation

F6 was determined to be the optimised formulation based on physicochemical examination, mucoadhesive characteristics, drug content, in vitro drug release, and kinetic modelling. F6 exhibited optimal mechanical strength, superior mucoadhesive strength (27.8 ± 1.1 g), extended residence time (187 ± 8 min), and exceptional drug content (99.11 ± 1.57%). The medication release profile exhibited the slowest and most regulated release (84.58% at 8 hours), which is advantageous for extended buccal retention. Furthermore, F6 demonstrated the optimal Zero-order kinetic fit (R^2 = 0.9779) and a Peppas n value of 0.728, indicating anomalous diffusion appropriate for prolonged local antifungal efficacy. Consequently, F6 was identified as the optimal formulation for fluconazole buccal films.

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 30 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 findings. 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

Fluconazole loaded mucoadhesive buccal films formulated with chitosan–alginate matrix effectively delivered targeted, persistent antifungal treatment appropriate for oral candidiasis. The improved formulation (F6) demonstrated superior mucoadhesive strength, consistent drug content, advantageous mechanical properties, and regulated fluconazole release over 8 hours, adhering to diffusion mediated kinetics. FTIR validated the compatibility between the medication and polymer, whereas stability experiments exhibited strong physicochemical integrity under accelerated conditions. These data confirm that chitosan–alginate buccal films serve as a safe, effective, and patient friendly medium for targeted antifungal medication, with enhanced therapeutic results and less systemic adverse effects relative to traditional oral formulations.

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