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INNOVATIVE ANTICANDIDAL MUCOADHESIVE VAGINAL TABLETS: DESIGN AND IN-VITRO ASSESSMENT

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ABSTRACT

Objective:

Candida albicans is the predominant yeast isolated from clinical specimens, frequently associated with vaginal thrush or vulvovaginal candidiasis (VVC) as a result of its overgrowth in the vaginal cavity. The ability of *C. albicans* to form biofilms complicates the treatment of candidiasis, rendering it resistant to standard antifungal therapies. The emergence of fluconazole (FCZ)-resistant *C. albicans* necessitates the development of innovative therapeutic approaches, either as standalone treatments or in conjunction with other agents. This study explores the synergistic effects of fluconazole and quercetin in the formulation of a mucoadhesive in-situ vaginal tablet aimed at targeting resistant strains of *C. albicans*. The mucoadhesive vaginal tablet formulation was developed and optimized through a 3^2 full factorial design (FFD), focusing on enhancing the properties of mucoadhesive and swelling polymers. Carbopol 934P (61.24% w/w) served as the swelling polymer, while HPMCK4M (63.15% w/w) was utilized as the mucoadhesive polymer. Comprehensive evaluations of the developed tablet were conducted, encompassing both pre-compression and post-compression assessments. In vitro studies included drug diffusion analyses, kinetic evaluations, product assays, and antifungal efficacy tests against resistant strains of *Candida albicans*. The optimized formulation

demonstrated satisfactory pre- and post-compression parameters of formulation. FCZ exhibited complete release within 90 minutes, whereas QCT released 99.55% within 150 minutes. The tablet maintained adhesion to the vaginal membrane for 273 minutes, ensuring the complete release of both FCZ and QCT. Kinetic analysis indicated that FCZ release adhered to the Korsmeyer-Peppas model, while QCT release conformed to the Higuchi model. The mucoadhesive vaginal formulation exhibited a synergistic effect against itraconazole-resistant *Candida albicans*. This mucoadhesive in-situ vaginal tablet formulation presents several advantages over oral dosage forms, including reduced metabolic degradation, enhanced bioavailability of quercetin, improved cosmetic acceptability, and increased patient adherence. Furthermore, the formulation is scalable and effectively targets drug-resistant strains of *Candida albicans*, making it particularly valuable in instances where fluconazole monotherapy proves ineffective.

Keywords: Mucoadhesive Vaginal Tablet, Fluconazole (FCZ), Quercetin (QCT), 3^2 Full Factorial Design (FFD), Antifungal activity

INTRODUCTION

Despite significant advancements in medical science, fungal diseases continue to pose a substantial threat to human health, with actual mortality rates estimated to be five times higher than officially reported **[1, 2]**. Over 90% of fungal infections are linked to Candida species, primarily *Candida albicans*, which predominantly affects the skin and mucous membranes **[3-7]**. Vulvovaginal candidiasis (VVC), commonly known as vaginal thrush, is a prevalent gynaecological condition caused by the overgrowth of yeast in the vagina, mainly due to *Candida albicans* **[8, 9]**. Approximately 75% of women experience VVC, with over 85% of cases attributable to *C. albicans* **[8-10]**. Research indicates that both free-floating Candida cells and biofilm formation contribute to antifungal resistance, complicating treatment strategies **[11-17]**.

Fluconazole (FCZ) is the first-line therapeutic agent for the prevention and treatment of mucosal and invasive Candida infections, including VVC, due to its favourable bioavailability and lower toxicity **[18-20]**. However, resistance rates of *C. albicans* to FCZ among VVC patients range from 10% to 20%, primarily due to excessive and indiscriminate antifungal use, leading to the emergence of multidrug-resistant (MDR) strains **[21-23]**. This highlights the urgent need for innovative therapies that can be employed as monotherapy or in combination with FCZ for treating FCZ-resistant *C. albicans* from VVC cases.

Quercetin (QCT) shows modest antifungal activity and effectively manages clinical *Candida albicans* biofilms while enhancing the susceptibility of FCZ-resistant isolates to FCZ **[24, 25]**. Studies indicate that

combining QCT and FCZ significantly reduces fungal load, eliminates hyphal forms, and alleviates mucosal epithelial inflammation, suggesting a potential synergistic effect in managing *C. albicans* infections **[26]**.

Traditional vaginal delivery methods, while effective, present challenges that hinder efficient antifungal drug delivery. Limitations of creams, suppositories, conventional tablets, and gels include discomfort, leakage, messiness, poor retention in the vaginal epithelium, and the need for frequent administration, all of which contribute to decreased patient compliance. Furthermore, these formulations often exhibit low oral bioavailability due to first-pass metabolism and suboptimal release patterns, impacting therapeutic efficacy and leading to patient reluctance in adhering to medication regimens **[27-30]**.

The formulation of a mucoadhesive vaginal tablet containing fluconazole (FCZ) and quercetin (QCT) represents an optimal strategy for achieving rapid and effective therapeutic action within the vaginal cavity. This formulation aims for a swift onset of action and prolonged drug retention, facilitating ease of application via an applicator. Key benefits include reduced drug metabolism, enhanced bioavailability of poorly soluble compounds like quercetin, improved cosmetic acceptability, increased patient adherence, scalability, and targeted efficacy against drug-resistant *Candida albicans* strains, thus providing a valuable alternative when fluconazole monotherapy is inadequate.

Current literature lacks substantial data on the formulation of a combined dosage form of fluconazole (FCZ) and quercetin (QCT). This investigation seeks to develop a mucoadhesive in-situ vaginal tablet utilizing FCZ and QCT to fill this knowledge gap. The mucoadhesive tablet formulation aims to overcome the limitations of conventional dosage forms by effectively adhering to the vaginal mucosal membrane **[31-32]**.

This study focuses on the development and optimization of a mucoadhesive vaginal tablet formulation using a 3^2 full factorial design, emphasizing the optimization of mucoadhesive and swelling polymers. Comprehensive evaluations of the formulated tablet included pre-compression and post-compression assessments, as well as in vitro evaluations comprising drug diffusion studies, kinetic analyses, product assays, and antifungal activity tests against resistant strains of *Candida albicans*.

MATERIALS AND METHODS

Materials

The Fluconazole (FCZ) standard was obtained from Rutu chemicals, located in Panoli, Gujarat, India. Quercetin, featuring 98.0% purity (HPLC-grade, molecular

weight 338.27, CAS No. 6151-25-3), was obtained from Sigma-Aldrich, Mumbai. HPMCK4M and Carbopol 934P were purchased from Colorcon Asia Pvt. Ltd., located in Goa, India. Avicel PH-102, was obtained from S.D. Fine chemicals, located in Vadodara, Gujarat, India. Talc and Magnesium stearate were purchased from Astron Chemicals, located in Ahmedabad, India. HP-β-cyclodextrin was acquired from S.A. Pharmachem Pvt. Ltd., located in Mumbai, Maharashtra, India.

Instrumentation

The following instruments were utilized for the formulation development and testing of mucoadhesive vaginal tablets: FTIR Spectrophotometer (FTIR6100) by JASCO, USA; Differential Scanning Calorimetry (DSC7020) by Hitachi, Japan; pH meter (Weltronix PM100) and Rotary tablet compression machine (Model RSB4-1, No. of station 10, Tooling B) by Karnavati engineering, Ahmedabad, India; Dissolution apparatus (TDT-08L) by Electrolab, Mumbai, India; Pfizer Hardness Tester (Tab-Machines T-SHT-17) by Mumbai, India; Roche Friabilator by Electrolab, Mumbai, India; Orbital shaker (CSI-24, BL) by Remi laboratory, Ahmedabad, India; UV-1800 and UV Probe 2.35 by Shimadzu, Japan. The AUW 220D Electronic balance, manufactured by Shimadzu Corp. in Japan, was used to measure the weight of all substances.

Solubility enhancement of Quercetin via HP-ß–Cyclodextrin Inclusion Complex

Quercetin's limited solubility and permeability hinder its therapeutic efficacy. This study utilized complexation with hydroxypropyl-β-cyclodextrin (HP-β-CD) to enhance solubility. Cyclodextrins (CDs), made of glucopyranoside sugar rings, improve drug solubility and bioavailability due to their unique structural properties **[33,34]**. HP-β-CDs are particularly valuable in pharmaceuticals for their cost-effectiveness and ability to encapsulate drugs, enhancing solubility and stability **[35]**.

Kneading Method

Quercetin and HP-ß-CD inclusion complexes were prepared by kneading at molar ratios of 1:1, 1:2, 1:3, 1:4, and 1:5. A water-ethanol (1:1) mixture was added to form a slurry, into which quercetin was gradually incorporated. After 60 minutes of trituration, the paste was dried at 45°C for 24 hours, sieved through a #40 sieve, and stored in a desiccator.

Phase Solubility Study

Phase solubility studies were conducted in water and simulated vaginal fluid (SVF, pH 7.0) following the method of Higuchi and Connors **[36]**. Quercetin-HP-ß-CD complexes at various molar ratios were added to 1 ml of water, agitated in an orbital shaker at 37±0.5°C for 24 hours, and then centrifuged at 8000 rpm for 10

minutes. The supernatant was filtered through a 0.45 μm Millipore filter, and Quercetin levels were measured using a zero-order UV spectrophotometric method at 258 nm ($y = 0.0649x + 0.012$, $R^2 = 0.9979$). The experiment was repeated three times in both water and SVF, and the solubility of pure Quercetin was also evaluated under identical conditions. The thermodynamic parameter Gibbs free energy (ΔG°) was utilized to evaluate the solubility of quercetin **[37]**.

Characterization of Quercetin-HP-β-Cyclodextrin Inclusion Complex using FTIR and DSC study

FTIR Spectroscopy Study

Infrared spectra were obtained using a JASCO FTIR-6100 spectrophotometer (4000-400 cm^{-1}) by dispersing the sample in KBr. The resolution was 0.15 cm^{-1} with a scan speed of 20 scans/second for both Quercetin and the Quercetin-HP-ß-CD inclusion complex.

DSC Study

Temperature characteristics were analysed using a HITACHI DSC 7020 in a nitrogen atmosphere. The samples were heated at 10°C/min from ambient temperature to the melting point, using an empty aluminum pan as a reference. Both Quercetin and the Quercetin-HP-ß-CD inclusion complex were analysed.

Formulation and Development of Mucoadhesive Vaginal Tablet

The mucoadhesive vaginal tablets were formulated using the direct compression technique with various polymer grades. Fluconazole was sieved through a #40 sieve, and the Quercetin-HP-ß-Cyclodextrin complex through a #44 sieve. Talc, diluent, and selected polymers were also sieved using #40. The mixtures were compressed into tablets averaging 830 mg using a Rotary tablet compression machine (Model RSB4-1, 10 stations). The optimized formulation comprises the active components enumerated in the **Table 1**.

Table 1: Composition of Optimized Mucoadhesive Vaginal Tablet

Each Mucoadhesive Vaginal Tablet Contained Following Ingredients			
Sr. No.	**Composition**	**Amount (mg)**	**Significance of Ingredient**
1	**Fluconazole**	**100**	**Antifungal**
2	**Quercetin-HP-B-Cyclodextrin Inclusion Complex**	**281.64**	**Antifungal and Biofilm inhibitors**
3	**Carbopol 934P**	**61.24**	**It is employed as a binder and controls the release of active medicament upon swelling.**
4	**HPMC K4 M**	**63.15**	**Mucoadhesive polymers**
5	**Avicel 102**	**304.61**	**Avicel facilitates effective dry blending, yielding tablets with high hardness, low friability, and excellent compressibility and colour stability.**
6	**Mg. Stearate**	**14**	**It is used as a lubricant additive to reduce hardness and increase disintegration time.**
7	**Talc**	**7**	**As a lubricant and diluent, it enhances powder flow and facilitates easy swallowing of tablets.**
Total Weight/tablet		**831.64**	

Optimization of Mucoadhesive In-situ Gel Formulation Using 3^2 Full Factorial Design In this study, a quality by design (QbD) approach was utilized, employing a design of experiments (DoE) methodology to systematically investigate the relationship between critical material attributes (CMAs) and critical quality attributes (CQAs). A 3^2 full factorial design (FFD) was established to evaluate all combinations of two independent variables at three levels. Specifically, the study focused on optimizing the polymer composition in vaginal tablets, with the variables being the concentration of the swelling polymer, Carbopol 934P (X1 = 50 to 150% w/w), and the concentration of the mucoadhesive polymer HPMCK4M (X2 = 50 to 150% w/w). All other material attributes and process parameters were maintained constant. The response factors analysed included the percentage cumulative drug release (CDR) of fluconazole (FCZ) at 60 minutes (Y1 ≥ 80%), the percentage CDR of quercetin (QCT) at 120 minutes (Y2 ≥ 80%), and the percentage swelling index (Y3 ≥ 60%). The experimental design comprised nine trials, facilitated by Design Expert 11.0.4.0 software (Stat-Ease, Inc., Minneapolis).

Evaluation Parameters of Mucoadhesive In-Situ Vaginal Tablet

Evaluation of Pre-compression Parameters

A precompression assessment evaluates the compressibility and flowability of a powdered mix, impacting weight variation and hardness **[38]**. Flowability affects die feeding and content uniformity **[39]**. The flowability of powder may be estimated by considering the angle of repose, bulk density, tapped density, Carr's compressibility index (CI), and Hausner ratio (HR) **[38-42]**.

Evaluation of Post-Compressional Parameters

Measuring tablet hardness and friability is essential to ensure they withstand abrasion or chipping during packing, handling, and shipping **[43]**. The post-compression parameters of the tablet encompass tablet dimensions, hardness, weight variation, and friability **[43-46]**.

Swelling Study

An appropriate swelling property will enhance the mucoadhesion and enable controlled release of the drug **[47]**. The vaginal tablet's swelling index was measured using Simulated Vaginal Fluid (SVF) at pH 7.00. The initial weight (w1) was recorded, and the tablet was placed in 10 ml of SVF (pH 7.0) in a petri dish at 37±1°C for 4 hours. The tablet was then reweighed, and the resulting weight (w2) was recorded. The formula for calculating the swelling index is expressed as Formula : Swelling index = 100 * (w2-w1)/w1

pH

Tablets were immersed in 1 mL of distilled water for 2 hours, and the surface pH was measured with a calibrated digital pH meter by placing the electrode near the tablet surface. This procedure was repeated three times **[48,49]**. To mitigate mucosal irritation, it is essential to maintain the pH within the normal range of 3.8 to 4.5.

In-vitro Evaluation of Mucoadhesive Strength and Force of Adhesion

Place the vaginal tablet and fresh chicken pouch mucosal membrane on a plank or platform and wet with pH 7.0 SVF buffer. They are held in one balancing arm. After moistening the chicken pouch mucosal membrane with SVF (pH 7.0), the mucoadhesive vaginal tablet was gently placed for five minutes. To ensure a firm connection upon contact, a pre-load force is applied. The second arm positions the weights, which are gradually raised until gravity separates the tablet from the tissue. The experiments were conducted in triplicate, and average values with standard deviations were computed. The force of adhesion was expressed using formula: Force of adhesion (Newton) = (Mucoadhesion strength (g)/100)*9.81

Measurement of Mucoadhesion Time

The duration of mucoadhesion was determined by measuring the time it took for the tablet to detach from the mucous membrane of the chicken pouch. A locally modified USP paddle apparatus (dissolution test equipment type II) was used for measurement of mucoadhesive time. A mucoadhesive tablet was moistened with 1 droplet of SVF (pH 7) and carefully attached to the freshly exposed chicken pouch mucosal membrane for 30 seconds. The tablet along with mucus membrane was fixed using a glass slide and submerged in a dissolving bowl containing 250 mL of SVF at a temperature of 37±1°C. It was then attached to the paddle of the dissolution equipment. The vaginal cavity environment was replicated by swirling the paddle slowly for 5 minutes, and the adhesion of the tablet was assessed **[50]**.

Content Uniformity

The average weight of 20 tablets was first determined and then pulverized using a mortar and pestle. A powder equivalent to 10 mg of FCZ was dissolved in a 100 ml volumetric flask with methanol, shaken for 10 minutes, and filtered through Whatman filter paper no. 1. The resulting solution contained 100 µg/ml FCZ and 25 µg/ml QCT. Next, 4.4 ml of this solution was diluted to 10 ml with SVF at pH 7.0, resulting in a final concentration of 44 µg/ml FCZ and 11 µg/ml QCT. FCZ was measured at the ZCP of QCT (268.03 nm), and QCT was measured at 400 nm in accordance with our previously published validated first-order derivative UV-spectrophotometry method **[51]**.

In-Vitro Drug Release Study

A paddle stirrer operated at 50 rpm in 500 ml of SVF at pH 7.00, maintained at 37±0.5°C. The vaginal tablet, attached to a glass disc with cyanoacrylate glue, was placed at the vessel's bottom. Samples (5 ml) were collected at 5, 10, 20, 30, 45, 60, 90, 120, 150, and 180 minutes, with the medium replaced by fresh SVF. After filtration through 0.45 µm Whatman paper, drug content was analysed using a developed First-order UV spectrophotometry method with SVF pH 7.0 as the blank. The study was repeated three times **[51, 52-54]**.

Drug Release Kinetic Analysis

Several kinetic models, such as the zero order model, first order model, Higuhi model, and Korsmeyer-Peppas kinetic model, were used **[55, 56]**. The y-axis and x-axis of each in vitro kinetics model were graphed **[43, 57]**.

FTIR and DSC Study of Optimized Validated Batch

The drug polymer interaction study of final validated batch was assessed using previously mentioned process using FTIR Spectrophotometer (JASCO FTIR-6100, Japan) and differential scanning calorimetry (DSC 7020-HITACHI, Japan).

Antifungal Studies of Mucoadhesive Vaginal Tablet Formulation

The broth microdilution method was used to determine the minimum inhibitory concentrations (MICs) of FCZ alone and in combination with QCT against Itraconazole-resistant *C. albicans* isolates. This was performed in 96-well microtiter plates. The fungal suspension was prepared with a dilution of 10^3 CFU/ml in RPMI 1640 medium, with FCZ and QCT combined in a 4:1 ratio of developed tablet formulation. RPMI 1640 was added to each well to reach a final volume of 200 µL. A drug-free well served as a control, and wells containing only RPMI 1640 were used as negative controls. The plates were incubated at 35°C for 24 hours. Growth inhibition was visually assessed and quantified by measuring the optical density at 492 nm. The MIC80 is defined as the minimum concentration that inhibits 80% of yeast growth compared to the control.

RESULTS AND DISCUSSIONS

Solubility enhancement of Quercetin (QCT)

Phase Solubility Study

Table 2 shows QCT's limited solubility in water and SVF at pH 7.0. However, the QCT-HP-β-cyclodextrin inclusion complex significantly increased QCT solubility in both media. Using the minimum necessary amount of cyclodextrin is crucial, as excessive amounts can hinder complex formation and reduce drug bioavailability **[58]**. The high molecular weight of cyclodextrin can also pose challenges for incorporation into a vehicle **[59]**. A QCT to

HP-β-cyclodextrin ratio of 1:3 was found to increase QCT solubility in SVF at pH 7.0 by 0.26-fold and was chosen for the formulation of mucoadhesive vaginal tablets.

Characterization of Quercetin-HP-β-Cyclodextrin Complex by FTIR and DSC

FTIR Study

The IR spectra of quercetin showed distinct bands at 3274.54 cm^{-1} (broad C-OH stretch, phenol) (Peak band-1), 2888.84 cm^{-1} (C-H stretching, unsaturation) (Peak band-2), 2071.17 cm^{-1} (C-H bending, aromatic) (Peak band-3), 1662.34 cm^{-1} (C=O stretching, conjugated ketone) (Peak band-4), and 1604.48 cm^{-1} (C=C stretching, aromatic) (Peak band-5). In the FTIR spectrum of the Quercetin-HP-β-Cyclodextrin inclusion complex, peaks related to the aromatic ring system (2888.84 cm^{-1}, 2071.17 cm^{-1}, and 1604.48 cm^{-1}) were absent, indicating interaction with HP-β-Cyclodextrin's hydrophobic cavity. The 3274.54 cm^{-1} peak shifted to a lower wave number, and the 1662.34 cm^{-1} peak shifted to a higher wave number, suggesting weak interactions between these functional groups and HP-β-Cyclodextrin **(Figure 1)**.

DSC Study

The DSC thermogram of pure QCT showed two endothermic transitions: a Glass Transition (Tg) at 119°C, indicating water loss from hydrated quercetin, and a second at 323.3°C, signifying rapid liquefaction and confirming its crystalline nature **(Figure 2a)**. The absence of these peaks in the DSC spectrum of the QCT-HP-β-Cyclodextrin complex indicates that QCT is fully encapsulated within HP-β-Cyclodextrin, demonstrating strong interaction **(Figure 2b) [60-62]**.

Optimization of Polymers Concentration Using 3^2 Full Factorial Design (FFD)

For 3^2 factorial designs, a total of nine experiments were performed for two factors at three levels each. All the nine formulations were evaluated for Average % Cumulative Drug Release (CDR) of FCZ at 60 min, Average % CDR of QCT at 120 min, and % Swelling Index (SI). The relationship between the two independent variables (X1 and X2) and three dependent variables (Y1, Y2, and Y3) in the factorial design was determined using Design-Expert® 11.0.4.0 through multiple regression analysis (MLR) and ANOVA. The optimal mathematical model was selected based on correlation coefficients (R^2), coefficient values, and Fisher's ratio with P values, with statistical significance determined at a 5% level ($p < 0.05$). The nine experimental runs conducted are outlined in **Table 3**, which also includes the design matrix presented in actual values.

Data for all three responses were analysed using various statistical models. Responses

Y1 and Y2 yielded the highest adjusted and predicted R^2 values in the linear model, while response Y3 showed the highest values in the quadratic model, reflecting interaction effects between selected variables and responses. All responses demonstrated adequate precision (> 4) and significant P values (< 0.05). A higher Model F-value indicates model significance, and R^2 values close to 1 confirm the model's reliability. Regression statistical analysis of the three responses is presented in **Table 4**.

The data indicate that Factor X1 (Carbopol 934P concentration) and Factor X2 (HPMCK4M concentration) significantly impact Y1, Y2, and Y3. HPMCK4M concentration significantly affected the %CDR of FCZ and QCT, whereas Carbopol 934P had a more substantial effect on the % swelling index.

Validation of Design Model

The overlay plot, created by superimposing contour plots, identifies the common area for generating standard checkpoint batches, with the optimal region highlighted in yellow **(Figure 4)**. Three checkpoint sets were selected, and their mathematical models were validated against chosen CQAs to ensure alignment with anticipated values. The % prediction error for all responses was calculated to be less than 5% **(Table 4)**, indicating the high predictive accuracy of the developed model **[63, 64]**.

Figure 3 shows 2D and 3D plots illustrating the effect of independent variables on each response.

Evaluation Parameters of Mucoadhesive Vaginal Tablet (Check Point Batch)

Precompression Parameters

The optimal value for outstanding flow behaviour of the powder is indicated by an angle of repose with an optimum range of 25-30 θ, a Carr's Index with an ideal value below 20, and a Hausner ratio below 1.25. Batch F1 is the best suited batch that fulfils all the given requirements **(Table 6)**.

Post Compression Parameters

The ideal values for the post-compression parameters of the vaginal tablet are as follows: hardness should be between 4-10 kg/cm^2, friability should not exceed 1%, weight variation and thickness should not deviate more than 5% from the average, and the tablet's pH should be similar to the normal vaginal pH. Batches F1-F3 all meet these criteria **(Table 7)**.

Table 8 presents the % CDR of FCZ and QCT for the validation batch. Increased polymer concentration led to a higher swelling index, enhancing both mucoadhesion force and duration. In vitro drug release showed FCZ released almost entirely within 90-120 minutes, while QCT released in 150 minutes. Therefore, a mucoadhesion duration of around 150 minutes is ideal. Batch F1 is the most acceptable in this context since it had an

adhesion time of 273 minutes, while the other two batches, F2 and F3, took a little longer time which is unnecessary.

In-Vitro Drug Release Study

The results indicated that the FCZ had a drug release that mostly took place between 90-120 minutes (Figure 5a), whereas the release of QCT took place within 150 minutes **(Figure 5b)**.

Determination In-Vitro Kinetic Release

The data analysis revealed that FCZ adhered to the Korsmeyer-Peppas model, with correlation coefficients (R^2) of 0.9803 for Batch F1, 0.9819 for Batch F2, and 0.9917 for Batch F3 **(Figure 6a)**. In contrast, QCT conformed to the Higuchi model, exhibiting R^2 values of 0.9899 for Batch F1, 0.9881 for Batch F2, and 0.9894 for Batch F3 **(Figure 6b)**.

Assay of Mucoadhesive Vaginal Tablet

The method was used to measure FCZ and QCT in the vaginal tablets. The analysis was conducted in triplicate using First order derivative UV-spectrophotometry technique in SVF, pH 7.00. The findings reported that all three validation batches demonstrated that the FCZ assay ranged from 97.19% to 101.52%, while the QCT assay ranged from 97.79% to 100.44%. All three validation batches meet the requirements for content uniformity.

Drug Polymer Compatibility Study

Based on all evaluation data of check point validation batches, Batch F1 is the best and should be used for further verification of drug-polymer/excipient compatibility, particularly in FTIR and DSC studies.

FTIR Spectroscopy Study

The FTIR spectrum of the optimized formulation (F1 batch) in **Figure 7** showed characteristic peaks for FCZ: 3282.25 cm^{-1} (C-OH stretching), 2915.84 cm^{-1} (C-H stretching, alkane), 1623.77 cm^{-1} and 1508.06 cm^{-1} (C=C stretching, aromatic), and 1149.37 cm^{-1} (C-F stretching). The disappearance of the 1272.68 cm^{-1} peak (C-N stretching) indicated minimal interaction between FCZ and excipients. In contrast, QCT displayed strong interactions with HP-β-CD, evidenced by the loss of several functional group peaks, including 3274.54 cm^{-1} (C-OH stretch), 2888.84 cm^{-1} (C-H stretching), 2071.17 cm^{-1} (C-H bending), 1662.34 cm^{-1} (C=O stretching), and 1604.48 cm^{-1} (C=C stretching).

DSC Study

The DSC spectrum of the optimized mucoadhesive vaginal tablet formulation (F1 batch) in **Figure 8** provides insights into thermal properties and component interactions. The endothermic peak of FCZ, originally at 139°C, showed reduced intensity and shifted lower, indicating minimal interaction with excipients. In contrast, the endothermic peak of QCT, initially at 323°C, was absent in the F1 batch, suggesting significant interaction with the polymers and excipients.

Antifungal activity:

The MIC80 is defined as the minimum concentration required to inhibit 80% of yeast growth compared to the control. For itraconazole-resistant *Candida albicans*, the MIC for both FCZ and QCT standards was determined to be 1000 µg/mL. However, the mucoadhesive vaginal tablet formulations demonstrated a significantly lower MIC of 500 µg/mL against this resistant strain. The MIC value for the developed mucoadhesive vaginal gel formulation being half that of the individual drugs indicates a synergistic effect. This synergy between QCT and FCZ effectively reduces the fungal burden, showcasing the potential of the combination in combating resistant fungal infections.

Table 2: Solubility of Quercetin-HP-β-Cyclodextrin Inclusion Complex in Water and SVF, pH 7.0

Quercetin-HP-β-cyclodextrin Inclusion complex Molar ratio	Solubility in Water (mg/ml) (n=3)		Gibb's Free Energy (ΔG°) (n=3)		Increased fold of solubility (n=3)	
	Average	SD	Average	SD	Average	SD
Pure Quercetin	0.43	0.0065	-	-	-	-
01:01	0.54	0.0209	-547.77	196.6009	0.10	0.0040
01:02	0.71	0.0252	-712.70	410.2205	0.14	00048
01:03	0.88	0.0191	-539.22	337.8519	0.17	0.0037
01:04	1.48	0.0168	-1340.45	404.2274	0.28	0.0032
01:05	0.96	0.0407	1112.71	117.6744	0.18	0.0078
Quercetin-HP-β-cyclodextrin Inclusion complex Molar ratio	Solubility in SVF, pH 7.00 (mg/ml) (n=3)		Gibb's Free Energy (ΔG°) (n=3)		Increased fold of solubility (n=3)	
	Average	SD	Average	SD	Average	SD
Pure Quercetin	0.48	0.0464	-	-	-	-
01:01	0.59	0.0508	-532.08	25.3268	0.11	0.0098
01:02	0.78	0.0782	-733.19	466.2351	0.15	0.0150
01:03	1.36	0.0102	-1447.58	247.2544	0.26	0.0020
01:04	1.11	0.0644	520.53	165.8449	0.21	0.0124
01:05	0.97	0.0436	339.61	74.5473	0.19	0.0084

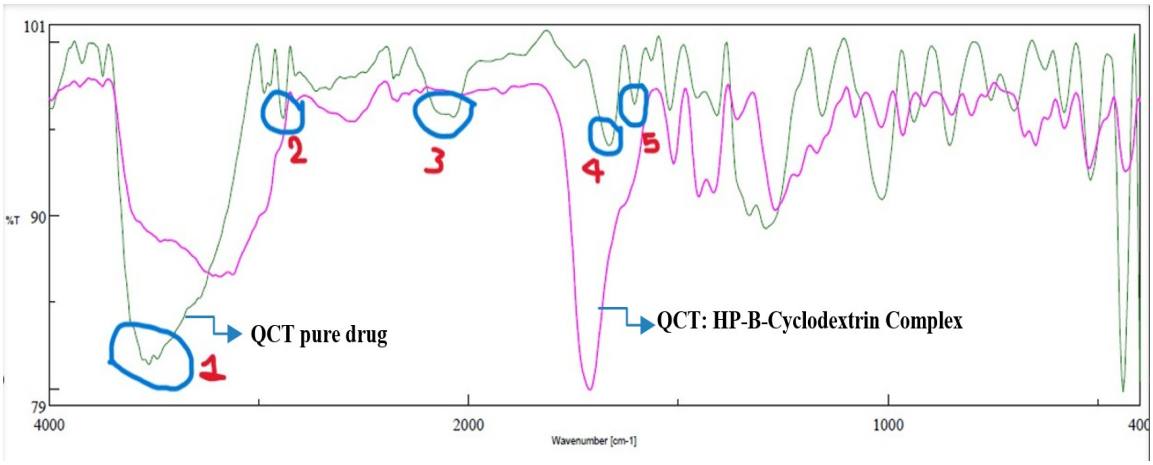


Figure 1: Overlay FTIR Spectrum of QCT and QCT:HP-B-Cyclodextrin Complex

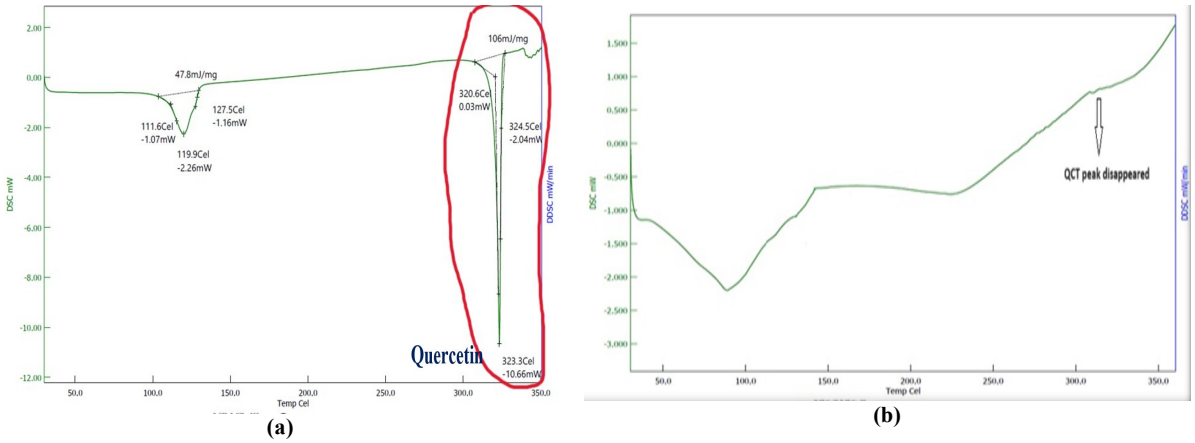


Figure 2: (a) DSC Spectrum of Quercetin (b) DSC Spectrum of Quercetin-HP-β-Cyclodextrin Inclusion Complex

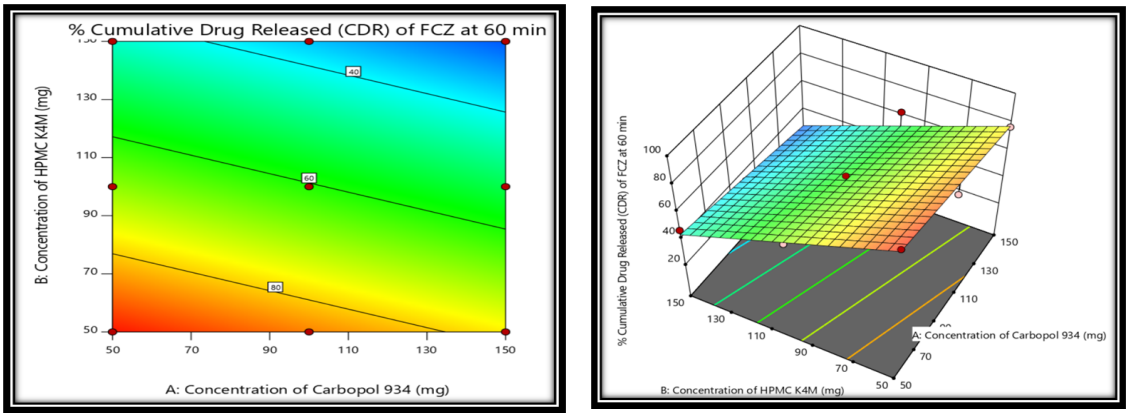
Table 3: 3^2 Full Factorial Design (FFD) Batches

Batch No.	Coded Value		Non coded Value		Average % Cumulative Drug Release (CDR) of FCZ at 60 min* ± SD (Y1)	Average % Cumulative Drug Release (CDR) of QCT at 120 min* ± SD (Y2)	% Swelling Index (SI)* ± SD (Y3)
	Factor 1	Factor 2	Factor 1	Factor 2			
	Conce. of Carbopol 934P (X1) (mg)	Conce. of HPMCK 4M (X2) (mg)	Conce. of Carbopol 934P (X1) (mg)	Conce. of HPMCK4M (X2) (mg)			
B1	1	-1	150	50	77.12 ± 1.6013	82.04 ± 1.1060	83.70 ± 0.8690
B2	-1	-1	50	50	67.24 ± 1.0869	78.67 ± 1.1530	68.50 ± 0.6950
B3	1	0	150	100	62.82 ± 1.0450	71.57 ± 1.2560	89.10 ± 1.1050
B4	-1	0	50	100	94.80 ± 0.3000	91.33 ± 1.0880	60.50 ± 1.0390
B5	0	0	100	100	63.87 ± 0.7308	77.48 ± 0.5050	87.50 ± 1.0900
B6	-1	1	50	150	32.82 ± 1.1312	69.62 ± 1.2950	95.70 ± 0.8370
B7	1	1	150	150	21.66 ± 1.1315	65.70 ± 1.1180	98.78 ± 0.7380
B8	0	1	100	150	78.49 ± 0.5656	86.06 ± 1.3120	79.30 ± 0.7620
B9	0	-1	100	50	46.95 ± 0.9550	70.93 ± 0.9400	76.70 ± 1.3110

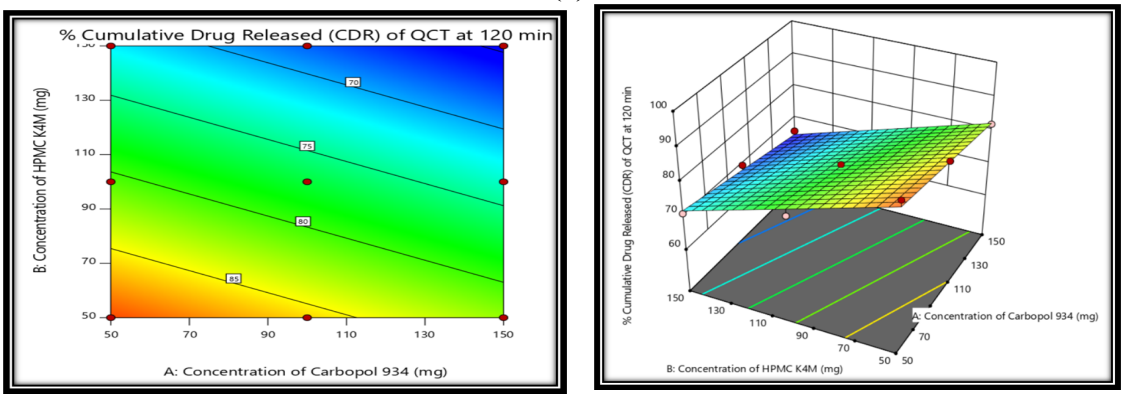
*n=3

Table 4: Regression statistical Analysis for the Observed Responses of 3^2 Full Factorial Design (FFD)

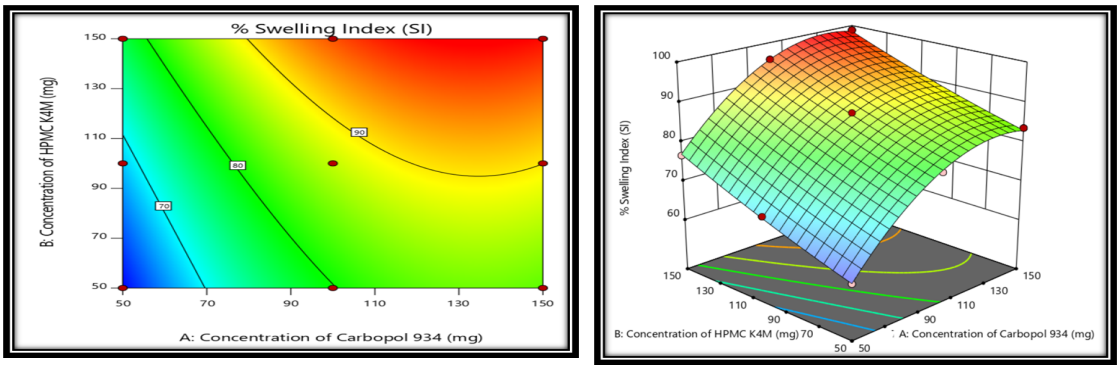
Statistical Parameters	Response Y1	Response Y2	Response Y3
Suggested Model	Linear	Linear	Quadratic
R^2	0.9481	0.9733	0.9983
Adjusted R^2	0.9307	0.9644	0.9954
Predicted R^2	0.8860	0.9365	0.9810
Adequate Precision	18.5886	27.2553	54.9267
PRESS Value	489.70	35.86	259.63
F-Value	54.75	109.39	345.36
P-Value	<0.0500	<0.0500	<0.0500
Polynomial Equation	Y= 60.64-7.90A-24.83B	Y= 77.04-3.60A-8.86B	$Y=87+10.98A+7.95B-0.2800AB-7.95A^2+0.7467B^2$



(a)



(b)



(c)

Figure 3: 2D and 3D contour plot for: a) Y1response, b) Y2 response, c) Y3 response

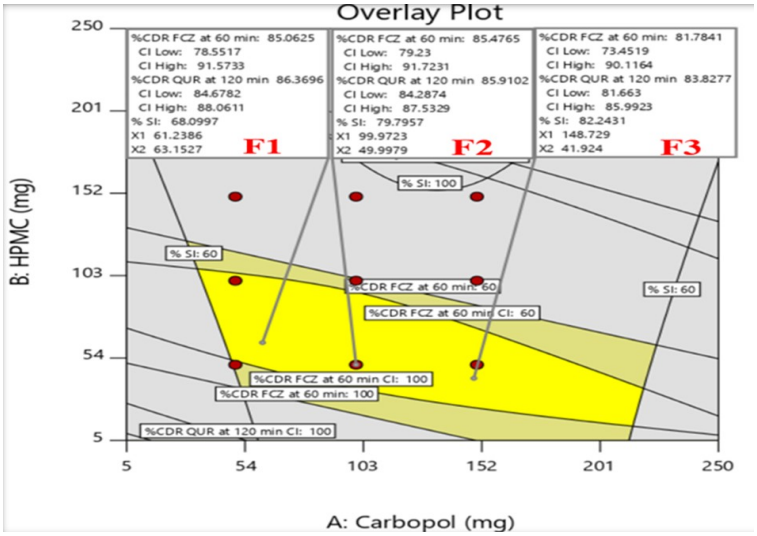


Figure 4: Overlay Plot Created by Design Expert Software

Table 5: Validation Data of Check Point Batches Generated from Design Space

Check point batches	% Cumulative Drug Released (CDR) of FCZ (Y1)			% Cumulative Drug Released (CDR) of QCT (Y2)			% Swelling Index (SI) at 4 h (Y3)		
	Pred. Value	Exp. value* ± SD	% Error	Pred. Value	Exp. value* ± SD	% Error	Pred. Value	Exp. value* ± SD	% Error
F1	85.06	84.05± 1.4908	1.19	86.37	85.12± 0.6768	1.45	68.1	66.79± 1.0627	1.93
F2	85.48	83.49± 0.5682	2.32	85.91	83.78± 1.2093	2.48	79.8	77.71± 1.0416	2.61
F3	81.78	79.59± 1.2239	2.68	83.83	80.99± 1.4304	3.39	82.24	78.91± 1.3721	4.06

*Average of three determination

Table 6: Results of Precompression Parameters

Check point batches	Angle of repose (θ)* ± SD	Bulk density (gm/cm^3)* ± SD	Tapped density (gm/cm^3)* ± SD	Carr's index* ± SD	Hausners ratio ± SD
	Precompression Parameters				
F1	25.97 ± 0.4190	0.44 ± 0.016	0.52 ±0.0047	15.89 ± 3.7796	1.19 ± 0.0540
F2	22.67 ± 0.3859	0.42 ± 0.0005	0.51 ±0.0047	17.54 ± 0.1600	1.21 ± 0.0020
F3	34.97 ± 0.1700	0.40 ± 0.0082	0.51 ±0.0047	23.57 ± 1.0247	1.31 ± 0.0180

*Average of three determination

Table 7: Results of Post Compression Parameters

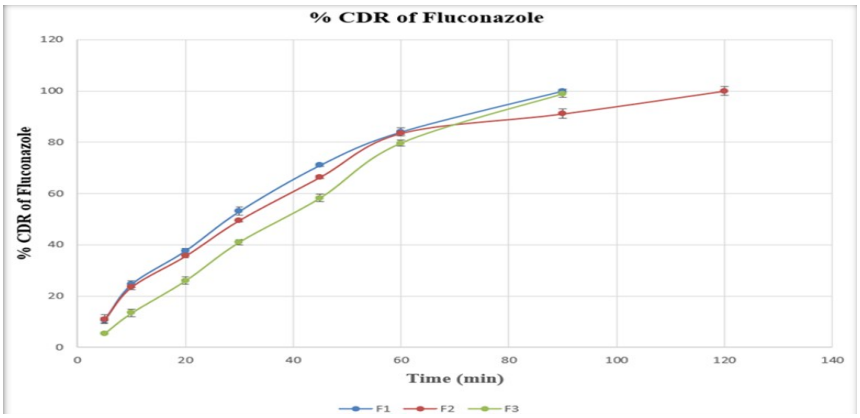
Check point batches	Hardness (kg/cm^2)* ± SD	Thickness (mm)* ± SD	Friability (%w/w) ± SD (n=10)	Tablet surface pH* ± SD	% Weigh Variation (n=20)
	Post Compression Parameters				
F1	6.40 ± 0.0216	6.30 ± 0.0816	0.08 ± 0.0047	4.63 ± 0.0082	831.53 ± 4.1356
F2	6.93 ± 0.1247	6.23 ± 0.0471	0.07 ± 0.0082	4.63 ±0.0094	830.38 ±4.1675
F3	7.20 ± 0.0816	6.20 ± 0.0816	0.04 ± 0.0082	4.58 ±0.0047	829.87 ± 4.2515

*Average of three determination

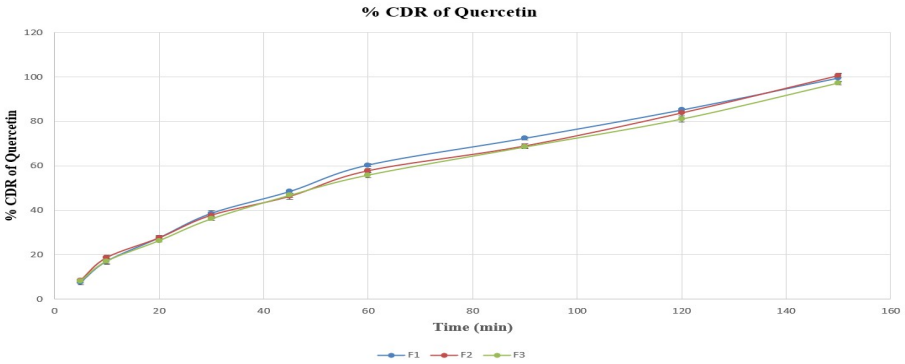
Table 8: % CDR (Cumulative Drug Release), % Swelling Index (SI), Force of Adhesion and Mucoadhesion Time

Check point batches	% Cumulative Drug Released (CDR) of FCZ at 60 min* ±SD	% Cumulative Drug Released (CDR) of QCT at 120 min* ± SD	% Swelling Index (SI)* ±SD	Force of adhesion (Newton)* ± SD	Mucoadhesion Time (min)* ± SD
F1	84.05±1.4908	85.12±0.6768	66.79±1.0627	0.366±0.0082	273.117±1.3328
F2	83.49±0.5682	83.78±1.2093	77.71±1.0416	0.375±0.0073	291.43±1.7310
F3	79.59±1.2239	80.99±1.4304	78.91±1.3721	0.417±0.0051	312.35±0.5779

*Average of three determination

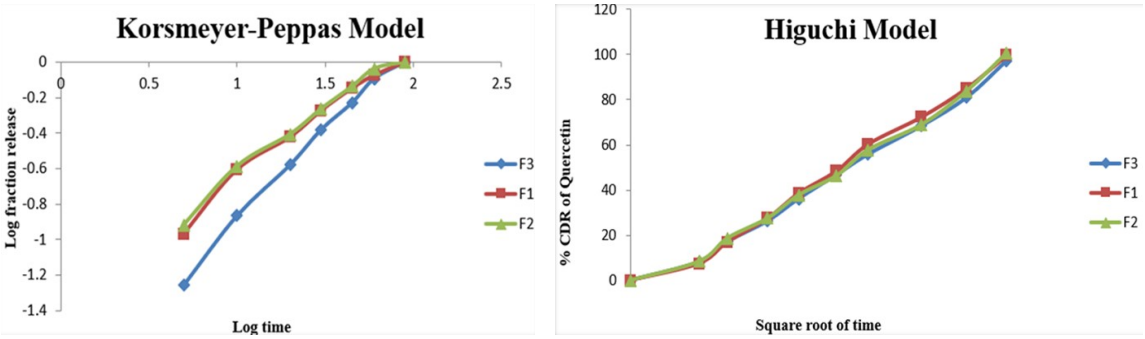


(a)



(b)

Figure 5: (a) %CDR of FCZ (b) %CDR of QCT



(a) (b)

Figure 6: (a) Kinetic Models of F1-F3 batches): a) Korsmeyer-Peppas Model of FCZ (b) Higuchi Model of QCT

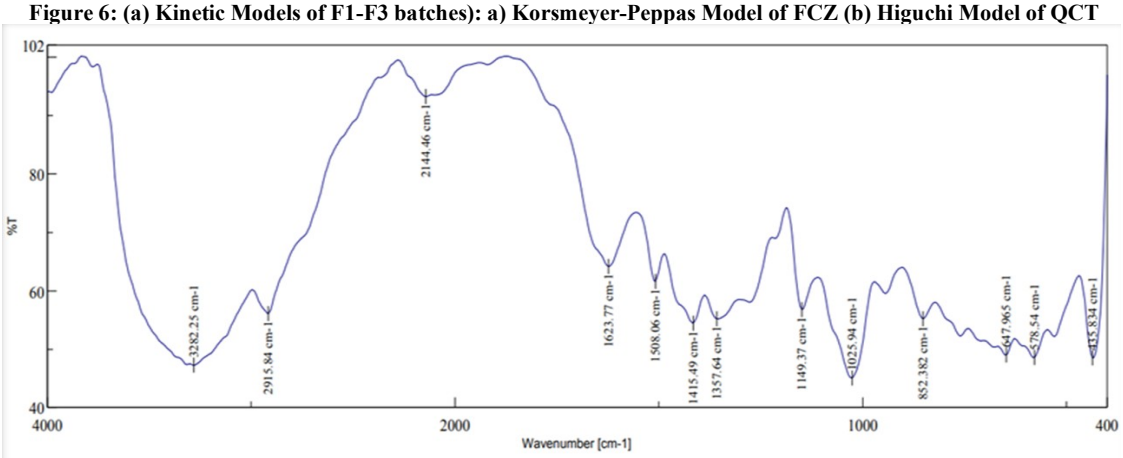


Figure 7: FTIR spectrum of optimized formulation (F1 batch)

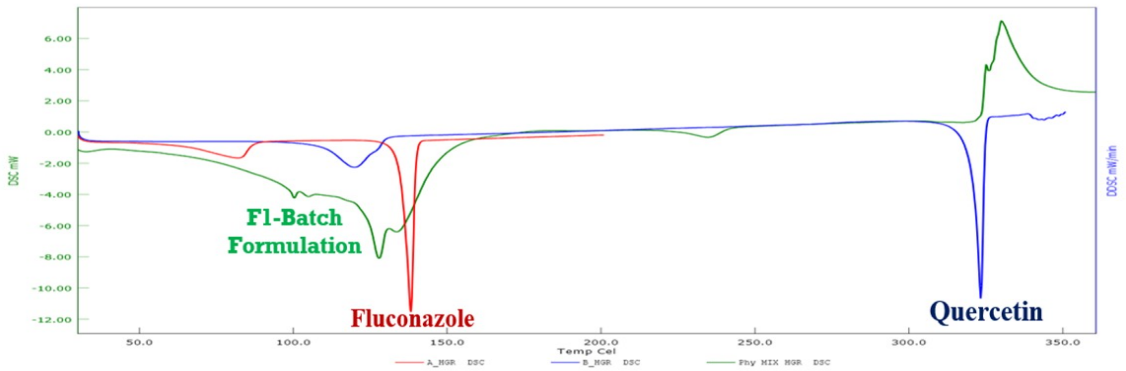


Figure 8: DSC Spectrum of FCZ, QCT and Sample (F1 batch)

CONCLUSION

To achieve rapid and effective therapeutic action within the vaginal cavity, the development of a mucoadhesive vaginal tablet incorporating FCZ and QCT represents an optimal strategy for vaginal administration. This formulation not only facilitates a swift onset of action but also prolongs the drug's residence time in the vaginal cavity. Designed for ease of application via an applicator, the tablet enhances user convenience.

The formulation offers several significant advantages, including minimized drug metabolism and improved bioavailability for poorly soluble compounds such as quercetin. Furthermore, it enhances cosmetic acceptability, promotes patient adherence, allows for scalability, and provides targeted efficacy against drug-resistant strains of *Candida albicans*. Consequently, this formulation is particularly beneficial in scenarios where fluconazole alone proves ineffective. The optimized formulation is detailed in Table 1.

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